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# Title

Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis

# Authors

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#### Abstract

#### Background

To eliminate mother-to-child transmission (MTCT) of hepatitis B virus (HBV), peripartum antiviral prophylaxis (PAP) may be required for HBV-infected pregnant women with a high risk of MTCT despite infant immunoprophylaxis. We conducted a systematic review and meta-analysis for the efficacy and safety of PAP, in order to inform the 2020 WHO guidelines.

# Methods

We searched four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chineselanguage (CNKI/Wanfang) databases for randomized (RCT) and non-randomized controlled trials (non-RCT) of PAP versus placebo or no PAP published through March 28<sup>th</sup>, 2019. Two reviewers independently extracted data. Odds ratios (OR) were pooled for the efficacy of PAP to reduce the risk of MTCT. Subgroup analyses were performed on the timing of initiating/stopping antivirals.

#### Findings

Of 7463 articles identified, 129 studies were included. The pooled ORs for RCTs were similar, at 0.10 (95% CI: 0.03-0.35) for 19 studies of tenofovir disoproxil fumarate (TDF), 0.16 (0.10-0.26) for 40 studies of lamivudine, and 0.14 (0.09-0.21) for 83 studies of telbivudine. The results were similar for non-RCTs. Subgroup analysis identified that initiation in the second trimester may be more beneficial than the third trimester (OR 0.23, 95% CI: 0.09-0.59). We found no increased risk of any infant or maternal safety measures following PAP, except for studies of lamivudine and telbivudine that detected drug-resistant mutations in some treated mothers.

Interpretation

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PAP is highly effective at reducing the risk of HBV MTCT. Our findings support the 2020 WHO recommendation of administering antivirals during pregnancy, specifically TDF, for the prevention of HBV MTCT.

Funding

WHO

#### **Research in context**

#### Evidence before this study.

Major international guidelines for the management of chronic hepatitis B virus (HBV) infection recommend the administration of peripartum antiviral prophylaxis (PAP) to pregnant women with high HBV viral load to prevent mother-to-child transmission (MTCT). The 2015 WHO guidelines utilized a systematic review and meta-analysis on the efficacy, safety, and costeffectiveness of PAP for the prevention of HBV MTCT. The systematic review only identified limited and low-quality evidence at that time; consequently, the WHO could not make a formal recommendation for use of PAP. Furthermore, only English-language databases were searched, although the majority of studies investigating the efficacy of PAP have been conducted in China and reported in Chinese journals that are not indexed in the English-language databases. Also, since that time, the results of several high-quality clinical trials have been published, especially for tenofovir disoproxil fumarate (TDF), a key first-line anti-HBV therapy.

#### Added value of this study.

Through a comprehensive search that widely covered both the English- and Chinese-language databases, this is the largest and most up-to-date systematic review and meta-analysis on this topic, including more than twice the number of studies compared to previously published systematic reviews. Furthermore, we thoroughly excluded studies with potentially overlapping patient populations. We found high efficacy of three antiviral therapy regimens, including TDF 300 mg (19 studies), lamivudine 100-150 mg (40 studies), and telbivudine 600 mg (83 studies), with protective ORs between 0.10 and 0.16 for RCTs and between 0.09 and 0.17 for non-RCTs. The large number of studies included enabled subgroup analysis on possible sources of

heterogeneity. Although efficacy did not vary by the timing of PAP discontinuation, we found that starting earlier in the second trimester might be more efficacious than in the third trimester. There was no evidence that the use of PAP is associated with an increased risk of fetal death, neonatal death, preterm birth, congenital abnormalities, postpartum hemorrhage, or postpartum hepatitis flare. Almost all studies sysmatically provided both hepatitis B birth dose vaccine (HepB-BD) and immune globulin (HBIG) to neonates, and no study evaluated an HBIG-free strategy.

#### Implications of all the available evidence.

In light of the findings of this meta-analysis, the WHO has made a recommendation for administration of TDF 300 mg starting from the 28<sup>th</sup> week of pregnancy until at least birth, in addition to the recommendation for at least three doses of hepatitis B vaccination including HepB-BD. Most studies were conducted in Asia, potentially limiting the applicability of findings to other regions with high HBV prevalence such as Africa. Research on the efficacy of PAP without HBIG is urgently needed, given the limited access to HBIG in many low- and middle-income countries.

## Introduction

Chronic infection with hepatitis B virus (CHB) represents a serious global health problem, affecting 257 million persons worldwide and causing 900,000 deaths annually due to chronic liver diseases such as cirrhosis and liver cancer.<sup>1</sup> In 2016, the World Health Organization (WHO) developed a global strategy to eliminate hepatitis B as a public health threat by 2030, with a goal to reduce its incidence by 90%, and its mortality by 65%.<sup>2</sup> To meet these objectives, it is crucial to eliminate mother-to-child transmission (MTCT) of HBV, because chronic infection is more likely to develop when infection occurs early in life, particularly at birth through MTCT.<sup>3</sup> Moreover, the risk of developing chronic liver diseases may be higher in those who acquired HBV infection through MTCT compared to those who acquire it through horizontal transmission later in life.<sup>4,5</sup>

To prevent MTCT, the WHO recommends that all infants receive at least three doses of hepatitis B vaccine, with the first dose administered within 24 hours of life.<sup>6</sup> However, the birth dose of hepatitis B vaccine (HepB-BD), even if given to neonates along with combined passive immunoprophylaxis using hepatitis B immune globulin (HBIG), does not prevent all MTCT,<sup>7</sup> particularly in those born to mothers with high viremia, as reported in a companion systematic review (*Boucheron P et al.*).<sup>8-10</sup> Consequently, MTCT remains a significant contributor to HBV incidence globally, and supplementary interventions to further decrease MTCT are needed.<sup>11</sup>

In 2014, the WHO commissioned a systematic review to examine the efficacy and safety of antiviral therapy administered during pregnancy for the prevention of MTCT. This review was restricted to English-language articles and identified only one observational study assessing the efficacy of tenofovir disoproxil fumarate (TDF), a key first-line anti-HBV therapy. Moreover,

there was limited evaluation of potential harms associated with the use of antivirals during pregnancy. Consequently, the WHO did not make a formal recommendation at that time.<sup>12</sup> Since then, several clinical trials using TDF have been published, and further evidence has become available regarding the risk of postpartum hepatitis flare in mothers after cessation of antivirals as well as for changes in bone mineral density in the infant.<sup>13-16</sup> We thus conducted an updated systematic review, searching both English- and Chinese-langauge databases, and meta-analysis on the efficacy and safety of peripartum antiviral prophylaxis (PAP) for prevention of MTCT, in order to inform the new WHO guidelines.<sup>17</sup>

#### Methods

Search strategy and selection criteria

We followed a protocol pre-registered in PROSPERO (CRD42019134614), and reported according to PRISMA guidelines.<sup>18</sup> Because many studies on HBV MTCT have been published in Chinese-language articles not indexed in Engligh-language databases, we searched four English-language (PubMed/EMBASE/Scopus/CENTRAL) and two Chinese-language (CNKI/Wanfang) databases from inception until March 28<sup>th</sup>, 2019. The search strategies used terms covering HBV AND antiviral therapy AND pregnancy (Appendix A). We also manually searched the references of included studies. There were no language restrictions. Conference abstracts were not considered.

We considered randomized controlled trials (RCT) or non-randomized controlled trials (non-RCT) that enrolled pregnant women with CHB, who received antiviral prophylaxis anytime during pregnancy, and reported the following outcomes: (i) MTCT, indicated by infant HBsAg positivity and/or HBV DNA positivity at 6-12 months of age; and (ii) any infant/maternal adverse events. The following antivirals were considered: adefovir (ADV), emtricitabine (FTC), entecavir (ETV), lamivudine (LAM), telbivudine (LdT), tenofovir alafenamide fumarate (TAF), and TDF. Control groups received no intervention or placebo. Non-RCTs were eligible if they were described as prospective or retrospective cohort studies, with control populations composed of pregnant women with CHB followed during the same time period but who did not receive antiviral prophylaxis (e.g. unwilling). Non-RCTs with a high risk of bias on the Newcastle Ottawa scale (i.e. score  $\leq$ 5) were excluded.<sup>19</sup> Throughout the paper, we used the term "peripartum antiviral prophylaxis (PAP)" rather than "peripartum antiviral therapy" in order to distinguish between antivirals that are given only for a few months surrounding pregnancy and delivery to prevent MTCT (the former) and antivirals given to women/mothers over a longer period, most often lifelong, for their own health benefit (the latter).

Two investigators independently: screened titles and abstracts for all publications identified through the English-language (AF and KY) and Chinese-language databases (YL and TZ); reviewed identified full-text papers; extracted data using a pre-piloted form (Appendix B); and assessed risk of bias using the Cochrane Collaboration tool for RCTs and the Newcastle-Ottawa Scale for non-RCTs (Appendix C).<sup>19,20</sup> A third reviewer resolved any discrepancies (YS). The following data were extracted: study characteristics, primary endpoint (HBsAg detected in infants at 6-12 months of age), secondary endpoint (HBV DNA in infants at 6-12 months), and maternal and infant safety outcomes including fetal/neonatal death, preterm birth, congenital

abnormalities, postpartum hemorrhage, postpartum hepatitis flare, antiviral resistance, and infant bone mineral density. Articles from the same study sites that had overlapping recruitment periods, enrolment criteria, and treatment types were considered to evaluate the same study population unless specifically indicated otherwise by corresponding authors, who we attempted to contact in all cases. Where multiple articles of the same study population were published, only the most recent article was included unless the risk of bias was lower in a different article.

#### Data analysis

The efficacy of PAP was assessed by pooling odds ratios (OR) for RCTs and non-RCTs separately. The primary and secondary endpoints were MTCT based on infant HBsAg positivity and HBV DNA positivity, respectively. The safety of PAP was assessed by pooling risk differences (RDs), rather than ORs, in order to include studies without events. Per-protocol analysis, with the denominator being the number of children with complete follow-up, was performed. If  $\geq 3$  studies were eligible for the analysis/sub-analysis, then estimates were pooled using the DerSimonian-Laird random-effects model. Statistical heterogeneity was assessed using the  $I^2$  statistic. Subgroup analyses were performed for the primary endpoint on the following potential sources of heterogeneity: study design (RCT vs non-RCT), WHO region, timing of treatment start/discontinuation, maternal characteristics (mean viral load at inclusion, HBeAg, HIV/HCV/HDV co-infections, HBV genotypes), infant immunoprophylaxis regimen (HBIG, HepB-BD), language used to report the work, quality of the study for non-RCTs, sample size (smaller studies with N≤30 in either treated or control group versus larger studies with N>30 in both treated and control group), and maternal viral load criteria (pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women

versus other than that). The presence of subgroup effects was evaluated using the fixed-effects inverse-variance method. In addition to *a priori* defined subgroup analysis looking at differences by the time of treatment initiation, and in order to further explore optimal timing of PAP, *post hoc* meta-analyses were performed including only studies with multiple treatment arms. These analyses directly compared the efficacy, viral load prior to treatment initiation, and viral load prior to delivery, for participants with earlier (2<sup>nd</sup> trimester) versus later (3<sup>rd</sup> trimester) start. The latter two analyses involved pooling mean differences in viral load at the various timepoints in order to generate the standardized mean difference (SMD). Also *post hoc*, where possible we examined differences in safety outcomes as per timing of treatment initiation. Where there were  $\geq 10$  studies,<sup>21</sup> small sample effects, a potential marker for publication bias, were evaluated using funnel plots and Egger's test. Analyses were done using STATA 13 (StataCorp LP, CollegeStation, TX). The evidence quality for primary efficacy analyses and safety analyses were evaluated using the GRADE framework,<sup>22</sup> based on risk of bias, inconsistency, imprecision, indirectness, and reporting bias.

# Role of the funding source

This project was funded by the WHO. The funder formulated the review questions, but had no role in study design, data collection, analysis, interpretation, or report writing. The corresponding author had full access to all data in the study and was ultimately responsible for the decision to submit for publication.

# Results

Study selection

Of 7463 articles identified, 595 were assessed in full text, and 129 original studies (reported in 158 articles) ultimately met eligibility criteria: 33 RCTs and 96 non-RCTs (Figure 1). These studies initially enrolled a total of 18,112 HBV-infected mothers (9573 treated, 8539 untreated) and 17,582 of the infants that born to these mothers had complete follow-up (9411 from treated mothers, 8171 from non-treated mothers). The following antivirals were evaluated using meta-analysis: TDF 300 mg (19 studies, 1092 mothers/1072 infants), <sup>13-15,23-44</sup> LAM 100-150 mg (40 studies, 2080 mothers/2007 infants), <sup>32-35,39,45-88</sup> LdT 600 mg (83 studies, 6036 mothers/5971 infants). <sup>30,38,42,43,46,50,56,60,62,64,76,79,80,85,89-173</sup> No meta-analysis was done for the two eligible studies on LdT 100 mg (65 mothers/65 infants)<sup>51,174</sup> or for the one study each on ADV 10 mg (42 mothers/42 infants).<sup>175</sup> and ADV 500 mg (258 mothers/254 infants);<sup>176</sup> these results are summarized in Appendix D.

Study characteristics (Appendix E)

Most studies (121/129, 93.8%) took place in China. One study was conducted in both China and the Philippines, and one study each was conducted in Japan, Taiwan, Thailand, Australia, Egypt, Turkey, and Ireland. Only eight studies reported HBV genotypes for all enrolled mothers: genotypes B/C in seven Asian studies;<sup>24,29,39,76,128,139,160</sup> and genotypes B/C/D/E in one Irish study.<sup>67</sup> In 79/129 studies (61.2%), the inclusion criteria specified a high (>5.0 log10 IU/mL) maternal viral load threshold at baseline for all participants. Most studies exclusively included HBeAg-positive women (83/129, 64.3%), 9 studies included a mix of HBeAg-positive and HBeAg-negative women, and one study exclusively included HBeAg-negative women;<sup>165</sup> the remaining 36 studies (27.9%) did not report on HBeAg positivity. All of the included studies

either excluded women co-infected with HIV, HCV, or HDV, or did not report on their prevalence. In most studies (102/129, 79.1%), timely HepB-BD and HBIG were provided to neonates; 27 studies did not clearly indicate timely administration of HepB-BD and HBIG.

#### Risk of bias within studies

Of the five RCTs evaluating TDF, two had low risk of bias for the majority of the main criteria;<sup>13,14</sup> the remaining three had a high/unclear risk of bias for the majority of criteria.<sup>24,26,27</sup> None of the RCTs investigating LAM (n=8) or LdT (n=21) achieved a 'low risk of bias' rating on the majority of the main criteria; most were either high/unclear risk for performance bias (blinding of study personnel), detection bias (blinding of outcome assessment), and attrition bias (high loss to follow-up or no reporting of loss to follow-up) (Appendix F). Of the 96 non-RCTs, 29 had a high risk of bias with a score of 6 while 67 had low risk of bias with a score ranging 7-9. There were no differences in the distributions of risk of bias scores across non-RCTs examining the three main treatment regimens (Appendix G).

# Overall efficacy

PAP was associated with a significant reduction in HBsAg positivity in infants aged 6-12 months in both RCTs and non-RCTs. The pooled ORs in RCTs were: 0.10 (95% CI: 0.03-0.35) for TDF, 0.16 (0.10-0.26) for LAM, and 0.14 (0.09-0.21) for LdT (Figure 2). Statistical heterogeneity was not present ( $I^2$ =0.0%) in any of the analyses, and the three antiviral regimens were similar in efficacy without any statistically significant difference (p=0.78). The pooled ORs in non-RCTs were: 0.17 (95% CI: 0.10-0.29) for TDF, 0.17 (0.12-0.24) for LAM, and 0.09 (0.06-0.12) for LdT. Between RCTs and non-RCTs, no significant differences in treatment efficacy were observed for each type of antiviral; therefore, these were merged for subsequent subgroup analysis. Similar efficacies were observed when using infant HBV DNA positivity as an endpoint. There was no statistical heterogeneity ( $I^2$ =0.0%) seen in any of the meta-analyses that used HBV DNA positivity as an endpoint, besides that of RCTs using LAM ( $I^2$ =39.8%) where only five studies were included and one outlier (OR=1.28, 95%CI: 0.20-8.32)<sup>45</sup> contributed all observed heterogeneity (Appendix H). The individual characteristics (where available) of infants with MTCT despite maternal TDF 300 mg prophylaxis can be found in Appendix I.

# Efficacy by subgroups

Efficacy did not vary according to mean maternal viral load at baseline (6.0-6.9, 7.0-7.9, 8.0-8.9 log10 IU/ml), the timing of PAP discontinuation (at delivery, 4-8, 12, 24 weeks postpartum), infant immunoprophylaxis regimen, language used to report the study (English, Chinese), risk of bias score for non-RCTs (high, 6; intermediate, 7; low, 8-9), study sample size ( $\leq$ 30 participants versus >30 participants in each group), or maternal viral load criteria (Appendices J-R). Although LAM 100-150 mg was associated with greater efficacy with earlier initiation, compared with later initiation, the interaction was not statistically significant (p=0.06) (Table 1). *Post hoc meta-analyses* of studies that directly compared different treatment starting times (2<sup>nd</sup> vs 3<sup>rd</sup> trimester) suggested that starting in the 2<sup>nd</sup> trimester might be more effective at reducing MTCT risk (OR 0.23, 95% CI: 0.09-0.59) (Figure 3). In the same set of analyses, while baseline viral load did not differ between women in these two timing groups prior to treatment (SMD=0.01, 95%CI: -0.16-0.19), women starting treatment earlier (in the second trimester) had significantly reduced viral load prior to delivery (SMD=-0.62, 95% CI: -0.77- -0.46) (Appendix S).

#### Maternal safety

There was no evidence that PAP was associated with an increased risk of fetal death or postpartum hemorrhage, however, the number of events was small and the estimates were imprecise (Table 2, Appendices T-V). There was also no association between cessation of TDF (four studies), LAM (six studies), or LdT (three studies) and increased risk of postpartum flare, based on evaluation for flare at a fixed time in the intervention group and a matched period in the control group. The definition of flare varied across studies; however, most cases were mild and spontaneously recovered, and none progressed to hepatic decompensation (Appendix V). One TDF study investigated antiviral resistance for all women and found no HBV mutations related to antiviral therapy.<sup>24</sup> In contrast, 2/4 studies of LAM and 3/7 studies of LdT detected drug-resistant mutations in some treated mothers; meta-analysis was not possible because of considerable variation in timing of testing and population tested.<sup>32,61,67,76,85,110,119,121,133,139,148</sup> There were no differences in risk of any maternal safety outcomes by timing of treatment initiation (Appendix W).

#### Infant safety

There was no evidence that PAP was associated with an increased risk of neonatal death, preterm birth, and congenital abnormalities, however, given the small number of events these estimates were imprecise (Table 2, Appendices X-Z). Only one TDF study investigated bone mineral density changes in children in both groups, with no statistically significant difference detected.<sup>14,15</sup> There were no differences in risk of any infant safety outcomes by timing of treatment initiation (Appendix W). There was heterogeneity ( $I^2$ =43.0%) in the meta-analysis of the risk of preterm birth following LAM 100-150 mg which could be largely contributed to two outlying studies, both of which were non-RCTs that started treatment very early (pre-pregnancy or in the first trimester) (Appendix Y).<sup>64,72</sup>

Risk of bias across studies

Funnel plots and the Egger's test did not indicate small sample effects in RCTs. In non-RCTs, however, there was evidence of potential small sample effects for the efficacy of each of the treatment types (Appendix AA).

#### GRADE assessment

The GRADE evidence quality for the primary endpoint, based on RCTs, was high for TDF and moderate for LAM and LdT (due to high/unclear risk of bias in most studies). Although GRADE was lower for non-RCTs, these studies' results were consistent with RCTs. For some safety outcomes evaluated by RCTs, including fetal death, neonatal death, and congenital abnormalities, GRADE was ranked as moderate for TDF and low for LAM and LdT. In contrast, GRADE for postpartum hemorrhage and postpartum flare were low or very low for all types of antivirals (Appendix AB). It was not possible to do GRADE evidence quality analysis for antiviral resistance.

## Discussion

This systematic review and meta-analysis found evidence to support the efficacy and safety of PAP using three different types of nucleos(t)ide analogues; namely, TDF, LAM, and LdT. Meta-analysis of RCTs showed that these antivirals were associated with large and similar reductions

in the likelihood of MTCT. For safety outcomes, there was no evidence for an increased risk associated with any of the antivirals examined, though some findings were based on small number of events. However, this systematic review confirmed the low barrier to resistance of early generation nucleos(t)ide analogues (LAM and LdT).<sup>12,177</sup> Consequently, WHO recommends TDF for HBV-infected women with high viral load to prevent MTCT.

An important strength of this systematic review is its comprehensive search, which covered both English- and Chinese-language databases, leading to the inclusion of more than twice the number of studies compared to previous systematic reviews on this topic.<sup>178-184</sup> The large number of studies included enabled us to perform subgroup analyses for efficacy, and safety evaluations of rarer outcomes. In addition, efforts were employed to exclude articles evaluating the same patient group, in order to avoid doublecounting and overweighting of the same study samples; the inclusion of overlapping patient populations in other systematic reviews has been criticized.<sup>185</sup> We also excluded poorly conducted non-RCTs with a high risk of bias. Subsequently, there was no evidence of heterogeneity in efficacy estimates between Englishversus Chinese-language studies, nor between studies with smaller versus larger sample sizes.

The optimal timing to start and stop PAP has not been well established. Different guidelines recommend varying schedules, ranging from starting at 24-28 to 28-32 weeks of gestation, and from stopping at childbirth to 12 weeks postpartum.<sup>186,187</sup> Our *post hoc* analyses suggest that starting in the second trimester might be more efficacious than in the third trimester, and that this may be linked to increased viral load reduction in women treated earlier. However, this finding should be cautiously interpreted as it is based on a small number of studies (4),<sup>37,87,94,139</sup> and events (23 total). Moreover, only two of the included studies in this *post hoc* analysis

administered TDF. More research is needed on this topic prior to making any conclusions. WHO recommends starting PAP from the 28<sup>th</sup> week of pregnancy, pending additional evidence to support earlier administration.

No difference was observed in the efficacy of PAP when cessation was at the time of childbirth versus at 4-8 weeks postpartum, suggesting that PAP could be stopped immediately after delivery. Another concern, however, is postpartum hepatitis flare. In HBV-infected pregnant women without concurrent antiviral therapy, rapid changes in maternal immunity being suppressed during pregnancy followed by its reconstitution after childbirth could trigger postpartum flare. Early studies have reported that initiating antivirals during pregnancy and its withdrawal at delivery might further increase the risk of postpartum flare.<sup>188</sup> Our meta-analysis did not observe any difference in the risk of postpartum flare between the treated group following discontinuation of PAP and controls; however, none of these comparative studies stopped PAP at the time of child delivery. In four included studies where all women were HBeAg-positive, and which reported on flare only in the treated group, the range of flare risk for women stopping treatment at childbirth was 3.5-19.2% (Appendix V).<sup>67,84,109,145</sup> This range overlaps with that previously reported for non-treated HBeAg-positive women (14.2-40.0%).<sup>189,190</sup> Few studies were included in the safety meta-analysis for postpartum flare and the GRADE evidence quality was low or very low for all treatment types for this outcome. There was also important heterogeneity in all meta-analyses for all treatments that evaluated flare, this is likely explained by the minimal number of eligible studies, as well as important differences in both the safety outcome definitions used and the treatment regimen timing across these studies. The vast majority of all flares described in the studies were mild and self-limiting; only a few required antiviral therapy, and none developed hepatic decompensation.

Our review had potential limitations. Only 6% (2/33) of the RCTs were assessed as having an overall low risk of bias (Appendix F). Very few (18%, 6/33) of the included RCTs presented adequate details of loss-to-follow-up,<sup>13,14,,26,89,103,106</sup> which limited our ability to perform intention-to-treat meta-analysis. Furthermore, although non-RCTs with a very high risk of bias were excluded from analysis, 31% of the remaining non-RCTs had a score of 6 (high) on the Newcastle-Ottawa scale, indicating multiple methodological limitations (Appendix G). Many of the included studies had small sample sizes ( $\leq 30$  infants) in either the treated or control group, although sensitivity analysis showed no difference in efficacy estimates between smaller and larger studies for any treatment type (Appendix Q). Some subgroup meta-analyses had few (i.e. <5) eligible studies, such as those examining differences in efficacy by mean maternal viral load at baseline (Appendix L), and therefore, these results should be interpreted cautiously. This is a meta-analysis of aggregate data, and some topics were limited in examining, such as differences in efficacy by maternal viral load, may be better evaluated using a meta-analysis of individual participant data. Importantly, the vast majority of included studies were conducted in Asia, particularly in China. Of the seven studies conducted outside of China, only one from each of Thailand and Taiwan had >30 participants in both treated and control groups. Therefore, there is very limited representation of diverse populations in this meta-analysis and the applicability of our study findings to other regions is uncertain. For example, in sub-Saharan Africa, another area with a high HBV prevalence, the major HBV genotypes, the natural history of CHB, and the current standard of care, all differ from Asia.<sup>191,192</sup> Many African countries have limited coverage of HepB-BD, and are without access to either HBIG or HBV DNA testing. No studies evaluated the efficacy of PAP without HBIG (i.e. with HepB-BD alone), indicating an important research

gap. A field evaluation is ongoing to assess the efficacy of HepB-BD plus PAP versus HepB-BD alone.<sup>193</sup>

Based on the evidence provided by this study as well as a companion systematic review that addressed HBV DNA thresholds for identifying pregnant women at risk of MTCT (*Boucheron P et al.*), the WHO recommends administering TDF to HBV-infected pregnant women with high viral load ( $\geq$ 5.3 log10 IU/mL ( $\geq$ 200,000 IU/mL)) from the 28<sup>th</sup> week of pregnancy until at least childbirth to prevent MTCT, in addition to three doses of hepatitis B vaccination including HepB-BD. In order to accelerate global HBV elimination by 2030, it is essential to promote the uptake of PAP into routine healthcare, particularly in LMICs that bear the highest HBV disease burden.

# **Contributors**

AF, JVH, RC, MB, and YS formulated the research questions. AF and YS developed the study protocol, analysed the data, and wrote the manuscript. AF and YL developed the search strategy. AF, YL, KY, TZ, and PB performed the systematic review. All authors reviewed the manuscript and approved the final version.

# **Declaration of interests**

RC received personal fees from the WHO. The rest of the authors declare no competing interests.

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| Subgroup                        |  | Г              | <b>TDF 300 mg (n=19)</b> | LAN  | M 100-150 mg (n=40 | )                | L    | LdT 600 mg (n=83) |                  |      |
|---------------------------------|--|----------------|--------------------------|------|--------------------|------------------|------|-------------------|------------------|------|
|                                 |  | No. of studies | OR (95% CI)              | Р    | No. of studies     | OR (95% CI)      | Р    | No. of studies    | OR (95% CI)      | Р    |
| Study design                    | RCTs                                     | 5              | 0.10 (0.03-0.35)         | 0.47 | 8                  | 0.16 (0.10-0.26) | 0.80 | 21                | 0.14 (0.09-0.21) | 0.08 |
| Study design                    | Non-RCTs                                 | 14             | 0.17 (0.10-0.29)         | 0.47 | 32                 | 0.17 (0.12-0.24) | 0.80 | 62                | 0.09 (0.06-0.12) | 0.08 |
| Timing of PAP                   | <28 weeks                                | 10             | 0.10 (0.04-0.25)         |      | 7                  | 0.10 (0.04-0.26) |      | 24                | 0.08 (0.05-0.13) |      |
| initiation                      | 28 weeks                                 | 7              | 0.25 (0.13-0.48)         | 0.15 | 20                 | 0.16 (0.11-0.22) | 0.06 | 44                | 0.13 (0.10-0.18) | 0.20 |
| (median<br>gestational age)     | >28 weeks                                | 5              | 0.10 (0.03-0.29)         |      | 11                 | 0.31 (0.16-0.57) | Ť    | 13                | 0.09 (0.04-0.20) |      |
| <b>Т</b> С. А. В.               | At delivery                              | 5              | 0.11 (0.04-0.28)         |      | 13                 | 0.15 (0.10-0.23) |      | 16                | 0.10 (0.06-0.16) |      |
| discontinuation<br>(postpartum) | 4-8 weeks                                | 7              | 0.12 (0.04-0.34)         | 0.06 | 21                 | 0.23 (0.15-0.34) | 0.10 | 33                | 0.13 (0.09-0.19) | 0.49 |
|                                 | 12 weeks                                 | 2              | N/A                      | 0.90 | 2                  | N/A              | 0.19 | 8                 | 0.06 (0.02-0.16) |      |
|                                 | 24 weeks                                 | 0              | N/A                      |      | 0                  | N/A              |      | 6                 | 0.11 (0.04-0.29) |      |
| Mean maternal                   | 5.0-5.9                                  | 0              | N/A                      |      | 0                  | N/A              |      | 1                 | N/A              | 0.14 |
| viral load at                   | 6.0-6.9                                  | 0              | N/A                      | 0.96 | 4                  | 0.15 (0.06-0.37) | N/A  | 10                | 0.13 (0.07-0.23) |      |
| baseline (log                   | 7.0-7.9                                  | 3              | 0.10 (0.03-0.41)         | 0.90 | 1                  | N/A              | 1N/A | 13                | 0.06 (0.03-0.13) |      |
| IU/mL)                          | 8.0-8.9                                  | 3              | 0.11 (0.02-0.51)         |      | 2                  | N/A              |      | 1                 | N/A              |      |
| Maternal                        | Positive                                 | 11             | 0.09 (0.04-0.21)         |      | 30                 | 0.16 (0.12-0.23) |      | 52                | 0.11 (0.08-0.14) |      |
| HBeAg at                        | Negative                                 | 0              | N/A                      | N/A  | 0                  | N/A              | 0.45 | 1                 | N/A              | 0.65 |
| baseline                        | Mixed                                    | 1              | N/A                      |      | 4                  | 0.26 (0.08-0.82) |      | 6                 | 0.09 (0.04-0.21) |      |
| Infant immuno-                  | Timely HepB-<br>BD & HBIG                | 14             | 0.15 (0.09-0.27)         |      | 31                 | 0.18 (0.13-0.24) |      | 64                | 0.10 (0.08-0.14) |      |
| prophylaxis<br>regimen          | No or unclear<br>timely HepB-<br>BD/HBIG | 5              | 0.16 (0.06-0.43)         | 0.89 | 9                  | 0.13 (0.06-0.25) | 0.38 | 18                | 0.10 (0.06-0.16) | 0.83 |

Table 1. Efficacy of peripartum antiviral prophylaxis (PAP) in the prevention of MTCT\*, by subgroups

\* MTCT is defined as HBsAg positivity in infants aged 6-12 months.

<sup>†</sup> Non-important heterogeneity ( $I^2 = 7.7\%$ ) in the subgroup of >28 weeks may or may not render the p-value non-valid.

| Table 2. | Safety | of | peripa | rtum    | antiviral | prop | hv]    | laxis   |
|----------|--------|----|--------|---------|-----------|------|--------|---------|
|          | Survey |    | peripa | I UMIII |           | PLOP | •• J · | 1002310 |

|                 |         | <b>TDF 300</b> | mg (N=19) | )        | L       | LAM 100-150 mg (N=40) |         |          |         | LdT 600 mg (N=83) |         |          |  |
|-----------------|---------|----------------|-----------|----------|---------|-----------------------|---------|----------|---------|-------------------|---------|----------|--|
| Safety          | No. of  | Eve            | vents/ RD |          | No. of  | Eve                   | nts/    | RD       | No. of  | Ever              | nts/    | RD       |  |
| measure         | atudioa | Participants   |           | (95%     | INU. UI | Participants          |         | (95%     | NU. UI  | Participants      |         | (95%     |  |
|                 | studies | Treated        | Control   | CI)      | studies | Treated               | Control | CI)      | studies | Treated           | Control | CI)      |  |
| Maternal safety |         |                |           |          |         |                       |         |          |         |                   |         |          |  |
|                 |         |                |           | 0.003    |         |                       |         | 0.000    |         |                   |         | -0.001   |  |
| Fetal death     | 19      | 3/1097         | 1/881     | (-0.006- | 39      | 1/2003                | 9/2087  | (-0.006- | 81      | 3/5645            | 20/5823 | (-0.003- |  |
|                 |         |                |           | 0.012)   |         |                       |         | 0.005)   |         |                   |         | 0.002)   |  |
| Doctnortum      |         |                |           | -0.001   |         |                       |         | 0.008    |         | 9 125/1729        | 116/    | -0.001   |  |
| homorrhage      | 6       | 9/365          | 7/256     | (-0.024- | 8       | 98/611                | 61/752  | (-0.012- | 19      |                   | 2020    | (-0.010- |  |
| nemorrhage      |         |                |           | 0.022)   |         |                       |         | 0.028)   |         |                   | 2020    | 0.008)   |  |
| Destructure     |         |                |           | -0.020   |         |                       |         | -0.020   |         |                   |         | 0.022    |  |
| Postpartum      | 4       | 28/356         | 20/327    | (-0.082- | 6       | 59/447                | 34/568  | (-0.071- | 3       | 27/431            | 26/565  | (-0.064- |  |
| nepatius nare   |         |                |           | 0.041)*  |         |                       |         | 0.030)*  |         |                   |         | 0.109)†  |  |
|                 |         |                |           |          | Inf     | ant safety            |         |          |         |                   |         |          |  |
| Neenetal        |         |                |           | 0.000    |         |                       |         | 0.000    |         |                   |         | 0.000    |  |
| Neonatai        | 19      | 2/1079         | 1/858     | (-0.009- | 39      | 1/2010                | 1/2093  | (-0.006- | 82      | 2/5752            | 0/5863  | (-0.002- |  |
| death           |         |                |           | 0.009)   |         |                       |         | 0.006)   |         |                   |         | 0.003)   |  |
|                 |         |                |           | -0.003   |         |                       |         | 0.000    |         |                   | 120/    | -0.001   |  |
| Preterm birth   | 9       | 19/622         | 22/479    | (-0.024- | 10      | 14/609                | 11/399  | (-0.025- | 24      | 105/2427          | 120/    | (-0.010- |  |
|                 |         |                |           | 0.019)   |         |                       |         | 0.025)*  |         |                   | 2191    | 0.008)   |  |
| C               |         |                |           | -0.002   |         |                       |         | 0.003    |         |                   |         | 0.000    |  |
| Congenital      | 14      | 4/802          | 5/687     | (-0.013- | 16      | 8/845                 | 5/953   | (-0.007- | 40      | 11/3585           | 9/2983  | (-0.004- |  |
| abnormalities   |         |                |           | 0.009)   |         |                       |         | 0.014)   |         |                   |         | 0.004)   |  |

Abbreviations: n, number of studies that reported on this safety outcome in a way that could be combined in the meta-analysis; RD, weighted risk difference.

\* Moderate to substantial heterogeneity in estimate ( $I^2 \ge 30\% \& < 75\%$ )

† Considerable heterogeneity ( $I^2 \ge 75\%$ )





#### Figure 2. Efficacy of peripartum antiviral prophylaxis in the prevention of MTCT\*

| Author         | Year      | Country       | in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control | OR (95% CI)       |
|----------------|-----------|---------------|-----------------------|------------------------|----------------------|--------------------|-------------------|
| Randomised     | controlle | d trials      |                       |                        |                      | <br>               |                   |
| Jourdain G     | 2018      | Thailand      | 26-29                 | 8                      | 0/149                | 3/147              | 0.14 (0.01, 2.7   |
| Lin Y          | 2018      | China         | 24                    | 4                      | 0/58                 | 4/52               | 0.09 (0.00, 1.7   |
| Liu MH         | 2017      | China         | 28-30                 | 0                      | 1/20                 | 6/20               | 0.12 (0.01, 1.1   |
| Pan CQ         | 2016      | China         | 30-32                 | 4                      | 0/92                 | 6/88               | 0.07 (0.00, 1.2   |
| Yu CY          | 2018      | China         | 24                    | 4                      | 0/30                 | 4/30               | 0.10 (0.00, 1.8   |
| Subtotal (I-so | quared =  | 0.0%, p = 0   | .997)                 |                        |                      | $\sim$             | > 0.10 (0.03, 0.3 |
|                |           |               |                       |                        |                      | _                  |                   |
| Non-randomis   | sed conti | rolled trials |                       |                        |                      |                    |                   |
| Celen MK       | 2013      | Turkey        | 18-27                 | 4                      | 0/21                 | 2/23               | • 0.20 (0.01, 4.4 |
| Chen HL        | 2015      | Taiwan        | 30-32                 | 4                      | 1/65                 | 6/56               | 0.13 (0.02, 1.1   |
| Chen WJ        | 2017      | China         | 28                    | 0                      | 1/30                 | 16/44              | 0.06 (0.01, 0.4   |
| Gong Q         | 2017      | China         | 1-6                   | NR                     | 1/44                 | 7/44               | 0.12 (0.01, 1.0   |
| Greenup AJ     | 2014      | Australia     | 32                    | 12                     | 1/69                 | 2/10               | 0.06 (0.00, 0.7   |
| He LL          | 2018      | China         | 28                    | NR                     | 13/50                | 17/35              | 0.37 (0.15, 0.9   |
| Hu MF          | 2018      | China         | <0-28                 | NR                     | 1/89                 | 3/30               | 0.10 (0.01, 1.0   |
| Huang Q        | 2017      | China         | 24-28                 | 12                     | 0/20                 | 3/20               | 0.12 (0.01, 2.5   |
| Wakano Y       | 2018      | Japan         | 22-28                 | 4-8                    | 0/2                  | 2/3                | 0.12 (0.00, 4.6   |
| Wan JY         | 2017      | China         | 28                    | 0                      | 3/74                 | 7/42               | • 0.21 (0.05, 0.8 |
| Wang HB        | 2018      | China         | 20-36                 | NR                     | 0/100                | 2/20               | 0.04 (0.00, 0.8   |
| Xiao XH        | 2017      | China         | 28                    | 0 or 4                 | 0/60                 | 1/61               | 0.33 (0.01, 8.3   |
| Zhang BF       | 2018      | China         | 24-28                 | 0                      | 0/39                 | 15/75              | 0.05 (0.00, 0.8   |
| Zhou Y         | 2018      | China         | 24-28                 | 0                      | 0/60                 | 5/36               | 0.05 (0.00, 0.8   |
| Subtotal (I-so | quared =  | 0.0%, p = 0   | .860)                 |                        |                      | <                  | > 0.17 (0.10, 0.2 |
|                |           |               |                       |                        |                      | Г<br>I             |                   |
| Overall (I-squ | uared = ( | 0.0%, p = 0.9 | 972)                  |                        |                      | 4                  | > 0.16 (0.09, 0.2 |
|                |           |               |                       |                        |                      | 1                  |                   |
|                |           |               |                       |                        |                      |                    |                   |

Figure 2A. Efficacy of tenofovir disoproxil fumarate (TDF) 300 mg, by study design

\* MTCT is defined as HBsAg positivity in infants aged 6-12 months.

# Figure 2B. Efficacy of lamivudine (LAM) 100-150 mg, by study design

|                          |           |                    | Тх              |                  |           |               |              |
|--------------------------|-----------|--------------------|-----------------|------------------|-----------|---------------|--------------|
| A                        |           | O                  | start in weeks  | Tx end in        | Events,   | Events,       |              |
| Author                   | rear      | Country            | gestation       | weeks postpartum | Treatment |               | OR (95% C    |
| Randomised               | controlle | ed trials          |                 |                  |           |               |              |
| Bai XW                   | 2011      | China              | 28              | 4                | 3/30      | 8/25          | 0.24 (0.05,  |
| Chen SM                  | 2017      | China              | 28              | NR               | 1/30      | 10/30         | 0.07 (0.01,  |
| Guo YZ                   | 2008      | China              | 28              | 0                | 3/70      | 13/40         | 0.09 (0.02,  |
| Ji YY                    | 2015      | China              | 28              | 4                | 2/65      | 12/65         | 0.14 (0.03,  |
| Li ZG                    | 2015      | China              | 28              | 6                | 1/25      | 4/25          | 0.22 (0.02,  |
| Tian XQ                  | 2015      | China              | 28              | 0                | 11/110    | 49/110        | 0.14 (0.07,  |
| Xu WM                    | 2009      | China, Philippines | 30-34           | 4                | 3/49      | 5/41          | 0.47 (0.11,  |
| Yang HW                  | 2014      | China              | 28              | 4                | 1/53      | 4/53          | 0.24 (0.03,  |
| Subtotal (I-so           | quared =  | = 0.0%, p = 0.794) |                 |                  |           | $\diamond$    | 0.16 (0.10,  |
|                          |           | and the states     |                 |                  |           | 1             |              |
| Non-randomi              | sea cont  | rolled trials      |                 |                  | 1 (00     | 5/00          | 0 4 4 /0 00  |
| Cherry VC                | 2018      | China              | 20              | 4                | 1/33      | 5/20          | 0.14 (0.02,  |
|                          | 2011      | China              | 32              | 4                | 8/30      |               | 1.21 (0.36,  |
| Feng HF                  | 2007      | China              | ∠o<br>Anutina a | 4<br>ND          | //48      | 10/42         | 0.28 (0.10,  |
| Foaud HM                 | 2019      | Egypt              | Anytime         | NR               | 0/29      | 1/30          | 0.33 (0.01,  |
| GeYL                     | 2015      | China              | 28-30           | 12               | 0/16      | 3/22          | 0.17 (0.01,  |
| Greenup AJ               | 2014      | Australia          | 32              | 2                | 0/43      | 2/10          | 0.04 (0.00,  |
| Han YP                   | 2014      | China              | 28              | 6                | 1/30      | 4/30          | 0.22 (0.02,  |
| Han ZH                   | 2005      | China              | 28              | 0                | 0/43      | 5/35          | 0.06 (0.00,  |
| He T                     | 2018      | China              | 1st Trimester   | NR               | 0/29      | 4/34          | 0.11 (0.01,  |
| Jackson V                | 2015      | Ireland            | 32              | 0                | 0/21      | 1/6           | 0.09 (0.00,  |
| Jiang HX                 | 2012      | China              | 20-34           | 0                | 0/164     | 8/92          | 0.03 (0.00,  |
| Li G                     | 2006      | China              | 28              | 0                | 1/35      | 7/32          | 0.11 (0.01,  |
| Li JH                    | 2017      | China              | 28              | 4                | 1/33      | 8/27          | 0.07 (0.01,  |
| _i WF                    | 2006      | China              | 24              | 0                | 1/36      | 7/44          | 0.15 (0.02,  |
| Ma J                     | 2006      | China              | Pre-pregnancy   | NR               | 0/18      | 9/16          | 0.02 (0.00,  |
| Pan CQ                   | 2017      | China              | 13-30           | 4                | 0/160     | 5/89          | 0.05 (0.00,  |
| Ren CJ                   | 2016      | China              | 28              | 0                | 2/67      | 10/72         | 0.19 (0.04,  |
| Ren YJ                   | 2011      | China              | 28              | 0                | 1/30      | 13/155        | 0.38 (0.05,  |
| Shen ML                  | 2016      | China              | 26              | 4                | 0/60      | 11/28         | 0.01 (0.00,  |
| Su TB                    | 2009      | China              | 32              | 0                | 5/128     | 13/120        | 0.33 (0.12,  |
| Tang X                   | 2009      | China              | 33              | 4                | 0/17      | 4/24          | 0.13 (0.01.  |
| Wakano Y                 | 2018      | Japan              | 28-32           | 4-8              | 0/3       | 2/3           | 0.09 (0.00.  |
| Wang DM                  | 2016      | China              | 28-30           | 12               | 1/42      | 5/20          | 0.07 (0.01.  |
| Wang EJ                  | 2012      | China              | 28              | 4                | 1/32      | 5/27          | 0.14 (0.02.  |
| Nang TM                  | 2005      | China              | Pre-pregnancy   | 0                | 0/32      | 8/32          | 0.04 (0.00   |
| Wang W                   | 2014      | China              | 28              | 4                | 0/35      | 2/28          | 0 15 (0 01   |
| ruan QE                  | 2012      | China              | 27              | 4                | 1/32      | 3/32          | 0.31 (0.03   |
| Zena YM                  | 2013      | China              | 28              | Variable (0.4.6) | 0/90      | 3/30          | 0.04 (0.00,  |
| Zhang H                  | 2014      | China              | 28-30           | 4                | 0/52      | 10/352        | • 0.31 (0.02 |
| Zhang VE                 | 20109     | China              | 28              | . 4              | 3/50      | 16/50         | 0.14 (0.02,  |
|                          | 20100     | China              | 20-28           | NB               | 5/112     | 28/95         | 0.14 (0.04,  |
| Zhu M                    | 2013      | China              | 20-20           | 0                | 0/04      | 0/24          | 0.11 (0.04,  |
| Citul IVI<br>Rubtatal /! | 2014      | - 0.0% n - 0.680   | 20              | v                | 2/24      | 3/24          | 0.15 (0.03,  |
| วนมเงเลเ (I-S            | -uared =  | = 0.0%, p = 0.686) |                 |                  |           | ¥             | 0.17 (0.12,  |
| Overall (I-sq            | uared =   | 0.0%, p = 0.830)   |                 |                  |           | <b>O</b>      | 0.17 (0.13,  |
|                          |           |                    |                 |                  |           |               |              |
|                          |           |                    |                 |                  |           |               |              |
|                          |           |                    |                 |                  |           | .001 .01 .1 1 | 10           |

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| Author              | Year             | Country        | start in weeks gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |                                       | OR (95% CI)                            |
|---------------------|------------------|----------------|--------------------------|------------------------|----------------------|--------------------|---------------------------------------|--|
| Randomised o        | ontrolled trials |                |                          |                        |                      |                    |                                       |  |
| Bai HL              | 2013             | China          | 28-32                    | 4                      | 0/27                 | 4/30               |                                       | 0.11 (0.01, 2.09)                      |
| Chen SM             | 2017             | China          | 28                       | NR                     | 0/30                 | 10/30              |                                       | 0.03 (0.00, 0.58)                      |
| Fu PX               | 2016             | China          | 24-28                    | 4                      | 1/100                | 3/100              |                                       | 0.33 (0.03, 3.19)                      |
| Guan ZF<br>Guo HJ   | 2017             | China          | 24                       | 4                      | 6/28                 | 6/26               |                                       | 0.03 (0.00, 0.51)                      |
| Huang HY            | 2016             | China          | 20-28                    | 0                      | 16/90                | 23/30              |                                       | 0.07 (0.02, 0.18)                      |
| Ji YY               | 2015             | China          | 28                       | 4                      | 3/65                 | 12/65              |                                       | 0.21 (0.06, 0.80)                      |
| Li SF               | 2015             | China          | 28                       | 24                     | 0/60                 | 6/60               |                                       | 0.07 (0.00, 1.26)                      |
| LU QY<br>PengMi     | 2016             | China          | 28                       | U<br>NB                | 2/152                | 12/132             |                                       | 0.13 (0.03, 0.61)                      |
| Shi QW              | 2017             | China          | 24                       | 0                      | 3/100                | 12/100             |                                       | 0.23 (0.06, 0.83)                      |
| Wang HY             | 2018             | China          | 12-14                    | 24                     | 0/40                 | 6/40               |                                       | 0.07 (0.00, 1.21)                      |
| Xie PY              | 2016             | China          | 28                       | 4                      | 1/60                 | 4/60               |                                       | 0.24 (0.03, 2.19)                      |
| Xing Y              | 2018             | China          | 28                       | 4                      | 0/30                 | 7/30               |                                       | 0.05 (0.00, 0.95)                      |
| Zhang LJ            | 2015             | China          | 28-32                    | 4                      | 0/30                 | 4/30               |                                       | 0.10 (0.00, 1.88)                      |
| Zhang Y             | 2018             | China          | Pre-pregnancy            | NR                     | 0/34                 | 13/34              |                                       | 0.02 (0.00, 0.41)                      |
| Zhao DB             | 2010             | China          | 28                       | 4                      | 1/30                 | 3/30               |                                       | 0.31 (0.03, 3.17)                      |
| Zhao Y              | 2017             | China          | 12                       | 12                     | 0/40                 | 5/40               |                                       | 0.08 (0.00, 1.49)                      |
| Zhu J<br>Zhu J P    | 2017             | China          | 28                       | 0                      | 1/60                 | 8/54               |                                       | 0.10 (0.01, 0.81)                      |
| Subtotal (I-sou     | uared = 0.0%.    | p = 0.561)     | 20                       | 4                      | 0/30                 | 5/50               | 0                                     | 0.14 (0.09, 0.21)                      |
|                     |                  | ,              |                          |                        |                      |                    | · · · · · · · · · · · · · · · · · · · |  |
| Non-randomise       | ed controlled tr | ials           |                          |                        |                      |                    | <u>.</u>                              |  |
| Chen CY             | 2015             | China          | 1st Trimester            | NR                     | 1/42                 | 7/40               |                                       | 0.11 (0.01, 0.98)                      |
| Chen OR             | 2018             | China          | 28                       | 4                      | 0/29                 | 5/98               |                                       | 0.06 (0.00, 1.20)                      |
| Chen WJ             | 2017             | China          | 28                       | 0                      | 4/79                 | 16/44              |                                       | 0.09 (0.03, 0.30)                      |
| Chen ZX             | 2017             | China          | 13-32                    | NR                     | 1/41                 | 15/89              |                                       | 0.12 (0.02, 0.97)                      |
| Cui ZL              | 2015             | China          | 28                       | 4                      | 1/50                 | 13/46              |                                       | 0.05 (0.01, 0.42)                      |
| Deng Y              | 2015             | China          | 24-36                    | 4                      | 0/82                 | 4/75               |                                       | 0.10 (0.01, 1.82)                      |
| Ding XP<br>Fan I ⊻  | 2018             | China          | 28                       | 4<br>24                | 0/38                 | 4/38<br>6/60       |                                       | 0.10 (0.01, 1.92)                      |
| Feng XM             | 2017             | China          | 28                       | 4                      | 1/36                 | 7/36               |                                       | 0.12 (0.01, 1.02)                      |
| Gao P               | 2016             | China          | 1st Trimester            | 0                      | 1/51                 | 9/51               |                                       | 0.09 (0.01, 0.77)                      |
| Ge YL               | 2015             | China          | 28-30                    | 12                     | 0/20                 | 3/22               |                                       | 0.14 (0.01, 2.81)                      |
| Han GR              | 2015             | China          | 20-32                    | NR                     | 0/358                | 8/86               | · · · · ·                             | 0.01 (0.00, 0.23)                      |
| Han YP              | 2014             | China          | 28<br>1et Trimester      | 6<br>ND                | 0/30                 | 4/30               |                                       | 0.10 (0.00, 1.88)                      |
| Hu WH               | 2016             | China          | 28                       | 28                     | 0/46                 | 4/34<br>5/40       | ī                                     | 0.07 (0.00, 1.30)                      |
| Hu Y                | 2018             | China          | 28-32                    | 3-4                    | 0/105                | 2/122              |                                       | 0.23 (0.01, 4.81)                      |
| Huang Q             | 2017             | China          | 24-28                    | 12                     | 0/20                 | 3/20               |                                       | 0.12 (0.01, 2.53)                      |
| Jiang S             | 2017             | China          | 28                       | NR                     | 1/44                 | 15/44              |                                       | 0.04 (0.01, 0.36)                      |
| Jiang XN            | 2013             | China          | 26-30                    | NR                     | 1/65                 | 8/51               |                                       | 0.08 (0.01, 0.70)                      |
| LICM                | 2017             | China          | 28<br><0-28              | 4<br>NB                | 1/30                 | 8/30<br>9/25       |                                       | 0.09 (0.01, 0.82)                      |
| LIYH                | 2017             | China          | 28                       | ~36                    | 1/30                 | 5/32               | · · · · · · · · · · · · · · · · · · · | 0.19 (0.02, 1.70)                      |
| Li ZY               | 2018             | China          | 28                       | NR                     | 4/41                 | 9/41               | L                                     | 0.38 (0.11, 1.37)                      |
| Liu CY              | 2014             | China          | 28                       | 4                      | 1/34                 | 8/34               |                                       | 0.10 (0.01, 0.84)                      |
| Liu J               | 2017             | China          | 30                       | NR                     | 0/97                 | 2/28               |                                       | 0.05 (0.00, 1.17)                      |
| Liu XB              | 2016             | China          | 28-36                    | 4                      | 1/82                 | 5/20<br>19/78      |                                       | 0.07 (0.00, 1.34)                      |
| Lou JJ              | 2010             | China          | 28                       | 4                      | 0/125                | 3/58               |                                       | 0.06 (0.00, 1.24)                      |
| Pan YC              | 2017             | China          | 32                       | 0                      | 0/81                 | 21/370             |                                       | 0.10 (0.01, 1.66)                      |
| Peng BA             | 2012             | China          | 28                       | 0                      | 1/40                 | 10/40              | +                                     | 0.08 (0.01, 0.63)                      |
| Qiu B               | 2016             | China          | <0-24                    | 0                      | 4/120                | 12/60              |                                       | 0.14 (0.04, 0.45)                      |
| Shen MI             | 2015             | China          | 26                       | 24                     | 2/46                 | 11/40              | <u> </u>                              | 0.01 (0.00, 0.22)                      |
| Sheng Q             | 2018a            | China          | 24-32                    | 0                      | 0/79                 | 2/21               |                                       | 0.05 (0.00, 1.06)                      |
| Sheng Q             | 2018b            | China          | 24-28                    | 0                      | 0/66                 | 5/46               |                                       | 0.06 (0.00, 1.05)                      |
| Sun W               | 2017             | China          | 12-28                    | 12                     | 0/123                | 12/65              |                                       | 0.02 (0.00, 0.30)                      |
| Sun WH              | 2015             | China          | 12-28                    | 12                     | 0/84                 | 8/46               |                                       | 0.03 (0.00, 0.48)                      |
| Tan Z               | 2019             | China          | <14-28                   | NB                     | 0/171                | 15/320             |                                       | 0.06 (0.00, 1.81)                      |
| Tian JH             | 2018             | China          | Anytime                  | NR                     | 0/135                | 7/203              |                                       | 0.10 (0.01, 1.71)                      |
| Tian RH             | 2016             | China          | 28                       | 4                      | 3/318                | 17/374             |                                       | 0.20 (0.06, 0.69)                      |
| Wang B              | 2016             | China          | 28                       | 4                      | 0/110                | 16/187             |                                       | 0.05 (0.00, 0.79)                      |
| Wang DM             | 2016             | China          | 28-30                    | 12                     | 1/36                 | 5/20               |                                       | 0.09 (0.01, 0.80)                      |
| Wang EJ<br>Wang HR  | 2012             | China          | ∠o<br>20-36              | 4<br>NB                | 0/100                | 5/2/<br>2/20       |                                       | 0.07 (0.00, 1.37)<br>0.04 (0.00, 0.80) |
| Wang J              | 2017             | China          | 24-28                    | NR                     | 1/329                | 9/65               |                                       | 0.02 (0.00, 0.15)                      |
| Wang TD             | 2015             | China          | 28                       | 4                      | 0/53                 | 8/52               |                                       | 0.05 (0.00, 0.87)                      |
| Wang WP             | 2012             | China          | <27-28                   | 0                      | 0/47                 | 20/198             |                                       | 0.09 (0.01, 1.54)                      |
| Wu Q                | 2015             | China<br>Chira | 24-32                    | 0 or 4                 | 0/204                | 14/95              |                                       | 0.01 (0.00, 0.23)                      |
| Xiao XH<br>Yao LE   | 2017             | China          | 28                       | U or 4                 | 0/62                 | 1/61               |                                       | 0.32 (0.01, 8.08)                      |
| Yao ZC              | 2014             | China          | 28                       | 4                      | 0/28                 | 4/30               |                                       | 0.10 (0.01, 2.01)                      |
| Zhang BF            | 2018             | China          | 24-28                    | 0                      | 0/36                 | 15/75              |                                       | 0.05 (0.00, 0.92)                      |
| Zhang GH            | 2018             | China          | 28                       | 4                      | 0/40                 | 3/40               |                                       | 0.13 (0.01, 2.65)                      |
| Zhang H             | 2014             | China          | 28-30                    | 4                      | 0/257                | 10/352             |                                       | 0.06 (0.00, 1.09)                      |
| ∠hang X<br>Zhang V⊑ | 2015             | China          | 28                       | 12                     | 0/48                 | 5/47<br>16/60      | *                                     | 0.08 (0.00, 1.48)                      |
| Zhang TF<br>Zhao J  | 20100            | China          | 20                       | <br>0                  | 0/41                 | 23/202             |                                       | 0.09 (0.01, 1.55)                      |
| Zheng JC            | 2018             | China          | 28                       | 4                      | 0/23                 | 8/37               |                                       | 0.07 (0.00, 1.35)                      |
| Zhou YJ             | 2014             | China          | 1st Trimester            | 0                      | 1/53                 | 6/34               |                                       | 0.09 (0.01, 0.78)                      |
| Yue X               | 2014             | China          | Anytime                  | NR                     | 0/31                 | 0/30               | <u> </u>                              | (Excluded)                             |
| Subtotal (I-squ     | uared = 0.0%,    | p = 1.000)     |                          |                        |                      |                    | •                                     | 0.09 (0.06, 0.12)                      |
| Overall (Leave      | ared = 0.0% p    | = 0.999)       |                          |                        |                      |                    |                                       | 0.10 (0.08.0.13)                       |
| overall (r-squa     | a.su = 0.0 %, p  | - 0.000)       |                          |                        |                      |                    | Y I                                   | 3.10 (0.00, 0.10)                      |
|                     |                  |                |                          |                        |                      |                    | · · · · · · · · · · · · · · · · · · · |  |
|                     |                  |                |                          |                        |                      |                    |                                       | 1                                      |
|                     |                  |                |                          |                        |                      |                    | .001 .01 .1 1                         | 10                                     |

# Figure 2C. Efficacy of telbivudine (LdT) 600 mg, by study design $T_{x}$ Tx end

## Figure 3. Efficacy of earlier versus later initiation of peripartum antiviral prophylaxis in the prevention of MTCT\*

|              |          |             | Treatment  | Early         | Events, | Late        | Events,    |            |                      |      |     |
|--------------|----------|-------------|------------|---------------|---------|-------------|------------|------------|----------------------|------|-----|
| Author       | Year     | Country     | type       | start time    | early   | start time  | late       |            | OR (95% CI)          |      |     |
| Pre-pregna   | ncy vs   | during pre  | gnancy     |               |         |             |            |            |                      |      |     |
| Hu MF        | 2018     | China       | TDF 300    | Pre-pregnancy | 0/29    | 14-28 weeks | 1/60 —     |            | → 0.67 (0.03, 17.01) |      |     |
| Li N         | 2016     | China       | LDT 600    | Pre-pregnancy | 0/35    | 28 weeks    | 1/30       | -          | - 0.28 (0.01, 7.06)  |      |     |
| Qiu B        | 2016     | China       | LDT 600    | Pre-pregnancy | 0/60    | 24 weeks    | 4/60 🗲     |            | 0.10 (0.01, 1.97)    |      |     |
| Subtotal (I  | -square  | d = 0.0%,   | p = 0.695) |               |         |             |            | >          | 0.25 (0.04, 1.54)    |      |     |
|              |          |             |            |               |         |             |            |            |                      |      |     |
| 1st trimeste | er vs 2n | d trimeste  | r          |               |         |             |            |            |                      |      |     |
| Sun W        | 2017     | China       | LDT 600    | 12 weeks      | 0/62    | 20-28 weeks | 0/61       |            | (Excluded)           |      |     |
| Sun WH       | 2015     | China       | LDT 600    | 12 weeks      | 0/43    | 20-28 weeks | 0/41       |            | (Excluded)           |      |     |
| Tan Z        | 2016     | China       | LDT 600    | <14 weeks     | 0/34    | 14-28 weeks | 0/137      |            | (Excluded)           |      |     |
| Subtotal (I  | -square  | d = .%, p : | = .)       |               |         |             |            |            | . (., .)             |      |     |
|              |          |             |            |               |         |             |            |            |                      |      |     |
| 2nd trimest  | er vs 3ı | d trimeste  | r          |               |         |             |            |            |                      |      |     |
| Hu MF        | 2018     | China       | TDF 300    | 14 weeks      | 0/30    | 28 weeks    | 1/30       |            | - 0.32 (0.01, 8.24)  |      |     |
| Huang HY     | 2016     | China       | LDT 600    | 20 weeks      | 6/60    | 28 weeks    | 10/30      |            | 0.22 (0.07, 0.69)    |      |     |
| Liu Y        | 2016     | China       | LDT 600    | 13-27 weeks   | 0/24    | 28-32 weeks | 1/33       | *          | → 0.44 (0.02, 11.33) |      |     |
| Zhou DS      | 2013     | China       | LAM 100    | 20 weeks      | 0/49    | 28 weeks    | 5/64 🔶     | *          | 0.11 (0.01, 2.03)    |      |     |
| Han GR       | 2015     | China       | LDT 600    | 20-27 weeks   | 0/256   | 28-32 weeks | 0/102      |            | (Excluded)           |      |     |
| Pan CQ       | 2017     | China       | LAM 100    | 13-26 weeks   | 0/66    | 28-30 weeks | 0/94       |            | (Excluded)           |      |     |
| Wang HB      | 2016     | China       | LDT 600    | 20 weeks      | 0/20    | 28 weeks    | 0/20       |            | (Excluded)           |      |     |
| Wang HB      | 2018     | China       | TDF 300    | 20 weeks      | 0/20    | 28 weeks    | 0/20       |            | (Excluded)           |      |     |
| Wang WP      | 2012     | China       | LDT 600    | <27 weeks     | 0/22    | 28 weeks    | 0/25       |            | (Excluded)           |      |     |
| Subtotal (I  | -square  | d = 0.0%,   | p = 0.928) |               |         |             |            | $\diamond$ | 0.23 (0.09, 0.59)    |      |     |
|              |          |             |            |               |         |             |            |            |                      |      |     |
|              |          |             |            |               |         |             |            |            |                      |      |     |
|              |          |             |            |               |         |             | I          |            | <u> </u>             |      |     |
|              |          |             |            |               |         |             | .01        | .1 1       | 10                   |      |     |
| MTCT         | Г        | is          | define     | ed as         | H       | łBsAg       | positivity | in         | infants aged         | 6-12 | , m |

\*

## **Supplementary Appendix**

Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child

transmission of hepatitis B virus: a systematic review and meta-analysis

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Roger Chou, Marc Bulterys, Yusuke Shimakawa

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| LAM 100-150 mg   | 258  |
| LdT 600 mg   | 262  |

# Appendix A: Search strategies

Database: PubMed

# Date searched: March 28<sup>th</sup>, 2019

| Item | Search words   | #<br>Records |
|------|--|--------------|
| 1    | "hepatitis b"[MeSH] OR "hepatitis b virus"[MeSH]   | 63 464       |
| 2    | hepatitis b[Text] OR type b hepatitis[Text] OR hepatitis type<br>b[Text] OR hbv[Text] OR vhb[Text] OR hep b[Text] OR<br>hbsag[Text] OR hbs ag[Text] OR hbs antigen*[Text]  | 98 948       |
| 3    | 1 OR 2   | 98 948       |
| 4    | <ul> <li>"antiviral agents" [MeSH] OR "nucleosides" [MeSH] OR</li> <li>"nucleotides" [MeSH] OR "adefovir" [Supplementary</li> <li>Concept] OR "emtricitabine" [MeSH] OR</li> <li>"entecavir" [Supplementary Concept] OR</li> <li>"lamivudine" [MeSH] OR "telbivudine" [MeSH] OR</li> <li>"tenofovir" [MeSH]</li> </ul>   | 822 520      |
| 5    | <ul> <li>antiviral*[Text] OR nucleoside*[Text] OR</li> <li>nucleotide*[Text] OR (nucleos*[Text] AND analog*[Text])</li> <li>OR (nucleot*[Text] AND analog*[Text]) OR NA[Text] OR</li> <li>adefovir[Text] OR hepsera[Text] OR preveon[Text] OR bis-</li> <li>POM PMEA[Text] OR GS 840[Text] OR ADV[Text] OR</li> <li>emtricitabine[Text] OR emtriva[Text] OR FTC[Text] OR</li> <li>entecavir[Text] OR baraclude[Text] OR ETV[Text] OR</li> <li>lamivudine[Text] OR sebivo[Text] OR tyzeka[Text] OR</li> <li>LdT[Text] OR tenofovir[Text] OR viread[Text] OR</li> <li>TDF[Text] OR vemlidy[Text] OR TAF[Text]</li> </ul> | 755 458      |
| 6    | 4 OR 5   | 1 335<br>890 |
| 7    | "pregnancy"[MeSH] OR "pregnant women"[MeSH] OR<br>"maternal-fetal relations"[MeSH] OR "infectious disease<br>transmission, vertical"[MeSH] OR "pregnancy<br>complications, infectious"[MeSH] OR "prenatal<br>diagnosis"[MeSH]  | 870 293      |
| 8    | pregnan*[Text] OR trimest*[Text] OR gestation*[Text] OR<br>antepartum[Text] OR ante-partum[Text] OR<br>prepartum[Text] OR pre-partum[Text] OR<br>intrapartum[Text] OR intra-partum[Text] OR<br>peripartum[Text] OR peri-partum[Text] OR  | 1 793<br>242 |

|    | antenatal*[Text] OR ante-natal*[Text] OR prenatal*[Text]  |       |
|----|---|-------|
|    | OR pre-natal*[Text] OR perinatal*[Text] OR peri-          |       |
|    | natal*[Text] OR intrauterine[Text] OR intra-uterine[Text] |       |
|    | OR inutero[Text] OR in utero[Text] OR                     |       |
|    | transplacental*[Text] OR placenta*[Text] OR               |       |
|    | vertical*[Text] OR congenital*[Text] OR mother*[Text] OR  |       |
|    | matern*[Text] OR fetomaternal*[Text] OR                   |       |
|    | foetomaternal*[Text] OR fetal*[Text] OR foetal*[Text] OR  |       |
|    | fetus[Text] OR foetus[Text] OR offspring[Text] OR         |       |
|    | MTCT[Text] OR TME[Text]                                   |       |
| 9  | 7 OR 8  | 1 803 |
|    |   | 794   |
| 10 | 3 AND 6 AND 9   | 1004  |

### Database: Embase Classic + Embase via OvidSP (1947-2019 March 26th)

Date searched: March 28<sup>th</sup> 2019

| Item | Search words  | #       |
|------|---|---------|
|      |   | Records |
| 1    | exp hepatitis B/ OR exp Hepatitis B virus/                  | 120 132 |
| 2    | (hepatitis b OR type b hepatitis OR hepatitis type b OR hbv | 158 928 |
|      | OR vhb OR hep b OR hbsag OR hbs ag OR hbs                   |         |
|      | antigen*).mp.   |         |
| 3    | 1 OR 2  | 158 928 |
| 4    | exp antiviral therapy/ OR exp antivirus agent/ OR exp       | 1 657   |
|      | nucleoside/ OR exp nucleotide/ OR exp adefovir/ OR exp      | 284     |
|      | adefovir dipivoxil/ OR exp emtricitabine/ OR exp entecavir/ |         |
|      | OR exp lamivudine/ OR exp telbivudine/ OR exp tenofovir/    |         |
|      | OR exp tenofovir disoproxil/ OR exp tenofovir alafenamide/  |         |
| 5    | (antiviral* OR nucleoside* OR nucleotide* OR (nucleos*      | 1 421   |
|      | AND analog*) OR (nucleot* AND analog*) OR NA OR             | 448     |
|      | adefovir OR hepsera OR preveon OR bis-POM PMEA OR           |         |
|      | GS 840 OR ADV OR emtricitabine OR emtriva OR FTC            |         |
|      | OR entecavir OR baraclude OR ETV OR lamivudine OR           |         |
|      | epivir OR 3TC OR telbivudine OR sebivo OR tyzeka OR         |         |
|      | LdT OR tenofovir OR viread OR TDF OR vemlidy OR             |         |
|      | TAF).mp.  |         |
| 6    | 4 OR 5  | 2 708   |
|      |   | 549     |
| 7    | exp pregnancy/ OR exp pregnant women/ OR exp mother         | 807 598 |
|      | fetus relationship/ OR exp vertical transmission/ OR exp    |         |
|      | pregnancy complication/ OR exp prenatal diagnosis/          |         |
| 8    | (pregnan* OR trimest* OR gestation* OR antepartum OR        | 2 268   |
|      | ante-partum OR prepartum OR pre-partum OR intrapartum       | 793     |
|      | OR intra-partum OR peripartum OR peri-partum OR             |         |
|      | antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR     |         |
|      | perinatal* OR peri-natal* OR intrauterine OR intra-uterine  |         |
|      | OR inutero OR in utero OR transplacental* OR placenta*      |         |
|      | OR vertical* OR congenital* OR mother* OR matern* OR        |         |
|      | fetomaternal* OR foetomaternal* OR fetal* OR foetal* OR     |         |
|      | fetus OR foetus OR offspring OR MTCT OR TME).mp.            |         |
| 9    | 7 OR 8  | 2 274   |
|      |   | 006     |
| 10   | 3 AND 6 AND 9   | 3 069   |

# Database: Scopus

Date searched: March 28<sup>th</sup> 2019

| r    |  |         |
|------|--|---------|
| Item | Search words   |         |
|      |  | Records |
| 1    | TITLE-ABS-KEY ("hepatitis b" OR "type b hepatitis" OR      | 138 899 |
|      | "hepatitis type b" OR "hbv" OR "vhb" OR "hep b" OR         |         |
|      | "hbsag" OR "hbs ag" OR "hbs antigen*")                     |         |
|      |  |         |
| 2    | TITLE-ABS-KEY ("antiviral*" OR "nucleoside*" OR            | 1 781   |
|      | "nucleotide*" OR ("nucleos*" AND "analog*") OR             | 759     |
|      | ("nucleot*" AND "analog*") OR "NA" OR "adefovir" OR        |         |
|      | "hepsera" OR "preveon" OR "bis-POM PMEA" OR "GS            |         |
|      | 840" OR "ADV" OR "emtricitabine" OR "emtriva" OR           |         |
|      | "FTC" OR "entecavir" OR "baraclude" OR "ETV" OR            |         |
|      | "lamivudine" OR "epivir" OR "3TC" OR "telbivudine" OR      |         |
|      | "sebivo" OR "tyzeka" OR "LdT" OR "tenofovir" OR            |         |
|      | "viread" OR "TDF" OR "vemlidy" OR "TAF")                   |         |
| 3    | TITLE-ABS-KEY ("pregnan*" OR "trimest*" OR                 | 2 892   |
|      | "gestation*" OR "antepartum" OR "ante-partum" OR           | 112     |
|      | "prepartum" OR "pre-partum" OR "intrapartum" OR "intra-    |         |
|      | partum" OR "peripartum" OR "peri-partum" OR                |         |
|      | "antenatal*" OR "ante-natal*" OR "prenatal*" OR "pre-      |         |
|      | natal*" OR "perinatal*" OR "peri-natal*" OR "intrauterine" |         |
|      | OR "intra-uterine" OR "inutero" OR "in utero" OR           |         |
|      | "transplacental*" OR "placenta*" OR "vertical*" OR         |         |
|      | "congenital*" OR "mother*" OR "matern*" OR                 |         |
|      | "fetomaternal*" OR "foetomaternal*" OR "fetal*" OR         |         |
|      | "foetal*" OR "fetus" OR "foetus" OR "offspring" OR         |         |
|      | "MTCT" OR "TME")   |         |
|      |  |         |
| 4    | #1 AND #2 AND #3   | 1 810   |

# Database: CENTRAL Database (The Cochrane Library)

Date searched: March 28<sup>th</sup> 2019

| Item | Search words                                      | # Trials and |
|------|---|--------------|
|      |   | Reviews      |
| 1    | hepatitis b [MeSH, exp] OR hepatitis b virus      | 2 462        |
|      | [MeSH, exp]                                       |              |
|      |   |              |
| 2    | "hepatitis b" OR "type b hepatitis" OR "hepatitis | 7 692        |
|      | type b" OR hbv OR vhb OR "hep b" OR hbsag         |              |
|      | OR "hbs ag" OR "hbs antigen" OR "hbs antigens"    |              |
| 3    | 1 OR 2  | 7 692        |
| 4    | antiviral agents [MeSH, exp] OR nucleosides       | 17 552       |
|      | [MeSH, exp] OR nucleotides [MeSH, exp] OR         |              |
|      | emtricitabine [MeSH, exp] OR lamivudine           |              |
|      | [MeSH, exp] OR telbivudine [MeSH, exp] OR         |              |
|      | tenofovir [MeSH, exp]                             |              |
| 5    | antiviral* OR nucleoside* OR nucleotide* OR       | 34 424       |
|      | (nucleos* AND analog*) OR (nucleot* AND           |              |
|      | analog*) OR NA OR adefovir OR hepsera OR          |              |
|      | preveon OR "bis-POM PMEA" OR "GS 840" OR          |              |
|      | ADV OR emtricitabine OR emtriva OR FTC OR         |              |
|      | entecavir OR baraclude OR ETV OR lamivudine       |              |
|      | OR epivir OR 3TC OR telbivudine OR sebivo OR      |              |
|      | tyzeka OR LdT OR tenofovir OR viread OR TDF       |              |
|      | OR vemlidy OR TAF                                 |              |
| 6    | 4 OR 5  | 44 913       |
| 7    | pregnancy [MeSH, exp] OR pregnant women           | 8 802        |
|      | [MeSH, exp] OR maternal-fetal relations [MeSH,    |              |
|      | exp] OR infectious disease transmission, vertical |              |
|      | [MeSH, exp] OR pregnancy complications,           |              |
|      | infectious [MeSH, exp] OR prenatal diagnosis      |              |
|      | [MeSH, exp]                                       |              |
| 8    | pregnan* OR trimest* OR gestation* OR             | 74 080       |
|      | antepartum OR ante-partum OR prepartum OR         |              |
|      | pre-partum OR intrapartum OR intra-partum OR      |              |
|      | peripartum OR peri-partum OR antenatal* OR        |              |
|      | ante-natal* OR prenatal* OR pre-natal* OR         |              |
|      | perinatal* OR peri-natal* OR intrauterine OR      |              |
|      | intra-uterine OR inutero OR "in utero" OR         |              |
|      | transplacental* OR placenta* OR vertical* OR      |              |
|      | congenital* OR mother* OR matern* OR              |              |
|      | fetomaternal* OR foetomaternal* OR fetal* OR      |              |

|    | foetal* OR fetus OR foetus OR offspring* OR<br>MTCT OR TME |        |
|----|--|--------|
| 9  | 7 OR 8   | 74 912 |
| 10 | 3 AND 6 AND 9  | 246    |

Database: CNKI

Date searched: March 28<sup>th</sup>, 2019

Search Strategy:

SU='乙型肝炎'+'乙肝'+'乙型肝炎病毒'+'乙肝病毒'+'HBV'+'乙型肝炎表面抗原'+'乙 肝表面抗原'AND SU='抗病毒'+'抗病毒药物'+'核苷'+'核苷酸'+'核苷类似物'+'核苷酸 类似物'+'NAs'+'阿德福韦酯'+'hepsera'+'preveon'+'bis-POM PMEA'+'GS 840'+'ADV'+' 恩 曲 他 滨 '+'emtriva'+'FTC'+' 恩 替 卡 韦 '+'baraclude'+'ETV'+' 拉 米 夫 定 '+'epivir'+'3TC'+'LAM'+' 替 比 夫 定 '+'sebivo'+'tyzeka'+'LdT'+' 替 诺 福 韦 酯 '+'viread'+'TDF'+'替诺福韦艾拉酚胺'+'vemlidy'+'TAF' AND SU='妊娠'+'怀孕'+'孕妇'+' 孕期'+'母胎'+'母亲'+'胎儿'+'子代'+'子女'+'垂直传播'+'产前'+'产时'+'产间'+'围产'+'出 生前'+'围生'+'宫内'+'跨胎盘'+'胎盘'+'母婴传播'+'预防母婴传播'+'阻断母婴传播'+'妊 娠并发症'+'产前诊断'+'先天'

65

Database: Wanfang

Date searched: March 28<sup>th</sup>, 2019

Search Strategy: 主题: ("乙型肝炎"+"乙肝"+"乙型肝炎病毒"+"乙肝病毒"+"HBV"+"乙型肝炎表面抗 原"+"乙肝表面抗原") and 主题: ("抗病毒"+"抗病毒药物"+"核苷"+"核苷酸"+"核苷类 似物 "+" 核 苷 酸 类 似物 "+"NAs"+" 阿 德 福 韦 酯 "+"hepsera"+"preveon"+"bis-POM PMEA"+"GS 840"+"ADV"+" 恩 曲 他 滨 "+"emtriva"+"FTC"+" 恩 替 卡 韦 "+"baraclude"+"ETV"+" 拉 米 夫 定 "+"epivir"+"3TC"+"LAM"+" 替 比 夫 定 "+"sebivo"+"tyzeka"+"LdT"+" 替诺福韦酯"+"viread"+"TDF"+" 替诺福韦艾拉酚胺 "+"vemlidy"+"TAF") and 主题: ("妊娠"+"怀孕"+"孕妇"+"孕期"+"母胎"+"母亲"+"胎 儿"+"子代"+"子女"+"垂直传**播**"+"产前"+"产时"+"产间"+"围产"+"出生前"+"围**生**"+" 宫内"+" 跨胎盘"+" 胎盘"+" 母婴传播"+" 预防母婴传播"+" 阻断母婴传播"+" 妊娠并发 **症**"+"产前诊断"+"先天")

#### Appendix B: List of variables present on data extraction tool

#### 1. Publication details

- First author
- Year
- Journal
- Language

#### 2. Methods

- Country
- Study design
- Purpose of study
- Recruitment period
- Recruitment setting (regional details, number of sites)
- Inclusion criteria
- Exclusion criteria
- Intervention arm treatment including birth dose vaccination and/or HBIg administration if relevant
- Intervention Treatment schedule (including birth dose vaccination and/or HBIg administration if relevant) and timing (including hours since birth for birth dose/HBIg)
- Control arm treatment
- Control arm treatment schedule and timing
- Infant treatment 1. Birth dose vaccination (dose, manufacturer)
- Infant treatment 1. Birth dose vaccination (detail the number of hours since birth)
- Infant treatment 2. HBIg (dose, manufacturer)
- Infant treatment 2. HBIg (detail the number of hours since birth)
- Infant treatment 3. Non-birth dose vaccination (dose, manufacturer)
- Infant treatment 3. Non-birth dose vaccination (schedule)
- Infant treatment 4. Any other treatment (e.g., antiviral therapy in infants)
- Follow-up schedule (mothers)
- Follow-up schedule (infants)

#### 3. Number (No.) of participants at enrolment

- No. of women assessed for eligibility
- No. of women who underwent randomization (or included if non-randomized)

#### 4. Women's characteristics in Treatment arm

- Treatment arm: No. of women assigned to treatment (or included if non-randomized)
- Treatment arm: No. of women with baseline characteristics reported
- Treatment arm: Mean treatment duration
- Treatment arm: Mean or median age
- Treatment arm: No. by ethnicity
- Treatment arm: No. positive for HBeAg
- Treatment arm: HBV DNA threshold used (IU/ml or copies/ml)
- Treatment arm: Mean or median HBV DNA

- Treatment arm: No. HDV positive
- Treatment arm: No. HCV positive
- Treatment arm: No. HIV positive
- Treatment arm: No. loss to F/U or regimen change

#### 5. Women's characteristics in control arm

- Control arm: No. of women assigned to control (or included if non-randomized)
- Control arm: No. of women with baseline characteristics reported
- Control arm: Mean treatment duration
- Control arm: Mean or median age
- Control arm: No. by ethnicity
- Control arm: No. positive for HBeAg
- Control arm: HBV DNA threshold used (IU/ml or copies/ml)
- Control arm: Mean or median HBV DNA
- Control arm: No. HDV positive
- Control arm: No. HCV positive
- Control arm: No. HIV positive
- Control arm: No. loss to F/U or regimen change
- 6. Infant outcomes at birth in treatment arm
  - No. of infants in treatment arm at birth
  - Treatment arm: No. of twins
  - Treatment arm: No. of triplets
  - Treatment arm: mean gestational age at birth (weeks)
  - Treatment arm: mean birthweight (kg)
  - Treatment arm: No. male
  - Treatment arm: No. by each type of delivery (vaginal or caesarean)
  - Treatment arm: No. of infants eventually assessed for all MTCT/ adverse event outcomes

#### 7. Infant outcomes at birth in control arm

- No. of infants in control arm at birth
- Control arm: No. of twins
- Control arm: No. of triplets
- Control arm: mean gestational age at birth (weeks)
- Control arm: mean birthweight (kg)
- Control arm: No. of male
- Control arm: No. by each type of delivery (vaginal or caesarean)
- Control arm: No. of infants eventually assessed for all MTCT/ adverse event outcomes

#### 8. MTCT definition

- MTCT definition used
- HBsAg assay method used to define MTCT
- HBV DNA assay method used to define MTCT
- Exact timing of 6-12 months assessment to define MTCT

#### 9. MTCT (intention-to-treat) in treatment arm

• Intention-to-treat or modified intention-to-treat definition used

- Denominator for intention-to-treat analysis: mothers assigned to intervention + twin/triplet
- No. of infants completed MTCT evaluation at 6-12 month timepoint
- No. of infants with HBsAg at 6-12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6-12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Intention-to-treat MTCT risk (defined by HBsAg)
- Intention-to-treat MTCT risk (defined by HBV DNA)

### **10. MTCT (per protocol) in treatment arm**

- Denominator for per-protocol analysis: mother-infant pairs completed the intervention treatment & completed MTCT evaluation at 6-12 months timepoint
- No. of infants with HBsAg at 6-12 months in mother-infant pairs completed the intervention treatment & completed MTCT evaluation at 6-12 months timepoint (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6-12 months in mother-infant pairs completed the intervention treatment & completed MTCT evaluation at 6-12 months timepoint (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Per-protocol MTCT risk (defined by HBsAg)
- Per-protocol MTCT risk (defined by HBV DNA)

### 11. MTCT (intention-to-treat) in control arm

- Denominator for intention-to-treat analysis: mothers assigned to control + twin/triplet
- No. of infants completed MTCT evaluation at 6-12 month timepoint
- No. of infants with HBsAg at 6-12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6-12 months (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Intention-to-treat MTCT risk (defined by HBsAg)
- Intention-to-treat MTCT risk (defined by HBV DNA)

## 12. MTCT (per protocol) in control arm

- Denominator for per-protocol analysis: mother-infant pairs completed the control treatment & completed MTCT evaluation at 6-12 months timepoint
- No. of infants with HBsAg at 6-12 months in mother-infant pairs completed the control treatment & completed MTCT evaluation at 6-12 months timepoint (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- No. of infants with HBV DNA at 6-12 months in mother-infant pairs completed the control treatment & completed MTCT evaluation at 6-12 months timepoint (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
- Per-protocol MTCT risk (defined by HBsAg)
- Per-protocol MTCT risk (defined by HBV DNA)
- 13. No. of infant adverse events in treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
  - Treatment arm: Foetal death
  - Treatment arm: Neonatal death (within 28 days)

- Treatment arm: Prematurity (give definition used)
- Treatment arm: Congenital abnormalities #
- Treatment arm: Congenital abnormalities: describe
- Treatment arm: Apgar score at 1 minute is <10
- Treatment arm: Sub-optimal bone density (give definition and the age at evaluation)
- Treatment arm: Any other event
- 14. No. of infant adverse events in control arm (list by maternal HBeAg, HBV DNA, HDV, HIV, where possible)
  - Control arm: Foetal death
  - Control arm: Neonatal death (within 28 days)
  - Control arm: Prematurity (give definition used)
  - Control arm: Congenital abnormalities #
  - Control arm: Congenital abnormalities: describe
  - Control arm: Apgar score at 1 minute is <10
  - Control arm: Sub-optimal bone density (give definition and the age at evaluation)
  - Control arm: Any other event

#### **15. Hepatitis flare**

• Definition of hepatitis flare used

# 16. No. of maternal adverse events in treatment arm (list by maternal HBeAg, HBV DNA, HDV, HIV, status where possible)

- Treatment arm: No. of women considered for adverse events
- Treatment arm: Foetal death or stillbirth
- Treatment arm: Hepatitis flare after treatment discontinuation
- Treatment arm: Postpartum hemorrhage
- Treatment arm: Antiviral resistance
- Treatment arm: Any other event

# 17. No. of maternal adverse events in control arm (list by maternal HBeAg, HBV DNA, HDV, HIV, status where possible)

- Control arm: No. of women considered for adverse events
- Control arm: Foetal death or stillbirth
- Control arm: Hepatitis flare after during a matched period
- Control arm: Postpartum hemorrhage
- Control arm: Antiviral resistance
- Control arm: Any other event

#### 18. Other

- Summary of study conclusions
- Funding by industry

## Appendix C: Risk of bias assessment tools

Guidance - Cochrane Collaboration's risk of bias assessment tool

|                | Courses of high     | Description                              | Deview extheria indement          |
|----------------|---------------------|--|-----------------------------------|
| Pige Domain    | Source or blas      | Description                              | Review author's judgment          |
| DiasDomain     |                     |  | Assess as low, unclear or high    |
|                |                     |  | risk of blas                      |
|                | Sequence            | Describe the method used to generate     | Selection bias (biased allocation |
| Selection bias | generation.         | the allocation sequence in sufficient    | to interventions) due to          |
|                |                     | detail to allow an assessment of         | inadequate generation of a        |
|                |                     | whether it should produce comparable     | randomized sequence               |
|                |                     | groups                                   |                                   |
|                | Allocation          | Describe the method used to conceal      | Selection bias (biased allocation |
|                | concealment.        | the allocation sequence in sufficient    | to interventions) due to          |
|                |                     | detail to determine whether              | inadequate concealment of         |
|                |                     | intervention allocations could have      | allocations before assignment     |
|                |                     | been foreseen before or during           | e                                 |
|                |                     | enrolment                                |                                   |
|                | Blindina of         | Describe all measures used if any to     | Performance bias due to           |
| Performance    | participants        | blind trial participants and researchers | knowledge of the allocated        |
| bias           | nersonnel and       | from knowledge of which intervention     | interventions by participants and |
|                | outcome assessors   | a participant received Provide any       | nersonnel during the study        |
|                | Assessments should  | information relating to whether the      | personner during the study        |
|                | he made for each    | intended blinding was effective          |                                   |
|                | main outcome (or    | intended binding was effective           |                                   |
|                | alass of outcomes)  |  |                                   |
|                | class of outcomes). | Describe all measured if and to          | Detection him des to be endeded   |
| Detection bias | Blinding of outcome | Describe all measures used, if any, to   | of the allocated interventions by |
| Detection bias | assessment          | bind outcome assessment from             | of the anocated interventions by  |
|                | Assessments should  | knowledge of which intervention a        | outcome assessment                |
|                | ha mada for aach    | participant received. Provide any        |                                   |
|                | be made for each    | information relating to whether the      |                                   |
|                | main outcome (or    | intended blinding was effective          |                                   |
|                | class of outcomes). | Describe the second terms of easterness  |                                   |
| Attrition bios |                     | Describe the completeness of outcome     | Attrition bias due to amount,     |
| ALLINUTIDIAS   | data. Assessments   | data for each main outcome, including    | nature, or handling of incomplete |
|                | should be made for  | attrition and exclusions from the        | outcome data                      |
|                | each main outcome   | analysis. State whether attrition and    |                                   |
|                | (or class of        | exclusions were reported, the numbers    |                                   |
|                | outcomes).          | in each intervention group (compared     |                                   |
|                |                     | with total randomized participants),     |                                   |
|                |                     | reasons for attrition or exclusions      |                                   |
|                |                     | where reported, and any reinclusions     |                                   |
|                |                     | in analyses for the review               |                                   |
| Den entire er  | Selective outcome   | State how the possibility of selective   | Reporting bias due to selective   |
| Reporting      | reporting.          | outcome reporting was examined by        | outcome reporting                 |
| blas           |                     | the review authors, and what was         |                                   |
|                |                     | found.                                   |                                   |
| Others L.      | Other sources of    | State any important concerns about       | Bias due to problems not covered  |
| Other blas     | bias.               | bias not addressed in the other          | elsewhere                         |
|                |                     | domains in the tool. If particular       |                                   |
|                |                     | questions/entries were pre-specified in  |                                   |
|                |                     | the review's protocol, responses         |                                   |
|                |                     | should be provided for each              |                                   |
|                |                     | question/entry.                          |                                   |

#### (Table taken directly Higgins JPT et al., 2011)
# Notes for filling out the table (adapted/made specific for this systematic review and meta-analysis from the *Cochrane Handbook 2008* and from *Higgins JPT et al.*, 2011):

- Within the table, summary descriptions should be provided in order to give an independent reader enough information to see why the specific judgment has been made. For example, if no information on sequence generation can be found in the article or correspondence with the author, you could enter "Comment: no information provided". If it states that patients were randomly allocated in the article, then you could copy out the phrase directly from the article, e.g. "Quote: "patients were randomly allocated". In any case, if you have doubts in whether or not the study actually did certain things that are mentioned in the article, please include an extra comment describing concern/contradiction in the article.
- When providing your judgment as a review author, indicate 'low risk' of bias, and 'high risk' of bias. If insufficient information is provided, then the judgment should be 'unclear' risk of bias.
  - See table 8.5c on pages 198-202 in the 2008 Cochrane Handbook for Systematic Reviews of Intervention (pages 223-227 of the PDF) for specific guidance on how to make your judgment.

#### Guidance - Newcastle - Ottawa Quality Assessment Scale for Cohort Studies

#### (Adapted to the systematic review questions)

<u>Note</u>: The below has been adapted for this specific meta-analysis from the guidance found on the Newcastle-Ottawa quality assessment group website (http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

#### SELECTION

#### 1) <u>Representativeness of the exposed cohort (0 or 1 star)</u>

a) Truly representative of the average HBV infected pregnant women in the community \*

- Women identified to carry HBsAg at a general antenatal care clinic or general practitioner with or without subsequently referral to the specialist obstetric care centre or hepatologist or infectious disease specialist
- Not part of a special group (e.g. all with recent treatment for hepatocellular carcinoma) then we might assume they reflect/are representative of HBV infected pregnant women in that community.

b) Somewhat representative of the average HBV infected pregnant women in the community \*

- e.g., women known to be chronically infected with HBV and have been followed by hepatologist or infectious disease specialist
- c) Selected group of users
  - eg. Women with severe liver disease (cirrhosis or hepatocellular carcinoma) only, part of a special group (HIV-infected women, intravenous drug users (IVDU)), women working in study centres/hospitals, etc
  - Please provide a comment if you believe that the exposed group does not match well the general community
- d) No description of the derivation of the cohort

#### 2) <u>Selection of the non-exposed cohort (0 or 1 star)</u>

a) Drawn from the same community as the exposed cohort \*

- Women presenting at the hospital, pregnant and with HBV (not, most of our studies should fall here in this review)
- b) Drawn from a different source
  - e.g. controls drawn from a historical sample
  - Please make a comment if you believe that the controls have been drawn from a different source
- c) No description of the derivation of the non exposed cohort

#### 3) <u>Ascertainment of exposure (exposure = treatment) (0 or 1 star)</u>

a) Valid method was used to ascertain adherence to the antiviral therapy\*

• Ideally with some mention of methods to ascertain maternal adherence to treatment (e.g., evaluation of pill count, immunoassay to detect serum/urine

metabolite of antiviral agents, or decrease in viral load levels subsequent to the treatment)

- b) Based on a secure record about adherence \*
  - Study staff have recorded good adherence to treatment based on self-report
  - Description on the treatment duration supports the confirmation of adherence by study staff.
- c) Data collection through registry
  - Care must be taken for a study based on registry data; having started antiviral during pregnancy does not necessarily guarantee that the women adhered to the treatment throughout the intended period.
- d) No description

## 4) <u>Demonstration that outcome of interest was not present at start of study (0 or 1 star)</u>

- a) Yes \star
  - This will always be yes in our case... for this study topic as the outcome of interest is HBV status in infants and infants are born during the course of the study

b) no

#### COMPARABILITY

#### 1) Comparability of cohorts on the basis of the design or analysis (0 or 1 or 2 star(s))

a) Study controls/is comparable for both HBV DNA level (within 1 log IU/ml) and HBeAg sero-status (within 10 % points)**\*** 

- The same threshold for HBV DNA level AND same HbeAg sero-status should be used for inclusion of treated and controls and/or the reported mean/median HBV DNA level and HbeAg sero-prevalence at baseline should be reported and should be similar.
- If not reported threshold or not reported mean/median and/or not similar then no star. If only one is reported/similar and the other not, then no star.

b) Study controls for child immunoprophylaxis at birth (birth dose vaccination, HBIG at birth) \*

• All have or all don't have or similar proportions across exposed and unexposed group with a similar timeliness. If not reported at all or very different proportions then no star.

#### OUTCOME

#### 1) Assessment of outcome (0 or 1 star)

- a) Independent blind assessment **\*** 
  - Examiner of infant outcome (e.g., laboratory staff) was blinded to the maternal exposure status.

b) Medical records related to outcome were seen and verified by study personnel, or there was record linkage \*

• In the case where testing is done as part of the study, and it is indicated that the same laboratory assays were used to test all infants, then it will be assumed that there was direct verification of test results by study personnel using these medical records.

c) No description

• If there is no description of laboratory methods (specifically, specifying which assay was used or indicating that all testing was done by study personnel or records were sent to study personnel) then no star will be given.

#### 2) <u>Was follow-up long enough for outcomes to occur (0 or 1 star)</u>

- a) Yes (at 6-12 months) **\*** 
  - Because we have defined our inclusion criteria for the review as testing needing to be done between 6 and 12 months, all of our studies should fall here.
- b) No
  - This should not be the case for any of our studies. Please provide a detailed comment if you think it is the case.

#### 3) Adequacy of follow up of cohorts (0 or 1 star)

a) Complete follow up - all subjects accounted for and lost to follow-up reported clearly as 0 \*

b) Subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % (or description provided of those lost) \*

c) Follow up rate < 80 % (select an adequate %) and no description of those lost

- d) No statement about LFU
  - If not reporting any LFU, and also not mentioning clearly that 'There were no cases 'LFU' then we should assume that LFU was not well reported, and this should not be given a star.

## Appendix D: Descriptions of other antiviral therapies included (<3 studies per regimen)

Telbivudine (LdT) 100 mg

Three studies were eligible for this meta-analysis that used telbivudine (LdT) 100 mg (*Ge JQ et al., 2015; Li ZG et al., 2015; Mu YSJ et al., 2018*). Of these, one was an RCT and two were non-RCTs. Of the non-RCTs, the risk of bias scores, according to the Newcastle-Ottawa scale, were 5 (high) and 6 (high), respectively (*Mu YSJ et al., 2018; Ge JQ et al., 2015*); as per protocol, studies with high risk of bias with scores of 5 or lower were excluded from analysis. Therefore, we describe only the basic details of two studies (one RCT and one non-RCT) here.

One RCT was performed that examined use of LdT 100 mg during pregnancy for the PMTCT of HBV (*Li ZG et al., 2015*). This study took place in China from 2013 to 2014. Treatment was started at 28 weeks of pregnancy, and stopped after 6 weeks postpartum. Birth dose vaccination and HBIg were given to all infants on the first day of life, and two further vaccinations were performed at 1 and 6 months of life. Of 25 infants whose mothers were treated during pregnancy, none were positive for HBsAg at 1 year of life, compared to 4 of 25 control infants at the same timepoint (OR=0.09, 95%CI: 0.01-1.84). Infant and maternal adverse events were not well described in the article.

One non-RCT, specifically, a retrospective cohort study, was performed that examined use of LdT 100 mg during pregnancy for the PMTCT of HBV (*Ge JQ et al., 2015*). This study took place in China from 2012 to 2013. Treatment was started between 28 and 32 weeks of pregnancy, and stopped after 6 weeks postpartum. Birth dose vaccination and HBIg were given to all infants within 12 hours of life, and two further vaccinations were performed at 1 and 6 months of life. Of 40 infants whose mothers were treated during pregnancy, one was positive for HBsAg at 12 months of life, compared to 11 of 40 control infants at the same timepoint (OR=0.07, 95%CI: 0.01-0.55). Most infant and maternal adverse events were not addressed in the article; however, authors did confirm that there were no congenital abnormalities in either the treated or control group at the time of birth.

#### Adefovir (ADV) 500 mg

One RCT was performed that examined use of ADV 500 mg during pregnancy for the PMTCT of HBV (*Feng Y et al., 2018*). This study took place in China in 2017. Treatment was started at 28 weeks of pregnancy, and stopped at the time of delivery. HBIg was given within 24 hours of life, a vaccination was given at '0 months', and two further vaccinations were performed at 1 and 6 months of life. Of 258 mothers treated during pregnancy, 254 infants were evaluated for MTCT, 6 were positive for HBsAg at 1 year of life, compared to 24 of 251 control infants at the same timepoint (OR=0.23, 95%CI: 0.09-0.57). Infant adverse events were not well described in the article. Of maternal adverse events, the authors did report that 5.4% (95%CI: 3.0-8.9) of women in the treated arm had postpartum hemorrhage, whereas this was 10.1% (95%CI: 6.7-14.4) in the control group.

#### Adefovir (ADV) 10 mg

One non-RCT, specifically, a prospective cohort study, was performed that examined use of ADV 10 mg during pregnancy for the PMTCT of HBV (*Fang HS et al., 2011*). This study took place in China from 2006 to 2008. Treatment with ADV was started prior to pregnancy in all women (end time not reported), and additionally, HBIg was given to women in both the treatment and control groups at 28, 32, and 36 weeks of gestation. Birth dose vaccination was done (timing unclear), and two further vaccinations were performed at 1 and 6 months of life. There was no mention of administration of HBIg to infants in the article. Of 42 infants whose mothers were treated during pregnancy, none were positive for HBsAg at 12 months of life, compared to 5 of 52 control infants at the same timepoint (OR=0.10, 95%CI: 0.01-1.89). Most infant and maternal adverse events were not addressed in the article; however, authors did confirm that there were no congenital abnormalities or cases of prematurity in either the treated or control group at the time of birth.

## Appendix E: Characteristics of the included studies by treatment type

## Aggregate study characteristics

| Treatme<br>nt        | #<br>Studi<br>es | Study<br>countries<br>(% studies)  | Study<br>design<br>(%<br>studies)                                       | Time<br>perio<br>d | #<br>Pregnant<br>women<br>included<br>(treated/no<br>t treated) | <b>HBeAg</b><br># studies/<br>total studies                                | Range of<br>mean<br>viral<br>load at<br>baseline<br>(#<br>studies<br>reporting<br>) | Range of<br>treatme<br>nt start<br>times          | Range of<br>treatme<br>nt<br>disconti<br>n-uation<br>times | # Infants<br>assessed<br>(of<br>mothers<br>treated/<br>untreated) | Infants<br>prophylax<br>is<br># studies/ total<br>studies |
|----------------------|------------------|--|---|--------------------|---|--|---|---|--|---|---|
| TDF<br>300 mg        | 19               | Australia<br>(5.3) China<br>(73.7) Japan<br>(5.3)<br>Taiwan<br>(5.3)<br>Thailand<br>(5.3)<br>Turkey<br>(5.3) | <b>RCT</b> =<br>5 (26.3)<br><b>non-</b><br><b>RCT</b> =<br>14<br>(73.7) | 2010-<br>2018      | 1974<br>(1092/882<br>)  | All positive:<br>11/19<br>All negative:<br>0/19<br>Mixed: 1/19<br>NR: 7/19 | 3.6 - 8.3<br>log10<br>IU/mL<br>(n=16)   | Pre-<br>pregnanc<br>y to 36<br>weeks<br>gestation | 0 to 12<br>weeks<br>post<br>partum                         | 1908<br>(1072/836<br>)  | HBIG,<br>Hep-B-<br>BD, infant<br>vaccines:<br>16/19       |
| LAM<br>100-150<br>mg | 40               | Australia<br>(2.5) China <sup>b</sup><br>(88.8)<br>Egypt (2.5)<br>Ireland<br>(2.5) Japan                     | <b>RCT</b> =<br>8 (20.0)<br><b>non-</b><br><b>RCT</b> =<br>32           | 2001-<br>2016      | 4200<br>(2080/212<br>0)   | All positive:<br>30/40<br>All negative:<br>0/40<br>Mixed: 4/40<br>NR: 6/40 | 6.0 - 8.7<br>log10<br>IU/mL<br>(n=26)   | Pre-<br>pregnanc<br>y to 34<br>weeks<br>gestation | 0 to 12<br>weeks<br>post<br>partum <sup>e</sup>            | 4051<br>(2007/204<br>4)   | HBIG,<br>Hep-B-<br>BD, infant<br>vaccines:<br>34/40       |

|               |    | (2.5)Phillipines <sup>b</sup> $(1.3)$ | (80.0)  |               |                          |   |                                      |   |                                    |                          |   |
|---------------|----|---------------------------------------|---|---------------|--------------------------|---|--------------------------------------|---|------------------------------------|--------------------------|---|
| LdT<br>600 mg | 83 | China<br>( <i>100.0</i> )             | <b>RCT</b> =<br>21<br>(25.3)<br><b>non-</b><br><b>RCT</b> =<br>62<br>(74.7) | 2001-<br>2016 | 12104<br>(6036/606<br>8) | All positive:<br>52/83<br>All negative:<br>1/83<br>Mixed: 6/83<br>NR: 24/83 | 2.0- 8.3<br>log10<br>IU/mL<br>(n=73) | Pre-<br>pregnanc<br>y to 36<br>weeks<br>gestation | 0 to 36<br>weeks<br>post<br>partum | 11768<br>(5971/579<br>7) | HBIG,<br>Hep-B-<br>BD, infant<br>vaccines:<br>78/83 |

**Note:** All percentages use as a denominator the total number of women/infants included/assessed studies with details reported. <sup>a</sup>In order to be considered as having 'full' prophylaxis, the study report needed to have mentioned clearly that infants were given all of HBIG at birth, HepB-BD, and subsequent HBV vaccinations in infancy. <sup>b</sup>One study took place in China and the Philippines – each have been counted as half for each country in this cell. <sup>c</sup>One study administered treatment 'anytime' which may have extended past 34 weeks gestation. <sup>d</sup>Two studies administered treatment 'anytime' which may have extended past 36 weeks gestation. <sup>e</sup>One study continued' treatment past 12 weeks for various and possibly indefinite periods for study participants.

## Individual study characteristics

| Gener   | al study de       | tails and o                | lesign   |     |   | Treate   | ed pregnant w                  | vomen (t     | x)   |                                   |        | Untreated p                    | regnant      | women (cont   | trol)                             | Infant ir                          | nmunopropl<br>infants) | nylaxis (all   |
|---|-------------------|----------------------------|--|-----|---|--|--------------------------------|--------------|--|-----------------------------------|--------|--------------------------------|--------------|---|-----------------------------------|------------------------------------|------------------------|--|
| Author,<br>year   | Country           | Recruit-<br>ment<br>period | Criteria<br>for<br>maternal<br>HBV<br>DNA (log<br>IU/mL) | #   | Treatme<br>(gestatio<br>/ Trea<br>disconti<br>(postp<br>wee   | ent start<br>n weeks)<br>tment<br>nuation<br>artum<br>eks) | Mean/<br>median age<br>(years) | HBeAg<br>(%) | Mean/<br>median<br>HBV<br>DNA at<br>baseline<br>(log<br>IU/mL) | # Infants<br>assessed<br>for MTCT | #      | Mean/<br>median age<br>(years) | HBeAg<br>(%) | Mean/<br>median<br>HBV DNA<br>at baseline<br>(log<br>IU/mL) | # Infants<br>assessed<br>for MTCT | HBIG at<br>birth,<br><i>timing</i> | HepB-BD,<br>timing     | Infant<br>vaccine,<br>dose 1 /dose<br>2 in<br>months |
|   |                   |                            |  |     |   |  |                                |              | TDF  | 300 mg                            |        |                                |              |   |                                   |                                    |                        |  |
|   | 1                 |                            |  |     | 1   |  | 1                              | Rando        | omized con   | trolled trials (                  | RCT)   | 1                              |              |   |                                   | 1                                  |                        | 1  |
| Jourdain<br>G, 2018 <sup>14,</sup><br><sup>15, 23</sup> | Thailand          | 2013-<br>2015              | None   | 168 | 26-29       8 $25.5$ 100       7.6       149       163 $26.7$ 100       7.3         24       4 $28.3$ 100       7.4       58       60 $28.1$ 100       7.7         30       30       30       30       30       30       30       30       30 |  |                                |              |  |                                   |        |                                |              |   |                                   | Yes,<br><3hr                       | Yes,<br><3hr           | Yes,<br>1/2/4/6                                      |
| Lin Y,<br>2018 <sup>24,25</sup>                         | China             | 2013-<br>2016              | ≥6.3   | 60  | 24  | 4  | 28.3<br>±3.6                   | 100          | 7.4  | 58                                | 60     | 28.1<br>±3.4                   | 100          | 7.7   | 52                                | Yes,<br><24hr                      | Yes,<br>12hr           | Yes,<br>1/6  |
| Liu MH,<br>2017 <sup>26</sup>                           | China             | 2014-<br>2016              | ≥5.3   | 20  | 28-30   | 0  | 30<br>[22-38]                  | 100          | 6.5  | 20                                | 20     | 29<br>[21-38]                  | 100          | 6.5   | 20                                | Yes,<br><24hr                      | Yes,<br><24hr          | Yes,<br>1/6  |
| Pan CQ,<br>2016 <sup>13</sup>                           | China             | 2012-<br>2013              | ≥5.3   | 100 | 30-32   | 4  | 27.4<br>±3.0                   | 100          | 8.2  | 92                                | 100    | 26.8<br>±3.0                   | 100          | 8.0   | 88                                | Yes,<br><12hr                      | Yes,<br><12hr          | Yes,<br>1/6  |
| Yu CY,<br>2018 <sup>27</sup>                            | China             | 2017                       | ≥6.0   | 30  | 24  | 4  | 26.8<br>±4.2                   | NR           | NR   | 30                                | 30     | 27.6<br>±3.6                   | NR           | NR  | 30                                | Yes,<br><24hr                      | Yes,<br><24hr          | NR   |
|   |                   |                            |  |     |   |  | No                             | on-rando     | mized cont   | rolled trials (                   | Non-RC | T)                             |              |   |                                   |                                    |                        |  |
| Celen<br>MK,<br>2013 <sup>28</sup>                      | Turkey            | 2010-<br>2012              | ≥6.3   | 21  | 18-27   | 4  | 28.2<br>±4.1                   | 100          | 8.3  | 21                                | 24     | 26.9<br>±2.9                   | 100          | 8.3   | 23                                | Yes,<br><24hr                      | No                     | Yes,<br>1/2/6  |
| Chen HL,<br>2015 <sup>29</sup>                          | China<br>(Taiwan) | 2011-<br>2013              | ≥7.5   | 62  | 30-32   | 4  | 32.4<br>±3.1                   | 100          | 8.3  | 65                                | 56     | 32.5<br>±3.2                   | 100          | 8.2   | 56                                | Yes,<br><24hr                      | Yes,<br>NR             | Yes,<br>1/6  |
| Chen WJ,<br>2017 <sup>30</sup>                          | China             | 2014-<br>2015              | ≥6.0   | 30  | 28  | 0  | 28.7<br>±5.7                   | 100          | 7.5  | 30                                | 44     | 29.9<br>±5.1                   | 100          | 7.5   | 44                                | Yes,<br>At birth                   | Yes,<br>At birth       | Yes,<br>1/6  |
| Gong Q,<br>2017 <sup>31</sup>                           | China             | 2015-<br>2016              | NR   | 44  | 1-6   | NR   | 29.1<br>±1.0                   | NR           | NR   | 44                                | 44     | 29.1<br>±1.2                   | NR           | NR  | 44                                | Yes,<br><24hr                      | Yes,<br><24hr          | Yes,<br>1/6  |
| Greenup<br>AJ,<br>2014 <sup>32-35</sup>                 | Australia         | 2007-<br>2013              | ≥7.0±0.5   | 62  | 32  | 12   | 30<br>±8.5                     | 94.8         | 7.9  | 69                                | 20     | 28±5                           | 100          | 8.0   | 10                                | Yes,<br>NR                         | Yes,<br>At birth       | Yes,<br>2/4/6  |

| He LL,<br>2018 <sup>36</sup>    | China | 2013-<br>2016 | NR                    | 50 | 28                | NR                            | 27.7<br>±3.2          | NR  | 3.6 | 50 | 35 | 26.3<br>±3.0          | NR  | 3.7 | 35 | Yes,<br><12hr           | Yes,<br><12hr        | Yes,<br>1/6          |
|---------------------------------|-------|---------------|-----------------------|----|-------------------|-------------------------------|-----------------------|-----|-----|----|----|-----------------------|-----|-----|----|-------------------------|----------------------|----------------------|
|                                 |       |               |                       | 30 | Pre-<br>pregnancy | Various<br>post-<br>pregnancy | 28.4<br>±1.4          | NR  | 7.4 | 29 |    |                       |     |     |    |                         |                      |                      |
| Hu MF,<br>2018 <sup>37</sup>    | China | 2016-<br>2018 | ≥6.0                  | 30 | 14                | Various<br>post-<br>pregnancy | 23.2<br>±3.3          | NR  | 7.5 | 30 | 30 | 26.3<br>±2.1          | NR  | 7.5 | 30 | Yes,<br>At birth        | Yes,<br>At birth     | Yes,<br>1/6          |
|                                 |       |               |                       | 30 | 28                | Various<br>post-<br>pregnancy | 24.4<br>±3.1          | NR  | 7.4 | 30 |    |                       |     |     |    |                         |                      |                      |
| Huang Q,<br>2017 <sup>38</sup>  | China | 2015          | ≥6.0                  | 20 | 24-28             | 12                            | 27.1<br>±2.4          | 100 | NR  | 20 | 20 | 27.0<br>±2.3          | 100 | NR  | 20 | Yes,<br><6hr            | Yes,<br><6hr         | Yes,<br>1/6          |
| Wakano<br>Y, 2018 <sup>39</sup> | Japan | 2011-<br>2015 | N/A                   | 2  | 22 or 28          | 4-8                           | [28-37]<br>All groups | 100 | 8.3 | 2  | 3  | [28-37]<br>All groups | 100 | 8.3 | 3  | Yes,<br><12 or<br><48hr | Yes (some),<br><12hr | Yes,<br>2/3/5 or 1/6 |
| Wan JY,<br>2017 <sup>40</sup>   | China | 2012-<br>2015 | ≥5.3                  | 74 | 28                | 0                             | 28.5<br>±4.2          | NR  | 7.7 | 74 | 42 | 27.9<br>±4.0          | NR  | 7.6 | 42 | NR                      | NR                   | NR                   |
|                                 |       |               |                       | 20 | 20                | NR                            | NR                    | NR  | 7.0 | 20 |    |                       |     |     |    |                         |                      |                      |
|                                 |       |               |                       | 20 | 24                | NR                            | NR                    | NR  | 7.1 | 20 |    |                       |     |     |    |                         |                      |                      |
| Wang HB,<br>2018 <sup>41</sup>  | China | 2013-<br>2016 | NR                    | 20 | 28                | NR                            | NR                    | NR  | 7.2 | 20 | 20 | NR                    | NR  | 7.2 | 20 | Yes,<br><24hr           | Yes, <24hr           | Yes, 1/6             |
|                                 |       |               |                       | 20 | 32                | NR                            | NR                    | NR  | 7.2 | 20 |    |                       |     |     |    |                         |                      |                      |
|                                 |       |               |                       | 20 | 36                | NR                            | NR                    | NR  | 6.7 | 20 |    |                       |     |     |    |                         |                      |                      |
| Xiao XH,<br>2017 <sup>42</sup>  | China | 2014-<br>2015 | ≥6.0                  | 60 | 28                | 0-4                           | 27.6<br>±3.2          | NR  | 7.6 | 60 | 60 | 28.5<br>±3.6          | NR  | 7.5 | 61 | Yes, NR                 | Yes, NR              | Yes, NR              |
| Zhang<br>BF, 2018 <sup>43</sup> | China | 2016-<br>2017 | $\geq 6.0$ (tx group) | 39 | 24-28             | 0                             | NR                    | 100 | 4.8 | 39 | 75 | NR                    | 100 | 6.0 | 75 | Yes,<br><6hr            | Yes,<br>At birth     | Yes,<br>1/6          |
| Zhou Y,<br>2018 <sup>44</sup>   | China | 2015-<br>2017 | ≥6.0                  | 60 | 24-28             | 0                             | 28<br>[21-38]         | 100 | 7.6 | 60 | 36 | 28<br>[23-39]         | 100 | 7.6 | 36 | Yes,<br><6hr            | Yes,<br><24hr        | Yes,<br>1/6          |

|                                    |                        |               |      |     |         |    |  |          | LAM 10     | 00-150 mg        |        |  |     |     |     |                              |                  |             |
|------------------------------------|------------------------|---------------|------|-----|---------|----|--|----------|------------|------------------|--------|--|-----|-----|-----|------------------------------|------------------|-------------|
|                                    |                        |               |      |     |         |    |  | Rando    | omized con | trolled trials ( | (RCT)  |  |     |     |     |                              |                  |             |
| Bai XW,<br>2011 <sup>45</sup>      | China                  | 2006-<br>2010 | NR   | 30  | 28      | 4  | NR   | NR       | NR         | 30               | 25     | NR   | NR  | NR  | 25  | Yes,<br><24hr (trt<br>group) | Yes,<br><24      | Yes,<br>1/6 |
| Chen SM,<br>2017 <sup>46</sup>     | China                  | 2013-<br>2014 | ≥4.3 | 30  | 28      | NR | 27.9<br>±3.6   | 100      | 7.5        | 30               | 30     | 27.5<br>±3.9   | 100 | 8.0 | 30  | Yes,<br>NR                   | Yes,<br>NR       | Yes,<br>NR  |
| Guo YZ,<br>2008 <sup>47-49</sup>   | China                  | 2003-<br>2006 | NR   | 70  | 28      | 0  | NR   | 100      | NR         | 70               | 40     | NR   | 100 | NR  | 40  | Yes,<br><6hr                 | Yes,<br>At birth | Yes,<br>1/6 |
| Ji YY,<br>2015 <sup>50</sup>       | China                  | 2010-<br>2013 | ≥5.3 | 65  | 28      | 4  | 26.2<br>±3.1   | 100      | 7.6        | 65               | 65     | 27.5<br>±4.1   | 100 | 7.7 | 65  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Li ZG,<br>2015 <sup>51</sup>       | China                  | 2013-<br>2014 | ≥4.3 | 25  | 28      | 6  | NR   | 100      | NR         | 25               | 25     | NR   | 100 | NR  | 25  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Tian XQ,<br>2015 <sup>52</sup>     | China                  | 2010-<br>2014 | ≥5.3 | 110 | 28      | 0  | 29±3   | 100      | 7.9        | 110              | 110    | 28±4   | 100 | 8.1 | 110 | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Xu WM,<br>2009 <sup>53,54</sup>    | China &<br>Philippines | NR            | ≥8.3 | 93  | 30-34   | 4  | 26<br>[19-32]  | 99       | 8.6        | 49               | 62     | 25<br>[20-36]  | 100 | 8.7 | 41  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Yang<br>HW,<br>2014 <sup>55</sup>  | China                  | 2010-<br>2013 | ≥5.3 | 53  | 28      | 4  | 29±4   | 100      | 7.3        | 53               | 53     | 28±4   | 100 | 7.3 | 53  | Yes,<br><24hr                | Yes,<br>At birth | Yes,<br>1/6 |
|                                    |                        |               |      |     |         |    | Na   | on-rando | mized cont | rolled trials (  | Non-RC | ( <b>T</b> )   |     |     |     |                              |                  |             |
| Chen QR,<br>2018 <sup>56</sup>     | China                  | 2014-<br>2016 | NR   | 33  | 28      | 4  | 25.0<br>±3.9   | 100      | 7.6        | 33               | 28     | 24.1<br>±4.7   | 100 | 7.7 | 28  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Cheng<br>YC,<br>2011 <sup>57</sup> | China                  | 2007-<br>2009 | ≥6.3 | 30  | 32      | 4  | 27±4   | 100      | 8.2        | 30               | 26     | 25±5   | 100 | 7.5 | 26  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Feng HF,<br>2007 <sup>58</sup>     | China                  | 2004-<br>2006 | ≥5.3 | 48  | 28      | 4  | NR   | 100      | 7.6        | 48               | 42     | NR   | 100 | 7.5 | 42  | Yes,<br><24hr                | Yes,<br><24hr    | Yes,<br>1/6 |
| Foaud<br>HM,<br>2019 <sup>59</sup> | Egypt                  | 2012-<br>2015 | NR   | 34  | Anytime | NR | $27.0$ $\pm 2.9 (tx in last)$ trimester) $27.7$ $\pm 4.0 (tx)$ | 44       | NR         | 29               | 39     | $27.4$ $\pm 4.6 (low)$ HBV DNA<br>group) 25.7<br>$\pm 4.3$ (diagnosed) | 13  | NR  | 30  | Yes,<br>At birth             | Yes,<br>At birth | Yes, 2/4/6  |

|  |           |               |            |     |                              |                | throughout<br>pregnancy) |     |     |     |    | too late for<br>tx) |     |     |    |                  |                  |               |
|--|-----------|---------------|------------|-----|------------------------------|----------------|--------------------------|-----|-----|-----|----|---------------------|-----|-----|----|------------------|------------------|---------------|
| Ge YL,<br>2015 <sup>60</sup>               | China     | NR            | ≥5.3       | 16  | 28-30                        | 12             | 27.9<br>±3.6             | 100 | 7.2 | 16  | 22 | 26.5<br>±4.2        | 100 | 6.9 | 22 | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6   |
| Greenup<br>AJ,<br>2014 <sup>32-35,61</sup> | Australia | 2007-<br>2013 | ≥7.0       | 48  | 32                           | 2              | 28±5                     | 96  | 7.7 | 43  | 20 | 28±5                | 100 | 8.0 | 10 | Yes,<br>NR       | Yes,<br>At birth | Yes,<br>2/4/6 |
| Han YP,<br>2014 <sup>62</sup>              | China     | 2010-<br>2012 | ≥4.3       | 30  | 28                           | 6              | 26±4                     | 100 | 7.6 | 30  | 30 | 26±4                | 100 | 7.7 | 30 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6   |
| Han ZH,<br>2005 <sup>63</sup>              | China     | 2001-<br>2003 | ≥4.9       | 43  | 28                           | 0              | NR                       | 100 | 6.4 | 43  | 35 | NR                  | 100 | NR  | 35 | Yes,<br><4hr     | No               | Yes,<br>2/3/6 |
| He T,<br>2018 <sup>64-66</sup>             | China     | 2008-<br>2016 | NR         | 27  | 1 <sup>st</sup><br>trimester | Contin-<br>ued | 29.2<br>±2.9             | 74  | 6.3 | 29  | 35 | 29.0<br>±3.6        | 80  | 6.3 | 34 | Yes,<br><6hr     | Yes,<br><12hr    | Yes,<br>1/6   |
| Jackson<br>V, 2015 <sup>67</sup>           | Ireland   | 2007-<br>2012 | ≥7.2       | 36  | 32                           | 0              | 26<br>[16-40]            | 100 | 8.1 | 21  | 9  | NR                  | 100 | NR  | 6  | Yes,<br><3hr     | Yes,<br><3hr     | Yes,<br>2/4/6 |
| Jiang HX,<br>2012 <sup>68</sup>            | China     | 2007-<br>2010 | ≥5.3       | 164 | 20-34                        | 0              | 27.3<br>±4.4             | 100 | 7.1 | 164 | 92 | 26.4<br>±3.2        | 100 | 7.2 | 92 | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6   |
| Li G,<br>2006 <sup>69</sup>                | China     | 2005-<br>2006 | NR         | 40  | 28                           | 0              | 24±3                     | 100 | NR  | 35  | 37 | 24±5                | 100 | NR  | 32 | Yes,<br><24hr    | No               | Yes,<br>1/2/7 |
| Li JH,<br>2017 <sup>70</sup>               | China     | 2012-<br>2016 | NR         | 33  | 28                           | 4              | 28.2<br>±6.3             | NR  | 8.0 | 33  | 27 | 29.4<br>±5.7        | NR  | 7.7 | 27 | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6   |
| Li WF,<br>2006 <sup>71</sup>               | China     | 2001-<br>2003 | ≥4.3       | 36  | 34                           | 0              | NR                       | 100 | 6.1 | 36  | 44 | NR                  | 100 | NR  | 44 | Yes,<br><6hr     | No               | Yes,<br>2/3/7 |
| Ma J,<br>2006 <sup>72</sup>                | China     | NR            | NR         | 18  | Pre-<br>pregnancy            | NR             | NR                       | 100 | NR  | 18  | 22 | NR                  | 100 | NR  | 16 | Yes,<br>At birth | Yes,<br>At birth | NR            |
| Pan CQ,                                    | China     | 2008-         | <u>5</u> 2 | 66  | 13-26                        | 4              | 27.7<br>±4.1             | 100 | 6.5 | 66  | 80 | 27.1                | 100 | 6.6 | 80 | Yes,             | Yes,             | Yes,          |
| 2017 <sup>73</sup>                         | Cnina     | 2015          | ≥3.3       | 94  | 28-30                        | 4              | 27.4<br>±3.5             | 100 | 6.5 | 94  | 89 | ±4.2                | 100 | 0.0 | 89 | <6hr             | <12hr            | 1/6           |
| Ren CJ,<br>2016 <sup>74</sup>              | China     | 2010-<br>2012 | ≥5.3       | 67  | 28                           | 0              | 25.8<br>±4.7             | 100 | 6.1 | 67  | 72 | 25.4<br>±5.1        | 100 | 6.1 | 72 | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6   |

| Ren YJ,<br>2011 <sup>75</sup>       | China | 2008-<br>2009 | NR   | 30  | 28                | 0   | NR                         | 100 | NR  | 30  | 155 | NR                         | 100 | NR  | 155 | Yes,<br><24hr           | Yes,<br>At birth     | Yes,<br>1/6    |
|-------------------------------------|-------|---------------|------|-----|-------------------|-----|----------------------------|-----|-----|-----|-----|----------------------------|-----|-----|-----|-------------------------|----------------------|----------------|
| Shen ML,<br>2016 <sup>76</sup>      | China | 2010-<br>2014 | ≥4.3 | 60  | 26                | 4   | NR                         | NR  | 6.1 | 60  | 28  | NR                         | NR  | 6.0 | 28  | Yes,<br><24hr           | Yes,<br>NR           | Yes,<br>NR     |
| Su TB,<br>2009 <sup>77</sup>        | China | 2004-<br>2007 | NR   | 128 | 32                | 0   | NR                         | NR  | NR  | 128 | 120 | NR                         | NR  | NR  | 120 | Yes,<br><2hr            | Yes,<br>3 days       | Yes,<br>1/6    |
| Tang X,<br>2009 <sup>78</sup>       | China | 2007-<br>2008 | ≥5.3 | 17  | 33                | 4   | NR                         | 100 | 6.6 | 17  | 24  | NR                         | 100 | 6.7 | 24  | Yes,<br><24hr           | Yes,<br><24hr        | Yes,<br>1/6    |
| Wakano<br>Y, 2018 <sup>39</sup>     | Japan | 2011-<br>2015 | NR   | 3   | 28-32             | 4-8 | [28-37]<br>All groups      | 100 | 8.3 | 3   | 3   | [28-37]<br>All groups      | 100 | 8.3 | 3   | Yes,<br><12 or<br><48hr | Yes (some),<br><12hr | Yes,<br>Varied |
| Wang<br>DM,<br>2016 <sup>79</sup>   | China | 2011-<br>2014 | ≥5.3 | 42  | 28-30             | 12  | 31.4<br>±7.3               | 100 | 7.1 | 42  | 20  | 31.7<br>±7.0               | 100 | 7.1 | 20  | NR                      | Yes,<br><24hr        | Yes,<br>1/6    |
| Wang EJ,<br>2012 <sup>80</sup>      | China | 2008-<br>2010 | ≥6.3 | 32  | 28                | 4   | 25.0<br>±3.8               | 100 | 7.6 | 32  | 27  | 24.0<br>±4.7               | 100 | 7.7 | 27  | Yes,<br><24hr           | Yes,<br><24hr        | Yes,<br>1/6    |
| Wang<br>TM,<br>2005 <sup>81</sup>   | China | 2001-<br>2003 | ≥5.7 | 32  | Pre-<br>pregnancy | 0   | NR                         | 100 | NR  | 32  | 32  | NR                         | 100 | NR  | 32  | NR                      | Yes,<br><12hr        | Yes,<br>1/6    |
| Wang W,<br>2014 <sup>82</sup>       | China | 2011-<br>2012 | NR   | 35  | 28                | 4   | 28.<br>4±3.8               | NR  | 7.4 | 35  | 28  | 27.2<br>±4.2               | NR  | 7.2 | 28  | Yes,<br><24hr           | Yes,<br>At birth     | Yes,<br>1/6    |
| Yuan QF,<br>2012 <sup>83</sup>      | China | 2010-<br>2011 | NR   | 30  | 27                | 4   | 26.5<br>±4.5<br>All groups | 100 | NR  | 32  | 30  | 26.5<br>±4.5<br>All groups | 100 | NR  | 32  | Yes,<br><24hr           | Yes,<br><24hr        | Yes,<br>6/12   |
|                                     |       |               |      | 30  | 28                | 0   | NR                         | 100 | 6.6 | 30  |     |                            |     |     |     |                         |                      |                |
| Zeng YM,<br>2013 <sup>84</sup>      | China | 2008-<br>2010 | ≥4.3 | 30  | 28                | 4   | NR                         | 100 | 6.6 | 30  | 30  | NR                         | 100 | 6.5 | 30  | Yes,<br>At birth        | Yes,<br>At birth     | Yes,<br>1/6    |
|                                     |       |               |      | 30  | 28                | 6   | NR                         | 100 | 6.5 | 30  |     |                            |     |     |     |                         |                      |                |
| Zhang H,<br>2014 <sup>85</sup>      | China | 2009-<br>2011 | ≥6.3 | 55  | 28-30             | 4   | 28.4<br>±7.1               | 100 | 6.9 | 52  | 374 | 29.0<br>±4.6               | 100 | 6.8 | 352 | Yes,<br><6hr            | Yes,<br><6hr         | Yes,<br>1/6    |
| Zhang<br>YF,<br>2010a <sup>86</sup> | China | 2006-<br>2007 | ≥5.3 | 50  | 28                | 4   | NR                         | 100 | 6.1 | 50  | 50  | NR                         | 100 | 6.1 | 50  | Yes,<br><24hr           | Yes,<br><24hr        | Yes,<br>1/6    |

| Zhou DS,                           | China | 2009-         | >5.3         | 49  | 20    | NR | 27.4<br>±6.7 | NR    | 6.8       | 49               | 05    | 29.2         | NR  | 6.9 | 95  | Yes,             | Yes,             | Yes,        |
|------------------------------------|-------|---------------|--------------|-----|-------|----|--------------|-------|-----------|------------------|-------|--------------|-----|-----|-----|------------------|------------------|-------------|
| 201387                             | China | 2012          | <u>_</u> J.J | 64  | 28    | NR | 28.1<br>±5.3 | NR    | 6.7       | 64               | 95    | ±6.1         |     | 0.9 | 75  | <12hr            | At birth         | 1/6         |
| Zhu M,<br>2014 <sup>88</sup>       | China | 2012-<br>2013 | NR           | 24  | 26    | 0  | NR           | 100   | NR        | 24               | 25    | NR           | 100 | NR  | 24  | Yes,<br><8hr     | Yes,<br><8hr     | Yes,<br>1/6 |
|                                    |       |               |              |     |       |    |              |       | LDT       | 600 mg           |       |              |     |     |     |                  |                  |             |
|                                    |       |               |              |     |       |    |              | Rando | mized con | trolled trials ( | (RCT) |              |     |     |     |                  |                  |             |
| Bai HL,<br>2013 <sup>89</sup>      | China | 2009-<br>2011 | ≥6.3         | 30  | 28-32 | 4  | NR           | NR    | 6.5       | 27               | 30    | NR           | NR  | 6.6 | 30  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Chen SM,<br>2017 <sup>46</sup>     | China | 2013-<br>2014 | ≥4.3         | 30  | 28    | NR | 27.4<br>±3.5 | 100   | 7.8       | 30               | 30    | 27.5<br>±3.9 | 100 | 8.0 | 30  | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
| Fu PX,<br>2016 <sup>90</sup>       | China | 2014-<br>2015 | NR           | 100 | 24-28 | 4  | 31.5<br>±1.5 | NR    | NR        | 100              | 100   | 31.7<br>±1.6 | NR  | NR  | 100 | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>NR  |
| Guan ZF,<br>2017 <sup>91,92</sup>  | China | 2005-<br>2015 | ≥6.3         | 12  | 24    | 12 | 26.5<br>±9.5 | 100   | 7.1       | 123              | 120   | 27.2<br>±9.4 | 100 | 7.1 | 122 | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Guo HJ,<br>2011 <sup>93</sup>      | China | 2008-<br>2010 | ≥6.3         | 25  | 28    | 4  | 28<br>±3     | 100   | 7.0       | 28               | 25    | 27±4         | 100 | 7.2 | 26  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
|                                    |       |               |              | 30  | 20    | 0  | 28.2<br>±3.5 | 100   | 7.3       | 30               |       |              |     |     |     |                  |                  |             |
| Huang<br>HY,<br>2016 <sup>94</sup> | China | 2012–<br>2013 | ≥5.3         | 30  | 24    | 0  | 28.6<br>±3.4 | 100   | 7.3       | 30               | 30    | 28.9<br>±3.5 | 100 | 7.2 | 30  | NR               | NR               | NR          |
|                                    |       |               |              | 30  | 28    | 0  | 28.4±<br>3.2 | 100   | 7.3       | 30               |       |              |     |     |     |                  |                  |             |
| Ji YY,<br>2015 <sup>50</sup>       | China | 2010-<br>2013 | ≥5.3         | 65  | 28    | 4  | 27.2<br>±3.6 | 100   | 7.7       | 65               | 65    | 27.5<br>±4.1 | 100 | 7.7 | 65  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Li SF,<br>2015 <sup>95</sup>       | China | 2012-<br>2014 | ≥6.3         | 60  | 28    | 24 | NR           | NR    | 6.9       | 60               | 60    | NR           | NR  | 6.7 | 60  | Yes,<br>At birth | No               | Yes,<br>1/6 |

| Lu QY,<br>2016 <sup>96</sup>       | China | 2013-<br>2014 | NR   | 152 | 28                           | 0  | [29-36]       | 47       | NR         | 152             | 132    | [29-36]       | 41  | NR  | 132 | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
|------------------------------------|-------|---------------|------|-----|------------------------------|----|---------------|----------|------------|-----------------|--------|---------------|-----|-----|-----|------------------|------------------|-------------|
| Peng ML,<br>2014 <sup>97</sup>     | China | 2011-<br>2012 | NR   | 30  | 28                           | NR | 25.9<br>±4.2  | 100      | 6.1        | 30              | 30     | 26.4<br>±4.4  | 100 | 6.1 | 30  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Shi QW,<br>2017 <sup>98</sup>      | China | NR            | ≥5.3 | 100 | 24                           | 0  | [23-40]       | NR       | 7.1        | 100             | 100    | [23-40]       | NR  | 6.9 | 100 | Yes,<br><2hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Wang<br>HY,<br>2018 <sup>99</sup>  | China | 2015-<br>2017 | ≥5.3 | 40  | 12-14                        | 24 | NR            | 100      | 6.8        | 40              | 40     | NR            | 100 | 6.9 | 40  | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1/6 |
| Xie PY,<br>2016 <sup>100</sup>     | China | 2015-<br>2015 | NR   | 60  | 28                           | 4  | 26.6<br>±12.5 | NR       | NR         | 60              | 60     | 26.1<br>±11.6 | NR  | NR  | 60  | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
| Xing Y,<br>2018 <sup>101</sup>     | China | 2013-<br>2015 | NR   | 30  | 28                           | 4  | 29.0<br>±6.0  | NR       | 6.5        | 30              | 30     | 29.5<br>±5.3  | NR  | 6.5 | 30  | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1   |
| Yang<br>HW,<br>2015 <sup>102</sup> | China | 2012-<br>2014 | ≥5.3 | 50  | 28                           | 4  | NR            | 100      | 6.1        | 50              | 50     | NR            | 100 | 6.1 | 50  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Zhang LJ,<br>2009 <sup>103</sup>   | China | 2007-<br>2008 | ≥6.3 | 31  | 28-32                        | 4  | NR            | NR       | 6.6        | 30              | 30     | NR            | NR  | 6.7 | 30  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Zhang Y,<br>2018 <sup>104</sup>    | China | 2015-<br>2017 | ≥6.3 | 34  | Pre-<br>pregnancy            | NR | 28.4<br>±3.1  | NR       | 6.6        | 34              | 34     | 28.0<br>±3.1  | NR  | 6.9 | 34  | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
| Zhao DB,<br>2010 <sup>105</sup>    | China | 2006-<br>2008 | NR   | 30  | 28                           | 4  | NR            | 100      | NR         | 30              | 30     | NR            | 100 | NR  | 30  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Zhao Y,<br>2017 <sup>106</sup>     | China | 2013-<br>2016 | ≥6.3 | 40  | 12                           | 12 | 28.1<br>±4.1  | 100      | 7.3        | 40              | 40     | 27.9<br>±3.9  | 100 | 7.2 | 40  | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Zhu J,<br>2017 <sup>107</sup>      | China | 2012-<br>2015 | NR   | 60  | 28                           | 0  | NR            | NR       | 7.4        | 60              | 60     | NR            | NR  | 6.9 | 54  | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Zhu LP,<br>2014 <sup>108</sup>     | China | 2011-<br>2012 | NR   | 30  | 28                           | 4  | NR            | NR       | 6.7        | 30              | 30     | NR            | NR  | 6.6 | 30  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
|                                    |       |               |      |     |                              |    | No            | on-rando | mized cont | rolled trials ( | Non-RC | <i>T</i> )    |     |     |     |                  |                  |             |
| Chen CY, 2015 <sup>109</sup>       | China | 2008-<br>2011 | ≥6.3 | 43  | 1 <sup>st</sup><br>trimester | NR | 29.7<br>±8.9  | 100      | 7.1        | 42              | 41     | 27.5<br>±6.6  | 100 | 7.0 | 40  | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |

| Chen F,<br>2016 <sup>110</sup>   | China | 2008-<br>2014 | ≥6.3 | 31  | Pre-<br>pregnancy            | NR             | 26.5<br>±4.0  | 100 | 6.9 | 31  | 33 | 26.0<br>±4.4 | 100 | 6.7 | 32 | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
|----------------------------------|-------|---------------|------|-----|------------------------------|----------------|---------------|-----|-----|-----|----|--------------|-----|-----|----|------------------|------------------|-------------|
| Chen QR,<br>2018 <sup>56</sup>   | China | 2014-<br>2016 | NR   | 29  | 28                           | 4              | 26.9<br>±4.3  | 100 | 7.8 | 29  | 28 | 24.1<br>±4.7 | 100 | 7.7 | 28 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Chen WJ,<br>2017 <sup>30</sup>   | China | 2014-<br>2015 | ≥6.0 | 79  | 28                           | 0              | 31.1<br>±6.3  | 100 | 8.3 | 79  | 44 | 29.9<br>±5.1 | 100 | 7.5 | 44 | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Chen ZX, 2017 <sup>111-113</sup> | China | 2001-<br>2015 | ≥5.3 | 43  | 13-32                        | NR             | 28.1<br>±6.7  | 70  | 6.5 | 41  | 89 | 26.2<br>±4.5 | 83  | 6.5 | 89 | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1/6 |
| Cui ZL,<br>2015 <sup>114</sup>   | China | 2013-<br>2014 | ≥5.3 | 50  | 28                           | 4              | 28.0<br>±1.8  | 100 | 7.1 | 50  | 50 | 27.6<br>±2.1 | 100 | 6.9 | 46 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Deng Y,<br>2015 <sup>115</sup>   | China | 2011-<br>2014 | ≥6.0 | 82  | 24-36                        | 4              | 25.4<br>±3.7  | NR  | 7.0 | 82  | 75 | 25.7<br>±3.6 | NR  | 7.0 | 75 | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Ding XP,<br>2018 <sup>116</sup>  | China | 2013-<br>2017 | ≥6.3 | 38  | 28                           | 4              | NR            | 100 | 7.3 | 38  | 38 | NR           | 100 | 7.2 | 38 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Fan LY,<br>2013 <sup>117</sup>   | China | 2010-<br>2011 | ≥5.3 | 58  | 28                           | 24             | 27.8<br>±3.0  | 100 | 6.9 | 58  | 60 | 29.0<br>±2.9 | 100 | 6.7 | 60 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Feng XM,<br>2017 <sup>118</sup>  | China | 2014-<br>2016 | ≥6.3 | 36  | 28                           | 4              | 29.6<br>±6.3  | 100 | 6.9 | 36  | 36 | 28.4<br>±5.1 | 100 | 6.7 | 36 | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Gao P,<br>2016 <sup>119</sup>    | China | 2012-<br>2014 | NR   | 51  | 1 <sup>st</sup><br>trimester | 0              | 28.4<br>±3.8  | NR  | 7.1 | 51  | 51 | 27.2<br>±3.6 | NR  | 7.0 | 51 | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
| Ge YL,<br>2015 <sup>60</sup>     | China | NR            | ≥5.3 | 20  | 28-30                        | 12             | 28.6<br>±3.5  | 100 | 7.1 | 20  | 22 | 26.5<br>±4.2 | 100 | 6.9 | 22 | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Han GR,                          | China | 2008-         | 5.2  | 257 | 20-27                        | Variable       | 27<br>[20-35] | 100 | 7.9 | 256 | 02 | 26           | 100 | 7.0 | 96 | Yes,             | Yes,             | Yes,        |
| 2015 <sup>120-125</sup>          | Cnina | 2010          | ≥3.3 | 105 | 28-32                        | Variable       | 28<br>[20-38] | 100 | 7.8 | 102 | 92 | [20-35]      | 100 | 7.9 | 80 | <3hr             | <12hr            | 1/6         |
| Han YP,<br>2014 <sup>62</sup>    | China | 2010-<br>2012 | ≥4.3 | 30  | 28                           | 6              | 26±4          | 100 | 7.7 | 30  | 30 | 26±4         | 100 | 7.7 | 30 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| He T,<br>2018 <sup>64,126</sup>  | China | 2008-<br>2016 | NR   | 32  | 1 <sup>st</sup><br>trimester | Contin-<br>ued | 29.2<br>±2.9  | 84  | 6.6 | 32  | 35 | 29.0<br>±3.6 | 80  | 6.2 | 34 | Yes,<br><6hr     | Yes,<br><12hr    | Yes,<br>1/6 |

| Hu WH,<br>2016 <sup>127</sup>    | China | 2013-<br>2015 | NR   | 46  | 28                | 28  | 28.9<br>±3.3 | NR  | 6.7 | 46  | 40  | 29.2<br>±3.4 | NR  | 6.6 | 40  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
|----------------------------------|-------|---------------|------|-----|-------------------|-----|--------------|-----|-----|-----|-----|--------------|-----|-----|-----|------------------|------------------|-------------|
| Hu Y,<br>2018 <sup>128,129</sup> | China | 2012-<br>2014 | NR   | 149 | 28-32             | 3-4 | 25.9<br>±3.7 | 100 | 7.4 | 105 | 179 | 26.4<br>±3.4 | 100 | 7.3 | 122 | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Huang Q,<br>2017 <sup>38</sup>   | China | 2015-<br>2015 | ≥6.0 | 20  | 24-28             | 12  | 26.8<br>±2.5 | 100 | NR  | 20  | 20  | 27.0<br>±2.3 | 100 | NR  | 20  | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1/6 |
| Jiang S,<br>2017 <sup>130</sup>  | China | 2015-<br>2016 | NR   | 44  | 28                | NR  | 28.3<br>±3.4 | NR  | 6.1 | 44  | 44  | NR           | NR  | 6.1 | 44  | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Jiang XN,<br>2013 <sup>131</sup> | China | 2010-<br>2011 | ≥4.3 | 65  | 26-30             | NR  | NR           | 100 | 6.0 | 65  | 51  | NR           | 100 | 5.9 | 51  | Yes,<br>NR       | Yes,<br>At birth | Yes,<br>1/6 |
| Li CM,<br>2017 <sup>132</sup>    | China | 2013-<br>2015 | ≥2.3 | 30  | 28                | 4   | 43.2<br>±1.3 | NR  | 6.1 | 30  | 30  | 43.2<br>±1.3 | NR  | 6.1 | 30  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Li N,                            | China | 2012-         | >1 2 | 35  | Pre-<br>pregnancy | NR  | NR           | NR  | 5.1 | 35  | 25  | ND           | ND  | 5.0 | 25  | Yes,             | Yes,             | Yes,        |
| <b>2016</b> <sup>133</sup>       | China | 2015          | 24.5 | 30  | 28                | NR  | NR           | NR  | 5.1 | 30  | 23  | INK          | INK | 5.0 | 23  | <6hr             | <6hr             | 1/6         |
| Li YH,<br>2017 <sup>134</sup>    | China | 2015-<br>2017 | ≥6.3 | 30  | 28                | ~36 | 29.5<br>±2.7 | 100 | 3.2 | 30  | 31  | 28.8<br>±3.5 | 100 | 3.2 | 32  | Yes,<br><24hr    | Yes,<br>NR       | Yes,<br>NR  |
| Li ZY,<br>2018 <sup>135</sup>    | China | 2015-<br>2016 | ≥5.3 | 41  | 28                | NR  | 26.2<br>±4.4 | 100 | 6.1 | 41  | 41  | 26.3<br>±4.2 | 100 | 6.1 | 41  | Yes,<br><24hr    | No               | Yes,<br>1/6 |
| Liu CY,<br>2014 <sup>136</sup>   | China | 2011-<br>2011 | ≥5.3 | 34  | 28                | 4   | 27.2<br>±3.6 | 100 | 7.1 | 34  | 34  | 26.9<br>±4.1 | 100 | 7.4 | 34  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Liu J,<br>2017 <sup>137</sup>    | China | 2013-<br>2015 | ≥6.0 | 102 | 30                | NR  | 27.8<br>±4.1 | 100 | 8.1 | 97  | 28  | 26.7<br>±3.9 | 100 | 8.1 | 28  | NR               | Yes,<br><12hr    | Yes,<br>1/6 |
| Liu XB,<br>2016 <sup>138</sup>   | China | 2014-<br>2015 | ≥6.0 | 20  | 28-36             | 4   | 25.4<br>±3.7 | 100 | 7.0 | 20  | 20  | 25.4<br>±3.6 | 100 | 7.0 | 20  | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Liu Y,                           | China | 2010-         | >6.0 | 50  | 4-27              | 4   | 27.9<br>±3.7 | 94  | 7.7 | 50  | 79  | 27.5         | 07  | 7.5 | 79  | Yes,             | Yes,             | Yes,        |
| 2016 <sup>139</sup>              | Cnina | 2012          | ≥0.0 | 32  | 28-32             | 4   | 28.3<br>±3.8 | 97  | 7.5 | 32  | /8  | ±3.5         | 97  | 1.5 | /8  | NR               | At birth         | 1/6         |

| Lou JJ,<br>2015 <sup>140</sup>       | China | 2012-<br>2013 | ≥4.6 | 127 | 28                | 4       | 30<br>±6      | 100 | 6.8  | 125 | 58  | 31±6          | 100 | 6.7 | 58  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
|--------------------------------------|-------|---------------|------|-----|-------------------|---------|---------------|-----|------|-----|-----|---------------|-----|-----|-----|------------------|------------------|-------------|
| Pan YC,<br>2017 <sup>141</sup>       | China | 2012-<br>2015 | ≥6.3 | 81  | 32                | 0       | 28.8<br>±3.3  | 100 | 8.3  | 81  | 453 | 27.6<br>±3.8  | 100 | 8.1 | 370 | Yes,<br><2hr     | Yes,<br><2hr     | Yes,<br>1/6 |
| Peng BA,<br>2012 <sup>142</sup>      | China | 2008-<br>2009 | ≥5.3 | 40  | 28                | 0       | NR            | 100 | 6.0  | 40  | 40  | NR            | 100 | 6.1 | 40  | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Qiu B,                               | China | 2009-         | >5.2 | 60  | Pre-<br>pregnancy | 0       | NR            | NR  | 6.91 | 60  | 60  | ND            | ND  | 6.9 | 60  | Yes,             | Yes,             | Yes,        |
| 2016 <sup>143</sup>                  | Cnina | 2014          | ≥3.3 | 60  | 24                | 0       | NR            | NR  | 6.9  | 60  | 00  | INK           | INK | 0.8 | 00  | <12hr            | <12hr            | 1/6         |
| Ren N,<br>2015 <sup>144</sup>        | China | 2011-<br>2014 | ≥5.3 | 46  | 28                | 24      | NR            | 100 | 7.2  | 46  | 46  | NR            | 100 | 7.5 | 46  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Shen ML,<br>2016 <sup>76</sup>       | China | 2010-<br>2014 | ≥4.3 | 60  | 26                | 4       | NR            | NR  | 5.9  | 61  | 28  | NR            | NR  | 6.0 | 28  | Yes,<br><24hr    | Yes,<br>NR       | Yes,<br>NR  |
| Sheng Q,<br>2018a <sup>145,146</sup> | China | 2013-<br>2015 | ≥5.0 | 91  | 24-32             | $0^{a}$ | 27.8<br>±4.2  | 100 | 8.1  | 79  | 21  | 26.8<br>±3.7  | 100 | 8.0 | 21  | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| Sheng Q,<br>2018b <sup>147</sup>     | China | 2016-<br>2016 | ≥6.3 | 66  | 24-28             | 0       | 31.3<br>±4.4  | 89  | 8.1  | 66  | 46  | 30.4<br>±4.2  | 89  | 7.9 | 46  | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| Sun W,                               | China | 2013-         | >6.2 | 62  | 12                | 12      | 28.9<br>±11.8 | 100 | 7.1  | 62  | 65  | 27.5          | 100 | 7.0 | 65  | Yes,             | Yes,             | Yes,        |
| 2017 <sup>148</sup>                  | China | 2015          | ≥0.5 | 61  | 20-28             | 12      | 29.7<br>±9.8  | 100 | 7.1  | 61  | 05  | ±12.9         | 100 | 7.0 | 03  | <6hr             | <12hr            | 1/6         |
| Sun WH,                              | China | 2009-         | >6.2 | 42  | 12                | 12      | 28.9<br>±11.8 | 100 | 7.1  | 43  | 45  | 27.5          | 100 | 7 1 | 16  | Yes,             | Yes,             | Yes,        |
| 2015 <sup>149,150</sup>              | China | 2013          | ≥0.5 | 41  | 20-28             | 12      | 29.7<br>±9.8  | 100 | 7.2  | 41  | 43  | ±12.9         | 100 | 7.1 | 40  | <6hr             | <6hr             | 1/6         |
| Tan J,<br>2019 <sup>151</sup>        | China | 2013-<br>2015 | NR   | 41  | 28                | 0       | NR            | NR  | 7.6  | 41  | 59  | NR            | NR  | 7.5 | 59  | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Tan Z,<br>2016 <sup>152</sup>        | China | 2012-<br>2015 | ≥6.0 | 145 | 14-28             | NR      | 29<br>[23-39] | 90  | 7.6  | 137 | 334 | 28<br>[20-41] | 85  | 7.6 | 320 | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |

|                                   |       |               | NR   | 37  | <14     | NR | 29<br>[20-38] | 65  | 2.0 | 34  |     |              |     |     |     |                  |                  |             |
|-----------------------------------|-------|---------------|------|-----|---------|----|---------------|-----|-----|-----|-----|--------------|-----|-----|-----|------------------|------------------|-------------|
| Tian JH,<br>2018 <sup>153</sup>   | China | 2000-<br>2017 | ≥4.6 | 135 | Anytime | NR | NR            | 100 | NR  | 135 | 203 | NR           | 100 | NR  | 203 | Yes,<br><6hr     | Yes,<br><12hr    | Yes,<br>1/6 |
| Tian RH,<br>2016 <sup>154</sup>   | China | 2013-<br>2013 | ≥6.0 | 318 | 28      | 4  | 27.2<br>±3.2  | 100 | 6.5 | 318 | 374 | 27.3<br>±3.2 | 100 | 6.6 | 374 | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Wang B,<br>2016 <sup>155</sup>    | China | 2011-<br>2012 | ≥6.0 | 110 | 28      | 4  | 24±5          | 100 | 7.9 | 110 | 187 | 24±4         | 100 | 7.9 | 187 | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
| Wang<br>DM,<br>2016 <sup>79</sup> | China | 2011-<br>2014 | ≥5.3 | 36  | 28-30   | 12 | 31.4<br>±7.3  | 100 | 7.1 | 36  | 20  | 31.7<br>±7.0 | 100 | 7.1 | 20  | NR               | Yes,<br><24hr    | Yes,<br>1/6 |
| Wang EJ,<br>2012 <sup>80</sup>    | China | 2008-<br>2010 | ≥6.3 | 28  | 28      | 4  | 27.0<br>±3.4  | 100 | 7.9 | 28  | 27  | 24.0<br>±4.7 | 100 | 7.7 | 27  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
|                                   |       |               |      | 20  | 20      | NR | NR            | NR  | 6.9 | 20  |     |              |     |     |     |                  |                  |             |
|                                   |       |               |      | 20  | 24      | NR | NR            | NR  | 7.2 | 20  |     |              |     |     |     |                  |                  |             |
| Wang HB,<br>2016 <sup>156</sup>   | China | 2013-<br>2016 | NR   | 20  | 28      | NR | NR            | NR  | 7.1 | 20  | 20  | NR           | NR  | 7.2 | 20  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
|                                   |       |               |      | 20  | 32      | NR | NR            | NR  | 7.2 | 20  |     |              |     |     |     |                  |                  |             |
|                                   |       |               |      | 20  | 36      | NR | NR            | NR  | 6.7 | 20  |     |              |     |     |     |                  |                  |             |
| Wang J,<br>2017 <sup>157</sup>    | China | 2010-<br>2015 | ≥6.0 | 329 | 24-28   | NR | 27.8<br>±3.7  | NR  | 7.8 | 329 | 65  | 27.6<br>±3.5 | NR  | 7.8 | 65  | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| Wang TD,<br>2015 <sup>158</sup>   | China | 2012-<br>2013 | ≥6.3 | 53  | 28      | 4  | 26.3<br>±3.1  | 100 | 7.3 | 53  | 52  | 25.8<br>±3.9 | 100 | 7.5 | 52  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Wang                              | China | 2010-         | >1 2 | 22  | <27     | 0  | NR            | 100 | 6.8 | 22  | 109 | ND           | 100 | 6.2 | 109 | Yes,             | Yes,             | Yes,        |
| 2012 <sup>159</sup>               | Cnina | 2011          | ≥4.3 | 25  | 28      | 0  | NR            | 100 | 6.7 | 25  | 198 | INK          | 100 | 0.3 | 198 | <6hr             | <6hr             | 1/6         |

| Wu QX,<br>2015 <sup>160,161</sup>       | China | 2008-<br>2014 | ≥6.0 | 279 | 24-32                        | 0 or 4 | 27<br>[17-38] | 100 | 7.2 | 204 | 171 | 28<br>[18-40] | 100 | 7.4 | 95  | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |
|---|-------|---------------|------|-----|------------------------------|--------|---------------|-----|-----|-----|-----|---------------|-----|-----|-----|------------------|------------------|-------------|
| Xiao XH,<br>2017 <sup>42</sup>          | China | 2014-<br>2015 | ≥6.0 | 60  | 28                           | 0 or 4 | 28.6<br>±3.2  | NR  | 7.5 | 62  | 60  | 28.5<br>±3.6  | NR  | 7.5 | 61  | Yes,<br>NR       | Yes<br>NR        | Yes,<br>NR  |
| Yao LF,<br>2014 <sup>162</sup>          | China | 2012-<br>2013 | ≥6.0 | 30  | 28-32                        | 6      | NR            | 100 | 7.3 | 30  | 30  | NR            | 100 | 8.2 | 30  | Yes,<br>NR       | Yes,<br>NR       | Yes,<br>NR  |
| Yao ZC,<br>2011 <sup>163,164</sup>      | China | 2008-<br>2010 | ≥5.3 | 28  | 28                           | 4      | NR            | NR  | 6.8 | 28  | 30  | NR            | NR  | 6.8 | 30  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Yue X, 2014 <sup>165</sup>              | China | 2007-<br>2012 | ≥5.3 | 31  | Any-<br>time                 | NR     | 29.7<br>±5.1  | 0   | 5.5 | 31  | 31  | 27.6<br>±2.9  | 0   | 5.6 | 30  | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Zhang<br>BF, 2018 <sup>43</sup>         | China | 2016-<br>2017 | ≥6.0 | 36  | 24-28                        | 0      | NR            | 100 | 5.0 | 36  | 75  | NR            | 100 | NR  | 75  | Yes,<br><6hr     | Yes,<br>At birth | Yes,<br>1/6 |
| Zhang<br>GH,<br>2018 <sup>166,167</sup> | China | 2012-<br>2014 | ≥6.3 | 40  | 28                           | 4      | NR            | 100 | NR  | 40  | 40  | NR            | 100 | NR  | 40  | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Zhang H,<br>2014 <sup>85</sup>          | China | 2009-<br>2011 | ≥5.3 | 263 | 28-30                        | 4      | 29.8<br>±6.3  | 100 | 6.9 | 257 | 374 | 29.0<br>±4.6  | 100 | 6.8 | 352 | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1/6 |
| Zhang X,<br>2015 <sup>168</sup>         | China | 2012-<br>2013 | ≥6.3 | 48  | 28                           | 12     | NR            | 100 | 7.0 | 48  | 47  | NR            | 100 | 6.8 | 47  | Yes,<br><24hr    | Yes,<br>At birth | Yes,<br>1/6 |
| Zhang<br>YF,<br>2010b <sup>169</sup>    | China | 2008-<br>2009 | ≥5.3 | 60  | 28                           | 4      | NR            | 100 | 6.1 | 60  | 60  | NR            | 100 | 6.1 | 60  | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6 |
| Zhao J,<br>2013 <sup>170</sup>          | China | 2010-<br>2011 | ≥6.3 | 41  | 20                           | 0      | NR            | 100 | NR  | 41  | 202 | NR            | 100 | NR  | 202 | Yes,<br><6hr     | Yes,<br><6hr     | Yes,<br>1/6 |
| Zheng JC,<br>2018 <sup>171</sup>        | China | 2012-<br>2015 | ≥5.3 | 23  | 28                           | 4      | NR            | 100 | NR  | 23  | 37  | NR            | 100 | NR  | 37  | Yes,<br><6hr     | Yes,<br><24hr    | Yes,<br>1/6 |
| Zhou YJ,<br>2014 <sup>172,173</sup>     | China | 2007-<br>2013 | ≥6.3 | 70  | 1 <sup>st</sup><br>trimester | 0      | NR            | NR  | NR  | 53  | 39  | NR            | NR  | NR  | 34  | Yes,<br>NR       | Yes,<br>At birth | Yes,<br>1/6 |

<sup>a</sup> 87/91 women stopped therapy at baseline and 4 others continued therapy

## Appendix F: Cochrane Collaboration's Risk of Bias Assessment Tool for RCTs

## TDF 300 mg

## A. English language studies

| Study<br>(year),                          | Selection bias  |  | Performance<br>bias   | Detection bias   | Attrition bias  |  |  | Reporting<br>bias   |
|---|---|--|---|--|---|--|--|---|
| (year),<br>journal,<br>No                 | Random<br>sequence  | Allocation   | Blinding of participants,   | Blinding of<br>outcome   | Incomplete outco  | ome data addressed   | l<br>Mother  | Selective   |
| 110.                                      | generation  | conceannent  | personnel   | assessment   | WICI  | mant Safety  | safety   | reporting   |
| Pan CQ,<br>(2016), N<br>Engl J<br>Med, 13 | Low risk<br>Quotes:<br>"Enrollment at<br>each center<br>was performed<br>with the use of<br>blocks and<br>randomized<br>for sample<br>balance. Using a<br>randomization<br>table, we<br>randomly<br>assigned 200<br>mothers,<br>in a 1:1 ratio" | High risk<br>Comment: no<br>concealment<br>described   | High risk<br>Quotes: "open-<br>label"   | High risk<br>Quotes: "open-label"  | Low risk<br>Comment: Loss to<br>follow-up detailed<br>carefully in Figure<br>1. Minimal loss to<br>follow-up (95% in<br>treated group,<br>88% in control<br>group), and <10%<br>points different<br>between control<br>and treated<br>groups. | Low risk<br>Comment:<br>Reports on all<br>infant adverse<br>events of interest<br>for 88% and<br>97.8% of control<br>and treated group,<br>respectively. This<br>excludes bone<br>density<br>measurements. | Low risk<br>Comment:<br>Reports on all<br>maternal<br>adverse events<br>of interest for<br>>95% of both<br>treated and<br>control<br>groups,<br>including<br>antiviral<br>resistance<br>testing. | Low risk<br>Comment: the<br>protocol is<br>available in a<br>separate<br>publication as<br>well as online<br>at NEJM.org.<br>The current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified. |
| Jourdain                                  | Low risk  | Low/Unclear  | Low Risk  | Low Risk   | Low Risk  | Low risk   | High risk  | Low risk  |
| G, (2018),<br>N Engl J<br>Med, 14         | Quotes:<br>"participants were<br>randomly<br>assigned in a 1:1<br>ratio"  | <b>Risk</b><br><i>Quotes:</i> "The<br>participants, the<br>trial staff on site<br>and at the<br>coordination | <i>Quotes:</i> "The participants, the trial staff on site and at the coordination center, the investigators and | <i>Quotes:</i> "The participants, the trial staff on site and at the coordination center, the investigators, and | <i>Comment:</i> 88 and<br>90% with full<br>follow-up in<br>treated and<br>control group   | <i>Comment</i> : 95 and<br>98% of infants<br>included in this<br>analysis from<br>treated and<br>control   | Comment:<br>although<br>>90% women<br>considered<br>until<br>discontinuatio  | <i>Comment:</i> the protocol is available in a separate publication as  |

|                                     | was performed<br>with the use of<br>permuted blocks<br>and stratified<br>according to trial<br>site"  | center, the<br>investigators, and<br>the laboratory<br>personnel were<br>unaware of the<br>trial-group<br>assignments"<br><i>Comment:</i> no<br>detail provided<br>about sealed<br>envelopes | the laboratory<br>personnel were<br>unaware of the trial-<br>group assignments."<br>"matching placebo<br>(similar to active<br>tablets minus the<br>active<br>pharmaceutical<br>ingredient)"   | personnel were<br>unaware of the trial-<br>group assignments."   | Numbers of<br>mothers/infants<br>withdrawn or<br>LFU detailed in<br>Figure 1. Similar<br>withdrawal/LFU<br>proportions in<br>each group and 1<br>fetal/ infant death<br>in each group.  | respectively. All<br>relevant adverse<br>events addressed,<br>including bone<br>mineral density<br>(although for this<br>variable, many<br>lost to follow-up,<br>would have to say<br>'high risk' ) | n of the trial<br>regimen, some<br>key adverse<br>events not<br>addressed<br>(e.g. antiviral<br>resistance,<br>postpartum<br>hemorrhage) | at NEJM.org.<br>The current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified.   |
|-------------------------------------|---|--|--|--|---|---|--|--|
| Lin Y,<br>(2018),<br>Sci Rep,<br>24 | Low risk<br>Quotes: "A<br>random number<br>table was used to<br>group<br>the pregnancies<br>into each group<br>(60 individuals<br>per group) based<br>on their<br>enrollment time.<br>Simple<br>randomization<br>was performed" | Low risk<br>Quotes: "sealed<br>envelopes were<br>used for<br>concealment of<br>the random<br>allocation."  | High risk<br>Quotes: "The<br>control individuals<br>did not receive anti-<br>viral treatment."<br>"The participants,<br>care providers<br>did not know<br>whether the patients<br>had accepted the<br>intervention."<br><i>Comment:</i><br>Information is<br>contradictory as it<br>says that<br>participants did not<br>receive treatment<br>(and no mention of<br>placebo) but also<br>that it is double<br>blinded. Unclear if<br>participants were<br>actually blinded | Low/Unclear Risk<br>Quotes: " persons<br>who examined the<br>viral DNA loads and<br>evaluated the<br>outcomes of the<br>patients did not know<br>whether the patients<br>had accepted the<br>intervention."<br><i>Comment:</i> It mentions<br>blinding but if<br>participants were not<br>properly blinded then<br>other staff etc can<br>easily understand<br>which treatment they<br>are on. | High risk<br>Comment: 100%<br>follow-up in<br>treated group but<br>87% in control.<br>This indicates that<br>blinding was<br>probably not done<br>well, and could<br>also introduce<br>bias with<br>dissimilar<br>proportions. No<br>breakdown of<br>LFU cases given. | High risk<br>Comment: same<br>numbers used and<br>therefore<br>comment as for<br>MTCT outcome.  | High risk<br>Comment:<br>same numbers<br>used and<br>therefore<br>comment as<br>for MTCT<br>outcome.                                     | Low risk<br>Comment: the<br>protocol is<br>available<br>online where<br>the article can<br>be accessed<br>on Scientific<br>Reports<br>website. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol. |

| Study    | Selection bias                  |                         | Performance bias               | Detection bias          | Attrition bias    |                    |                               | Reporting                 |
|----------|---------------------------------|-------------------------|--------------------------------|-------------------------|-------------------|--------------------|-------------------------------|---------------------------|
| (vear).  |                                 |                         |                                |                         |                   |                    |                               | bias                      |
| journal, | Random                          | Allocation              | Blinding of                    | Blinding of             | Incomplete outco  | ome data addressed | 1                             |                           |
| No.      | sequence                        | concealment             | participants,                  | outcome                 | мтст              | Infant Safety      | Mother                        | Selective                 |
|          | generation                      |                         | personnel                      | assessment              |                   |                    | safety                        | reporting                 |
| Yu CY    | , Low                           | Unclear                 | High risk                      | Unclear                 | Unclear           | High risk          | High risk                     | Low risk                  |
| (2018),  | $\mathbf{J}$ Quotes:            | method of               | group received liver           | study did not           | statement about   | numbers used as    | same numbers                  | protocol is               |
| of Pu    | <b>b</b> "60 cases of           | concealment not         | protecting treatment"          | address this            | LFU (not          | for MTCT           | used as for                   | available in              |
| Health   | with                            | described               | received antiviral             | outcome                 | LFU, and also not | congenital         | outcome.                      | section of the            |
| and Pro  | asymptomatic                    |                         | treatment with                 |                         | mentioning        | abnormality        | Women                         | article. The              |
|          | were selected and               |                         | <i>Comment</i> : the study did |                         | were no cases     | kev adverse        | until late                    | outcomes of               |
| mea, 27  | randomly divided                |                         | not address this               |                         | LFU)              | events not         | pregnancy.                    | interest that             |
|          | nto liver<br>protection group   |                         | outcome and no use of placebo  |                         |                   | addressed.         | Only elevated bile acid level | this meta-<br>analysis is |
|          | and tenofovir                   |                         | r                              |                         |                   |                    | and amniotic                  | recording                 |
|          | group, with 30<br>cases in each |                         |                                |                         |                   |                    | fluid turbidity<br>reported   | were pre-                 |
|          | group"                          |                         |                                |                         |                   |                    | Other key                     | that protocol.            |
|          | <i>Comment:</i> the             |                         |                                |                         |                   |                    | adverse events                |                           |
|          | describe the exact              |                         |                                |                         |                   |                    | this review                   |                           |
|          | random                          |                         |                                |                         |                   |                    | not addressed                 |                           |
|          | component in the                |                         |                                |                         |                   |                    | (e.g. hepatitis               |                           |
|          | generation                      |                         |                                |                         |                   |                    | flare after                   |                           |
|          | process                         |                         |                                |                         |                   |                    | discontinuatio                |                           |
|          |                                 |                         |                                |                         |                   |                    | n, antiviral                  |                           |
|          |                                 |                         |                                |                         |                   |                    | resistance)                   |                           |
| Liu Mł   | LOW                             | Unclear<br>Comments the | High risk                      | Unclear<br>Commonts the | Low risk          | High risk          | High risk                     | Low risk                  |
| (2017b), | Ouotes:                         | method of               | group received no              | study did not           | follow-up in both | numbers used as    | same numbers                  | protocol is               |
| Chinese  | "participants were              | concealment not         | antiviral treatment"           | address this            | treated and       | for MTCT           | used as for                   | available in              |
|          | randomly                        | described               | "The observation group         | outcome                 | control group     | outcome. Only      | МТСТ                          | the method                |

#### **B.** Chinese language studies

| Journal of | assigned in a 1:1  | received | l antiviral               |  | Apgar       | score,  | outcome.   |        | section   | of the |
|------------|--------------------|----------|---------------------------|--|-------------|---------|------------|--------|-----------|--------|
| ***        | ratio"             | treatme  | nt with TDF"              |  | premature   | labor,  | Women      |        | article.  | The    |
| Woman      | Comment: the       | Comme    | <i>nt</i> : the study did |  | congenital  |         | considere  | ed     | current   |        |
| and Child  | study did not      | not      | address this              |  | abnormality | y and   | until deli | ivery. | outcome   | es of  |
|            | describe the exact | outcom   | e and no                  |  | retarded    |         | Only       |        | interest  | that   |
| Health     | random             | mentior  | of placebo                |  | developme   | nt      | postpartu  | m      | this      | meta-  |
|            | component in the   |          |                           |  | reported.   | Other   | hemorrha   | ige    | analysis  | is     |
| Research,  | sequence           |          |                           |  | key         | adverse | reported.  |        | recordin  | g      |
| 26         | generation         |          |                           |  | events      | not     | Other      | key    | were      | pre-   |
| 20         | process            |          |                           |  | addressed.  |         | adverse e  | vents  | specified | d in   |
|            |                    |          |                           |  |             |         | not addre  | ssed.  | that prot | ocol.  |

## LAM 100-150 mg

## A. English language studies

| Study   | Selection bias   |   | Performance<br>bias  | Detection bias  | Attrition bias  |   |  | Reporting<br>bias  |
|---|--|---|--|---|---|---|--|--|
| journal,  | Random   | Allocation  | Blinding of  | Blinding of   | Incomplete outco  | ome data addressed  | 1  |  |
| No.   | sequence<br>generation   | concealment   | participants,<br>personnel   | outcome<br>assessment   | МТСТ  | Infant Safety   | Mother<br>safety   | Selective<br>reporting   |
| Xu WM<br>(2009),<br>Journal of<br>Viral<br>Hepatitis,<br>53 | High risk<br>Comment:<br>Mentions that<br>women were<br>randomly<br>assigned but does<br>not give any<br>indication of<br>method for<br>randomization. | Low/unclear risk<br>Quotes:<br>"After written<br>informed consent<br>was obtained,<br>participants were<br>randomly<br>assigned in a 1:1<br>ratio ~"<br>Comment: No<br>method for<br>allocation<br>concealment is<br>mentioned except<br>calling the trial<br>'blinded' and<br>'double-blind'.<br>However, from<br>the above quote it<br>seems that<br>randomization<br>occurred after<br>informed consent. | Low risk<br>Quotes: "To<br>preserve study<br>blinding, the<br>investigators were<br>instructed not to<br>determine serum<br>HBV DNA levels<br>locally while the<br>mother was<br>receiving blinded<br>treatment";<br>"matching placebo<br>orally once daily"<br>Comment: Calls the<br>trial blinded and<br>mentions some<br>extra efforts put in<br>to preserve blinding<br>with study<br>personnel. | Low risk<br>Quotes: "To preserve<br>study blinding, the<br>investigators were<br>instructed not to<br>determine serum<br>HBV DNA levels<br>locally while the<br>mother was receiving<br>blinded treatment"<br>Comment: Calls the<br>trial blinded and<br>mentions some extra<br>efforts put in to<br>preserve blinding with<br>study personnel<br>(specifically lab<br>personnel) | Unclear risk<br>Comment: All lost<br>to follow-up,<br>withdrawals, etc<br>detailed carefully<br>in text and a<br>figure within the<br>report.<br>Appropriate<br>analysis methods<br>used to consider<br>loss to follow-up<br>(e.g. mITT<br>analysis).<br>However, only<br>78% and 66%<br>retention in<br>treated and<br>control groups,<br>respectively<br>(these proportions<br>also differ by<br>>10% points) | High risk<br>Comment:<br>Though all the<br>infants were<br>included in this<br>analysis from<br>three arms,<br>respectively, some<br>key adverse<br>events including<br>prematurity,<br>Apgar and bone<br>density were not<br>reported. | High risk<br>Comment:<br>Though >90%<br>women were<br>included in<br>this analysis,<br>some key<br>adverse<br>events, were<br>not addressed<br>(e.g. antiviral<br>resistance,<br>postpartum<br>hemorrhage) | Unclear risk<br>Comment:<br>Both<br>reviewers<br>were unable to<br>find the trial<br>protocol<br>online. |

| Study   | Selection bias   |  | Performance bias   | Detection bias  | Attrition bias   |   |   | Reporting<br>bias   |
|---|--|--|--|---|--|---|---|---|
| journal,<br>No.   | Random<br>sequence<br>generation   | Allocation<br>concealment  | Blinding of<br>participants,<br>personnel  | Blindingofoutcomeassessment   | Incomplete outco   | ome data addressed<br>Infant Safety                                 | l<br>Mother<br>safety   | Selective<br>reporting  |
| Chen SM<br>(2017),<br>Journal of<br>China<br>Prescripti<br>on Drug,<br>46 | Low<br>risk/Unclear<br>Quotes:<br>"90 cases of<br>pregnant women<br>chronically<br>infected with<br>HBV were<br>selected and<br>randomly divided<br>into lamivudine<br>group, telbivudine<br>group, telbivudine<br>group, with 30<br>cases in each<br>group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | Unclear<br>Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation<br>groups received<br>antiviral treatment with<br>lamivudine or<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome               | Low risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol. |
| Ji YY<br>(2015),<br>Chin J<br>Postgrad                                    | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into  | UnclearComment:themethodofconcealmentnotdescribed                    | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral   | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also not  | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | <b>Unclear</b><br><i>Comment:</i> the<br>study did not<br>address this<br>outcome | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the  |

#### **B.** Chinese language studies

| Med, 50  | telbivudine group,<br>lamivudine group<br>and control group,<br>with 65 cases in<br>each group"   |  | treatment with<br>telbivudine or<br>lamivudine''<br><i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo  |   | mentioning<br>clearly that there<br>were no cases<br>LFU)  |  |   | article. But<br>not all of the<br>study's pre-<br>specified<br>primary<br>outcomes<br>have been<br>reported (e.g.<br>maternal liver<br>function after<br>antiviral<br>treatment).   |
|--|---|--|---|---|--|--|---|---|
| Li ZG<br>(2015),<br>World<br>Latest<br>Medicine<br>Informati<br>on, 51 | Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into lamivudine<br>group,<br>telbivudine group<br>and control group,<br>with 25 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | Unclear<br>Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>lamivudine or<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome                  | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome                               | Low risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol. |
| Tian XQ<br>(2015),<br>Shanxi<br>Med J, 52                              | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation<br>group and the   | UnclearComment:themethodofconcealmentnotdescribed                    | High risk<br>Quotes: "The control<br>group received HBIG"<br>"The observation group<br>received lamivudine on<br>the basis of HBIG for<br>the control group"<br>Comment: the study did  | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearlythat there   | High riskComment:Though all theinfants wereincluded in thisanalysis, somekey adverse | High risk<br>Comment:<br>Though all<br>women were<br>included in<br>this analysis,<br>the adverse | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more   |

|  | control group,<br>with 110 cases in<br>each group"   |  | not address this<br>outcome and no<br>mention of placebo  |   | were no cases<br>LFU)  | events including<br>Apgar and bone<br>density were not<br>reported.   | events<br>observed,<br>were not<br>addressed  | reported<br>primary<br>outcomes<br>were not pre-<br>specified<br>(mainly<br>maternal and<br>infantile<br>adverse<br>reactions)  |
|--|--|--|---|---|--|---|---|---|
| Yang HW<br>(2014),<br>Hebei<br>Medical<br>Journal,<br>55 | Low<br>risk/Unclear<br>Quotes:<br>"152 cases of<br>pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>I group, descrimental<br>group, 53, 53 and<br>46 cases in the<br>above three<br>groups,<br>respectively"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process; and<br>importantly,<br>there's a disparity<br>between the<br>number of cases<br>in the<br>experimental | <b>Unclear</b><br><i>Comment:</i> the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The<br>experimental II group<br>received HBIG" "The<br>experimental I group<br>received lamivudine on<br>the basis of HBIG"<br><i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo | <b>Unclear</b><br><i>Comment:</i> the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | High risk<br>Comment:<br>Though all the<br>infants were<br>included in this<br>analysis, some<br>key adverse<br>events including<br>Apgar and bone<br>density were not<br>reported. | High risk<br><i>Comment:</i><br>Though all<br>women were<br>included in<br>this analysis,<br>some key<br>adverse<br>events, were<br>not addressed<br>(e.g. antiviral<br>resistance) | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified<br>(mainly<br>maternal and<br>infantile<br>adverse<br>reactions) |

|                       | group and that of                 |                             |   |                         |                               |                         |                         |                           |
|-----------------------|-----------------------------------|-----------------------------|---|-------------------------|-------------------------------|-------------------------|-------------------------|---------------------------|
|                       | the control group                 | <b>T</b> T 1                | TT* 1 • 1   | <b>T</b> T 1            | <b>X</b> 7 <b>1</b>           | <b>T</b> T <b>1</b>     | <b>T</b> T <b>1</b>     | <b>T</b> • 1              |
| Bai XW                |                                   | Unclear<br>Commonte the     | High risk   | Unclear<br>Commonts the | Unclear<br>Commonte No        | Unclear<br>Commonts the | Unclear                 | Low risk                  |
| (2011),               | Quotes: "The                      | method of                   | group received no                                   | study did not           | statement about               | study did not           | study did not           | protocol is               |
| Maternal              | patients were<br>randomly divided | concealment no<br>described | "The observation group                              | address this outcome    | LFU (not<br>reporting any     | address this outcome    | address this outcome    | available in the method   |
| and Child             | into observation                  |                             | 1 received HBIG and                                 |                         | LFU, and also not             |                         |                         | section of the            |
| Health                | group 1,<br>observation group     |                             | the observation group 2<br>antiviral treatment with |                         | mentioning clearly that there |                         |                         | article. The current      |
| Care of               | 2 and control group, with 30, 30  |                             | lamivudine"<br><i>Comment</i> : the study did       |                         | were no cases<br>LFU)         |                         |                         | outcomes of interest that |
| China, 45             | and 25 cases,                     |                             | not address this                                    |                         |                               |                         |                         | this meta-                |
|                       | respectively"                     |                             | outcome and no                                      |                         |                               |                         |                         | analysis is               |
|                       | Comment: the                      |                             | mention of placebo                                  |                         |                               |                         |                         | recording                 |
|                       | study did not                     |                             |   |                         |                               |                         |                         | were pre-                 |
|                       | describe the exact                |                             |   |                         |                               |                         |                         | specified in              |
|                       | random                            |                             |   |                         |                               |                         |                         | that protocol.            |
|                       | component in the                  |                             |   |                         |                               |                         |                         |                           |
|                       | sequence                          |                             |   |                         |                               |                         |                         |                           |
|                       | generation                        |                             |   |                         |                               |                         |                         |                           |
|                       | process.                          |                             |   |                         |                               |                         |                         |                           |
|                       | Importantly,                      |                             |   |                         |                               |                         |                         |                           |
|                       | disparity exists                  |                             |   |                         |                               |                         |                         |                           |
|                       | between the                       |                             |   |                         |                               |                         |                         |                           |
|                       | number of cases                   |                             |   |                         |                               |                         |                         |                           |
|                       | in observation                    |                             |   |                         |                               |                         |                         |                           |
|                       | groups and                        |                             |   |                         |                               |                         |                         |                           |
|                       | control groups.                   |                             |   |                         |                               |                         |                         |                           |
| Guo V7                | Low                               | Unclear                     | High risk   | Unclear                 | Unclear                       | Unclear                 | Unclear                 | Low risk                  |
| 000 12                | risk/Unclear                      | Comment: the                | <i>Quotes:</i> "The control                         | <i>Comment:</i> the     | Comment: No                   | <i>Comment:</i> the     | <i>Comment:</i> the     | <i>Comment</i> : the      |
| (2008),               | Quotes: "The                      | method o                    | group received no                                   | study did not           | statement about               | study did not           | study did not           | protocol is               |
| Chin J of             | patients were<br>randomly divided | concealment no<br>described | "antiviral treatment"<br>"The observation group     | address this outcome    | LFU (not<br>reporting any     | address this outcome    | address this<br>outcome | available in the method   |
| Clinical              | into the                          |                             | received antiviral                                  |                         | LFU, and also not             |                         |                         | section of the            |
| <b>D</b> (1) <b>D</b> | observation group                 |                             | treatment with                                      |                         | mentioning                    |                         |                         | article. The              |
| Rational              | and the control                   |                             | lamivudine"   |                         | clearly that there            |                         |                         | current                   |
| Drug                  | group, with 70                    |                             | Comment: the study did                              |                         | were no cases                 |                         |                         | outcomes of               |
| ~                     | cases in the                      |                             | not address this                                    |                         | LFU)                          |                         |                         | interest that             |
|                       | observation group                 |                             | outcome and no                                      | 1                       |                               |                         |                         | this meta-                |

| Use, 47 | and 40 cases in    | mention of placebo |  |  | analysis is    |
|---------|--------------------|--------------------|--|--|----------------|
| ,       | the control group" |                    |  |  | recording      |
|         | Comment: the       |                    |  |  | were pre-      |
|         | study did not      |                    |  |  | specified in   |
|         | describe the exact |                    |  |  | that protocol. |
|         | random             |                    |  |  |                |
|         | component in the   |                    |  |  |                |
|         | sequence           |                    |  |  |                |
|         | generation         |                    |  |  |                |
|         | process;           |                    |  |  |                |
|         | importantly,       |                    |  |  |                |
|         | there's a huge     |                    |  |  |                |
|         | disparity between  |                    |  |  |                |
|         | the numbers of     |                    |  |  |                |
|         | cases in           |                    |  |  |                |
|         | observation and    |                    |  |  |                |
|         | control groups     |                    |  |  |                |

## LDT 600 mg

## A. English language studies

None

## **B.** Chinese language studies

| Selection bias                 |  | Performance bias   | Detection bias  | Attrition bias  |   |   | Reporting<br>bias  |
|--------------------------------|--|--|---|---|---|---|--|
| Random                         | Allocation   | Blinding of  | Blinding of   | Incomplete outco  | ome data addressed  | 1   |  |
| sequence                       | concealment  | participants,  | outcome   | МТСТ  | Infant Safety   | Mother  | Selective  |
| generation                     |  | personnel  | assessment  |   |   | safety  | reporting  |
| Low                            | Unclear  | High risk  | Unclear   | Unclear   | High risk   | Unclear   | High risk  |
| <b>risk/Unclear</b><br>Quotes: | <i>Comment:</i> the method of  | <i>Quotes:</i> "The experimental group   | <i>Comment:</i> the study did not   | <i>Comment:</i> No statement about  | <i>Comment:</i> same numbers used as  | <i>Comment:</i> the study did not   | <i>Comment</i> : the protocol is   |
| "80 cases of                   | concealment not  | received LdT" "The   | address this  | LFU (not  | for MTCT  | address this  | available in   |
| pregnant women<br>with chronic | described  | control individuals did<br>not receive antiviral   | outcome   | reporting any LFU, and also not   | outcome. Some<br>key adverse  | outcome   | the method section of the  |
| hepatitis B were               |  | treatment and were   |   | mentioning  | events not  |   | article. But   |
| into experimental              |  | given supportive   |   | clearly that there  | addressed (e.g.   |   | not all of the study's pre-  |
| group and control              |  | observation"   |   | LFU)  | neonatal death.   |   | specified  |
| group, 40 cases in             |  | Comment: the study did   |   | - /   | sub-optimal bone  |   | primary  |
| each group"                    |  | not address this   |   |   | density)  |   | outcomes   |
| <i>Comment:</i> the            |  | outcome and no   |   |   |   |   | have been  |
| study did not                  |  | mention of placebo   |   |   |   |   | reported (i.e.   |
| describe the exact             |  |  |   |   |   |   | maternal   |
| component in the               |  |  |   |   |   |   | more reported  |
| sequence                       |  |  |   |   |   |   | primary  |
| generation                     |  |  |   |   |   |   | outcomes   |
| process                        |  |  |   |   |   |   | were not pre-  |
|                                |  |  |   |   |   |   | specified  |
|                                |  |  |   |   |   |   | (body length,  |
|                                |  |  |   |   |   |   | pirth weight,  |
|                                | Selection bias Random sequence generation Low risk/Unclear Quotes: "80 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 40 cases in each group" Comment: the study did not describe the exact random component in the sequence generation process | Selection bias         Random<br>sequence<br>generation       Allocation<br>concealment         Low<br>risk/Unclear<br>Quotes:       Unclear<br>Comment: the<br>method of<br>concealment not<br>described         %0       cases of<br>pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>group and control<br>group, 40 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | Selection biasPerformance biasRandom<br>sequence<br>generationAllocation<br>concealmentBlinding of<br>participants,<br>personnelLow<br>risk/Unclear<br>Quotes:<br>"80 cases of<br>pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>group and control<br>group, 40 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generationHigh risk<br>Quotes: "The<br>experimental group<br>received LdT" "The<br>control individuals did<br>not receive antiviral<br>treatment or<br>of observation"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>processHigh risk<br>Quotes: "The<br>experimental<br>group and control<br>group, 40 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>processHigh risk<br>Quotes: "The<br>experimental<br>group and control<br>group and control<br> | Selection biasPerformance biasDetection biasRandom<br>sequence<br>generationAllocation<br>concealmentBlinding<br>participants,<br>personnelBlinding<br>of<br>assessmentLow<br>risk/Unclear<br>Quotes:<br>"80 cases of<br>pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>group and control<br>group, 40 cases in<br>each group"<br>Comment: the<br>study did not<br>describedHigh risk<br>Quotes:<br>"The<br>experimental group<br>received LdT" "The<br>control individuals did<br>not receive antiviral<br>treatment and were<br>given supportive<br>treatment or<br>observation"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placeboUnclear<br>Comment: he<br>study did not<br>describedSelection biasNot<br>concealment not<br>describedHigh risk<br>Quotes: "The<br>control individuals did<br>not receive antiviral<br>treatment and were<br>given supportive<br>treatment or<br>observation"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placeboUnclear<br>Comment: he<br>study did not<br>describedsequence<br>generation<br>processImage: sequence<br>generation<br>processImage: sequence<br>generationImage: sequence<br>generationgroup and control<br>describedImage: sequence<br>generation<br>processImage: sequence<br>generationImage: sequence<br>generationImage: sequence<br>generationgeneration<br>processImage: sequence<br>generationImage: sequence<br>generationImage: sequence<br>generationImage: sequence<br>generationgeneration<br>processImage: sequence<br>generationImage: sequence<br>generationImage: sequence<br>gene | Selection bias       Performance bias       Detection bias       Attrition bias         Random<br>sequence<br>generation       Allocation<br>concealment       Blinding<br>participants,<br>personnel       Blinding<br>outcome<br>assessment       Incomplete outcome<br>outcome<br>assessment         Low<br>risk/Unclear<br>Quotes:       Unclear<br>Comment: the<br>method of<br>pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>group and control<br>group, 40 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation       Unclear<br>Comment: the<br>supportive<br>treatment and were<br>given supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation of placebo       Unclear<br>Comment: the<br>supportive<br>treatment or<br>observation"<br>Comment: the<br>supportive<br>treatment or<br>observation of placebo       Unclear<br>Comment: the<br>supportive<br>treatment or<br>observation of placebo       Unclear<br>Comment: the<br>supportive<br>treatment or<br>observation of placebo | Selection bias       Performance bias       Detection bias       Attrition bias         Random sequence generation       Allocation concealment       Blinding of participants, personnel       Blinding of outcome assessment       Incomplete outcome data addressee         Low risk/Unclear Quotes:       Omment: the method of concealment not described       High risk Quotes:       Unclear Comment: the outcome and not mention of placebo       Unclear Comment: No statement about address this outcome and no mention of placebo       Unclear (comment: No statement about address this outcome and no mention of placebo       Unclear (comment: No statement about address this outcome and no mention of placebo       High risk (comment: he study did not address this outcome and no mention of placebo       Unclear (comment: No statement about addresse this outcome and no mention of placebo       High risk (comment: he study did not address this outcome and no mention of placebo       Unclear (comment: he study did not address this outcome and no mention of placebo       Unclear (comment: he study did not address this outcome and no mention of placebo       Unclear (comment: study did not address this outcome and no mention of placebo       Unclear (comment: study did not address this outcome and no mention of placebo       Unclear (comment: study did not address this outcome and no mention of placebo       Unclear (comment: study addressed (comme | Selection bias         Performance bias         Detection bias         Attrition bias           Random<br>sequence<br>generation         Allocation<br>concealment         Blinding<br>participants,<br>personnel         of<br>participants,<br>personnel         Blinding<br>outcome<br>assessment         fncomplete outcome data addresseet<br>outcome         Infant Safety<br>safety           Low<br>risk/Unclear<br>Quotes:         Unclear<br>Comment: the<br>method of<br>creacipeed LdT"         High risk<br>Quotes:         Unclear<br>Comment: the<br>study did not<br>address this<br>outcome         Unclear<br>Comment: the<br>study did not<br>address this         Unclear<br>Comment: the<br>study did not<br>address this         Unclear<br>Comment: the<br>study did not         Unclear<br>for MTCT<br>address this         Unclear<br>Comment: the<br>study did not         Unclear<br>for MTCT<br>address this         Unclear<br>for MTCT         Unclear<br>for MTCT         Unclear<br>for MTCT           Comment: the<br>study did not         Unclear<br>for MTCT |

|   |  |  |  |  |  |   |  | age and<br>congenital<br>abnormality)   |
|---|--|--|--|--|--|---|--|---|
| Xing Y<br>(2018),<br>Clinical<br>Research,<br>101   | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation<br>group and the<br>control group,<br>with 30 cases in<br>each group" | Unclear<br>Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received regular<br>liver protecting<br>treatment with<br>compound glycyrrhizin"<br>"The observation group<br>received LdT on the<br>basis of regular liver<br>protecting treatment for<br>the control group"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br><i>Comment:</i> the<br>study did not<br>address this<br>outcome | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | High risk<br>Comment: same<br>numbers used as<br>for MTCT<br>outcome. Only<br>Apgar score<br>reported. Some<br>key adverse<br>events not<br>addressed (e.g.<br>neonatal death,<br>prematurity,<br>congenital<br>abnormality, sub-<br>optimal bone<br>danaity) | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome  | Low risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that meta-<br>anal                                 |
| Zhang Y<br>(2018),<br>Chinese<br>Journal of<br>Woman<br>and Child<br>Health<br>Research,<br>104 | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation<br>group and the<br>control group,<br>with 34 cases in<br>each group" | Unclear<br>Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received regular<br>internal treatment" "The<br>observation group<br>received antiviral<br>treatment with<br>telbivudine on the basis<br>of regular internal<br>treatment for the control<br>group"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo           | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome        | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | High risk<br>Comment: same<br>numbers used as<br>for MTCT<br>outcome. Only<br>congenital<br>abnormality and<br>Apgar score<br>reported. Other<br>key adverse<br>events not<br>addressed.  | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Only CK<br>reported. Key<br>adverse events<br>not addressed. | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>not all of the<br>study's pre-<br>specified<br>primary<br>outcomes<br>have been<br>reported (e.g.<br>maternal<br>adverse<br>events, HBV<br>serological<br>markers). |
| Chen SM<br>(2017),  | Low<br>risk/Unclear<br>Quotes:   | UnclearComment:themethodof   | High risk<br>Quotes: "The control<br>group received no   | UnclearComment:thestudydidnot  | UnclearComment:Nostatementabout  | Unclear<br>Comment: the<br>study did not  | Unclear<br>Comment: the<br>study did not   | Low risk<br>Comment: the<br>protocol is   |

| Journal of  | "90 cases of   | concealment n   | not       | antiviral treatment"  | address t   | his               | LFU (not   | address this  | address this  | available in  |
|---|--|---|-----------|---|---|-------------------|--|---|---|---|
| Journal of<br>China<br>Prescripti<br>on Drug,<br>46                       | 90 cases of<br>pregnant women<br>chronically<br>infected with<br>HBV were<br>selected and<br>randomly divided<br>into lamivudine<br>group, telbivudine<br>group, telbivudine<br>group, telbivudine<br>group, with 30<br>cases in each<br>group"<br><i>Comment:</i> the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | described   | 101       | "The observation<br>groups received<br>antiviral treatment with<br>lamivudine or<br>telbivudine"<br><i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo  | outcome   | ms                | LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU)  | outcome   | outcome   | the method<br>section of the<br>article. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol.  |
| Guan ZF<br>(2017),<br>Acta Med<br>Univ Sci<br>Technol<br>Huazhong<br>, 91 | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation<br>group and the<br>control group,<br>with 120 cases in<br>each group"  | Unclear<br>Comment: the<br>method<br>concealment n<br>described | he of not | High risk<br>Quotes: "The control<br>group received liver<br>protecting treatment<br>with compound<br>glycyrrhizin" "The<br>observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no use of<br>placebo | Unclear<br>Comment:<br>study did in<br>address t<br>outcome | the<br>not<br>his | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | High risk<br>Comment: same<br>numbers used as<br>for MTCT<br>outcome. Only<br>Apgar score<br>reported. Other<br>key adverse<br>events not<br>addressed. | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only<br>postpartum<br>hemorrhage<br>reported.<br>Other key<br>adverse events<br>not addraesed | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal HBV<br>DNA and<br>ALT) |
| Shi QW<br>(2017),   | Low<br>risk/Unclear<br>Quotes:   | Unclear<br>Comment: the method                                  | he<br>of  | High risk<br>Quotes: "The control<br>group received HBIG"   | <b>Unclear</b><br><i>Comment:</i><br>study did n            | the<br>not        | UnclearComment:Nostatementabout  | High risk<br>Comment:   | High risk<br>Comment:   | High risk<br>Comment: the<br>protocol is  |

| Mod                | "200 cases of   | concealment not        | "The observation group   | address this                      | LFU (not  | Though all the  | Though all   | available in   |
|--------------------|---|------------------------|--|-----------------------------------|---|---|--|--|
| Diagn<br>Treat, 98 | pregnant women<br>with chronic<br>hepatitis B were<br>randomly divided<br>into experimental<br>group and control<br>group, 100 cases<br>in each group"<br><i>Comment:</i> the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | described              | received telbivulion group<br>received telbivuline on<br>the basis of HBIG for<br>the control group"<br><i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo | outcome                           | reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | infants were<br>included in this<br>analysis, some<br>key adverse<br>events including<br>neonatal death<br>and bone density<br>were not reported. | women were<br>included in<br>this analysis,<br>some key<br>adverse<br>events, were<br>not addressed<br>(e.g. antiviral<br>resistance,<br>postpartum<br>hemorrhage) | the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified<br>(mainly<br>maternal<br>adverse<br>reactions) |
| Zhao Y             | Low risk  | Low risk               | High risk  | Unclear                           | Low risk  | High risk   | High risk  | Low risk   |
| (2017), J          | <i>Quotes:</i><br>"Referring to   | <i>Quotes:</i> "sealed | <i>Quotes:</i> "The control group received   | <i>Comment:</i> the study did not | <i>Comment:</i> 100% follow-up in both  | <i>Comment:</i> same  | <i>Comment:</i>  | <i>Comment</i> : the protocol is   |
| Prac               | random number   | envelopes were         | compound glycyrrhizin"   | address this                      | treated and   | for MTCT  | used as for  | available in   |
| Hanadal            | table, the patients   | used for               | "The observation group   | outcome                           | control group   | outcome. Only   | MTCT   | the method   |
| Hepatol,           | the observation   | the random             | treatment with   |                                   |   | reported. Other   | Women  | article. The   |
| 106                | group and the   | allocation."           | telbivudine on the basis   |                                   |   | key adverse   | considered   | current  |
|                    | control group,  |                        | of compound  |                                   |   | events not  | until 12 weeks   | outcomes of  |
|                    | with 40 cases in  |                        | glycyrrhizin"  |                                   |   | addressed.  | after delivery.  | interest that  |
|                    | each group  |                        | not address this   |                                   |   |   | chill and rash   | analysis is  |
|                    |   |                        | outcome and no   |                                   |   |   | reported.  | recording  |
|                    |   |                        | mention of placebo   |                                   |   |   | Other key  | were pre-  |
|                    |   |                        |  |                                   |   |   | adverse events   | specified in that protocol   |
| Zhu J              | Low risk  | Unclear                | High risk  | Unclear                           | Unclear   | High risk   | High risk  | Low risk   |
| (2017)             | Quotes:   | Comment: the           | Quotes: "The control   | Comment: the                      | Comment: No   | Comment: same   | Comment:   | Comment: the   |
| (2017),            | "Referring to   | method of              | group received no  | study did no                      | statement about   | numbers used as   | same numbers   | protocol is  |
| Maternal           | table, the patients   | described              | "The observation group   | outcome                           | reporting anv   | outcome. Only   | MTCT   | the method   |
| and Child          | were divided into   |                        | received antiviral   |                                   | LFU, and also not   | Apgar score and   | outcome.   | section of the   |
| Health             | the observation   |                        | treatment with   |                                   | mentioning  | neonatal asphyxia   | Women  | article. The   |
| meann              | group and the   |                        | telbivudine"   |                                   | clearly that there  | reported. Other   | considered   | current  |

| Care of<br>China,<br>107                 | control group,<br>with 60 cases in<br>each group"   |   | <i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo   |  | were no cases<br>LFU); 6 cases of<br>foetal death in<br>control group  | key adverse<br>events not<br>addressed.                  | until delivery.<br>Only foetal<br>death and<br>postpartum<br>hemorrhage<br>reported.<br>Other key<br>adverse events<br>not addressed  | outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol.   |
|--|---|---|--|--|--|--|---|---|
| Fu PX<br>(2016),<br>Psycholog<br>ist, 90 | Low<br>risk/Unclear<br>Quotes:<br>"200 cases of<br>pregnant women<br>chronically<br>infected with<br>HBV were<br>randomly divided<br>into treated group<br>and control group,<br>with 100 cases in<br>each group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process | Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Comment: the<br>study did not<br>address this<br>outcome | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly that therewerenocasesLFU) | Comment: the<br>study did not<br>address this<br>outcome | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only CK<br>elevation<br>reported.<br>Other key<br>adverse events<br>not addressed | High risk<br><i>Comment:</i> the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>not all of the<br>study's pre-<br>specified<br>primary<br>outcomes<br>have been<br>reported (e.g.<br>maternal liver<br>function, viral<br>variants). One<br>or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal CK) |
| Huang<br>HY<br>(2016),<br>Chinese        | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation  | UnclearComment:themethodofconcealmentnotdescribed         | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>1, 2 and 3 received<br>antiviral treatment with  | UnclearComment:thestudydidnotaddressthisoutcome          | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioning                                  | UnclearComment:thestudydidnotaddressthisoutcome          | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome   | Low risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. The   |

| Journal of<br>Eugenics<br>and<br>Genetics,<br>94 | group 1, 2, 3 and<br>the control group,<br>with 30 cases in<br>each group"  | Unclear  | telbivudine at 20, 24<br>and 28 weeks,<br>respectively"<br><i>Comment:</i> the study did<br>not address this<br>outcome and no<br>mention of placebo  | Unclear   | clearly that there<br>were no cases<br>LFU)  | Unclear   | Unclear   | current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol.  |
|--|---|--|---|---|--|---|---|---|
| (2016),<br>Psycholog<br>ist, 100                 | Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>the observation<br>group and the<br>control group,<br>with 60 cases in<br>each group"  | <i>Comment:</i> the<br>method of<br>concealment not<br>described | Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br><i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo   | <i>Comment:</i> the<br>study did not<br>address this<br>outcome     | <i>Comment:</i> No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU)     | <i>Comment:</i> the<br>study did not<br>address this<br>outcome   | <i>Comment:</i> the<br>study did not<br>address this<br>outcome   | <i>Comment:</i> the<br>protocol is<br>available in<br>the method<br>section of the<br>article. The<br>current<br>outcomes of<br>interest that<br>this meta-<br>analysis is<br>recording<br>were pre-<br>specified in<br>that protocol |
| Lu QY<br>(2016),<br>Henan J<br>Prev<br>Med, 96   | Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control<br>group, with 152<br>cases in the<br>observation group<br>and 132 cases in<br>the control group"<br>Comment: the<br>study did not<br>describe the exact | UnclearComment:themethodofconcealmentnotdescribed                | High risk<br>Quotes: "The control<br>group received HBIG"<br>"The observation group<br>received telbivudine on<br>the basis of HBIG for<br>the control group"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | High risk<br>Comment:<br>Though all the<br>infants were<br>included in this<br>analysis, some<br>key adverse<br>events including<br>Apgar and bone<br>density were not<br>reported. | High risk<br>Comment:<br>Though all<br>women were<br>included in<br>this analysis,<br>some key<br>adverse<br>events, were<br>not addressed<br>(e.g. antiviral<br>resistance,<br>postpartum<br>hemorrhage) | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified<br>(mainly<br>maternal and<br>infantile      |
|   | random<br>component in the<br>sequence<br>generation<br>process; and<br>importantly,<br>there's a huge<br>disparity between<br>the number of<br>cases in the<br>observation group<br>and that of the<br>control group |  |   |   |  |   |   | adverse<br>reactions)   |
|---|---|--|---|---|--|---|---|---|
| Ji YY<br>(2015),<br>Chin J<br>Postgrad<br>Med, 50 | Low risk<br>Quotes:<br>"Referring to<br>random number<br>table, the patients<br>were divided into<br>telbivudine group,<br>lamivudine group<br>and control group,<br>with 65 cases in<br>each group"                  | Unclear<br>Comment: the<br>method of<br>concealment not<br>described | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine or<br>lamivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome                     | Unclear<br>Comment: the<br>study did not<br>address this<br>outcome                             | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>not all of the<br>study's pre-<br>specified<br>primary<br>outcomes<br>have been<br>reported (e.g.<br>maternal liver<br>function after<br>antiviral<br>treatment). |
| Li SF.<br>(2015),<br>World of<br>Mother<br>and    | Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control  | UnclearComment:themethodofconcealmentnotdescribed                    | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"  | UnclearComment:thestudydidnotaddressthisoutcome                     | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly that there  | High riskComment:samenumbersusedasforMTCToutcome.OnlyApgarscorereported.Otherkeyadverse | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more   |

| Infant, 95 | group, with 60<br>cases in each<br>group"<br><i>Comment:</i> the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process |                           | <i>Comment</i> : the study did<br>not address this<br>outcome and no<br>mention of placebo |                      | were no cases<br>LFU)     | events not<br>addressed. | until 6 months<br>after delivery.<br>Only adverse<br>reactions,<br>abnormal<br>pregnancy,<br>and CK<br>elevation<br>reported.<br>Other key<br>adverse events<br>not addressed | reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>abnormal<br>pregnancy).<br>One or more<br>outcomes of<br>interest in the<br>review are<br>reported<br>incompletely<br>so that they<br>cannot be<br>entered in a |
|------------|--|---------------------------|--|----------------------|---------------------------|--------------------------|---|--|
|            |  |                           |  |                      |                           |                          |   | meta-analysis<br>(e.g. Apgar<br>score).  |
| Yang HW    | Low  | Unclear                   | High risk  | Unclear              | Unclear                   | Unclear                  | High risk   | High risk  |
| 8          | risk/Unclear   | Comment: the              | Quotes: "The control   | Comment: the         | Comment: No               | Comment: the             | Comment:  | Comment: the   |
| (2015),    | Quotes: "The   | method of                 | group received no  | study did not        | statement about           | study did not            | same numbers  | protocol is  |
| Journal of | patients were randomly divided   | concealment not described | antiviral treatment"<br>"The observation group   | address this outcome | LFU (not<br>reporting any | address this outcome     | used as for<br>MTCT   | available in the method  |
| Hainan     | into the   |                           | received antiviral   |                      | LFU, and also not         |                          | outcome.  | section of the   |
| Madical    | intervention group   |                           | treatment with   |                      | mentioning                |                          | Women   | article. But   |
| Medical    | and the control  |                           | telbivudine"   |                      | clearly that there        |                          | considered  | one or more  |
| Universit  | group, with 50 cases in each   |                           | not address this   |                      | were no cases<br>LFU)     |                          | Only adverse  | reported<br>primary  |
| y, 102     | group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process   |                           | outcome and no<br>mention of placebo   |                      |                           |                          | reactions<br>reported.<br>Other key<br>adverse events<br>not addressed.   | outcomes<br>were not pre-<br>specified (e.g.<br>maternal<br>adverse<br>reactions)  |

| Peng ML   | Low   | Unclear  |                  | High risk  | Unclear  |                    | Unclear  | Unclear  |                    | Unclear  | Low risk  |
|---|---|--|------------------|--|--|--------------------|--|--|--------------------|--|---|
|   | risk/Unclear  | Comment:   | the              | Quotes: "The control   | Comment:   | the                | Comment: No  | Comment:   | the                | Comment: the   | Comment: the  |
| (2014),   | Quotes:   | method   | of               | group received HBIG"   | study did  | not                | statement about  | study did  | not                | study did not  | protocol is   |
| Chin I  | "60 cases of  | concealment  | not              | "The observation group   | address  | this               | LFU (not   | address  | this               | address this   | available in  |
| Chini J   | pregnant women  | described  |                  | received telbivudine on  | outcome  |                    | reporting any  | outcome  |                    | outcome  | the method  |
| Nosocomi  | with chronic  |  |                  | the basis of HBIG for  |  |                    | LFU, and also not  |  |                    |  | section of the  |
|   | hepatitis B were  |  |                  | the control group"   |  |                    | mentioning   |  |                    |  | article. The  |
| ol, 97  | randomly divided  |  |                  | <i>Comment</i> : the study did   |  |                    | clearly that there   |  |                    |  | current   |
|   | into experimental   |  |                  | not address this   |  |                    | were no cases  |  |                    |  | outcomes of   |
|   | group and control   |  |                  | outcome and no   |  |                    | LFU)   |  |                    |  | interest that   |
|   | group, 30 cases in  |  |                  | mention of placebo   |  |                    |  |  |                    |  | this meta-  |
|   | each group"   |  |                  |  |  |                    |  |  |                    |  | analysis is   |
|   | Comment: the  |  |                  |  |  |                    |  |  |                    |  | recording   |
|   | study did not   |  |                  |  |  |                    |  |  |                    |  | were pre-   |
|   | describe the exact  |  |                  |  |  |                    |  |  |                    |  | specified in  |
|   | random  |  |                  |  |  |                    |  |  |                    |  | that protocol.  |
|   | component in the  |  |                  |  |  |                    |  |  |                    |  |   |
|   | sequence  |  |                  |  |  |                    |  |  |                    |  |   |
|   | generation  |  |                  |  |  |                    |  |  |                    |  |   |
|   |   |  |                  |  |  |                    |  |  |                    |  |   |
|   | process   |  |                  |  |  |                    |  |  |                    |  |   |
| Zhu LP  | process<br>Low  | Unclear  |                  | High risk  | Unclear  |                    | Unclear  | Unclear  |                    | High risk  | High risk   |
| Zhu LP  | process<br>Low<br>risk/Unclear  | <b>Unclear</b><br><i>Comment:</i>                          | the              | High risk<br>Quotes: "The control  | Unclear<br>Comment:                                    | the                | Unclear<br>Comment: No   | Unclear<br>Comment:  | the                | High risk<br>Comment:  | High risk<br>Comment: the   |
| Zhu LP<br>(2014),   | process<br>Low<br>risk/Unclear<br>Quotes: "The  | Unclear<br>Comment:<br>method                              | the<br>of        | High risk<br>Quotes: "The control<br>group received no   | <b>Unclear</b><br><i>Comment:</i><br>study did         | the<br>not         | UnclearComment:Nostatementabout  | Unclear<br>Comment:<br>study did                                     | the<br>not         | High risk<br>Comment:<br>same numbers  | High risk<br>Comment: the<br>protocol is  |
| Zhu LP<br>(2014),<br>Chin J   | process       Low       risk/Unclear       Quotes:     "The       patients     were   | <b>Unclear</b><br><i>Comment:</i><br>method<br>concealment | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"   | Unclear<br>Comment:<br>study did<br>address            | the<br>not<br>this | UnclearComment:NostatementaboutLFU(not   | Unclear<br>Comment:<br>study did<br>address                          | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for   | High riskComment:protocolisavailablein  |
| Zhu         LP           (2014)            Chin         J   | process         Low         risk/Unclear         Quotes:       "The         patients       were         randomly divided  | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportingany   | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method  |
| Zhu         LP           (2014)            Chin         J           Mod                                   | process         Low         risk/Unclear         Quotes:       "The         patients       were         randomly divided         into       the   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also not  | <b>Unclear</b><br><i>Comment:</i><br>study did<br>address<br>outcome | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the  |
| Zhu LP<br>(2014),<br>Chin J<br>Mod Prug   | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservationgroup  | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioning  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women  | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But  |
| Zhu     LP       (2014)     J       Chin     J       Mod     L       Drug     L                           | process         Low         risk/Unclear         Quotes:       "The         patients       were         randomly divided         into       the         observation group         and       the control   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thatthere   | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered  | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more   |
| Zhu       LP         (2014),          Chin       J         Mod          Drug                              | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupandthe controlgroup,with30   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocases  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported   |
| Zhu       LP         (2014)       J         Chin       J         Mod       J         Drug       Appl, 108 | process<br>Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control<br>group, with 30<br>cases in each  | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this   | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | Comment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)   | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary  |
| Zhu       LP         (2014)       J         Chin       J         Mod       J         Drug       Appl, 108 | process<br>Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control<br>group, with 30<br>cases in each<br>group"  | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no                       | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes  |
| Zhu     LP       (2014)     J       Chin     J       Mod     Drug       Appl, 108                         | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupand the controlgroup, with 30cases in eachgroup"Comment:the  | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-   |
| Zhu     LP       (2014)     J       Chin     J       Mod     I       Drug     I       Appl, 108           | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupandthe controlgroup, with30casesingroup"Comment:thestudydidnot   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.                                    |
| ZhuLP(2014)JChinJModIDrugAppl, 108  | process<br>Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control<br>group, with 30<br>cases in each<br>group"<br>Comment: the<br>study did not<br>describe the exact           | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and<br>CK elevation   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal                        |
| ZhuLP(2014)JChinJMod-Drug-Appl, 108   | process<br>Low<br>risk/Unclear<br>Quotes: "The<br>patients were<br>randomly divided<br>into the<br>observation group<br>and the control<br>group, with 30<br>cases in each<br>group"<br>Comment: the<br>study did not<br>describe the exact<br>random | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and<br>CK elevation<br>reported.  | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal<br>adverse             |
| ZhuLP(2014)JChinJMod-Drug-Appl, 108   | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupandthe controlgroup, with30casesingroup"Comment:thestudydiddescribe the exactrandomcomponentin the   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | UnclearComment:NostatementaboutLFU(notreportinganyLFU, and also notmentioningclearly thattherewerenocasesLFU)  | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and<br>CK elevation<br>reported.<br>Other key                                     | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal<br>adverse<br>effects) |
| ZhuLP(2014)JChinJMod-Drug-Appl, 108   | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupandthe controlgroup, with30casesingroup, with30casesingroup"Comment:Comment:thestudydidnotdescribedescribetheexactrandomcomponentinthesequence                   | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and<br>CK elevation<br>reported.<br>Other key<br>adverse events                   | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal<br>adverse<br>effects) |
| ZhuLP(2014)JChinJMod-Drug-Appl, 108   | processLowrisk/UnclearQuotes:"Thepatientswererandomly dividedintotheobservation groupandthe controlgroup, with30casesingroup, with30casesingroup"Comment:Comment:thestudydidnotdescribe the exactrandomcomponent in thesequencegeneration             | Unclear<br>Comment:<br>method<br>concealment<br>described  | the<br>of<br>not | High risk<br>Quotes: "The control<br>group received no<br>antiviral treatment"<br>"The observation group<br>received antiviral<br>treatment with<br>telbivudine"<br>Comment: the study did<br>not address this<br>outcome and no<br>mention of placebo | Unclear<br>Comment:<br>study did<br>address<br>outcome | the<br>not<br>this | Unclear<br>Comment: No<br>statement about<br>LFU (not<br>reporting any<br>LFU, and also not<br>mentioning<br>clearly that there<br>were no cases<br>LFU) | Unclear<br>Comment:<br>study did<br>address<br>outcome               | the<br>not<br>this | High risk<br>Comment:<br>same numbers<br>used as for<br>MTCT<br>outcome.<br>Women<br>considered<br>until delivery.<br>Only adverse<br>reactions,<br>renal function<br>despair, and<br>CK elevation<br>reported.<br>Other key<br>adverse events<br>not addressed. | High risk<br>Comment: the<br>protocol is<br>available in<br>the method<br>section of the<br>article. But<br>one or more<br>reported<br>primary<br>outcomes<br>were not pre-<br>specified (e.g.<br>maternal<br>adverse<br>effects) |

| Bai HL     | Low                 | Unclear         | High risk                      | Unclear       | Low risk           | High risk       | High risk       | High risk       |
|------------|---------------------|-----------------|--------------------------------|---------------|--------------------|-----------------|-----------------|-----------------|
|            | risk/Unclear        | Comment: the    | Quotes: "The control           | Comment: the  | Comment: 100%      | Comment: same   | Comment:        | Comment: the    |
| (2013),    | Quotes: "The        | method of       | group received no              | study did not | follow-up in both  | numbers used as | same numbers    | protocol is     |
| China      | patients were       | concealment not | antiviral treatment"           | address this  | treated and        | for MTCT        | used as for     | available in    |
| Ciiiia     | randomly divided    | described       | "The observation group         | outcome       | control group      | outcome. Only   | MTCT            | the method      |
| Medical    | into the            |                 | received antiviral             |               |                    | CK elevation    | outcome.        | section of the  |
| <b>.</b>   | observation group   |                 | treatment with                 |               |                    | reported. Other | Women           | article. But    |
| Engineeri  | and the control     |                 | telbivudine"                   |               |                    | key adverse     | considered      | one or more     |
| ng 89      | group, with 30      |                 | <i>Comment</i> : the study did |               |                    | events not      | until delivery. | reported        |
| ng, 02     | cases in each       |                 | not address this               |               |                    | addressed.      | Only adverse    | primary         |
|            | group"              |                 | outcome and no                 |               |                    |                 | reactions,      | outcomes        |
|            | <i>Comment:</i> the |                 | mention of placebo             |               |                    |                 | renal function  | were not pre-   |
|            | study did not       |                 |                                |               |                    |                 | despair, and    | specified (e.g. |
|            | describe the exact  |                 |                                |               |                    |                 | CK elevation    | maternal and    |
|            | random              |                 |                                |               |                    |                 | reported.       | infantile       |
|            | component in the    |                 |                                |               |                    |                 | Other key       | adverse         |
|            | sequence            |                 |                                |               |                    |                 | adverse events  | effects). One   |
|            | generation          |                 |                                |               |                    |                 | not addressed.  | or more         |
|            | process             |                 |                                |               |                    |                 |                 | outcomes of     |
|            |                     |                 |                                |               |                    |                 |                 | merest in the   |
|            |                     |                 |                                |               |                    |                 |                 | reported        |
|            |                     |                 |                                |               |                    |                 |                 | incompletely    |
|            |                     |                 |                                |               |                    |                 |                 | so that they    |
|            |                     |                 |                                |               |                    |                 |                 | cannot be       |
|            |                     |                 |                                |               |                    |                 |                 | entered in a    |
|            |                     |                 |                                |               |                    |                 |                 | meta-analysis   |
|            |                     |                 |                                |               |                    |                 |                 | (e.g            |
|            |                     |                 |                                |               |                    |                 |                 | nostnartum      |
|            |                     |                 |                                |               |                    |                 |                 | hemorrhage)     |
|            |                     |                 |                                |               |                    |                 |                 | 8-/             |
| Guo HJ     | Low                 | Unclear         | Unclear                        | Unclear       | Unclear            | Unclear         | Unclear         | High risk       |
| (2011)     | risk/Unclear        | Comment: the    | Quotes: "The control           | Comment: the  | Comment: No        | Comment: the    | Comment: the    | Comment: the    |
| (2011),    | Quotes: "The        | method of       | group received placebo         | study did not | statement about    | study did not   | study did not   | protocol is     |
| Journal of | patients were       | concealment not | provided by the                | address this  | LFU (not           | address this    | address this    | available in    |
| oournur or | randomly divided    | described       | manufacturer" "The             | outcome       | reporting any      | outcome         | outcome         | the method      |
| Changzhi   | into the            |                 | observation group              |               | LFU, and also not  |                 |                 | section of the  |
| Modical    | observation group   |                 | received antiviral             |               | mentioning         |                 |                 | article. But    |
| wieuicai   | and the control     |                 | treatment with                 |               | clearly that there |                 |                 | one or more     |
| College,   | group, with 25      |                 | telbivudine"                   |               | were no cases      |                 |                 | reported        |
| 0 /        | cases in each       |                 | <i>Comment</i> : the study did |               | LFU)               |                 |                 | primary         |

| 93        | group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process |                               | not address this<br>outcome, though<br>mention of placebo |                                   |                                    |                                      |                                 | outcomes<br>were not pre-<br>specified (e.g.<br>maternal liver<br>function, total<br>bilirubin, and<br>HBV DNA).  |
|-----------|--|-------------------------------|---|-----------------------------------|------------------------------------|--------------------------------------|---------------------------------|---|
| Zhao DB   | Low  | Unclear                       | High risk   | Unclear                           | Unclear                            | Unclear                              | Unclear                         | High risk   |
| (2010),   | <i>Quotes:</i> "The  | <i>Comment:</i> the method of | <i>Quotes:</i> "The control group received no             | <i>Comment:</i> the study did not | <i>Comment:</i> No statement about | <i>Quotes:</i> "no adverse reactions | <i>Quotes:</i> "no adverse      | <i>Comment:</i> the protocol is   |
| Chin J    | randomly divided   | described                     | "The observation group                                    | address this                      | reporting any                      | groups of mothers                    | found in two                    | the method  |
| Mod       | into the   | austricea                     | received antiviral  |                                   | LFU, and also not                  | and infants"                         | groups of                       | section of the  |
| Drug      | observation group<br>and the control   |                               | treatment with telbivudine"                               |                                   | mentioning<br>clearly that there   | Comment:<br>insufficient             | mothers and<br>infants"         | article. But<br>one or more   |
| Appl, 105 | group, with 30<br>cases in each  |                               | <i>Comment</i> : the study did<br>not address this        |                                   | were no cases<br>LFU)              | reporting                            | <i>Comment:</i><br>insufficient | reported<br>primary   |
|           | group"<br>Comment: the<br>study did not<br>describe the exact<br>random<br>component in the<br>sequence<br>generation<br>process |                               | outcome and no<br>mention of placebo                      |                                   |                                    |                                      | reporting                       | outcomes<br>were not pre-<br>specified (e.g.<br>maternal and<br>infantile<br>adverse<br>reactions).<br>One or more<br>outcomes of<br>interest in the<br>review are<br>reported<br>incompletely<br>so that they<br>cannot be<br>entered in a<br>meta-analysis<br>(e.g. maternal<br>and infantile<br>adverse<br>reactions). |

| Zhang LJ | Low                 | Unclear         | High risk                      | Unclear       | Low risk          | High risk           | High risk       | High risk       |
|----------|---------------------|-----------------|--------------------------------|---------------|-------------------|---------------------|-----------------|-----------------|
|          | risk/Unclear        | Comment: the    | Quotes: "The control           | Comment: the  | Comment: 96.8%    | Comment: all        | Comment: All    | Comment: the    |
| (2009),  | Quotes: "The        | method of       | group received no              | study did not | and 100.0% with   | infants included in | women           | protocol is     |
| Chin I   | patients were       | concealment not | antiviral treatment"           | address this  | full follow-up in | this analysis from  | considered      | available in    |
| Chin 5   | randomly divided    | described       | "The observation group         | outcome       | treated and       | both treated and    | until delivery. | the method      |
| Hepatol, | into the            |                 | received antiviral             |               | control group     | control groups.     | Only adverse    | section of the  |
| 102      | observation group   |                 | treatment with                 |               | respectively.     | Only CK             | reactions,      | article. But    |
| 103      | and the control     |                 | telbivudine"                   |               | Similar follow-up | elevation           | renal function  | one or more     |
|          | group, with 31      |                 | <i>Comment</i> : the study did |               | proportions in    | reported. Other     | despair, and    | reported        |
|          | cases in the        |                 | not address this               |               | each group.       | key adverse         | CK elevation    | primary         |
|          | observation group   |                 | outcome and no                 |               |                   | events not          | reported.       | outcomes        |
|          | and 30 cases in     |                 | mention of placebo             |               |                   | addressed.          | Other key       | were not pre-   |
|          | the control group"  |                 |                                |               |                   |                     | adverse events  | specified (e.g. |
|          | <i>Comment:</i> the |                 |                                |               |                   |                     | not addressed.  | maternal and    |
|          | study did not       |                 |                                |               |                   |                     |                 | infantile       |
|          | describe the exact  |                 |                                |               |                   |                     |                 | adverse         |
|          | random              |                 |                                |               |                   |                     |                 | effects). One   |
|          | component in the    |                 |                                |               |                   |                     |                 | or more         |
|          | sequence            |                 |                                |               |                   |                     |                 | outcomes of     |
|          | generation          |                 |                                |               |                   |                     |                 | interest in the |
|          | process             |                 |                                |               |                   |                     |                 | review are      |
|          |                     |                 |                                |               |                   |                     |                 | reported        |
|          |                     |                 |                                |               |                   |                     |                 | incompletely    |
|          |                     |                 |                                |               |                   |                     |                 | so that they    |
|          |                     |                 |                                |               |                   |                     |                 | cannot be       |
|          |                     |                 |                                |               |                   |                     |                 | entered in a    |
|          |                     |                 |                                |               |                   |                     |                 | meta-analysis   |
|          |                     |                 |                                |               |                   |                     |                 | (e.g.           |
|          |                     |                 |                                |               |                   |                     |                 | postpartum      |
|          |                     |                 |                                |               |                   |                     |                 | nemorrhage).    |
|          |                     |                 |                                |               |                   |                     |                 |                 |

# Appendix G: Newcastle-Ottawa Risk of Bias Assessment Tool for non-RCTs

TDF 300 mg

#### A. English Language Observational Studies

|  |   |  |  | Demonstration        |   |  | Was follow-     |   | Total              |
|--|---|--|--|----------------------|---|--|-----------------|---|--------------------|
|  | Representa  | Selection of   |  | that outcome of      | Comparability of  |  | up long         |   | number             |
| Study  | tive-ness of  | the non-   |  | interest was         | cohorts on the basis  |  | enough for      | Adequacy of   | of stars           |
| (year),  | the exposed   | exposed  | Ascertainment  | not present at       | of the design or  | Assessment of  | outcomes        | follow up of  | (risk of           |
| journal, No.   | cohort  | cohort   | of exposure  | baseline             | analysis  | outcomes   | occur           | cohorts   | bias) <sup>a</sup> |
| Celen MK,<br>(2013),<br>World J<br>Gastroenter<br>ol, 28 | ★       At     least       somewhat       representative       of the average       HBV infected       pregnant | ★  | Do not provide<br>many details on<br>decrease of HBV<br>DNA levels, no<br>other discussion<br>of maternal<br>adherence.  | ★<br>Always the case | ★★         Comparable for HBV         DNA level and         comparable HBeAg         positive. Same regimen         for infant         immunoprophylaxis.                 | Describes testing<br>done and refers to<br>a central<br>laboratory<br>employed for this<br>study.                              | <b>★</b><br>Yes | None reported<br>(retrospective)  | 7<br>(low)         |
|  | woman   |  |  |                      |   |  |                 |   |                    |
| Greenup AJ<br>(2014), J<br>Hepatol, 32                   | ★     least       Somewhat     representative       of the average     HBV infected       pregnant     woman    | ★ Drawn from the same community (same inclusion and exclusion criteria also) | Reporting       on         adherence       within         the       paper,         reduction       of         load       used       to         assess       women's         response       to         treatment. | ★ Always the case    | Comparable for<br>HBV DNA level and<br>comparable HBeAg<br>positive. Same regimen<br>for infant<br>immunoprophylaxis and<br>confirmation that all<br>infants received it. | No details given<br>on laboratory<br>methods for<br>infants, and no<br>details of which<br>assay was used for<br>testing HBsAg | <b>★</b><br>Yes | > 20% LFU in<br>control group,<br>although <20% LFU<br>in two treatment<br>groups | 7<br>(low)         |

| Chen HL,  | *  | *   | 4   | 衣<br>文                      | **  | 4  | *               | *  | 9           |
|---|--|---|---|-----------------------------|---|--|-----------------|--|-------------|
| (2015),<br>Hepatology,<br>29                            | At least<br>somewhat<br>representative<br>of the average<br>HBV infected<br>pregnant<br>woman                    | Drawn from the<br>same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)   | Regular testing<br>(and pre-delivery<br>testing) of HBV<br>DNA levels were<br>correlated with<br>duration of<br>treatment in<br>mothers | Always the case             | Comparable for HBV<br>DNA level and<br>comparable HBeAg<br>positive. Same regimen<br>for infant<br>immunoprophylaxis.   | Describes test<br>assays used for<br>HBsAg and HBV<br>DNA and<br>acknowledges a<br>study laboratory. | Yes             | LFU reported and<br><20% LFU in all<br>treatment and<br>control groups | (low)       |
| Kochaksarei<br>GS, (2016) <sup>1</sup>                  | At least<br>somewhat<br>representative<br>of the average<br>HBV infected<br>pregnant<br>woman                    | Not same<br>population, the<br>untreated did<br>not have high<br>viremia or pre-<br>existing liver<br>disease,<br>whereas the<br>treated did. | Adherence is<br>mentioned but<br>was ascertained in<br>16/23 women<br>(<70%), and only<br>2/3rds had good<br>adherence.                 | <b>☆</b><br>Always the case | ★ Not comparable for<br>HBV DNA level or<br>HBeAg positive.<br>Apparently the same<br>regimen for infant<br>immunoprophylaxis,<br>however very few details<br>stated. | ★<br>Testing done<br>centrally, and<br>methods/assays<br>for testing<br>described.                   | <b>★</b><br>Yes | <80% follow-up in<br>both treated and<br>control groups                | 5<br>(high) |
| Wakano Y,<br>(2018), J<br>Obstet<br>Gynaecol<br>Res, 39 | Not<br>representative<br>of the general<br>population<br>(women<br>who've had a<br>child infected<br>previously) | ★<br>Drawn from<br>the same<br>community with<br>same inclusion<br>and exclusion<br>criteria.   | ★ >2 log reduction<br>of HBV DNA<br>levels in all<br>treated women  | <b>★</b><br>Always the case | Comparable for<br>HBV DNA level and<br>comparable HBeAg<br>positive. Different<br>immunoprophylaxis<br>regimens mixed amongst<br>the groups of treated and            | Laboratory assays<br>not well<br>described.  | <b>★</b><br>Yes | ★<br>100% retention  | 6<br>(high) |

<sup>&</sup>lt;sup>1</sup> Kochaksaraei GS, Castillo E, Osman M, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant participants in a low hepatitis B virus endemic region. *J Viral Hepat* 2016; **23(1)**:15-22.

|                             |               |                   |                     |                         | non-treated.           |              |  |  |
|-----------------------------|---------------|-------------------|---------------------|-------------------------|------------------------|--------------|--|--|
| <sup>a</sup> Risk of bias a | ssessments sh | ould be classifie | d as being either l | ow $(\geq 7)$ or high ( | < 7) by the Newcastle- | Ottawa scale |  |  |

|                |                   |                 |                    | Demonstration    | Comparability of       |                | Was follow- |           |                    |
|----------------|-------------------|-----------------|--------------------|------------------|------------------------|----------------|-------------|-----------|--------------------|
|                |                   | Selection of    |                    | that outcome of  | cohorts on the         |                | up long     | Adequacy  | Total              |
|                | Representative    | the non-        |                    | interest was not | basis of the           |                | enough for  | of follow | number of          |
| Study (year),  | -ness of the      | exposed         | Ascertainment      | present at       | design or              | Assessment     | outcomes    | up of     | stars (risk of     |
| journal, No.   | exposed cohort    | cohort          | of exposure        | baseline         | analysis               | of outcomes    | occur       | cohorts   | bias) <sup>a</sup> |
| He LL, (2018), | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | ★ Always the     | ★ Comparable           | な              | ★ Yes       | No        | 7 (low)            |
| Maternal and   | somewhat          | from the same   | was used to        | case             | for HBV DNA            | Laboratory     |             | statement |                    |
| Child Health   | representative of | community       | ascertain          |                  | levels at baseline but | methods        |             | OI LI'U   |                    |
| Care of China, | the average HBV   | (same inclusion | adherence to the   |                  | HBeAg sero-status      | described in   |             |           |                    |
| 36             | infected pregnant | and exclusion   | antiviral therapy  |                  | not described. Same    | detail (which  |             |           |                    |
| 50             | woman             | criteria also)  | (decrease in viral |                  | regimen for infant     | assay used),   |             |           |                    |
|                |                   |                 | load levels        |                  | immunoprophylaxis      | indicating use |             |           |                    |
|                |                   |                 | subsequent to the  |                  | at birth               | of a central   |             |           |                    |
|                |                   |                 | treatment)         |                  |                        | laboaratory    |             |           |                    |
|                |                   |                 |                    |                  |                        | and/or record  |             |           |                    |
|                |                   |                 |                    |                  |                        | linkage.       |             |           |                    |
| Hu MF,         | 🛠 At least        | 🛠 Drawn         | ✤ Valid method     | 🖈 Always the     | ★ Comparable           | *              | ★ Yes       | No        | 7 (low)            |
| (2018), Chin J | somewhat          | from the same   | was used to        | case             | for HBV DNA            | Laboratory     |             | of LEU    |                    |
| Drug Depend,   | representative of | community       | ascertain          |                  | levels at baseline but | methods        |             | of Li C   |                    |
| 37             | the average HBV   | (same inclusion | adherence to the   |                  | HBeAg sero-status      | described in   |             |           |                    |
|                | infected pregnant | and exclusion   | antiviral therapy  |                  | not described. Same    | detail (which  |             |           |                    |
|                | woman             | criteria also)  | (decrease in viral |                  | regimen for infant     | assay used),   |             |           |                    |
|                |                   |                 | load levels        |                  | immunoprophylaxis      | indicating use |             |           |                    |
|                |                   |                 | subsequent to the  |                  | at birth               | of a central   |             |           |                    |
|                |                   |                 | treatment)         |                  |                        | laboaratory    |             |           |                    |
|                |                   |                 |                    |                  |                        | and/or record  |             |           |                    |
|                |                   |                 |                    |                  |                        | linkage.       |             |           |                    |

### **B.** Chinese Language Observational Studies

| Wang HB,       | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | *    | Always th | Same threshold       | ₩Laboratory    | <b>⊀</b> Yes | No              | 7 (low)  |
|----------------|-------------------|-----------------|--------------------|------|-----------|----------------------|----------------|--------------|-----------------|----------|
| (2018), Chin J | somowhat          | from the same   | was used to        | 0000 |           | for HPV DNA lovel    | mathods        |              | statement       |          |
| Exp Clin       | representative of | community       | was used to        | case |           | but HBaAg sero       | described in   |              | of LFU          |          |
| Infact Dis 41  | the average HPV   | (same inclusion | adharanaa to tha   |      |           | status not described | detail (which  |              |                 |          |
| Infect D15, 41 | inforted program  | (same inclusion | antiviral thorapy  |      |           | Same regimen for     |                |              |                 |          |
|                | meeted pregnant   | and exclusion   | (doorsooo in virol |      |           | infont               | indianting use |              |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |           | iniant               | indicating use |              |                 |          |
|                |                   |                 | load levels        |      |           | immunoprophylaxis    | of a central   |              |                 |          |
|                |                   |                 | subsequent to the  |      |           | at birth             | laboaratory    |              |                 |          |
|                |                   |                 | treatment)         |      |           |                      | and/or record  |              |                 |          |
|                |                   |                 |                    |      |           |                      | linkage.       |              |                 |          |
| Zhang BF,      | 🛠 At least        | <b>↓</b> Drawn  | ★ Valid method     | *    | Always th | Same HBeAg           | No             | 🛠 Yes        | No              | 6 (high) |
| (2018), Chin J |                   |                 |                    |      | •         |                      | description    |              | statement       |          |
| Henatol 13     | somewhat          | from the same   | was used to        | case |           | sero-status but      |                |              | of LFU          |          |
| 11epatol, 45   | representative of | community       | ascertain          |      |           | different thresholds |                |              |                 |          |
|                | the average HBV   | (same inclusion | adherence to the   |      |           | for HBV DNA level.   |                |              |                 |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |           | Same regimen for     |                |              |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |           | infant               |                |              |                 |          |
|                |                   |                 | load levels        |      |           | immunoprophylaxis    |                |              |                 |          |
|                |                   |                 | subsequent to the  |      |           | at birth             |                |              |                 |          |
|                |                   |                 | treatment)         |      |           |                      |                |              |                 |          |
| Zhou Y,        | 🛠 At least        | 🖈 Drawn         | ★ Valid method     | *    | Always th | e ☆☆ Same            | *              | ★ Yes        | No<br>statement | 8 (low)  |
| (2018), New    | somewhat          | from the same   | was used to        | case |           | HBeAg sero-status    | Laboratory     |              | of LFU          |          |
| Medical        | representative of | community       | ascertain          |      |           | and same thresholds  | methods        |              |                 |          |
| Science, 44    | the average HBV   | (same inclusion | adherence to the   |      |           | for HBV DNA level.   | described in   |              |                 |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |           | Same regimen for     | detail (which  |              |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |           | infant               | assay used),   |              |                 |          |
|                |                   |                 | load levels        |      |           | immunoprophylaxis    | indicating use |              |                 |          |
|                |                   |                 | subsequent to the  |      |           | at birth             | of a central   |              |                 |          |
|                |                   |                 | treatment)         |      |           |                      | laboaratory    |              |                 |          |

|               |                    |                 |                    |      |           |   |                     | and/or record  |       |           |          |
|---------------|--------------------|-----------------|--------------------|------|-----------|---|---------------------|----------------|-------|-----------|----------|
|               |                    |                 |                    |      |           |   |                     | linkage.       |       |           |          |
| Chen WJ,      | 🛠 At least         | ★ Drawn         | ★ Valid method     | ķ    | Always th | e | ☆☆ Same             | *Laboratory    | ★ Yes | No        | 8 (low)  |
| (2017),       | _                  |                 |                    |      | 5         |   |                     |                |       | statement |          |
| Shandong      | somewhat           | from the same   | was used to        | case |           |   | HBeAg sero-status   | methods        |       | of LFU    |          |
|               | representative of  | community       | ascertain          |      |           |   | and same thresholds | described in   |       |           |          |
| Medicine, 30  | the average HBV    | (same inclusion | adherence to the   |      |           |   | for HBV DNA level.  | detail (which  |       |           |          |
|               | infected pregnant  | and exclusion   | antiviral therapy  |      |           |   | Same regimen for    | assay used),   |       |           |          |
|               | woman              | criteria also)  | (decrease in viral |      |           |   | infant              | indicating use |       |           |          |
|               |                    |                 | load levels        |      |           |   | immunoprophylaxis   | of a central   |       |           |          |
|               |                    |                 | subsequent to the  |      |           |   | at birth            | laboaratory    |       |           |          |
|               |                    |                 | treatment)         |      |           |   |                     | and/or record  |       |           |          |
|               |                    |                 |                    |      |           |   |                     | linkage.       |       |           |          |
| Gong Q,       | 🛠 At least         | <b>☆</b> Drawn  | ✤ Valid method     | ķ    | Always th | e | 🛠 Both HBeAg        | No             | ★ Yes | No        | 6 (high) |
| (2017), China | comowhat           | from the come   | was used to        | 2222 | -         |   | core status and     | description    |       | statement |          |
| Continuing    | somewhat           | from the same   | was used to        | case |           |   | sero-status and     |                |       | of LFU    |          |
| Madical       | the second and UDV | community       |                    |      |           |   | DNA lavel not       |                |       |           |          |
| Medical       | the average HBV    | (same inclusion | adherence to the   |      |           |   | DINA level not      |                |       |           |          |
| Education, 31 | infected pregnant  | and exclusion   | antiviral therapy  |      |           |   | described. Same     |                |       |           |          |
|               | woman              | criteria also)  | (decrease in viral |      |           |   | regimen for infant  |                |       |           |          |
|               |                    |                 | load levels        |      |           |   | immunoprophylaxis   |                |       |           |          |
|               |                    |                 | subsequent to the  |      |           |   | at birth            |                |       |           |          |
|               |                    |                 | treatment)         |      |           |   |                     |                |       |           |          |
| Huang Q,      | 🛠 At least         | ★ Drawn         | ✤ Valid method     | *    | Always th | e | <b>☆☆</b> Same      | No             | ★ Yes | No        | 7 (low)  |
| (2017),       | somowhat           | from the same   | was used to        | 2052 |           |   | UPa A a sara status | description    |       | statement |          |
| Oinghai       | somewhat           | nom the same    | was used to        | case |           |   | and some thresholds |                |       | of LFU    |          |
| Madical       | the average UDV    | (same inclusion | adharanaa ta th-   |      |           |   | for LIDV DNA low-1  |                |       |           |          |
| wieuical      | inforted areas i   | (same inclusion | autience to the    |      |           |   | Some regiment       |                |       |           |          |
| Journal, 38   | infected pregnant  | and exclusion   | anuviral therapy   |      |           |   | Same regimen for    |                |       |           |          |
|               | woman              | criteria also)  | (decrease in viral |      |           |   | iniant              |                |       |           |          |
|               |                    |                 | load levels        |      |           |   | immunoprophylaxis   |                |       |           |          |

|                         |                   |                       | subsequent to the  |      |        |     | at birth                                 |                |              |                 |          |
|-------------------------|-------------------|-----------------------|--------------------|------|--------|-----|--|----------------|--------------|-----------------|----------|
|                         |                   |                       | treatment)         |      |        |     |  |                |              |                 |          |
| Wan JY,<br>(2017) China | 🛠 At least        | <b>☆</b> Drawn        | ★ Valid method     | *    | Always | the | Same thresholds for<br>HBV DNA level but | ₩Laboratory    | ★ Yes        | No<br>statement | 6 (high) |
| (2017), China           | somewhat          | from the same         | was used to        | case |        |     | HBeAg sero-status                        | methods        |              | of LFU          |          |
| Tropical                | representative of | community             | ascertain          |      |        |     | not described.                           | described in   |              |                 |          |
| Medicine, 40            | the average HBV   | (same inclusion       | adherence to the   |      |        |     | Regimen for infant                       | detail (which  |              |                 |          |
|                         | infected pregnant | and exclusion         | antiviral therapy  |      |        |     | immunoprophylaxis                        | assay used),   |              |                 |          |
|                         | woman             | criteria also)        | (decrease in viral |      |        |     | at birth not                             | indicating use |              |                 |          |
|                         |                   |                       | load levels        |      |        |     | described                                | of a central   |              |                 |          |
|                         |                   |                       | subsequent to the  |      |        |     |  | laboaratory    |              |                 |          |
|                         |                   |                       | treatment)         |      |        |     |  | and/or record  |              |                 |          |
|                         |                   |                       |                    |      |        |     |  | linkage.       |              |                 |          |
| Xiao XH,                | At least          |                       | ★ Valid method     | *    | Alwaye | the | Same thresholds for                      | 4              | <b>∛</b> Vas | There is a      | 6 (high) |
| (2017).                 | At least          | V <sup>4</sup> Diawii | ve vand method     |      | Always | the | HBV DNA level but                        |                | 1 1 1 2 3    | description     |          |
| ( <u></u> ),            | somewhat          | from the same         | was used to        | case |        |     | HBeAg sero-status                        | Laboratory     |              | of LFU for      |          |
| Maternal and            | representative of | community             | ascertain          |      |        |     | not described.                           | methods        |              | the exposed     |          |
| Child Health            | the average HBV   | (same inclusion       | adherence to the   |      |        |     | Regimen for infant                       | described in   |              | but not for     |          |
| Care of China,          | infected pregnant | and exclusion         | antiviral therapy  |      |        |     | immunoprophylaxis                        | detail (which  |              | the control     |          |
| 42                      | woman             | criteria also)        | (decrease in viral |      |        |     | at birth not clearly                     | assay used),   |              | group           |          |
| 12                      |                   |                       | load levels        |      |        |     | described                                | indicating use |              |                 |          |
|                         |                   |                       | subsequent to the  |      |        |     |  | of a central   |              |                 |          |
|                         |                   |                       | treatment)         |      |        |     |  | laboaratory    |              |                 |          |
|                         |                   |                       |                    |      |        |     |  | and/or_record  |              |                 |          |
|                         |                   |                       |                    |      |        |     |  | und/or record  |              |                 |          |

#### LAM 100-150 mg

#### A. English Language Observational Studies

|             |                |                 |                    | Demonstration      |                          |                    | Was follow- |                   | Total              |
|-------------|----------------|-----------------|--------------------|--------------------|--------------------------|--------------------|-------------|-------------------|--------------------|
|             | Representa     | Selection of    |                    | that outcome of    | Comparability of         |                    | up long     |                   | number             |
|             | tive-ness of   | the non-        |                    | interest was       | cohorts on the basis     |                    | enough for  | Adequacy of       | of stars           |
| Study       | the exposed    | exposed         | Ascertainment      | not present at     | of the design or         | Assessment of      | outcomes    | follow up of      | (risk of           |
| (year)      | cohort         | cohort          | of exposure        | baseline           | analysis                 | outcomes           | occur       | cohorts           | bias) <sup>a</sup> |
| Greenup AJ  | *              | な               | *                  | ★ Always the       | <b>☆☆</b> Comparable for | No details given   | *           | > 20% LFU in      | 7                  |
| (2014), J   | At least       | Drawn from the  | Reporting on       | case               | HBV DNA level and        | methods for        | Yes         | although <20% LFU | (low)              |
| Hepatol, 32 | somewhat       | same            | adherence within   |                    | comparable HBeAg         | infants, and no    |             | in two treatment  |                    |
|             | representative | community       | the paper,         |                    | positive. Same regimen   | details of which   |             | groups            |                    |
|             | of the average | (same inclusion | reduction of viral |                    | for infant               | assay was used for |             |                   |                    |
|             | HBV infected   | and exclusion   | load used to       |                    | immunoprophylaxis and    | testing HBsAg      |             |                   |                    |
|             | pregnant       | criteria also)  | assess women's     |                    | confirmation that all    |                    |             |                   |                    |
|             | woman          |                 | response to        |                    | infants received it.     |                    |             |                   |                    |
|             |                |                 | treatment.         |                    |                          |                    |             |                   |                    |
| Zhang H     | *              | な               | *                  | *                  | <b>44</b>                | *                  | *           | *                 | 9                  |
| (2014),     | At least       | Drawn from      | Monthly HBV        | Always the case    | Comparable for HBV       | Describes testing  | Yes         | LFU reported and  | (low)              |
| Hepatology, | somewhat       | the same        | DNA level testing  | Thinkings are case | DNA level and            | done and refers to | 100         | <20% LFU in all   |                    |
| 85          | representative | community       | was done to check  |                    | comparable HBeAg         | a central          |             | treatment and     |                    |
|             | of the average | (same inclusion | maternal           |                    | positive. Same regimen   | laboratory         |             | control groups    |                    |
|             | HBV infected   | and exclusion   | adherence          |                    | for infant               | employed for this  |             | 8F-               |                    |
|             | pregnant       | criteria also)  | uunoronoo          |                    | immunoprophylaxis        | study              |             |                   |                    |
|             | woman          |                 |                    |                    |                          | studyt             |             |                   |                    |
| Jackson V   |                |                 |                    |                    | HBV DNA level and        |                    |             | <80% retention in | 6                  |
|             | *              | *               | *                  | *                  | HBeAg not described in   | *                  | *           | both treated and  |                    |
| (2015), Eur | At least       | Drawn from the  | Mentions good      | Always the case    | control group. Mentions  | Laboratory         | Yes         | control groups    | (high)             |

| J          | Clin   | somewhat       | same             | treatment          |                 | that all infants received | assays described,                     |     |                       |          |
|------------|--------|----------------|------------------|--------------------|-----------------|---------------------------|---------------------------------------|-----|-----------------------|----------|
| Miarah     | -<br>- | representative | community        | compliance in all  |                 | the same regimen for      | with indication of                    |     |                       |          |
| MICIOU     | 101    | of the average | (same inclusion  | but one patient,   |                 | infant                    | record linkage                        |     |                       |          |
| Infect     | Dis,   | HBV infected   | and exclusion    | and measures       |                 | immunoprophylaxis,        | (results viewed                       |     |                       |          |
| 67         |        | pregnant       | criteria also)   | decrease in viral  |                 | however, in the control   | retrospectively in                    |     |                       |          |
|            |        | woman          | ,                | load in 35/36      |                 | group, many women         | medical records)                      |     |                       |          |
|            |        |                |                  | women taking       |                 | defaulted from            | , , , , , , , , , , , , , , , , , , , |     |                       |          |
|            |        |                |                  | treatment just     |                 | care/moved to other       |                                       |     |                       |          |
|            |        |                |                  | prior to delivery  |                 | maternities, so this does |                                       |     |                       |          |
|            |        |                |                  | and saw a          |                 | not seem well verified.   |                                       |     |                       |          |
|            |        |                |                  | significant        |                 |                           |                                       |     |                       |          |
|            |        |                |                  | decrease in most   |                 |                           |                                       |     |                       |          |
|            |        |                |                  | patients (also     |                 |                           |                                       |     |                       |          |
|            |        |                |                  | show these results |                 |                           |                                       |     |                       |          |
|            |        |                |                  | in a figure in the |                 |                           |                                       |     |                       |          |
|            |        |                |                  | paper).            |                 |                           |                                       |     |                       |          |
| Liu        | CP     |                | Many more        | Some limited data  |                 | <u> </u>                  |                                       |     | No loss to follow-up  | 5 (high) |
| $(2015)^2$ | C1     | 72             | women            | presented on       | 72              | 73                        | 72                                    | 72  | described because it  | 5 (ingh) |
| (2015)     |        | At least       | included in the  | decrease of        | Always the case | HBV DNA level and/or      | Laboratory                            | Yes | was a retrospective   |          |
|            |        | somewhat       | control group    | maternal viral     |                 | HBeAg not described for   | assays described,                     |     | cohort study (or      |          |
|            |        | representative | (highly          | load, but no       |                 | both treated and control  | with indication of                    |     | listed as such) where |          |
|            |        | of the average | disproportionate | mention of linking |                 | groups. Similar infant    | record linkage                        |     | the infants needed to |          |
|            |        | HBV infected   | which could      | this with          |                 | prophylaxis between       | (results viewed                       |     | have had test results |          |
|            |        | pregnant       | indicate non-    | compliance/adher   |                 | treated and control       | retrospectively in                    |     | at the testing        |          |
|            |        | woman          | similarity with  | ence/time on       |                 | groups.                   | medical records)                      |     | timepoint (this is    |          |
|            |        |                | the treated)     | treatment, and no  |                 |                           |                                       |     | therefore             |          |
|            |        |                |                  | detailed results   |                 |                           |                                       |     | misclassified as a    |          |
|            |        |                |                  | provided.          |                 |                           |                                       |     | cohort study, and     |          |
|            |        |                |                  |                    |                 |                           |                                       |     |                       |          |

<sup>&</sup>lt;sup>2</sup> Liu CP, Zeng YL, Zhou M, et al. Factors Associated with Mother-to-child Transmission of Hepatitis B Virus Despite Immunoprophylaxis. *Intern Med* 2015; **54(7)**: 711-716.

|              |                |                  |                    |                 |   |                    |     | has a high risk of    |        |
|--------------|----------------|------------------|--------------------|-----------------|---|--------------------|-----|-----------------------|--------|
|              |                |                  |                    |                 |   |                    |     | bias for loss to      |        |
|              |                |                  |                    |                 |   |                    |     | follow-up)            |        |
| Pan CQ       | *              | Same             | Some data          | な               | **  | *                  | *   | No loss to follow-up  | 6      |
| (2017). J    | ,              | population and   | presented on       | ,               | , ,   | ,                  | ,   | described because it  | (high) |
|              | At least       | criteria,        | decrease of        | Always the case | Comparable for HBV  | Reference to the   | Yes | was a retrospective   | (      |
| Viral Hepat, | somewhat       | however, no      | maternal viral     |                 | DNA level and   | hospital's         |     | cohort study (or      |        |
| 73           | representative | indication of    | load, but no       |                 | comparable HBeAg  | centralized        |     | listed as such) where |        |
|              | of the average | how this group   | mention of linking |                 | positive. Same regimen  | laboratory and     |     | the infants needed to |        |
|              | HBV infected   | was chosen       | this with          |                 | for infant  | linkage to medical |     | have had test results |        |
|              | pregnant       | (usually says    | compliance/adher   |                 | immunoprophylaxis   | records for        |     | at the testing time-  |        |
|              | woman          | 'unwillingness', | ence/time on       |                 |   | assessing infant   |     | point (this is        |        |
|              |                | for example)     | treatment.         |                 |   | outcome.           |     | therefore             |        |
|              |                |                  | Additionally,      |                 |   |                    |     | misclassified as a    |        |
|              |                |                  | because of study   |                 |   |                    |     | cohort study, and     |        |
|              |                |                  | design             |                 |   |                    |     | has a high risk of    |        |
|              |                |                  | (retrospective)    |                 |   |                    |     | bias for loss to      |        |
|              |                |                  | there is low/no    |                 |   |                    |     | follow-up)            |        |
|              |                |                  | chance of          |                 |   |                    |     |                       |        |
|              |                |                  | adherence          |                 |   |                    |     |                       |        |
|              |                |                  | monitoring.        |                 |   |                    |     |                       |        |
| He T         | 4              | 4                | *                  | *               | -<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>-<br>- | 4                  | 4   | Retrospective cohort  | 8      |
| (2018).      |                |                  |                    |                 |   |                    |     | mentioned but no      | (low)  |
|              | At least       | Drawn from the   | Detailed           | Always the case | Comparable for HBV  | Linkage to         | Yes | loss to follow-up     | (10)   |
| Hepatol Int, | somewhat       | same             | information on     |                 | DNA level and   | medical records    |     | described, no         |        |
| 64           | representative | community with   | reduction of viral |                 | comparable HBeAg  |                    |     | mention of how        |        |
|              | of the average | same inclusion   | load given,        |                 | positive. Same regimen  |                    |     | there was perfect     |        |
|              | HBV infected   | and exclusion    | including specific |                 | for infant  |                    |     | retention.            |        |
|              | pregnant       | criteria.        | data for each      |                 | immunoprophylaxis   |                    |     |                       |        |
|              | woman          |                  | women (every one   |                 |   |                    |     |                       |        |
|              |                |                  | had a -6 to -8 log |                 |   |                    |     |                       |        |

|             |                |                 | reduction)        |                 |                           |                      |     |                       |        |
|-------------|----------------|-----------------|-------------------|-----------------|---------------------------|----------------------|-----|-----------------------|--------|
| Wakano Y    | Not            | な               | *                 | <b>X</b>        | *                         | Laboratory assays    | 4   | *                     | 6      |
| (2018), J   | representative | ,               |                   | ,               |                           | not well             |     |                       | (high) |
| Obstat      | of the general | Drawn from      | >2 log reduction  | Always the case | Comparable for HBV        | described.           | Yes | 100% retention        |        |
| Obster      | population     | the same        | of HBV DNA        |                 | DNA level and             |                      |     |                       |        |
| Gynaecol    | (women         | community with  | levels in all     |                 | comparable HBeAg          |                      |     |                       |        |
| Res, 39     | who've had a   | same inclusion  | treated women     |                 | positive. Different       |                      |     |                       |        |
|             | child infected | and exclusion   |                   |                 | immunoprophylaxis         |                      |     |                       |        |
|             | previously)    | criteria.       |                   |                 | regimens mixed amongst    |                      |     |                       |        |
|             |                |                 |                   |                 | the groups of treated and |                      |     |                       |        |
|             |                |                 |                   |                 | non-treated.              |                      |     |                       |        |
| Foaud HM    | <b>X</b>       | Control group   | *                 | な               | 4                         | 4                    | な   | <80% follow-up at     | 6      |
| (2019).     | ,              | was comprised   | ,                 | ,               | ,                         | ,                    | r   | 6-12 months in        | (high) |
| Arch I      | Truly          | of women who    | States that women | Always the case | HBeAg proportion not      | Lab testing done     | Yes | control group,        | ( 8 /  |
| Arab J      | representative | were not a      | were given        |                 | comparable, and HBV       | centrally as part of |     | though ~86%           |        |
| Gastroenter | of the average | candidate for   | lamivudine        |                 | DNA at baseline not       | the study,           |     | follow-up in treated  |        |
| ol, 59      | HBV infected   | lamivudine      | monthly and were  |                 | given. Same regimen for   | laboratory assays    |     | group at that         |        |
|             | pregnant       | (likely to be   | questioned        |                 | infant                    | for defining infant  |     | timepoint. (Note: at  |        |
|             | woman          | quite different | regarding         |                 | immunoprophylaxis         | outcome              |     | later timepoint, that |        |
|             |                | from those who  | compliance at     |                 |                           | described.           |     | study defined, there  |        |
|             |                | received it)    | each visit.       |                 |                           |                      |     | was >80% followup)    |        |

|                       |                   |                 |                    | Demonstration    | Comparability of       |                | Was follow- |              |                    |
|-----------------------|-------------------|-----------------|--------------------|------------------|------------------------|----------------|-------------|--------------|--------------------|
|                       |                   | Selection of    |                    | that outcome of  | cohorts on the         |                | up long     | Adequacy     | Total              |
|                       | Representative    | the non-        |                    | interest was not | basis of the           |                | enough for  | of follow    | number of          |
| Study (year),         | -ness of the      | exposed         | Ascertainment      | present at       | design or              | Assessment     | outcomes    | up of        | stars (risk of     |
| journal, No.          | exposed cohort    | cohort          | of exposure        | baseline         | analysis               | of outcomes    | occur       | cohorts      | bias) <sup>a</sup> |
| Chen QR               | 🖈 At least        | ★ Drawn         | No description     | 🖈 Always the     | ★★ Same                | No             | ★ Yes       | No           | 6 (high)           |
| (2018),               | aamarrikat        | from the come   |                    |                  | UDe A e corre status   | description    |             | statement    |                    |
| Maternal and          | somewhat          | from the same   |                    | case             | HBeAg sero-status      |                |             | of LFU       |                    |
| Child Health          | the average HBV   | (same inclusion |                    |                  | HBV DNA levels at      |                |             |              |                    |
|                       | infected pregnant | and exclusion   |                    |                  | haseline Same          |                |             |              |                    |
| Care of China,        | woman             | criteria also)  |                    |                  | regimen for infant     |                |             |              |                    |
| 56                    | woman             | cinterna aiso)  |                    |                  | immunoprophylaxis      |                |             |              |                    |
|                       |                   |                 |                    |                  | at birth               |                |             |              |                    |
| Li IH (2017)          |                   | ×               |                    |                  | ~                      |                |             | None         | 7 (low)            |
| Chinese               | 72                | 72              | ✓ Valid method     | 72               | <b>★</b> Comparable    | 72             | 72          | reported     | , (1011)           |
| Chinese               | At least          | Drawn from      | was used to        | Always the case  | for HBV DNA            | Indication of  | Yes (always | (retrospecti |                    |
| General               | somewhat          | the same        | ascertain          |                  | levels at baseline but | record         | the case)   | ve)          |                    |
| Practice, 70          | representative of | community       | adherence to the   |                  | HBeAg sero-status      | linkage        |             |              |                    |
|                       | the average HBV   | (same inclusion | antiviral therapy  |                  | not described. Same    | (results       |             |              |                    |
|                       | infected pregnant | and exclusion   | (decrease in viral |                  | regimen for infant     | viewed         |             |              |                    |
|                       | woman             | criteria also)  | load levels        |                  | immunoprophylaxis.     | retrospectivel |             |              |                    |
|                       |                   |                 | subsequent to the  |                  |                        | y in medical   |             |              |                    |
|                       |                   |                 | treatment)         |                  |                        | records)       |             |              |                    |
| Ren CJ (2016),        | 🛠 At least        | ★ Drawn         | ★ Valid method     | Always the       | ★★ Same HBeA₀          | 4              | ⊀ Yes       | No           | 8 (low)            |
| J Med Theor &         |                   |                 |                    |                  |                        |                |             | statement    |                    |
| Prac 74               | somewhat          | from the same   | was used to        | case             | sero-status and same   | Laboratory     |             | of LFU       |                    |
| 1 Iuc, / <del>1</del> | representative of | community       | ascertain          |                  | thresholds for HBV     | methods        |             |              |                    |
|                       | the average HBV   | (same inclusion | adherence to the   |                  | DNA level. Same        | described in   |             |              |                    |

## **B.** Chinese Language Observational Studies

|                | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   | detail (which  |       |                 |          |
|----------------|-------------------|-----------------|--------------------|------|------------|----------------------|----------------|-------|-----------------|----------|
|                | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),   |       |                 |          |
|                |                   |                 | load levels        |      |            | at birth             | indicating use |       |                 |          |
|                |                   |                 | subsequent to the  |      |            |                      | of a central   |       |                 |          |
|                |                   |                 | treatment)         |      |            |                      | laboaratory    |       |                 |          |
|                |                   |                 |                    |      |            |                      | and/or record  |       |                 |          |
|                |                   |                 |                    |      |            |                      | linkage.       |       |                 |          |
| Shen ML        | At loost          |                 | Valid mathad       | *    | Almong the | Same thresholds for  | *              | Var   | No              | 6 (high) |
| (2016), WCJD,  | r At least        |                 |                    |      | Always the | HBV DNA level but    | r              | r ies | statement       |          |
| (2010), (1002, | somewhat          | from the same   | was used to        | case |            | HBeAg sero-status    | Laboratory     |       | of LFU          |          |
| /6             | representative of | community       | ascertain          |      |            | not described.       | methods        |       |                 |          |
|                | the average HBV   | (same inclusion | adherence to the   |      |            | Regimen for infant   | described in   |       |                 |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |            | immunoprophylaxis    | detail (which  |       |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |            | at birth not clearly | assay used),   |       |                 |          |
|                |                   |                 | load levels        |      |            | described            | indicating use |       |                 |          |
|                |                   |                 | subsequent to the  |      |            |                      | of a central   |       |                 |          |
|                |                   |                 | treatment)         |      |            |                      | laboaratory    |       |                 |          |
|                |                   |                 |                    |      |            |                      | and/or record  |       |                 |          |
|                |                   |                 |                    |      |            |                      | linkage.       |       |                 |          |
| Wang DM        | 🛠 At least        | ★ Drawn         | ★ Valid method     | ☆    | Always the | <b>☆☆</b> Same HBeAg | *              | ★ Yes | No<br>statement | 8 (low)  |
| (2016),        | somewhat          | from the same   | was used to        | case |            | sero-status and same | Laboratory     |       | of LFU          |          |
| Chinese        | representative of | community       | ascertain          |      |            | thresholds for HBV   | methods        |       |                 |          |
| Hepatology,    | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      | described in   |       |                 |          |
| 79             | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   | detail (which  |       |                 |          |
| 17             | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),   |       |                 |          |
|                |                   |                 | load levels        |      |            | at birth             | indicating use |       |                 |          |
|                |                   |                 | subsequent to the  |      |            |                      | of a central   |       |                 |          |
|                |                   |                 | treatment)         |      |            |                      | laboaratory    |       |                 |          |
|                |                   |                 |                    |      |            |                      | and/or record  |       |                 |          |
|                |                   |                 |                    |      |            |                      | linkage.       |       |                 |          |

| Ge YL (2015), | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | *    | Always th  | e ★★ Same HBeAg       | No             | <b>☆</b> Yes | No        | 7 (low) |
|---------------|-------------------|-----------------|--------------------|------|------------|-----------------------|----------------|--------------|-----------|---------|
| Chin J Clin   | somewhat          | from the same   | was used to        | case |            | sero-status and same  | description    |              |           |         |
| Pharmacol, 60 | representative of | community       | ascertain          | cuse |            | thresholds for HBV    |                |              | OI LI'U   |         |
|               | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same       |                |              |           |         |
|               | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    |                |              |           |         |
|               | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     |                |              |           |         |
|               |                   | ,               | load levels        |      |            | at birth              |                |              |           |         |
|               |                   |                 | subsequent to the  |      |            |                       |                |              |           |         |
|               |                   |                 | treatment)         |      |            |                       |                |              |           |         |
| Han YP        |                   | × -             |                    |      |            |                       | No             | ×            | No        | 7 (low) |
| (2014) Habai  | At least          | → Drawn         | ✓ Valid method     | 74   | Always th  | Same HBeAg            | description    | ★ Yes        | statement | . ()    |
| (2014), Hebel | somewhat          | from the same   | was used to        | case |            | sero-status and same  |                |              | of LFU    |         |
| Medical       | representative of | community       | ascertain          |      |            | thresholds for HBV    |                |              |           |         |
| Journal, 62   | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same       |                |              |           |         |
|               | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    |                |              |           |         |
|               | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     |                |              |           |         |
|               |                   |                 | load levels        |      |            | at birth              |                |              |           |         |
|               |                   |                 | subsequent to the  |      |            |                       |                |              |           |         |
|               |                   |                 | treatment)         |      |            |                       |                |              |           |         |
| Wang W        | 🛠 At least        | 🖈 Drawn         | ★ Valid method     | *    | Always th  | Comparable for        | *              | X Ves        | No        | 7 (low) |
| (2014), Hebei | , ni loust        | , Diuvii        | , , , , und method | ,    | riiwayo ai |                       | r              | , 105        | statement |         |
| Madiaal       | somewhat          | from the same   | was used to        | case |            | HBV DNA levels        | Laboratory     |              | of LFU    |         |
| Wieulcal      | representative of | community       | ascertain          |      |            | but HBeAg sero-       | methods        |              |           |         |
| Journal, 82   | the average HBV   | (same inclusion | adherence to the   |      |            | status not described. | described in   |              |           |         |
|               | infected pregnant | and exclusion   | antiviral therapy  |      |            | Same regimen for      | detail (which  |              |           |         |
|               | woman             | criteria also)  | (decrease in viral |      |            | infant                | assay used),   |              |           |         |
|               |                   |                 | load levels        |      |            | immunoprophylaxis     | indicating use |              |           |         |
|               |                   |                 | subsequent to the  |      |            | at birth              | of a central   |              |           |         |
|               |                   |                 | treatment)         |      |            |                       | laboaratory    |              |           |         |
|               |                   |                 |                    |      |            |                       | and/or record  |              |           |         |

|  |  |   |   |                   |  | linkage.  |                          |                           |          |
|--|--|---|---|-------------------|--|---|--------------------------|---------------------------|----------|
| Zhu M (2014),                          | <b>A</b>   | *   | ★ Valid method  | な                 | Comparable for   | *   | な                        | No<br>statement           | 6 (high) |
| Hebei<br>Medicine, 88                  | At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman   | Drawn from<br>the same<br>community   | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the                               | Always the case   | HBeAg sero-status<br>but HBV DNA<br>levels not described.<br>Same regimen for<br>infant<br>immunoprophylaxis.  | Laboratory<br>assays<br>described   | Yes (always<br>the case) | of LFU                    |          |
| Zeng YM                                |  | * -   | treatment)  |                   |  | The second se   |                          | No                        | 7 (low)  |
| (2013), J Med<br>Res, 84               | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | ⊀ Always the case | Same HBeAg<br>sero-status and same<br>thresholds for HBV<br>DNA level.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not<br>described clearly | ★<br>Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage. | ⊀ Yes                    | statement<br>of LFU       | / (IOW)  |
| Zhou DS<br>(2013), Hainan<br>Med J, 87 | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | ★ Drawn from the same community (same inclusion and exclusion criteria also)                | No description  | ★ Always the case | ★ Same thresholds<br>for HBV DNA level<br>but HBeAg sero-<br>status not described.<br>Same regimen for<br>infant<br>immunoprophylaxis                  | ★<br>Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use   | ★ Yes                    | No<br>statement<br>of LFU | 6 (high) |

|  |  |  |   |      |            | at birth   | of a central   |           |  |          |
|--|--|--|---|------|------------|--|--|-----------|--|----------|
|  |  |  |   |      |            |  | laboaratory  |           |  |          |
|  |  |  |   |      |            |  | and/or record  |           |  |          |
|  |  |  |   |      |            |  | linkage.   |           |  |          |
| Jiang HX   | At least   |  | Valid method  | *    | Always the | ★★ Same HBeAg  | **   | 🕸 Vas     | No                                     | 8 (low)  |
| (2012), Chin J   | r At least   | Je Diawii  | v vand method   |      | Always the | V V Same HBeAg   |  | 1 1 1 2 3 | statement                              |          |
| Hanatal 69   | somewhat   | from the same  | was used to   | case |            | sero-status and same   | Laboratory   |           | of LFU                                 |          |
| Hepatol, 68  | representative of  | community  | ascertain   |      |            | thresholds for HBV   | methods  |           |  |          |
|  | the average HBV  | (same inclusion  | adherence to the  |      |            | DNA level. Same  | described in   |           |  |          |
|  | infected pregnant  | and exclusion  | antiviral therapy   |      |            | regimen for infant   | detail (which  |           |  |          |
|  | woman  | criteria also)   | (decrease in viral  |      |            | immunoprophylaxis  | assay used),   |           |  |          |
|  |  |  | load levels   |      |            | at birth   | indicating use   |           |  |          |
|  |  |  | subsequent to the   |      |            |  | of a central   |           |  |          |
|  |  |  | treatment)  |      |            |  | laboaratory  |           |  |          |
|  |  |  |   |      |            |  | and/or record  |           |  |          |
|  |  |  |   |      |            |  | linkage.   |           |  |          |
| Wang EJ  | ¥  |  | A   | ¥    | A.1 (1     | ATA C LIDA   | ¥  | dr v      | No                                     | 8 (low)  |
| -  | 14 AT 100 CT   |  | A Valid method  | - m  | Always the | NAME NAME HREAG  | n in   | r Yes     |  |          |
| (2012)   | At least   | P Diawii   | v vand method   | ,    | 2          | , , balle fiberig  | ,  |           | statement                              |          |
| (2012),  | somewhat   | from the same  | was used to   | case | 2          | sero-status and same   | Laboratory   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese                                       | somewhat<br>representative of  | from the same<br>community   | was used to ascertain   | case | 2          | sero-status and same<br>thresholds for HBV   | Laboratory methods   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General                            | somewhat<br>representative of<br>the average HBV                               | from the same<br>community<br>(same inclusion                                    | was used to<br>ascertain<br>adherence to the  | case | ž          | sero-status and same<br>thresholds for HBV<br>DNA level. Same  | Laboratory<br>methods<br>described in  |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant          | from the same<br>community<br>(same inclusion<br>and exclusion                   | was used to<br>ascertain<br>adherence to the<br>antiviral therapy   | case | Ĩ          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant                                  | Laboratory<br>methods<br>described in<br>detail (which   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral   | case | ŗ          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis             | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels  | case | ŗ          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the   | case | Ţ          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central   |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment)                                 | case |            | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory                              |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment)                                 | case |            | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record             |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment)                                 | case |            | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage. |           | statement<br>of LFU                    |          |
| (2012),<br>Chinese<br>General<br>Practice, 80            | somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment)                                 | case | -          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage. |           | statement<br>of LFU<br>No              | 6 (high) |
| (2012),<br>Chinese<br>General<br>Practice, 80<br>Yuan QF | <pre>representative of the average HBV infected pregnant woman</pre>           | from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment)<br>Adherence/compli<br>ance not | case | -          | sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage. | *         | statement<br>of LFU<br>No<br>statement | 6 (high) |

| Chinese          | somewhat          | the same        | data presented on  |                 | but HBV DNA level    | record         | the case)    |           |         |
|------------------|-------------------|-----------------|--------------------|-----------------|----------------------|----------------|--------------|-----------|---------|
| Manipulation     | representative of | community       | decrease in HBV    |                 | not described. Same  | linkage        |              |           |         |
| &                | the average HBV   | (same inclusion | DNA levels         |                 | regimen for infant   |                |              |           |         |
| Rehabilitation   | infected pregnant | and exclusion   |                    |                 | immunoprophylaxis.   |                |              |           |         |
| Medicine 83      | woman             | cinterna aiso)  |                    |                 |                      |                |              |           |         |
| Change VC        |                   |                 |                    |                 |                      |                |              | No        | 9 (low) |
| Cheng IC         | 🛠 At least        | <b>☆</b> Drawn  | 🛠 Valid method     | 🛠 Always the    | <b>☆☆</b> Same HBeAg | な              | ⊀ Yes        | statement | 8 (IOW) |
| (2011),          | somewhat          | from the same   | was used to        | case            | sero-status and same | Laboratory     |              | of LFU    |         |
| Zhejiang         | representative of | community       | ascertain          |                 | thresholds for HBV   | methods        |              |           |         |
| Practical        | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      | described in   |              |           |         |
| Medicine, 57     | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   | detail (which  |              |           |         |
|                  | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    | assay used),   |              |           |         |
|                  |                   |                 | load levels        |                 | at birth             | indicating use |              |           |         |
|                  |                   |                 | subsequent to the  |                 |                      | of a central   |              |           |         |
|                  |                   |                 | treatment)         |                 |                      | and/or record  |              |           |         |
|                  |                   |                 |                    |                 |                      | linkage.       |              |           |         |
| Ren YJ (2011).   | ~                 |                 | <b>N</b>           | ~               |                      | ×              |              | No        | 7 (low) |
| Hebei Medical    | 74                | 74              | ★ Valid method     | 74              | Comparable for       | 72             | 74           | statement | . ()    |
|                  | At least          | Drawn from      | was used to        | Always the case | HBeAg sero-status    | Laboratory     | Yes (always  | of LFU    |         |
| Journal, 75      | somewhat          | the same        | ascertain          |                 | but not for HBV      | assays         | the case)    |           |         |
|                  | representative of | community       | adherence to the   |                 | DNA level. Same      | described      |              |           |         |
|                  | the average HBV   |                 | antiviral therapy  |                 | regimen for infant   |                |              |           |         |
|                  | infected pregnant |                 | (decrease in viral |                 | immunoprophylaxis.   |                |              |           |         |
|                  | woman             |                 | load levels        |                 |                      |                |              |           |         |
|                  |                   |                 | treatment)         |                 |                      |                |              |           |         |
| Zhang VF         | N -               |                 | h.                 |                 |                      | No             |              | No        | 7(10w)  |
| $(2010_{\rm r})$ | ⊀ At least        | 🛠 Drawn         | ✓ Valid method     | Always the      | ⊀⊀ Same HBeAg        | description    | <b>⊀</b> Yes | statement | / (IOW) |
| (2010a),         | somewhat          | from the same   | was used to        | case            | sero-status and same | -              |              | of LFU    |         |

| Journal of      | representative of | community       | ascertain          |                 | thresholds for HBV   |                |             |                 |            |
|-----------------|-------------------|-----------------|--------------------|-----------------|----------------------|----------------|-------------|-----------------|------------|
| Practical       | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      |                |             |                 |            |
| Obstetrics and  | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   |                |             |                 |            |
| Gynecology,     | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    |                |             |                 |            |
| 86              |                   |                 | subsequent to the  |                 | ut onth              |                |             |                 |            |
| 80              |                   |                 | treatment)         |                 |                      |                |             |                 |            |
| Su TB (2009)    |                   |                 | Do not provide     |                 |                      |                |             | No              | 6 (high)   |
| Su ID (2007),   | *                 | *               | any details on     | **              | 🛠 Both HBeAg         | *              | *           | statement       | 0 (IIIgII) |
| Chinese         | At least          | Drawn from      | adherence.         | Always the case | sero-status and HBV  | Testing done   | Yes (always | of LFU          |            |
| Journal of      | somewhat          | the same        |                    |                 | DNA not described.   | centrally in   | the case)   |                 |            |
| Coal Industry   | representative of | community       |                    |                 | Same regimen for     | the hospital   |             |                 |            |
| Medicine, 77    | the average HBV   | (same inclusion |                    |                 | infant               | that study     |             |                 |            |
| ,               | infected pregnant | and exclusion   |                    |                 | immunoprophylaxis.   | staffs worked  |             |                 |            |
|                 | woman             | criteria also)  |                    |                 |                      | in.            |             |                 |            |
| Tang X          | 🛠 At least        | <b>★</b> Drawn  | ★ Valid method     | 🛠 Always the    | <b>☆☆</b> Same HBeAg | *              | ★ Yes       | No<br>statement | 8 (low)    |
| (2009), Jiangxi | somewhat          | from the same   | was used to        | case            | sero-status and same | Laboratory     |             | of LFU          |            |
| Medical         | representative of | community       | ascertain          |                 | thresholds for HBV   | methods        |             |                 |            |
| Journal, 78     | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      | described in   |             |                 |            |
|                 | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   | detail (which  |             |                 |            |
|                 | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    | assay used),   |             |                 |            |
|                 |                   |                 | load levels        |                 | at birth             | indicating use |             |                 |            |
|                 |                   |                 | subsequent to the  |                 |                      | of a central   |             |                 |            |
|                 |                   |                 | treatment)         |                 |                      | laboaratory    |             |                 |            |
|                 |                   |                 |                    |                 |                      | and/or record  |             |                 |            |
|                 |                   |                 |                    |                 |                      | linkage.       |             |                 |            |
| Feng HF         | 🖈 At least        | 🛠 Drawn         | 🛠 Valid method     | 🛠 Always the    | <b>☆☆</b> Same HBeAg | 4              | ★ Yes       | No              | 8 (low)    |
| (2007), J Appl  | somewhat          | from the same   | was used to        | case            | sero-status and same | Laboratory     |             | statement       |            |
| Clin Pediatr,   | representative of | community       | ascertain          | cube            | thresholds for HBV   | methods        |             | OI LFU          |            |

| 58            | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      | described in   |             |           |         |
|---------------|-------------------|-----------------|--------------------|-----------------|----------------------|----------------|-------------|-----------|---------|
|               | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   | detail (which  |             |           |         |
|               | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    | assay used),   |             |           |         |
|               |                   |                 | load levels        |                 | at birth             | indicating use |             |           |         |
|               |                   |                 | subsequent to the  |                 |                      | of a central   |             |           |         |
|               |                   |                 | treatment)         |                 |                      | laboaratory    |             |           |         |
|               |                   |                 |                    |                 |                      | and/or record  |             |           |         |
|               |                   |                 |                    |                 |                      | linkage.       |             |           |         |
| Li G (2006),  | *                 | *               | ★ Valid method     | *               | Comparable           | *              | *           | *         | 8 (low) |
| Journal of    | At least          | Drawn from      | was used to        | Always the case | HBala sero status    | Laboratory     | Vac (always | IEU       |         |
| Wenzhou       | somewhat          | the same        | ascertain          | Aiways the ease | hut HBV DNA          | Laboratory     | the case)   | reported  |         |
| Medical       | representative of | community       | adherence to the   |                 | levels not described | described      | the ease)   | and <20%  |         |
|               | the average HBV   | (same inclusion | antiviral therapy  |                 | Same regimen for     | described      |             | I EU in   |         |
| College, 69   | infected pregnant | and exclusion   | (decrease in viral |                 | infant               |                |             | both      |         |
|               | woman             | criteria also)  | load levels        |                 | immunoprophylavis    |                |             | treatment |         |
|               | woman             | cinteria also)  | subsequent to the  |                 | minunopropriytaxis.  |                |             | group and |         |
|               |                   |                 | treatment)         |                 |                      |                |             | control   |         |
|               |                   |                 | treatment)         |                 |                      |                |             | group     |         |
| L: WE (2006)  |                   |                 |                    |                 |                      |                |             | No        | 8 (low) |
| LI WF (2000), | 🖈 At least        | 🛠 Drawn         | 🛠 Valid method     | 🛠 Always the    | <b>☆☆</b> Same HBeAg | Laboratory     | ⊀ Yes       | statement | 8 (IOW) |
| Chinese       | somewhat          | from the same   | was used to        | case            | sero-status and same | methods        |             | of I FU   |         |
| Hepatology,   | representative of | community       | ascertain          |                 | thresholds for HBV   | described in   |             | of Li C   |         |
| 71            | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      | detail (which  |             |           |         |
|               | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   | assay used),   |             |           |         |
|               | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    | indicating use |             |           |         |
|               |                   |                 | load levels        |                 | at birth             | of a central   |             |           |         |
|               |                   |                 | subsequent to the  |                 |                      | laboaratory    |             |           |         |
|               |                   |                 | treatment)         |                 |                      | and/or record  |             |           |         |
|               |                   |                 |                    |                 |                      | linkage.       |             |           |         |

| Ma J (2006),    | *                 | *               | ★ Valid method     | *               | Comparable HBeAg     | *                   | 4              | No        | 6 (high) |
|-----------------|-------------------|-----------------|--------------------|-----------------|----------------------|---------------------|----------------|-----------|----------|
| China Practical | At least          | Drawn from      | was used to        | Always the case | sero-status but HBV  | Laboratory          | Ves (always    | statement |          |
| Medical, 72     | somewhat          | the same        | ascertain          | riways the case | DINA levels not      | assavs              | the case)      | OI LFU    |          |
|                 | representative of | community       | adherence to the   |                 | for infort           | described           | une euse)      |           |          |
|                 | the average HBV   | (same inclusion | antiviral therapy  |                 | ior miant            | desenteed           |                |           |          |
|                 | infected pregnant | and exclusion   | (decrease in viral |                 | immunoprophylaxis    |                     |                |           |          |
|                 | woman             | criteria also)  | load levels        |                 | not described        |                     |                |           |          |
|                 | woman             | enteria aiso)   | subsequent to the  |                 |                      |                     |                |           |          |
|                 |                   |                 | treatment)         |                 |                      |                     |                |           |          |
| Here 711        |                   |                 | treatment)         |                 |                      |                     |                | No        | Q (1)    |
| Han ZH          | 🖈 At least        | 🗱 Drawn         | 🛠 Valid method     | 🖈 Always the    | <b>☆☆</b> Same HBeAg | <b>★</b> Laboratory | 🛠 Yes          | statement | 8 (IOW)  |
| (2005), Chin J  | somewhat          | from the same   | was used to        | case            | sero-status and same | methods             |                | of I FU   |          |
| Intern Med, 63  | representative of | community       | ascertain          |                 | thresholds for HBV   | described in        |                | of Li C   |          |
|                 | the average HBV   | (same inclusion | adherence to the   |                 | DNA level. Same      | detail (which       |                |           |          |
|                 | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   | assay used),        |                |           |          |
|                 | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    | indicating use      |                |           |          |
|                 |                   | ,               | load levels        |                 | at birth             | of a central        |                |           |          |
|                 |                   |                 | subsequent to the  |                 |                      | laboaratory         |                |           |          |
|                 |                   |                 | treatment)         |                 |                      | and/or record       |                |           |          |
|                 |                   |                 | ,                  |                 |                      | linkage.            |                |           |          |
| Wang TM         |                   | <u>۲</u>        |                    |                 |                      | No                  |                | No        | 6 (high) |
| (2005)          | At least          | 🗚 Drawn         | ✓ Valid method     | Always the      | ★ Same HBeAg         | description         | <b>≯</b> ¥ Yes | statement | ° (g)    |
| (2005),         | somewhat          | from the same   | was used to        | case            | sero-status but HBV  | 1                   |                | of LFU    |          |
| Chinese         | representative of | community       | ascertain          |                 | DNA level not        |                     |                |           |          |
| Journal of      | the average HBV   | (same inclusion | adherence to the   |                 | described. Same      |                     |                |           |          |
| Eugenics and    | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant   |                     |                |           |          |
| Constine 91     | woman             | criteria also)  | (decrease in viral |                 | immunoprophylaxis    |                     |                |           |          |
| Genetics, 81    |                   |                 | load levels        |                 | at birth             |                     |                |           |          |
|                 |                   |                 | subsequent to the  |                 |                      |                     |                |           |          |
|                 |                   |                 | treatment)         |                 |                      |                     |                |           |          |

### LDT 600 mg

### A. English Language Observational Studies

|              |                |                 |                   | Demonstration    |                        |                    | Was follow- |                  | Total              |
|--------------|----------------|-----------------|-------------------|------------------|------------------------|--------------------|-------------|------------------|--------------------|
|              | Representa     | Selection of    |                   | that outcome of  | Comparability of       |                    | up long     |                  | number             |
| Study        | tive-ness of   | the non-        |                   | interest was     | cohorts on the basis   |                    | enough for  | Adequacy of      | of stars           |
| (year),      | the exposed    | exposed         | Ascertainment     | not present at   | of the design or       | Assessment of      | outcomes    | follow up of     | (risk of           |
| journal, No. | cohort         | cohort          | of exposure       | baseline         | analysis               | outcomes           | occur       | cohorts          | bias) <sup>a</sup> |
| Zhang H,     | *              | *               | 4                 | 衣<br>文           | <b>衣</b> 衣             | 衣<br>文             | <b>Å</b>    | 衣<br>文           | 9                  |
| (2014),      | At least       | Drawn from      | Monthly HBV       | Always the case  | Comparable for HBV     | Describes testing  | Ves         | LEU reported and | (low)              |
| Hepatology,  | somewhat       | the same        | DNA level testing | Thiways the case | DNA level and          | done and refers to | 103         | 20% LEU in all   |                    |
| 85           | representative | community       | was done to check |                  | comparable HBeAg       | a central          |             | treatment and    |                    |
| 05           | of the average | (same inclusion | maternal          |                  | positive Same regimen  | laboratory         |             | control groups   |                    |
|              | HBV infected   | and exclusion   | adherence         |                  | for infant             | amployed for this  |             | control groups   |                    |
|              | pregnant       | criteria also)  | adherence         |                  | immunoprophylaxis      | study              |             |                  |                    |
|              | woman          | cinena aiso)    |                   |                  |                        | study.             |             |                  |                    |
| Har CD       | woman          |                 |                   |                  |                        |                    |             |                  | 0                  |
| Hall GK,     | *              | *               | 4                 | *                | **                     | *                  | *           | *                | 9                  |
| (2015), J    | At least       | Drawn from      | Regular testing   | Always the case  | Comparable for HBV     | Describes test     | Yes         | LFU reported and | (low)              |
| Viral Hepat, | somewhat       | the same        | (and pre-delivery |                  | DNA level and          | assays used for    |             | <20% LFU in all  |                    |
| 120          | representative | community       | testing) of HBV   |                  | comparable HBeAg       | HBsAg and HBV      |             | treatment and    |                    |
|              | of the average | (same inclusion | DNA levels were   |                  | positive. Same regimen | DNA of infants     |             | control groups   |                    |
|              | HBV infected   | and exclusion   | done in mothers   |                  | for infant             | and describes that |             |                  |                    |
|              | pregnant       | criteria also)  | and each treated  |                  | immunoprophylaxis      | samples were       |             |                  |                    |
|              | woman          |                 | mother had at     |                  |                        | taken by study     |             |                  |                    |
|              |                |                 | least a 3-log     |                  |                        | personnel          |             |                  |                    |
|              |                |                 | decrease in HBV   |                  |                        | themselves         |             |                  |                    |
|              |                |                 | DNA level prior   |                  |                        | (meaning they      |             |                  |                    |
|              |                |                 | to delivery.      |                  |                        | would have direct  |             |                  |                    |

|             |                |                 |                    |                 |                          | linkage to results) |          |                       |        |
|-------------|----------------|-----------------|--------------------|-----------------|--------------------------|---------------------|----------|-----------------------|--------|
| Liu CP,     | 4              | Many more       | Some limited data  | な               | *                        | 4                   | 4        | No loss to follow-up  | 5      |
| $(2015)^3$  | , ,            | women in the    | presented on       | ,               |                          |                     | <b>,</b> | described because it  | (high) |
| ()          | At least       | control group   | decrease of        | Always the case | HBV DNA level and/or     | Laboratory          | Yes      | was a retrospective   | (8/    |
|             | somewhat       | when compared   | maternal viral     |                 | HBeAg not described for  | assays described,   |          | cohort study (or      |        |
|             | representative | to the treated  | load, but no       |                 | both treated and control | with indication of  |          | listed as such) where |        |
|             | of the average | group – this    | mention of linking |                 | groups. Similar infant   | record linkage      |          | the infants needed to |        |
|             | HBV infected   | could indicate  | this with          |                 | prophylaxis between      | (results viewed     |          | have had test results |        |
|             | pregnant       | dissimilarity   | compliance/adher   |                 | treated and control      | retrospectively in  |          | at the testing        |        |
|             | woman          | between the two | ence/time on       |                 | groups.                  | medical records)    |          | timepoint (this is    |        |
|             |                | groups          | treatment, and no  |                 |                          |                     |          | therefore             |        |
|             |                |                 | detailed results   |                 |                          |                     |          | misclassified as a    |        |
|             |                |                 | provided.          |                 |                          |                     |          | cohort study, and     |        |
|             |                |                 |                    |                 |                          |                     |          | has a high risk of    |        |
|             |                |                 |                    |                 |                          |                     |          | bias for loss to      |        |
|             |                |                 |                    |                 |                          |                     |          | follow-up)            |        |
| Wu QX,      | 4              | 4               | 4                  | *               | 女女                       | 4                   | *        | <80% follow-up for    | 8      |
| (2015).     |                |                 |                    |                 |                          |                     |          | both treated and      | (low)  |
| (linical    | At least       | Drawn from      | Fairly detailed    | Always the case | Comparable for HBV       | Laboratory          | Yes      | control groups        | (10)   |
| Clinical    | somewhat       | the same        | data provided on   |                 | DNA level and            | assays described    |          |                       |        |
| Gastroenter | representative | community       | maternal viral     |                 | comparable HBeAg         | in detail with      |          |                       |        |
| ology and   | of the average | (same inclusion | load decrease.     |                 | positive. Same regimen   | indication that     |          |                       |        |
| Hepatology  | HBV infected   | and exclusion   | >80% of women      |                 | for infant               | testing (and        |          |                       |        |
| 1.00        | pregnant       | criteria also)  | taking treatment   |                 | immunoprophylaxis.       | viewing of          |          |                       |        |
| 160         | woman          |                 | had >2 log         |                 |                          | medical records,    |          |                       |        |
|             |                |                 | decrease in viral  |                 |                          | was done by study   |          |                       |        |
|             |                |                 | load compared to   |                 |                          | personnel)          |          |                       |        |
|             |                |                 | none of the        |                 |                          |                     |          |                       |        |

<sup>&</sup>lt;sup>3</sup> Liu CP, Zeng YL, Zhou M, et al. Factors Associated with Mother-to-child Transmission of Hepatitis B Virus Despite Immunoprophylaxis. *Intern Med* 2015; **54(7)**: 711-716.

|            |                |                  | controls.          |                 |   |                      |          |                      |          |
|------------|----------------|------------------|--------------------|-----------------|---|----------------------|----------|----------------------|----------|
| Liu Y,     | *              | *                | Some limited data  | *               | *   | *                    | <b>4</b> | Loss to follow-up    | 6        |
| (2016),    | ,              | ,                | presented on       | ,               | ,   | ,                    | r        | not mentioned and    | (high)   |
| Ueneteleev | At least       | Drawn from       | decrease of        | Always the case | HBV DNA level and   | Laboratory assays    | Yes      | flow-chart of        |          |
| Hepatology | somewhat       | the same         | maternal viral     |                 | HBeAg comparable  | described in detail  |          | patients not given.  |          |
| Research,  | representative | community        | load, but no       |                 | between treated and non   | with indication      |          | This may indicate    |          |
| 139        | of the average | (same inclusion  | mention of linking |                 | treated groups. Infant  | that testing (and    |          | omitting of loss to  |          |
|            | HBV infected   | and exclusion    | this with          |                 | immunoprophylaxis not   | viewing of           |          | follow-up details    |          |
|            | pregnant       | criteria also)   | compliance/adher   |                 | described clearly (no   | medical records,     |          | rather than perfect  |          |
|            | woman          |                  | ence/time on       |                 | timing of HBIg).  | was done by study    |          | (100%) retention,    |          |
|            |                |                  | treatment, and no  |                 |   | personnel)           |          | and does not allow   |          |
|            |                |                  | detailed results   |                 |   |                      |          | one to assume the    |          |
|            |                |                  | provided.          |                 |   |                      |          | latter.              |          |
| Tan Z,     | 47             | None (Arm 1)     | Adherence or       | *               | +x (A mm 1) +x +x (A mm 2)  | *                    | 4        | *                    | 6 (high) |
| (2016)     |                | ₹ (Amm 2)        | compliance to      | r               | $\mathbf{P}(\operatorname{AIII} 1) = \mathbf{P}(\operatorname{AIII} 2)$ |                      | ~        |                      | (Arm 1)  |
| (2010),    | Truly          | r (Anii 2)       | treatment not      | Always the case | Comparable for HBV  | Lab testing done     | Yes      | >80% follow-up in    |          |
| Medicine,  | representative | For arm 2 it is  | examined, little   |                 | DNA level and   | centrally as part of |          | across all treatment | 8 (low)  |
| 152        | of the average | drawn from the   | data on tracking   |                 | comparable HBeAg  | the study,           |          | arms and control     | (Arm 2)  |
|            | HBV infected   | same             | of viral load      |                 | positive for the second   | laboratory assays    |          | groups.              |          |
|            | pregnant       | community        | decrease.          |                 | treatment arm compared  | for defining infant  |          |                      |          |
|            | woman          | (same inclusion  |                    |                 | to the control arm. For   | outcome              |          |                      |          |
|            |                | and exclusion    |                    |                 | the first arm of the study  | described.           |          |                      |          |
|            |                | criteria also).  |                    |                 | they are not comparable.  |                      |          |                      |          |
|            |                | However, arm 1   |                    |                 | Same regimen for infant   |                      |          |                      |          |
|            |                | is not           |                    |                 | immunoprophylaxis.  |                      |          |                      |          |
|            |                | comparable       |                    |                 |   |                      |          |                      |          |
|            |                | with the control |                    |                 |   |                      |          |                      |          |
|            |                | group.           |                    |                 |   |                      |          |                      |          |
| Chen ZX,   | *              | *                | Adherence/compli   | *               | 4   | 4                    | 4        | Loss to follow-up    | 6        |
| (2017) I   |                |                  | ance not           | <i>v</i> ^      |   |                      | r        | not mentioned and    | (high)   |
| (_017), 5  | At least       | Drawn from the   | mentioned and no   | Always the case | Comparable for HBV  | Lab testing done     | Yes      | flow-chart of        | (        |

| infect, 111 | somewhat       | same            | data presented on  |                 | DNA level but more than  | centrally as part of |     | patients not given.  |         |
|-------------|----------------|-----------------|--------------------|-----------------|--------------------------|----------------------|-----|----------------------|---------|
|             | representative | community       | decrease in HBV    |                 | 10% points different for | the study,           |     | This may indicate    |         |
|             | of the average | (same inclusion | DNA levels         |                 | HBeAg positive. Same     | laboratory assays    |     | omitting of loss to  |         |
|             | HBV infected   | and exclusion   |                    |                 | regimen for infant       | for defining infant  |     | follow-up details    |         |
|             | pregnant       | criteria also)  |                    |                 | immunoprophylaxis        | outcome              |     | rather than perfect  |         |
|             | woman          |                 |                    |                 |                          | described.           |     | (100%) retention,    |         |
|             |                |                 |                    |                 |                          |                      |     | and does not allow   |         |
|             |                |                 |                    |                 |                          |                      |     | one to assume the    |         |
|             |                |                 |                    |                 |                          |                      |     | latter.              |         |
| Sun W,      | 47             | 4               | ¥                  | *               | **                       | Laboratory assays    | *   | Loss to follow-up    | 7       |
| (2017)      |                |                 |                    |                 |                          | used not well        | ~   | not mentioned and    | (low)   |
|             | At least       | Drawn from the  | HBV DNA            | Always the case | Comparable for HBV       | described            | Yes | flow-chart of        | (10 11) |
| BMC         | somewhat       | same            | changes specified  |                 | DNA level and            |                      |     | patients not given.  |         |
| Gastroenter | representative | community with  | with some detai.   |                 | comparable HBeAg         |                      |     | This may indicate    |         |
| ology, 148  | of the average | same inclusion  | ~7 log decrease in |                 | positive. Same regimen   |                      |     | omitting of loss to  |         |
|             | HBV infected   | and exclusion   | both treatment     |                 | for infant               |                      |     | follow-up details    |         |
|             | pregnant       | criteria.       | groups compared    |                 | immunoprophylaxis        |                      |     | rather than perfect  |         |
|             | woman          | Mentions        | to the control     |                 |                          |                      |     | (100%) retention,    |         |
|             |                | allocation of   | group.             |                 |                          |                      |     | and does not allow   |         |
|             |                | women into      |                    |                 |                          |                      |     | one to assume the    |         |
|             |                | three groups    |                    |                 |                          |                      |     | latter.              |         |
| He T,       | *              | 4               | *                  | *               | 44                       | 4                    | 4   | Retrospective cohort | 8       |
| (2018).     | ,              | ,               | ŗ                  | ,               | , ,                      | ,                    | r   | mentioned but no     | (low)   |
| Honotol Int | At least       | Drawn from the  | Detailed           | Always the case | Comparable for HBV       | Linkage to           | Yes | loss to follow-up    |         |
| nepator mi, | somewhat       | same            | information on     |                 | DNA level and            | medical records      |     | described, no        |         |
| 64          | representative | community with  | reduction of viral |                 | comparable HBeAg         |                      |     | mention of how       |         |
|             | of the average | same inclusion  | load given,        |                 | positive. Same regimen   |                      |     | there was perfect    |         |
|             | HBV infected   | and exclusion   | including specific |                 | for infant               |                      |     | retention.           |         |
|             | pregnant       | criteria.       | data for each      |                 | immunoprophylaxis        |                      |     |                      |         |
|             | woman          |                 | women (every one   |                 |                          |                      |     |                      |         |
|             |                |                 | had a -6 to -8 log |                 |                          |                      |     |                      |         |

|              |                |                | reduction)         |                 |                         |                      |     |                     |         |
|--------------|----------------|----------------|--------------------|-----------------|-------------------------|----------------------|-----|---------------------|---------|
| Hu Y,        | な              | 4              | 4                  | な               | 女女                      | 4                    | な   | Only ~70 % follow-  | 8       |
| (2018), J    |                | ,              |                    |                 |                         | ,                    |     | up between 7 to 12  | (low)   |
| Viral Hapat  | At least       | Drawn from     | Detailed info on   | Always the case | Comparable for HBV      | Lab testing done     | Yes | months (although    | ` ´ ´   |
| vitat Hepat, | somewhat       | the same       | reduction of viral |                 | DNA level and           | centrally as part of |     | some others were    |         |
| 128          | representative | community with | load given, only   |                 | comparable HBeAg        | the study,           |     | included and tested |         |
|              | of the average | same inclusion | ~5% of women in    |                 | positive. Same regimen  | laboratory assays    |     | at 13-14 months     |         |
|              | HBV infected   | and exclusion  | the treated group  |                 | for infant              | for defining infant  |     | not actually        |         |
|              | pregnant       | criteria.      | did not have a     |                 | immunoprophylaxis       | outcome              |     | completely lost to  |         |
|              | woman          |                | reduction below    |                 |                         | described.           |     | follow-up)          |         |
|              |                |                | 2x10^7 log         |                 |                         |                      |     |                     |         |
| Sheng QJ,    | *              | *              | *                  | *               | **                      | *                    | *   | *                   | 9       |
| (2018a), Int |                | ,              |                    |                 |                         | ,                    |     | ,                   | (low)   |
| I mad Sai    | At least       | Drawn from     | Mentions careful   | Always the case | Comparable for HBV      | Lab testing done     | Yes | >80% follow-up in   | Ì Í     |
| J med Sci,   | somewhat       | the same       | monitoring of      |                 | DNA level and           | centrally as part of |     | both treatment and  |         |
| 145          | representative | community with | HBV DNA level      |                 | comparable HBeAg        | the study,           |     | control group       |         |
|              | of the average | same inclusion | for checking       |                 | positive. Same regimen  | laboratory assays    |     |                     |         |
|              | HBV infected   | and exclusion  | maternal           |                 | for infant              | for defining infant  |     |                     |         |
|              | pregnant       | criteria.      | adherence/changin  |                 | immunoprophylaxis       | outcome              |     |                     |         |
|              | woman          |                | g treatment        |                 |                         | described.           |     |                     |         |
|              |                |                | regimen when       |                 |                         |                      |     |                     |         |
|              |                |                | needed.            |                 |                         |                      |     |                     |         |
| Sheng QJ,    | *              | 4              | 4                  | 4               | 4                       | 4                    | *   | No description of   | 7       |
| (2018b)      |                |                |                    |                 |                         |                      |     | any loss to follow- | (low)   |
| (20100),     | At least       | Drawn from     | Mentions that all  | Always the case | Comparable for HBV      | Lab testing done     | Yes | up or confirmation  | (10 11) |
| Medicine,    | somewhat       | the same       | treated women      |                 | DNA level. HBeAg        | centrally as part of |     | that there was no   |         |
| 147          | representative | community with | received 8 weeks   |                 | comparability not clear | the study,           |     | loss-to-follow-up.  |         |
|              | of the average | same inclusion | of therapy.        |                 | as they only give the   | laboratory assays    |     |                     |         |
|              | HBV infected   | and exclusion  | Provides detailed  |                 | proportion overall of   | for defining infant  |     |                     |         |
|              | pregnant       | criteria.      | information on     |                 | women who were          | outcome              |     |                     |         |
|              | woman          |                | decrease in HBV    |                 | HBeAg positive. Same    | described.           |     |                     |         |
| 1            | 1              | 1              | 1                  | 1               |                         | 1                    | 1   | 1                   | 1       |

|  | DNA level for   | regimen   | for     | infant |  |  |
|--|-----------------|-----------|---------|--------|--|--|
|  | treated cohort. | immunopro | ophylax | cis    |  |  |

|   |  |   |   | Demonstration     | Comparability of   |  | Was follow- |                           |                    |
|---|--|---|---|-------------------|--|--|-------------|---------------------------|--------------------|
|   |  | Selection of  |   | that outcome of   | cohorts on the   |  | up long     | Adequacy                  | Total              |
|   | Representative   | the non-  |   | interest was not  | basis of the   |  | enough for  | of follow                 | number of          |
| Study (year),   | -ness of the   | exposed   | Ascertainment   | present at        | design or  | Assessment   | outcomes    | up of                     | stars (risk of     |
| journal, No.  | exposed cohort   | cohort  | of exposure   | baseline          | analysis   | of outcomes  | occur       | cohorts                   | bias) <sup>a</sup> |
| Tan J, (2019),<br>J Prac Hepatol,<br>151                                    | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | ★     Valid       method was used     to       to     ascertain       adherence     to the       antiviral     therapy       (decrease     in viral       load     levels       subsequent     to the       treatment)     to the | Always the case   | Comparable for<br>HBV DNA levels at<br>baseline but HBeAg<br>sero-status not<br>described. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | ↓<br>Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory | ★ Yes       | No<br>statement<br>of LFU | 7 (low)            |
|   |  |   |   |                   |  | and/or record<br>linkage.  |             |                           |                    |
| Chen QR,<br>(2018),<br>Maternal and<br>Child Health<br>Care of China,<br>56 | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | No description  | ★ Always the case | ★★SameHBeAgsero-statusandcomparableHBV DNA levels atbaseline.baseline.Sameregimenforinfantimmunoprophylaxisat birth                                    | No<br>description  | ¥ Yes       | No<br>statement<br>of LFU | 6 (high)           |
| DingXP,(2018), HealthResearch, 116  | ★ At least somewhat  | ★ Drawn from the same   | ★ Valid method was used to  | Always the        | <b>★</b> ★ Same<br>HBeAg sero-status   | No<br>description  | ★ Yes       | No<br>statement<br>of LFU | 7 (low)            |

#### **B.** Chinese Language Observational Studies

|                | representative of | community       | ascertain          |      |              | and compar      | rable  |                   |             |                 |          |
|----------------|-------------------|-----------------|--------------------|------|--------------|-----------------|--------|-------------------|-------------|-----------------|----------|
|                | the average HBV   | (same inclusion | adherence to the   |      |              | HBV DNA leve    | els at |                   |             |                 |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |              | baseline. S     | Same   |                   |             |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |              | regimen for in  | nfant  |                   |             |                 |          |
|                |                   |                 | load levels        |      |              | immunoprophyla  | axis   |                   |             |                 |          |
|                |                   |                 | subsequent to the  |      |              | at birth        |        |                   |             |                 |          |
|                |                   |                 | treatment)         |      |              |                 |        |                   |             |                 |          |
| Li ZY, (2018), | *                 | な               | 🛠 Valid method     | *    |              | XX Compar       | rable  | <b>À</b>          | *           | None            | 8 (low)  |
| Drug           | <b>V</b>          | ,               | v vand method      | ,    |              | , , Compar      | rabic  |                   | ,           | reported        |          |
| Evaluation     | At least          | Drawn from      | was used to        | Alwa | ays the case | for HBeAg s     | sero-  | Indication of     | Yes (always | (retrospecti    |          |
| Evaluation     | somewhat          | the same        | ascertain          |      |              | status and H    | HBV    | record            | the case)   | ve)             |          |
| Research, 135  | representative of | community       | adherence to the   |      |              | DNA level. S    | Same   | linkage           |             |                 |          |
|                | the average HBV   | (same inclusion | antiviral therapy  |      |              | regimen for in  | nfant  | (results          |             |                 |          |
|                | infected pregnant | and exclusion   | (decrease in viral |      |              | immunoprophyla  | axis.  | viewed            |             |                 |          |
|                | woman             | criteria also)  | load levels        |      |              |                 |        | retrospectivel    |             |                 |          |
|                |                   |                 | subsequent to the  |      |              |                 |        | y in medical      |             |                 |          |
|                |                   |                 | treatment)         |      |              |                 |        | records)          |             |                 |          |
| Tian JH,       | 🛠 At least        | Drawn           | No description     | *    | Always the   | <b>☆☆</b> s     | Same   | *                 | ★ Yes       | No<br>statement | 7 (low)  |
| (2018), Ciiiia | somewhat          | from the same   |                    | case |              | threshold for H | HBV    | Laboratory        |             | of LFU          |          |
| & Foreign      | representative of | community       |                    |      |              | DNA level and s | same   | methods           |             |                 |          |
| Medical        | the average HBV   | (same inclusion |                    |      |              | HBeAg sero-st   | tatus  | described in      |             |                 |          |
| Treatment, 153 | infected pregnant | and exclusion   |                    |      |              | used. Same regi | imen   | detail (which     |             |                 |          |
|                | woman             | criteria also)  |                    |      |              | for in          | nfant  | assay used),      |             |                 |          |
|                |                   |                 |                    |      |              | immunoprophyla  | axis   | indicating use    |             |                 |          |
|                |                   |                 |                    |      |              | at birth        |        | of a central      |             |                 |          |
|                |                   |                 |                    |      |              |                 |        | laboaratory       |             |                 |          |
|                |                   |                 |                    |      |              |                 |        | and/or record     |             |                 |          |
|                |                   |                 |                    |      |              |                 |        | linkage.          |             |                 |          |
| Zhang BF,      | 🛠 At least        | <b>≯</b> Drawn  | ★ Valid method     | *    | Always the   | ★ Same HB       | BeAg   | No<br>description | ★ Yes       | No<br>statement | 6 (high) |

| (2018), Chin J | somewhat          | from the same   | was used to        | case |            | sero-status but      |                   |       | of LFU          |         |
|----------------|-------------------|-----------------|--------------------|------|------------|----------------------|-------------------|-------|-----------------|---------|
| Hepatol, 43    | representative of | community       | ascertain          |      |            | different thresholds |                   |       |                 |         |
| <b>I</b> , -   | the average HBV   | (same inclusion | adherence to the   |      |            | for HBV DNA level.   |                   |       |                 |         |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |            | Same regimen for     |                   |       |                 |         |
|                | woman             | criteria also)  | (decrease in viral |      |            | infant               |                   |       |                 |         |
|                |                   |                 | load levels        |      |            | immunoprophylaxis    |                   |       |                 |         |
|                |                   |                 | subsequent to the  |      |            | at birth             |                   |       |                 |         |
|                |                   |                 | treatment)         |      |            |                      |                   |       |                 |         |
| Zhang GH,      | 🖈 At least        | 🖈 Drawn         | ★ Valid method     | *    | Always the | <b>☆☆</b> Same       | No<br>description | ★ Yes | No<br>statement | 7 (low) |
| (2018), China  | somewhat          | from the same   | was used to        | case |            | HBeAg sero-status    | <u>1</u>          |       | of LFU          |         |
| Health Care &  | representative of | community       | ascertain          |      |            | and same thresholds  |                   |       |                 |         |
| Nutrition, 166 | the average HBV   | (same inclusion | adherence to the   |      |            | for HBV DNA level.   |                   |       |                 |         |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |            | Same regimen for     |                   |       |                 |         |
|                | woman             | criteria also)  | (decrease in viral |      |            | infant               |                   |       |                 |         |
|                |                   |                 | load levels        |      |            | immunoprophylaxis    |                   |       |                 |         |
|                |                   |                 | subsequent to the  |      |            | at birth             |                   |       |                 |         |
|                |                   |                 | treatment)         |      |            |                      |                   |       |                 |         |
| Zheng JC,      | 🛠 At least        | <b>☆</b> Drawn  | No description     | *    | Always the | <b>☆☆</b> Same       | *                 | ⊀ Yes | No              | 7 (low) |
| (2018), China  | somewhat          | from the same   |                    | case |            | HBeAg sero-status    | Laboratory        |       | of I FU         |         |
| Rural          | representative of | community       |                    |      |            | and same thresholds  | methods           |       | of Li C         |         |
| Medicine, 171  | the average HBV   | (same inclusion |                    |      |            | for HBV DNA level.   | described in      |       |                 |         |
|                | infected pregnant | and exclusion   |                    |      |            | Same regimen for     | detail (which     |       |                 |         |
|                | woman             | criteria also)  |                    |      |            | infant               | assay used),      |       |                 |         |
|                |                   |                 |                    |      |            | immunoprophylaxis    | indicating use    |       |                 |         |
|                |                   |                 |                    |      |            | at birth             | of a central      |       |                 |         |
|                |                   |                 |                    |      |            |                      | laboaratory       |       |                 |         |
|                |                   |                 |                    |      |            |                      | and/or record     |       |                 |         |
|                |                   |                 |                    |      |            |                      | linkage.          |       |                 |         |
| Chen WJ,     | 🖈 At least        | <b>★</b> Drawn  | ★ Valid method     | *    | Always | the | **        | Same        | *              | <b>☆</b> Yes | No        | 8 (low) |
|--------------|-------------------|-----------------|--------------------|------|--------|-----|-----------|-------------|----------------|--------------|-----------|---------|
| (2017),      | comparished       | from the come   | was used to        | 0000 | -      |     | IID a A a | core status | Laboratory     |              | statement |         |
| Shandong     | somewhat          | community       | was used to        | case |        |     | and same  | thresholds  | methods        |              | of LFU    |         |
| Medicine 30  | the average HBV   | (same inclusion | adherence to the   |      |        |     | for HBV   | DNA level   | described in   |              |           |         |
| Wedlenie, 50 | infected pregnant | and exclusion   | antiviral therapy  |      |        |     | Same re   | orimen for  | detail (which  |              |           |         |
|              | woman             | criteria also)  | (decrease in viral |      |        |     | infant    | gimen ioi   | assay used)    |              |           |         |
|              | woman             | cinterna aiso)  | load levels        |      |        |     | immunon   | rophylaxis  | indicating use |              |           |         |
|              |                   |                 | subsequent to the  |      |        |     | at birth  | торнуваль   | of a central   |              |           |         |
|              |                   |                 | treatment)         |      |        |     | at onth   |             | laboaratory    |              |           |         |
|              |                   |                 | treatment)         |      |        |     |           |             | and/or record  |              |           |         |
|              |                   |                 |                    |      |        |     |           |             | linkage        |              |           |         |
| Eang VM      |                   |                 |                    |      |        |     |           |             | iiiikuge.      |              | No        | 9 (low) |
| reng Aw,     | 🛠 At least        | 🖈 Drawn         | ✤ Valid method     | *    | Always | the | 44        | Same        | *              | 🛠 Yes        | statement | 8 (IOW) |
| (2017),      | somewhat          | from the same   | was used to        | case |        |     | HBeAg     | sero-status | Laboratory     |              | of LEU    |         |
| Clinical     | representative of | community       | ascertain          |      |        |     | and same  | thresholds  | methods        |              | of Er C   |         |
| Research and | the average HBV   | (same inclusion | adherence to the   |      |        |     | for HBV   | DNA level.  | described in   |              |           |         |
| Practice 118 | infected pregnant | and exclusion   | antiviral therapy  |      |        |     | Same re   | gimen for   | detail (which  |              |           |         |
| 1140400, 110 | woman             | criteria also)  | (decrease in viral |      |        |     | infant    |             | assay used),   |              |           |         |
|              |                   |                 | load levels        |      |        |     | immunop   | rophylaxis  | indicating use |              |           |         |
|              |                   |                 | subsequent to the  |      |        |     | at birth  |             | of a central   |              |           |         |
|              |                   |                 | treatment)         |      |        |     |           |             | laboaratory    |              |           |         |
|              |                   |                 |                    |      |        |     |           |             | and/or record  |              |           |         |
|              |                   |                 |                    |      |        |     |           |             | linkage.       |              |           |         |
| Huang Q,     | At least          |                 | Valid mathed       | *    | Alwova | the | 4747      | Sama        | No             | ⊀ Vas        | No        | 7 (low) |
| (2017)       | P At least        | r Diawii        | r vand method      |      | Always | the |           | Same        | description    | r ies        | statement |         |
| (2017),      | somewhat          | from the same   | was used to        | case |        |     | HBeAg     | sero-status |                |              | of LFU    |         |
| Qingnai      | representative of | community       | ascertain          |      |        |     | and same  | thresholds  |                |              |           |         |
| Medical      | the average HBV   | (same inclusion | adherence to the   |      |        |     | for HBV   | DNA level.  |                |              |           |         |
| Journal, 38  | infected pregnant | and exclusion   | antiviral therapy  |      |        |     | Same re   | gimen for   |                |              |           |         |
|              | woman             | criteria also)  | (decrease in viral |      |        |     | infant    |             |                |              |           |         |

|                |                   |                 | load levels        |                 | immunoprophylaxis     |                     |              |           |          |
|----------------|-------------------|-----------------|--------------------|-----------------|-----------------------|---------------------|--------------|-----------|----------|
|                |                   |                 | subsequent to the  |                 | at birth              |                     |              |           |          |
|                |                   |                 | treatment)         |                 |                       |                     |              |           |          |
| Jiang S,       | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | 🛠 Always the    | ★ Comparable for      | No<br>description o | <b>☆</b> Yes | No        | 6 (high) |
| (2017), Diet   | somewhat          | from the same   | was used to        | case            | HBV DNA level but     | description a       |              |           |          |
| Health, 130    | representative of | community       | ascertain          | cuse            | HBeAg sero-status     |                     |              | OI LFU    |          |
|                | the average HBV   | (same inclusion | adherence to the   |                 | not described Same    |                     |              |           |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |                 | regimen for infant    |                     |              |           |          |
|                | meeted pregnant   | and exclusion   | (decrease in viral |                 | immunonnonhulouis     |                     |              |           |          |
|                | woman             | criteria also)  |                    |                 | ininiunopropriyaxis   |                     |              |           |          |
|                |                   |                 | load levels        |                 | at birth              |                     |              |           |          |
|                |                   |                 | subsequent to the  |                 |                       |                     |              |           |          |
|                |                   |                 | treatment)         |                 |                       |                     |              |           |          |
| Li CM, (2017), | *                 | *               | 🛠 Valid method     | *               | ★ Comparable          | Laboratory          | *            | No        | 6 (high) |
| Northern       | A. 1 .            | D (             |                    | 41 4            |                       | assays used         |              | statement |          |
| Pharmacy 132   | At least          | Drawn from      | was used to        | Always the case | for HBV DNA level     | not well            | Yes (always  | of LFU    |          |
| 1 harmacy, 152 | somewhat          | the same        | ascertain          |                 | but HBeAg sero-       | described           | the case)    |           |          |
|                | representative of | community       | adherence to the   |                 | status not described. |                     |              |           |          |
|                | the average HBV   | (same inclusion | antiviral therapy  |                 | Same regimen for      |                     |              |           |          |
|                | infected pregnant | and exclusion   | (decrease in viral |                 | infant                |                     |              |           |          |
|                | woman             | criteria also)  | load levels        |                 | immunoprophylaxis.    |                     |              |           |          |
|                |                   |                 | subsequent to the  |                 |                       |                     |              |           |          |
|                |                   |                 | treatment)         |                 |                       |                     |              |           |          |
| Li YH, (2017), | At least          |                 | ★ Valid method     | Always the      | tata Sama             | 4                   | Var          | No        | 8 (low)  |
| Northern       | At least          | P Diawii        | vand method        | Always the      | Jane Same             | <b>F</b> -          | 105          | statement |          |
|                | somewhat          | from the same   | was used to        | case            | HBeAg sero-status     | Laboratory          |              | of LFU    |          |
| Pharmacy, 134  | representative of | community       | ascertain          |                 | and same thresholds   | methods             |              |           |          |
|                | the average HBV   | (same inclusion | adherence to the   |                 | for HBV DNA level.    | described in        |              |           |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |                 | Same regimen for      | detail (which       |              |           |          |
|                | woman             | criteria also)  | (decrease in viral |                 | infant                | assay used),        |              |           |          |
|                |                   |                 | load levels        |                 | immunoprophylaxis     | indicating use      |              |           |          |

|   |  |  | subsequent to the   |                          |                          | at birth   | of a central                         |                |  |                     |
|---|--|--|---|--------------------------|--------------------------|--|--------------------------------------|----------------|--|---------------------|
|   |  |  | treatment)  |                          |                          |  | laboaratory                          |                |  |                     |
|   |  |  |   |                          |                          |  | and/or record                        |                |  |                     |
|   |  |  |   |                          |                          |  | linkage.                             |                |  |                     |
| Liu J, (2017),  | At loost   |  | Valid mathad  | ¥                        | Always the               | tata somo  | No                                   | ★ Vac          | There is a                                 | 7 (low)             |
| Maternal and  | At least   |  | vanu method   |                          | Always the               | Same Same  | description                          | F 165          | description                                |                     |
|   | somewhat   | from the same  | was used to   | case                     |                          | HBeAg sero-status  |                                      |                | of LFU for                                 |                     |
| Child Health  | representative of  | community  | ascertain   |                          |                          | and comparable for   |                                      |                | the exposed                                |                     |
| Care of China,  | the average HBV  | (same inclusion  | adherence to the  |                          |                          | HBV DNA levels.  |                                      |                | but not for                                |                     |
| 137   | infected pregnant  | and exclusion  | antiviral therapy   |                          |                          | Same regimen for   |                                      |                | the control                                |                     |
|   | woman  | criteria also)   | (decrease in viral  |                          |                          | infant   |                                      |                | group                                      |                     |
|   |  |  | load levels   |                          |                          | immunoprophylaxis  |                                      |                |  |                     |
|   |  |  | subsequent to the   |                          |                          | at birth   |                                      |                |  |                     |
|   |  |  | treatment)  |                          |                          |  |                                      |                |  |                     |
|   |  |  |   |                          |                          |  |                                      |                |  |                     |
| Luo DX,   | At least   | X Duraum   | Valid mathed  | 47                       | Almoria the              | Comparable for   | No                                   | Vac            | No   | 5 (high)            |
| Luo DX,   | 🛠 At least   | 🗱 Drawn  | ★ Valid method  | *                        | Always the               | Comparable for<br>HBV DNA levels   | No<br>description                    | 🛠 Yes          | No<br>statement                            | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★ At least somewhat  | ★ Drawn from the same  | ★ Valid method<br>was used to   | <b>☆</b><br>case         | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-  | No<br>description                    | 🛠 Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★     At     least       somewhat     representative     of  | ★ Drawn from the same community  | ★ Valid method<br>was used to<br>ascertain  | <b>☆</b><br>case         | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.   | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★Atleastsomewhatrepresentativeofthe averageHBV   | ★ Drawn from the same community (same inclusion  | ★ Valid method<br>was used to<br>ascertain<br>adherence to the  | <b>☆</b><br>case         | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant   | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant  | ★ Drawn from the same community (same inclusion and exclusion  | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy   | *<br>case                | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis  | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★Atleastsomewhatrepresentativeofthe averageHBVinfectedpregnantwoman  | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)                    | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral)  | *<br>case                | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly  | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman   | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)                    | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels                                    | <b>★</b><br>case         | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described                                 | No<br>description                    | ⊀ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman   | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)                    | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the               | <b>★</b><br>case         | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described                                 | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup>                              | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman   | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)                    | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | <b>↓</b> X<br>case       | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described                                 | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)            |
| Luo DX,<br>(2017) <sup>4</sup><br>Pan YC,                   | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman   | ★ Drawn from the same community (same inclusion and exclusion criteria also)                                   | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | tx<br>case               | Always the               | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described                                 | No<br>description                    | ★ Yes          | No<br>statement<br>of LFU                  | 5 (high)<br>8 (low) |
| Luo DX,<br>(2017) <sup>4</sup><br>Pan YC,<br>(2017) L Clin  | ★     At     least       somewhat     representative     of       the average     HBV       infected     pregnant       woman     HBV  | ★   Drawn     from the same   community     (same inclusion   and exclusion     and exclusion   criteria also) | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | ☆<br>case                | Always the<br>Always the | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described<br>★★ Same                      | No<br>description                    | ☆ Yes          | No<br>statement<br>of LFU                  | 5 (high)<br>8 (low) |
| Luo DX,<br>(2017) <sup>4</sup><br>Pan YC,<br>(2017), J Clin | ★       At       least         somewhat       of         representative       of         the average       HBV         infected       pregnant         woman       At         At       least         somewhat       Somewhat | ★     Drawn       from the same     community       (same inclusion       and exclusion       criteria also)   | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | tx<br>case<br>tx<br>case | Always the<br>Always the | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described<br>★★ Same<br>HBeAg sero-status | No<br>description<br>★<br>Laboratory | ★ Yes<br>★ Yes | No<br>statement<br>of LFU<br>★<br>Subjects | 5 (high)<br>8 (low) |

<sup>&</sup>lt;sup>4</sup> Luo D, He K. A study on the effect of telbivudine to interrupt mother-to-child transmission of hepatitis B virus and nursing intervention. *Chin J Woman Child Health Res* 2017; **28 (2)**: 626.

|                | the average HBV   | (same inclusion |                    |      |            | for HBV DNA level.    | described in   |       | follow up   |          |
|----------------|-------------------|-----------------|--------------------|------|------------|-----------------------|----------------|-------|-------------|----------|
|                | infected pregnant | and exclusion   |                    |      |            | Same regimen for      | detail (which  |       | unlikely to |          |
|                | woman             | criteria also)  |                    |      |            | infant                | assay used),   |       | introduce   |          |
|                |                   |                 |                    |      |            | immunoprophylaxis     | indicating use |       | bias, small |          |
|                |                   |                 |                    |      |            | at birth              | of a central   |       | number lost |          |
|                |                   |                 |                    |      |            |                       | laboaratory    |       |             |          |
|                |                   |                 |                    |      |            |                       | and/or record  |       |             |          |
|                |                   |                 |                    |      |            |                       | linkage.       |       |             |          |
| Wang J,        | 🛠 At least        |                 | ★ Valid method     | *    | Always the | Same thresholds       | No             | ¥ Ves | No          | 6 (high) |
| (2017).        | , At least        | , Diawii        | v vand memod       | ,.   | Aiways the | v Same unesholds      | description    | 103   | statement   |          |
| (Lot 1)),      | somewhat          | from the same   | was used to        | case |            | for HBV DNA level     |                |       | of LFU      |          |
| Chinese        | representative of | community       | ascertain          |      |            | but HBeAg sero-       |                |       |             |          |
| Journal of     | the average HBV   | (same inclusion | adherence to the   |      |            | status not described. |                |       |             |          |
| Woman and      | infected pregnant | and exclusion   | antiviral therapy  |      |            | Same regimen for      |                |       |             |          |
| Child Health   | woman             | criteria also)  | (decrease in viral |      |            | infant                |                |       |             |          |
| D              |                   |                 | load levels        |      |            | immunoprophylaxis     |                |       |             |          |
| Research, 157  |                   |                 | subsequent to the  |      |            | at birth              |                |       |             |          |
|                |                   |                 | treatment)         |      |            |                       |                |       |             |          |
| Xiao XH,       | ⊀ At least        | ★ Drawn         | ★ Valid method     | Å    | Always the | Same thresholds for   | *              | ⊀ Yes | There is a  | 6 (high) |
| (2017),        | _                 |                 |                    |      | 5          | HBV DNA level but     |                |       | description |          |
| Maternal and   | somewhat          | from the same   | was used to        | case |            | HBeAg sero-status     | Laboratory     |       | of LFU for  |          |
|                | representative of | community       | ascertain          |      |            | not described.        | methods        |       | the exposed |          |
| Child Health   | the average HBV   | (same inclusion | adherence to the   |      |            | Regimen for infant    | described in   |       | but not for |          |
| Care of China, | infected pregnant | and exclusion   | antiviral therapy  |      |            | immunoprophylaxis     | detail (which  |       | the control |          |
| 42             | woman             | criteria also)  | (decrease in viral |      |            | at birth not clearly  | assay used),   |       | group       |          |
|                |                   |                 | load levels        |      |            | described             | indicating use |       |             |          |
|                |                   |                 | subsequent to the  |      |            |                       | of a central   |       |             |          |
|                |                   |                 | treatment)         |      |            |                       | laboaratory    |       |             |          |
|                |                   |                 |                    |      |            |                       | and/or record  |       |             |          |
|                |                   |                 |                    |      |            |                       | linkage.       |       |             |          |

| Chen F,<br>(2016), Journal<br>of Practical<br>Medicine, 110               | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | <b>☆</b><br>case | Always the | ★ Same HBeAg<br>sero-status and same<br>thresholds for HBV<br>DNA level.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described     | ↓<br>Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkaga | ★ Yes | No<br>statement<br>of LFU | 7 (low)  |
|---|--|---|---|------------------|------------|--|--|-------|---------------------------|----------|
| Gao P, (2016),<br>J Medical<br>Forum, 119                                 | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | ¢<br>case        | Always the | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Regimen for infant<br>immunoprophylaxis<br>at birth not clearly<br>described | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage.     | ★ Yes | No<br>statement<br>of LFU | 6 (high) |
| Hu WH,<br>(2016), Journal<br>of Qiqihar<br>University of<br>Medicine, 127 | ★ At least<br>somewhat<br>representative of<br>the average HBV<br>infected pregnant<br>woman | Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also)   | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral)  | <b>☆</b><br>case | Always the | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Same regimen for<br>infant   | ↓<br>Laboratory<br>methods<br>described in<br>detail (which<br>assay used),  | ★ Yes | No<br>statement<br>of LFU | 7 (low)  |

|   |   |  | load levels   |                  |            | immunoprophylaxis  | indicating use    |              |                           |          |
|---|---|--|---|------------------|------------|--|-------------------|--------------|---------------------------|----------|
|   |   |  | subsequent to the   |                  |            | at birth   | of a central      |              |                           |          |
|   |   |  | treatment)  |                  |            |  | laboaratory       |              |                           |          |
|   |   |  |   |                  |            |  | and/or record     |              |                           |          |
|   |   |  |   |                  |            |  | linkage.          |              |                           |          |
| Li N, (2016),<br>Medical<br>Innovation of<br>China, 133 | ★Atleastsomewhatrepresentativeofthe averageHBVinfectedpregnantwoman | ★Drawnfrom the samecommunity(same inclusionand exclusioncriteria also) | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral | <b>☆</b><br>case | Always the | Comparable for<br>HBV DNA levels<br>but HBeAg sero-<br>status not described.<br>Same regimen for<br>infant | No<br>description | ★ Yes        | No<br>statement<br>of LFU | 6 (high) |
|   |   |  | load levels   |                  |            | immunoprophylaxis  |                   |              |                           |          |
|   |   |  | subsequent to the   |                  |            | at birth   |                   |              |                           |          |
|   |   |  | treatment)  |                  |            |  |                   |              |                           |          |
| Liu XB,   | 🖈 At least  | <b>★</b> Drawn   | ★ Valid method  | *                | Always the | <b>☆☆</b> Same HBeAg   | No<br>description | ★ Yes        | No<br>statement           | 7 (low)  |
| (2016), Journal   | somewhat  | from the same  | was used to   | case             |            | sero-status and same   | -                 |              | of LFU                    |          |
| of  | representative of   | community  | ascertain   |                  |            | thresholds for HBV   |                   |              |                           |          |
| Contemporary  | the average HBV   | (same inclusion  | adherence to the  |                  |            | DNA level. Same  |                   |              |                           |          |
| Clinical  | infected pregnant   | and exclusion  | antiviral therapy   |                  |            | regimen for infant   |                   |              |                           |          |
| Madiaina 120  | woman   | criteria also)   | (decrease in viral  |                  |            | immunoprophylaxis  |                   |              |                           |          |
| Medicine, 158   |   |  | load levels   |                  |            | at birth   |                   |              |                           |          |
|   |   |  | subsequent to the treatment)  |                  |            |  |                   |              |                           |          |
| Qiu B, (2016),  | 🛠 At least  | <b>☆</b> Drawn   | ★ Valid method  | *                | Always the | ★ Same thresholds  | 4                 | <b>☆</b> Yes | No                        | 7 (low)  |
| J Prac Hepatol,<br>143                                  | somewhat  | from the same  | was used to   | case             |            | for HBV DNA level  | Laboratory        |              | statement<br>of LFU       |          |
|   | the average HRV   | (same inclusion  | adherence to the  |                  |            | status not described   | described in      |              |                           |          |
|   | infected pregnant   | and exclusion  | antiviral therapy   |                  |            | Same regimen for   | detail (which     |              |                           |          |

|                | woman             | criteria also)  | (decrease in viral |                 | infant               | assay used),   |              |           |          |
|----------------|-------------------|-----------------|--------------------|-----------------|----------------------|----------------|--------------|-----------|----------|
|                |                   |                 | load levels        |                 | immunoprophylaxis    | indicating use |              |           |          |
|                |                   |                 | subsequent to the  |                 | at birth             | of a central   |              |           |          |
|                |                   |                 | treatment)         |                 |                      | laboaratory    |              |           |          |
|                |                   |                 |                    |                 |                      | and/or record  |              |           |          |
|                |                   |                 |                    |                 |                      | linkage.       |              |           |          |
| Shen ML,       | At loost          |                 | Valid method       | Always the      | Same thresholds for  | 4              | <b>∛</b> Vas | No        | 6 (high) |
| (2016) WCID    | r At least        | r Diawii        | r vand method      | r Always the    | HBV DNA level but    |                | r ies        | statement |          |
| (2010), WCJD,  | somewhat          | from the same   | was used to        | case            | HBeAg sero-status    | Laboratory     |              | of LFU    |          |
| 76             | representative of | community       | ascertain          |                 | not described.       | methods        |              |           |          |
|                | the average HBV   | (same inclusion | adherence to the   |                 | Regimen for infant   | described in   |              |           |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |                 | immunoprophylaxis    | detail (which  |              |           |          |
|                | woman             | criteria also)  | (decrease in viral |                 | at birth not clearly | assay used),   |              |           |          |
|                |                   |                 | load levels        |                 | described            | indicating use |              |           |          |
|                |                   |                 | subsequent to the  |                 |                      | of a central   |              |           |          |
|                |                   |                 | treatment)         |                 |                      | laboaratory    |              |           |          |
|                |                   |                 |                    |                 |                      | and/or record  |              |           |          |
|                |                   |                 |                    |                 |                      | linkage.       |              |           |          |
| Tian RH,       | 🖈 At least        | → Drawn         | No description     | Always the      | XX Same HBeAg        | No             | ⊀ Yes        | No        | 6 (high) |
| (2016),        | , ni loust        | , Diuvii        |                    | , niways the    | , , Sume Hiberig     | description    | , 105        | statement |          |
| Chinasa        | somewhat          | from the same   |                    | case            | sero-status and same |                |              | of LFU    |          |
| Clillese       | representative of | community       |                    |                 | thresholds for HBV   |                |              |           |          |
| Journal of     | the average HBV   | (same inclusion |                    |                 | DNA level. Same      |                |              |           |          |
| Clinical       | infected pregnant | and exclusion   |                    |                 | regimen for infant   |                |              |           |          |
| Research, 154  | woman             | criteria also)  |                    |                 | immunoprophylaxis    |                |              |           |          |
| resourch, is i |                   |                 |                    |                 | at birth             |                |              |           |          |
| Wang B,        | *                 | 4               | ★ Valid method     | *               | ★★ Comparable        | *              | <b>X</b>     | No        | 8 (low)  |
| (2016),        |                   |                 |                    |                 | Comparable           | ,              |              | statement |          |
| Chinese        | At least          | Drawn from      | was used to        | Always the case | for HBeAg sero-      | Laboratory     | Yes (always  | of LFU    |          |
|                | somewhat          | the same        | ascertain          |                 | status and HBV       | assays         | the case)    |           |          |
| Remedies &     | representative of | community       | adherence to the   |                 | DNA level. Same      | described      |              |           |          |

| Clinics, 155    | the average HBV   | (same inclusion | antiviral therapy  |      |            | regimen for infant   |                   |       |                 |          |
|-----------------|-------------------|-----------------|--------------------|------|------------|----------------------|-------------------|-------|-----------------|----------|
|                 | infected pregnant | and exclusion   | (decrease in viral |      |            | immunoprophylaxis.   |                   |       |                 |          |
|                 | woman             | criteria also)  | load levels        |      |            |                      |                   |       |                 |          |
|                 |                   |                 | subsequent to the  |      |            |                      |                   |       |                 |          |
|                 |                   |                 | treatment)         |      |            |                      |                   |       |                 |          |
| Wang DM,        | 🖈 At least        | <b>☆</b> Drawn  | ★ Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg | <b>Å</b>          | ★ Yes | No<br>statement | 8 (low)  |
| (2016),         | somewhat          | from the same   | was used to        | case |            | sero-status and same | Laboratory        |       | of LFU          |          |
| Chinese         | representative of | community       | ascertain          |      |            | thresholds for HBV   | methods           |       |                 |          |
| Hepatology,     | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      | described in      |       |                 |          |
| 79              | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   | detail (which     |       |                 |          |
|                 | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),      |       |                 |          |
|                 |                   |                 | load levels        |      |            | at birth             | indicating use    |       |                 |          |
|                 |                   |                 | subsequent to the  |      |            |                      | of a central      |       |                 |          |
|                 |                   |                 | treatment)         |      |            |                      | laboaratory       |       |                 |          |
|                 |                   |                 |                    |      |            |                      | and/or record     |       |                 |          |
|                 |                   |                 |                    |      |            |                      | linkage.          |       |                 |          |
| Wang HB,        | 🖈 At least        | 🗱 Drawn         | ★ Valid method     | な    | Always the | ★ Comparable for     | No<br>description | 🛠 Yes | No<br>statement | 6 (high) |
| (2016), Journal | somewhat          | from the same   | was used to        | case |            | HBV DNA level but    |                   |       | of LFU          |          |
| of Practical    | representative of | community       | ascertain          |      |            | HBeAg sero-status    |                   |       |                 |          |
| Medicine, 156   | the average HBV   | (same inclusion | adherence to the   |      |            | not described. Same  |                   |       |                 |          |
|                 | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   |                   |       |                 |          |
|                 | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    |                   |       |                 |          |
|                 |                   |                 | load levels        |      |            | at birth             |                   |       |                 |          |
|                 |                   |                 | subsequent to the  |      |            |                      |                   |       |                 |          |
|                 |                   |                 | treatment)         |      |            |                      |                   |       |                 |          |

| Zhang R,       | 🛃 At least        | 🖈 Drawn         | No description     | *    | Always the  | HBeAg sero-status    | No             | 🛠 Ves | No        | 4 (high) |
|----------------|-------------------|-----------------|--------------------|------|-------------|----------------------|----------------|-------|-----------|----------|
| $(2016)^5$     | , ni loust        | , Diawii        |                    | ,    | riiwayo ule | and threshold for    | description    | , 105 | statement |          |
|                | somewhat          | from the same   |                    | case |             | HBV DNA level not    |                |       | of LFU    |          |
|                | representative of | community       |                    |      |             | described. Regimen   |                |       |           |          |
|                | the average HBV   | (same inclusion |                    |      |             | for infant           |                |       |           |          |
|                | infected pregnant | and exclusion   |                    |      |             | immunoprophylaxis    |                |       |           |          |
|                | woman             | criteria also)  |                    |      |             | at birth not clearly |                |       |           |          |
|                |                   |                 |                    |      |             | described            |                |       |           |          |
| Chen CY,       | At logst          |                 | Valid mathad       | *    | Almong the  | Sama HBaAg           | 4              | ★ Vas | No        | 7 (low)  |
| (2015), Chin J | At least          | P Diawii        | v vand method      |      | Always the  | - Same HBEAg         |                | 105   | statement |          |
|                | somewhat          | from the same   | was used to        | case |             | sero-status and same | Laboratory     |       | of LFU    |          |
| Hepatol, 109   | representative of | community       | ascertain          |      |             | thresholds for HBV   | methods        |       |           |          |
|                | the average HBV   | (same inclusion | adherence to the   |      |             | DNA level.           | described in   |       |           |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |             | Regimen for infant   | detail (which  |       |           |          |
|                | woman             | criteria also)  | (decrease in viral |      |             | immunoprophylaxis    | assay used),   |       |           |          |
|                |                   |                 | load levels        |      |             | at birth not clearly | indicating use |       |           |          |
|                |                   |                 | subsequent to the  |      |             | described            | of a central   |       |           |          |
|                |                   |                 | treatment)         |      |             |                      | laboaratory    |       |           |          |
|                |                   |                 |                    |      |             |                      | and/or record  |       |           |          |
|                |                   |                 |                    |      |             |                      | linkage.       |       |           |          |
| Cui ZL,        | ★ At least        | ★ Drawn         | ★ Valid method     | *    | Always the  | XX Same HBeAg        | *              | ★ Yes | No        | 8 (low)  |
| (2015),        |                   |                 |                    |      |             |                      |                |       | statement |          |
| IMHGN 114      | somewhat          | from the same   | was used to        | case |             | sero-status and same | Laboratory     |       | of LFU    |          |
| 11/11/010, 114 | representative of | community       | ascertain          |      |             | thresholds for HBV   | methods        |       |           |          |
|                | the average HBV   | (same inclusion | adherence to the   |      |             | DNA level. Same      | described in   |       |           |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |             | regimen for infant   | detail (which  |       |           |          |
|                | woman             | criteria also)  | (decrease in viral |      |             | immunoprophylaxis    | assay used),   |       |           |          |
|                |                   |                 | load levels        |      |             | at birth             | indicating use |       |           |          |

<sup>&</sup>lt;sup>5</sup> Zhang R, Lu F, Liu M. Analysis of nursing management of antiviral intrauterine interruption of patients with HBV during pregnancy. *China Health Industry* 2016; **13 (31)**: 145-147.

|   |                   |                 | subsequent to the  |      |            |                       | of a central  |              |            |          |
|---|-------------------|-----------------|--------------------|------|------------|-----------------------|---------------|--------------|------------|----------|
|   |                   |                 | treatment)         |      |            |                       | laboaratory   |              |            |          |
|   |                   |                 |                    |      |            |                       | and/or record |              |            |          |
|   |                   |                 |                    |      |            |                       | linkage.      |              |            |          |
| Deng Y,                                 | 🛠 At least        | <b>★</b> Drawn  | ★ Valid method     | ¥    | Always the | Same thresholds       | No            | <b>☆</b> Yes | No         | 6 (high) |
| (2015), Chin J                          | somewhat          | from the same   | was used to        | Case | ·          | for HBV DNA level     | description   |              | statement  |          |
| Hepatol, 115                            | representative of | community       | was used to        | case |            | but HBaAg sero        |               |              | of LFU     |          |
| 1 /                                     | the average HPV   | (some inclusion | adharanaa ta tha   |      |            | status not described  |               |              |            |          |
|   | inforted another  | (same inclusion | autierine to the   |      |            | Status not described. |               |              |            |          |
|   | unected pregnant  | and exclusion   | (decrease in viral |      |            | same regimen for      |               |              |            |          |
|   | woman             | cificila also)  | load lovels        |      |            | immun on son bylowic  |               |              |            |          |
|   |                   |                 | ioad levels        |      |            | nininunopropriyiaxis  |               |              |            |          |
|   |                   |                 | subsequent to the  |      |            | at birth              |               |              |            |          |
| ~ |                   |                 | treatment)         |      |            |                       | N             |              | <b>N</b> 7 |          |
| Ge YL,                                  | 🛠 At least        | <b>★</b> Drawn  | 🛠 Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg  | No            | <b>☆</b> Yes | No         | 7 (low)  |
| (2015), Chin J                          | somewhat          | from the same   | was used to        | case |            | sero-status and same  | description   |              | statement  |          |
| Clin                                    | representative of | community       | ascertain          | euse |            | thresholds for HBV    |               |              | 01 LFU     |          |
| Pharmacol 60                            | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level Same        |               |              |            |          |
| Tharmacon, oo                           | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    |               |              |            |          |
|   | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     |               |              |            |          |
|   | Wollian           | cificilia also) | load levels        |      |            | at hirth              |               |              |            |          |
|   |                   |                 | subsequent to the  |      |            | at onth               |               |              |            |          |
|   |                   |                 | treatment)         |      |            |                       |               |              |            |          |
| Lon II (2015)                           |                   |                 | (ioutificity)      |      |            |                       |               |              | No         | 9 (low)  |
| Lou JJ, (2013),                         | 🛠 At least        | <b>⊀</b> Drawn  | 🛠 Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg  | *             | ★ Yes        | statement  | 8 (IOW)  |
| Chinese                                 | somewhat          | from the same   | was used to        | case |            | sero-status and same  | Laboratory    |              | of I FU    |          |
| Journal of                              | representative of | community       | ascertain          |      |            | thresholds for HBV    | methods       |              | 01110      |          |
| Microecology,                           | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same       | described in  |              |            |          |
| 140                                     | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    | detail (which |              |            |          |
| 170                                     | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     | assay used),  |              |            |          |

|  |                   |   | load levels   |                    |            | at birth   | indicating use   |       |                           |         |
|--|-------------------|---|---|--------------------|------------|--|--|-------|---------------------------|---------|
|  |                   |   | treatment)  |                    |            |  | laboaratory  |       |                           |         |
|  |                   |   | treatment)  |                    |            |  | and/or record  |       |                           |         |
|  |                   |   |   |                    |            |  | linkage  |       |                           |         |
| Ren N, (2015),<br>China<br>Medicine and<br>Pharmacy, 144 |                   | ★ Drawn<br>from the same<br>community<br>(same inclusion<br>and exclusion<br>criteria also) | ★ Valid method<br>was used to<br>ascertain<br>adherence to the<br>antiviral therapy<br>(decrease in viral<br>load levels<br>subsequent to the<br>treatment) | <b>↓</b> ×<br>case | Always the | Same HBeAg<br>sero-status and same<br>thresholds for HBV<br>DNA level. Same<br>regimen for infant<br>immunoprophylaxis<br>at birth | Laboratory<br>methods<br>described in<br>detail (which<br>assay used),<br>indicating use<br>of a central<br>laboaratory<br>and/or record<br>linkage. | ⊀ Yes | No<br>statement<br>of LFU | 8 (low) |
| Sun WH,  | 🛠 At least        | <b>↓</b> Drawn  | ★ Valid method  | *                  | Always the | ★★ Same HBeAg  | *  | ★ Yes | No                        | 8 (low) |
| (2015), Chin J   | somewhat          | from the same   | was used to   | case               |            | sero-status and same   | Laboratory   |       | of LFU                    |         |
| Hepatol, 149   | representative of | community   | ascertain   |                    |            | thresholds for HBV   | methods  |       |                           |         |
|  | the average HBV   | (same inclusion   | adherence to the  |                    |            | DNA level. Same  | described in   |       |                           |         |
|  | infected pregnant | and exclusion   | antiviral therapy   |                    |            | regimen for infant   | detail (which  |       |                           |         |
|  | woman             | criteria also)  | (decrease in viral  |                    |            | immunoprophylaxis  | assay used),   |       |                           |         |
|  |                   |   | load levels   |                    |            | at birth   | indicating use   |       |                           |         |
|  |                   |   | subsequent to the   |                    |            |  | of a central   |       |                           |         |
|  |                   |   | treatment)  |                    |            |  | laboaratory  |       |                           |         |
|  |                   |   |   |                    |            |  | and/or record  |       |                           |         |
|  |                   |   |   |                    |            |  | linkage.   |       |                           |         |
| Wang TD,   | 🛠 At least        | 🖈 Drawn   | ★ Valid method  | 4                  | Always the | ★★ Same HBeAg  | *  | 🛠 Yes | No<br>statement           | 8 (low) |

| (2015), China  | somewhat          | from the same     | was used to        | case |            | sero-status and same  | Laboratory     |       | of LFU    |          |
|----------------|-------------------|-------------------|--------------------|------|------------|-----------------------|----------------|-------|-----------|----------|
| Pharmaceutica  | representative of | community         | ascertain          |      |            | thresholds for HBV    | methods        |       |           |          |
| 1. 150         | the average HBV   | (same inclusion   | adherence to the   |      |            | DNA level. Same       | described in   |       |           |          |
| 15, 158        | infected pregnant | and exclusion     | antiviral therapy  |      |            | regimen for infant    | detail (which  |       |           |          |
|                | woman             | criteria also)    | (decrease in viral |      |            | immunoprophylaxis     | assay used),   |       |           |          |
|                |                   |                   | load levels        |      |            | at birth              | indicating use |       |           |          |
|                |                   |                   | subsequent to the  |      |            |                       | of a central   |       |           |          |
|                |                   |                   | treatment)         |      |            |                       | laboaratory    |       |           |          |
|                |                   |                   |                    |      |            |                       | and/or record  |       |           |          |
|                |                   |                   |                    |      |            |                       | linkage.       |       |           |          |
| Zhang X,       | A 1               | <b>X</b> D        | Valid mathed       | -tr  | A 1 41     |                       | ۲۲.            | N Var | No        | 8 (low)  |
| (2015) I Prac  | r At least        | r Drawn           | r valid method     | r    | Always the | r r Same HBeAg        | r              | r Yes | statement |          |
| (2015), 5 11ac | somewhat          | from the same     | was used to        | case |            | sero-status and same  | Laboratory     |       | of LFU    |          |
| Hepatol, 168   | representative of | community         | ascertain          |      |            | thresholds for HBV    | methods        |       |           |          |
|                | the average HBV   | (same inclusion   | adherence to the   |      |            | DNA level. Same       | described in   |       |           |          |
|                | infected pregnant | and exclusion     | antiviral therapy  |      |            | regimen for infant    | detail (which  |       |           |          |
|                | woman             | criteria also)    | (decrease in viral |      |            | immunoprophylaxis     | assay used),   |       |           |          |
|                |                   |                   | load levels        |      |            | at birth              | indicating use |       |           |          |
|                |                   |                   | subsequent to the  |      |            |                       | of a central   |       |           |          |
|                |                   |                   | treatment)         |      |            |                       | laboaratory    |       |           |          |
|                |                   |                   |                    |      |            |                       | and/or record  |       |           |          |
|                |                   |                   |                    |      |            |                       | linkage.       |       |           |          |
| Chen YL,       | No description    | No description    | Valid method       | 47   | Almong the | Comparable for        | No             | ⊀ Vas | No        | 4 (high) |
| $(2014)^{6}$   | of the derivation | of the derivation | > vand method      |      | Always the | r Comparable for      | description    | r les | statement |          |
| (2011)         | of the cohort     | of the non        | was used to        | case |            | HBV DNA levels        |                |       | of LFU    |          |
|                |                   | exposed cohort    | ascertain          |      |            | but HBeAg sero-       |                |       |           |          |
|                |                   |                   | adherence to the   |      |            | status not described. |                |       |           |          |
|                |                   |                   | antiviral therapy  |      |            | Same regimen for      |                |       |           |          |

<sup>&</sup>lt;sup>6</sup> Chen Y, Gao X, Li J. Telbivudine combined with hepatitis B vaccine to interrupt hepatitis B virus intrauterine infection. *Acta Universitatis Medicinalis Nanjing (Natural Science)* 2014; **34 (1)**: 67-68.

|                 |                   |                 | (decrease in viral |      |            | infant                |                |              |           |         |
|-----------------|-------------------|-----------------|--------------------|------|------------|-----------------------|----------------|--------------|-----------|---------|
|                 |                   |                 | load levels        |      |            | immunoprophylaxis     |                |              |           |         |
|                 |                   |                 | subsequent to the  |      |            | at birth              |                |              |           |         |
|                 |                   |                 | treatment)         |      |            |                       |                |              |           |         |
| Han YP,         | 🛠 At least        | <b>★</b> Drawn  | ★ Valid method     | ☆    | Always the | <b>≭</b> ≭ Same HBeAg | No             | <b>☆</b> Yes | No        | 7 (low) |
| (2014), Hebei   | somewhat          | from the same   | was used to        | case |            | sero-status and same  | description    |              | of LEL    |         |
| Medical         | representative of | community       | ascertain          | euse |            | thresholds for HBV    |                |              | 01 LFU    |         |
| Journal, 62     | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same       |                |              |           |         |
|                 | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    |                |              |           |         |
|                 | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     |                |              |           |         |
|                 |                   |                 | load levels        |      |            | at birth              |                |              |           |         |
|                 |                   |                 | subsequent to the  |      |            |                       |                |              |           |         |
|                 |                   |                 | treatment)         |      |            |                       |                |              |           |         |
| Liu CY,         | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | ¥    | Always the | <b>☆☆</b> Same HBeAg  | *              | <b>☆</b> Yes | No        | 8 (low) |
| (2014), Journal | somewhat          | from the same   | was used to        | case |            | sero-status and same  | Laboratory     |              | statement |         |
| of Yanan        | representative of | community       | ascertain          |      |            | thresholds for HBV    | methods        |              | OI LI'U   |         |
| University,     | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same       | described in   |              |           |         |
| 136             | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant    | detail (which  |              |           |         |
| 150             | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis     | assay used),   |              |           |         |
|                 |                   |                 | load levels        |      |            | at birth              | indicating use |              |           |         |
|                 |                   |                 | subsequent to the  |      |            |                       | of a central   |              |           |         |
|                 |                   |                 | treatment)         |      |            |                       | laboaratory    |              |           |         |
|                 |                   |                 |                    |      |            |                       | and/or record  |              |           |         |
|                 |                   |                 |                    |      |            |                       | linkage.       |              |           |         |
| Yao LF,         | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | *    | Always the | ★ Same HBeAg          | *              | ★ Yes        | No        | 7 (low) |
| (2014), Chin J  | 1                 |                 | 1                  | ,    |            | 1                     | <b>x</b> 1     |              | statement |         |
| Obstet          | somewhat          | from the same   | was used to        | case |            | sero-status and same  | Laboratory     |              | of LFU    |         |
| Cumaaal         | representative of | community       | ascertain          |      |            | thresholds for HBV    | methods        |              |           |         |
| Gynecol         | the average HBV   | (same inclusion | adherence to the   |      |            | DINA level.           | described in   |              |           |         |

| Pediatr, 162   | infected pregnant | and exclusion   | antiviral therapy  |      |            | Regimen for infant   | detail (which     |       |                 |          |
|----------------|-------------------|-----------------|--------------------|------|------------|----------------------|-------------------|-------|-----------------|----------|
|                | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),      |       |                 |          |
|                |                   |                 | load levels        |      |            | at birth not clearly | indicating use    |       |                 |          |
|                |                   |                 | subsequent to the  |      |            | described            | of a central      |       |                 |          |
|                |                   |                 | treatment)         |      |            |                      | laboaratory       |       |                 |          |
|                |                   |                 |                    |      |            |                      | and/or record     |       |                 |          |
|                |                   |                 |                    |      |            |                      | linkage.          |       |                 |          |
| Yue X, (2014), | At least          |                 | ★ Valid method     | **   | Alwaye the | XX Same HBeAg        | No                | Var   | 44              | 8 (low)  |
| Chin J Infect  | At least          | P Diawii        | v vand method      |      | Always the | Same HBeAg           | description       | 105   |                 |          |
| Div 165        | somewhat          | from the same   | was used to        | case |            | sero-status and same |                   |       | Complete        |          |
| Dis, 165       | representative of | community       | ascertain          |      |            | thresholds for HBV   |                   |       | follow-up       |          |
|                | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      |                   |       |                 |          |
|                | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   |                   |       |                 |          |
|                | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    |                   |       |                 |          |
|                |                   |                 | load levels        |      |            | at birth             |                   |       |                 |          |
|                |                   |                 | subsequent to the  |      |            |                      |                   |       |                 |          |
|                |                   |                 | treatment)         |      |            |                      |                   |       |                 |          |
| Zhou YJ,       | 🛠 At least        | 🖈 Drawn         | No description     | *    | Always the | Comparable           | *                 | ★ Yes | No<br>statement | 6 (high) |
| (2014), Chin J | somewhat          | from the same   |                    | case |            | HBeAg sero-status    | Laboratory        |       | of LFU          |          |
| Hepatol, 172   | representative of | community       |                    |      |            | and same thresholds  | methods           |       |                 |          |
|                | the average HBV   | (same inclusion |                    |      |            | for HBV DNA level.   | described in      |       |                 |          |
|                | infected pregnant | and exclusion   |                    |      |            | Regimen for infant   | detail (which     |       |                 |          |
|                | woman             | criteria also)  |                    |      |            | immunoprophylaxis    | assay used),      |       |                 |          |
|                |                   |                 |                    |      |            | at birth not         | indicating use    |       |                 |          |
|                |                   |                 |                    |      |            | described clearly    | of a central      |       |                 |          |
|                |                   |                 |                    |      |            |                      | laboaratory       |       |                 |          |
|                |                   |                 |                    |      |            |                      | and/or record     |       |                 |          |
|                |                   |                 |                    |      |            |                      | linkage.          |       |                 |          |
| Fan LY,        | ★ At least        | <b>★</b> Drawn  | ★ Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg | No<br>description | ¥ Yes | No<br>statement | 7 (low)  |

| (2013), J Med   | somewhat          | from the same   | was used to        | case |            | sero-status and same |                   |       | of LFU    |         |
|-----------------|-------------------|-----------------|--------------------|------|------------|----------------------|-------------------|-------|-----------|---------|
| Res. 117        | representative of | community       | ascertain          |      |            | thresholds for HBV   |                   |       |           |         |
| ,               | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      |                   |       |           |         |
|                 | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   |                   |       |           |         |
|                 | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    |                   |       |           |         |
|                 |                   |                 | load levels        |      |            | at birth             |                   |       |           |         |
|                 |                   |                 | subsequent to the  |      |            |                      |                   |       |           |         |
|                 |                   |                 | treatment)         |      |            |                      |                   |       |           |         |
| Jiang XN,       | 🛠 At least        | 🗱 Drawn         | ★ Valid method     | *    | Always the | 🛠 Same HBeAg         | No<br>description | ★ Yes | *         | 7 (low) |
| (2013), J Chin  | somewhat          | from the same   | was used to        | case |            | sero-status and same |                   |       | Complete  |         |
| Hepatol, 131    | representative of | community       | ascertain          |      |            | thresholds for HBV   |                   |       | follow-up |         |
|                 | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level.           |                   |       |           |         |
|                 | infected pregnant | and exclusion   | antiviral therapy  |      |            | Regimen for infant   |                   |       |           |         |
|                 | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    |                   |       |           |         |
|                 |                   |                 | load levels        |      |            | at birth not         |                   |       |           |         |
|                 |                   |                 | subsequent to the  |      |            | described clearly    |                   |       |           |         |
|                 |                   |                 | treatment)         |      |            |                      |                   |       |           |         |
| Zhao J, (2013), | At least          |                 | No description     | *    | Always the | ★ K Same HBeAg       | *                 | 🛃 Vas | No        | 7 (low) |
| China           | r Ai Itasi        |                 |                    | ,    | Aiways uic | r r same merg        |                   | F 105 | statement |         |
| Clinician 170   | somewhat          | from the same   |                    | case |            | sero-status and same | Laboratory        |       | of LFU    |         |
| Clinician, 170  | representative of | community       |                    |      |            | thresholds for HBV   | methods           |       |           |         |
|                 | the average HBV   | (same inclusion |                    |      |            | DNA level. Same      | described in      |       |           |         |
|                 | infected pregnant | and exclusion   |                    |      |            | regimen for infant   | detail (which     |       |           |         |
|                 | woman             | criteria also)  |                    |      |            | immunoprophylaxis    | assay used),      |       |           |         |
|                 |                   |                 |                    |      |            | at birth             | indicating use    |       |           |         |
|                 |                   |                 |                    |      |            |                      | of a central      |       |           |         |
|                 |                   |                 |                    |      |            |                      | laboaratory       |       |           |         |
|                 |                   |                 |                    |      |            |                      | and/or record     |       |           |         |
|                 |                   |                 |                    |      |            |                      | linkage.          |       |           |         |

| Peng BA,     | 🛠 At least        | 🖈 Drawn         | ★ Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg | No             | <b>☆</b> Yes | No              | 7 (low) |
|--------------|-------------------|-----------------|--------------------|------|------------|----------------------|----------------|--------------|-----------------|---------|
| (2012), Chin | somewhat          | from the same   | was used to        | case |            | sero-status and same | description    |              |                 |         |
| Pharm J, 142 | representative of | community       | ascertain          | euse |            | thresholds for HBV   |                |              | OI LI'U         |         |
|              | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      |                |              |                 |         |
|              | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   |                |              |                 |         |
|              | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    |                |              |                 |         |
|              |                   |                 | load levels        |      |            | at birth             |                |              |                 |         |
|              |                   |                 | subsequent to the  |      |            |                      |                |              |                 |         |
|              |                   |                 | treatment)         |      |            |                      |                |              |                 |         |
| Wang EJ,     | 🛠 At least        | <b>★</b> Drawn  | ★ Valid method     | *    | Always the | ★★ Same HBeAg        | *              | ★ Yes        | No              | 8 (low) |
| (2012),      | somewhat          | from the same   | was used to        | case |            | sero-status and same | Laboratory     |              | of LFU          |         |
| Chinese      | representative of | community       | ascertain          |      |            | thresholds for HBV   | methods        |              |                 |         |
| General      | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      | described in   |              |                 |         |
| Practice, 80 | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   | detail (which  |              |                 |         |
| 1100000,00   | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),   |              |                 |         |
|              |                   |                 | load levels        |      |            | at birth             | indicating use |              |                 |         |
|              |                   |                 | subsequent to the  |      |            |                      | of a central   |              |                 |         |
|              |                   |                 | treatment)         |      |            |                      | laboaratory    |              |                 |         |
|              |                   |                 |                    |      |            |                      | and/or record  |              |                 |         |
|              |                   |                 |                    |      |            |                      | linkage.       |              |                 |         |
| Wang WP,     | 🛠 At least        | <b>☆</b> Drawn  | ★ Valid method     | *    | Always the | <b>☆☆</b> Same HBeAg | *              | ★ Yes        | No<br>statement | 8 (low) |
| (2012), Prog | somewhat          | from the same   | was used to        | case |            | sero-status and same | Laboratory     |              | of LFU          |         |
| Obstet       | representative of | community       | ascertain          |      |            | thresholds for HBV   | methods        |              |                 |         |
| Gynecol, 159 | the average HBV   | (same inclusion | adherence to the   |      |            | DNA level. Same      | described in   |              |                 |         |
|              | infected pregnant | and exclusion   | antiviral therapy  |      |            | regimen for infant   | detail (which  |              |                 |         |
|              | woman             | criteria also)  | (decrease in viral |      |            | immunoprophylaxis    | assay used),   |              |                 |         |
|              |                   |                 | load levels        |      |            | at birth             | indicating use |              |                 |         |
|              |                   |                 | subsequent to the  |      |            |                      | of a central   |              |                 |         |

|                |                   |                 | treatment)         |       |               |                       | laboaratory    |          |              |            |
|----------------|-------------------|-----------------|--------------------|-------|---------------|-----------------------|----------------|----------|--------------|------------|
|                |                   |                 |                    |       |               |                       | and/or record  |          |              |            |
|                |                   |                 |                    |       |               |                       | linkage        |          |              |            |
|                |                   |                 |                    |       |               |                       | initiage.      |          | NT.          |            |
| Yao ZC,        | 🛠 At least        | 🗱 Drawn         | 🛠 Valid method     | *     | Always the    | ★ Same thresholds     | 4              | 🛠 Yes    | No           | 7 (low)    |
| (2011), J Clin |                   |                 |                    |       |               |                       |                |          | statement    |            |
| Hapatal 162    | somewhat          | from the same   | was used to        | case  |               | for HBV DNA level     | Laboratory     |          | of LFU       |            |
| nepatol, 105   | representative of | community       | ascertain          |       |               | but HBeAg sero-       | methods        |          |              |            |
|                | the average HBV   | (same inclusion | adherence to the   |       |               | status not described. | described in   |          |              |            |
|                | infected pregnant | and exclusion   | antiviral therapy  |       |               | Same regimen for      | detail (which  |          |              |            |
|                | woman             | criteria also)  | (decrease in viral |       |               | infant                | assay used),   |          |              |            |
|                |                   |                 | load levels        |       |               | immunoprophylaxis     | indicating use |          |              |            |
|                |                   |                 | subsequent to the  |       |               | at birth              | of a central   |          |              |            |
|                |                   |                 | treatment)         |       |               |                       | laboaratory    |          |              |            |
|                |                   |                 | ,                  |       |               |                       | and/or record  |          |              |            |
|                |                   |                 |                    |       |               |                       | linkaga        |          |              |            |
|                |                   |                 |                    |       |               |                       | iiiikage.      |          |              |            |
| Zhang YF,      | 🖈 At least        | ★ Drawn         | ★ Valid method     | *     | Always the    | ★★ Same HBeAg         | No             | ★ Yes    | No           | 7 (low)    |
| (2010b),       |                   |                 |                    |       | 2             |                       | description    |          | statement    |            |
|                | somewhat          | from the same   | was used to        | case  |               | sero-status and same  |                |          | of LFU       |            |
| ADRJ, 169      | representative of | community       | ascertain          |       |               | thresholds for HBV    |                |          |              |            |
|                | the average HBV   | (same inclusion | adherence to the   |       |               | DNA level. Same       |                |          |              |            |
|                | infected pregnant | and exclusion   | antiviral therapy  |       |               | regimen for infant    |                |          |              |            |
|                | woman             | criteria also)  | (decrease in viral |       |               | immunoprophylaxis     |                |          |              |            |
|                |                   |                 | load levels        |       |               | at birth              |                |          |              |            |
|                |                   |                 | subsequent to the  |       |               |                       |                |          |              |            |
|                |                   |                 | treatment)         |       |               |                       |                |          |              |            |
| an:1 c 1:      |                   |                 |                    |       | •. <b>1</b> • |                       |                | 1 .1 .   |              |            |
| "Risk of bias  | s assessments     | should be       | classified as      | being | either lov    | w (≥ 7) or            | high (< 7)     | by the N | vewcastle-Ot | tawa scale |

## **Appendix H: Efficacy on the infants' HBV DNA positivity**

- TDF 300 mg (infants' HBV DNA positivity)
  - Overall pooled OR= 0.09 (95% CI: 0.04-0.20), p<0.001, I<sup>2</sup>=0%
  - RCTs only (n=4): pooled OR=0.11 (95%CI: 0.03-0.43), p=0.001, I<sup>2</sup>=0%
  - Non-RCTs only (n=7): pooled OR=0.07 (95%CI: 0.03-0.21), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between RCTs and non-RCTs was 0.64

| Author        | Year      | Country       | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |     |                   |     | OR (95% Cl)       | Events,<br>Treatment | Events,<br>Control |
|---------------|-----------|---------------|-----------------------------------|----------------------------------|-----|-------------------|-----|-------------------|----------------------|--------------------|
| Randomised    | l control | lled trials   |                                   |                                  |     |                   |     |                   |                      |                    |
| Jourdain G    | 2018      | Thailand      | 26-29                             | 8                                |     |                   |     | 0.14 (0.01, 2.70) | 0/149                | 3/147              |
| Lin Y         | 2018      | China         | 24                                | 4                                |     |                   |     | 0.05 (0.00, 0.93) | 0/58                 | 7/52               |
| Liu MH        | 2017      | China         | 28-30                             | 0                                |     |                   |     | 0.21 (0.02, 2.08) | 1/20                 | 4/20               |
| Pan CQ        | 2016      | China         | 30-32                             | 4                                |     | -                 | -   | 0.07 (0.00, 1.24) | 0/92                 | 6/88               |
| Subtotal (I-s | squared   | = 0.0%, p     | = 0.868)                          |                                  |     | $\langle \rangle$ |     | 0.11 (0.03, 0.43) | 1/319                | 20/307             |
| Non-random    | iised co  | ntrolled tria | ls                                |                                  |     |                   |     |                   |                      |                    |
| Chen WJ       | 2017      | China         | 28                                | 0                                |     | -                 | _   | 0.05 (0.00, 0.85) | 0/30                 | 11/44              |
| Hu MF         | 2018      | China         | <0-28                             | NR                               | _   |                   |     | 0.10 (0.01, 1.02) | 1/89                 | 3/30               |
| Wan JY        | 2017      | China         | 28                                | 0                                |     |                   |     | 0.08 (0.00, 1.50) | 0/74                 | 3/42               |
| Wang HB       | 2018      | China         | 20-36                             | NR -                             |     | -                 | _   | 0.04 (0.00, 0.80) | 0/100                | 2/20               |
| Xiao XH       | 2017      | China         | 28                                | 0 or 4                           |     |                   |     | 0.20 (0.01, 4.18) | 0/60                 | 2/61               |
| Zhang BF      | 2018      | China         | 24-28                             | 0                                |     | -                 |     | 0.06 (0.00, 1.01) | 0/39                 | 13/75              |
| Zhou Y        | 2018      | China         | 24-28                             | 0                                |     |                   | _   | 0.06 (0.00, 1.14) | 0/60                 | 4/36               |
| Subtotal (I-s | squared   | = 0.0%, p     | = 0.992)                          |                                  |     | $\Leftrightarrow$ |     | 0.07 (0.03, 0.21) | 1/452                | 38/308             |
| Overall (I-so | quared :  | = 0.0%, p =   | 0.998)                            |                                  |     |                   |     | 0.09 (0.04, 0.20) | 2/771                | 58/615             |
|               |           |               |                                   | .001                             | .01 | .1                | 1 1 | 0                 |                      |                    |

## • LAM 100-150 mg (infants' HBV DNA positivity)

- Overall pooled OR= 0.16 (95% CI: 0.11-0.23), p<0.001, I<sup>2</sup>=0.0%
- RCTs only: pooled OR= 0.22 (95% CI: 0.10-0.47), p<0.001, I<sup>2</sup>=39.8%
- Non-RCTs only: pooled OR=0.14 (95%CI: 0.09-0.23), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between RCTs and non-RCTs was 0.47

| s<br>28<br>28<br>28<br>Philippines 30-34<br>28 | 4<br>0<br>0                                 |   | - 1.28 (0.20, 8.32)<br>0 10 (0.03, 0.33)                         | 3/30   |   |
|--|---|---|--|--|---|
| 28<br>28<br>28<br>Philippines 30-34<br>28      | 4<br>0<br>0                                 |   | <ul> <li>1.28 (0.20, 8.32)</li> <li>0.10 (0.03, 0.33)</li> </ul> | 3/30   |   |
| 28<br>28<br>Philippines 30-34<br>28            | 0<br>0                                      |   | 0 10 (0 03 0 33)   |  | 2/25  |
| 28<br>Philippines 30-34<br>28                  | 0   |   | 0.10 (0.00, 0.00)  | 4/70   | 15/40   |
| Philippines 30-34<br>28                        | 4   |   | 0.13 (0.06, 0.29)  | 9/110  | 44/110  |
| 28   | 4   |   | 0.32 (0.09, 1.12)  | 4/49   | 9/41  |
|  | 4   |   | 0.32 (0.03, 3.18)  | 1/53   | 3/53  |
| o, p = 0.156)                                  |   | $\diamond$  | 0.22 (0.10, 0.47)  | 21/312   | 73/269  |
| trials   |   |   |  |  |   |
| 32   | 4   |   | 0.25 (0.07, 0.92)  | 4/30   | 10/26   |
| 28   | 4   |   | 0.28 (0.10, 0.77)  | 7/48   | 16/42   |
| Anytime  | NR —  |   | - 0.33 (0.01, 8.52)  | 0/29   | 1/30  |
| 28-30  | 12  |   | 0.17 (0.01, 3.51)  | 0/16   | 3/22  |
| 1st Trimester                                  | NR  |   | 0.11 (0.01, 2.23)  | 0/29   | 4/34  |
| 20-34  | 0   |   | 0.03 (0.00, 0.53)  | 0/164  | 8/92  |
| 28   | 0   | -   | 0.13 (0.01, 1.12)  | 1/35   | 6/32  |
| 28   | 4   | •   | 0.06 (0.01, 0.53)  | 1/33   | 9/27  |
| 13-30  | 4   | *   | 0.05 (0.00, 0.88)  | 0/160  | 5/89  |
| 28-30  | 12  | •   | 0.07 (0.01, 0.68)  | 1/42   | 5/20  |
| Pre-pregnancy                                  | 0   |   | 0.08 (0.00, 1.45)  | 0/32   | 5/32  |
| 28   | 4   | *   | 0.08 (0.00, 1.49)  | 0/35   | 4/28  |
| 27   | 4   |   | 0.47 (0.08, 2.75)  | 2/32   | 4/32  |
| 28   | Variable (0,4,6)                            | -   | 0.04 (0.00, 0.87)  | 0/90   | 3/30  |
| 28-30  | 4 —   |   | 0.31 (0.02, 5.38)  | 0/52   | 10/352  |
| 28   | 4 —   | + 1   | 0.10 (0.02, 0.45)  | 2/50   | 15/50   |
| 20-28  | NR -  |   | 0.10 (0.03, 0.33)  | 3/113  | 21/95   |
| 26   | 0   |   | 0.09 (0.01, 0.77)  | 1/24   | 8/24  |
| , p = 0.935)                                   |   | $\diamond$  | 0.14 (0.09, 0.23)  | 22/1014  | 137/1057  |
| p = 0.801)                                     |   | <b>\$</b>   | 0.16 (0.11, 0.23)  | 43/1326  | 210/132   |
| ,<br>p   | 28<br>20-28<br>26<br>p = 0.935)<br>= 0.801) | 28 4 —<br>20-28 NR ·<br>26 0 · · · ·<br>p = 0.935)<br>= 0.801)<br>I I<br>.001 .01 | $\begin{array}{cccccccccccccccccccccccccccccccccccc$             | 28     4     0.10 (0.02, 0.45)       20-28     NR     0.10 (0.03, 0.33)       26     0     0.09 (0.01, 0.77)       0.14 (0.09, 0.23)     0.16 (0.11, 0.23)       1     1 | $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ |

## • LdT 600 mg (infants' HBV DNA positivity)

- Overall pooled OR= 0.08 (95% CI: 0.06-0.11), p<0.001, I<sup>2</sup>=0.0%
- RCTs only: pooled OR= 0.11 (95% CI: 0.05-0.26), p<0.001,  $I^2=0\%$
- Non-RCTs only: pooled OR=0.07 (95%CI: 0.05-0.10), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between RCTs and non-RCTs was 0.29

| Author         Year           Randomised controlled<br>Fu PX         2016           Guo HJ         2011           Wang HY         2018           Zhang Y         2018           Zhao DE         2010           Zhao PS         2017           Zhao DE         2010           Zhao PS         2017           Zhao PS         2017           Subtotal (I-Squared = 0           Non-randomised control           Chen CY         2015           Chen F         2016           Chen WJ         2017           Cui ZL         2015           Feng XM         2017           Cui ZL         2015           Fan LY         2013           Feng XM         2017           Gao P         2016           Ga VL         2015           Han GR         2015           Hu Y         2018           Jiang S         2017           Li CM         2017           Li X         2018           Jiang S         2017           Li X         2018           Li X         2018           Li X         2016           <   | Country<br>tirials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | start in weeks<br>gestation<br>24-28<br>28<br>12-14<br>28<br>Pre-pregnancy<br>28<br>12<br>28<br>888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>1st Trimester<br>24-36<br>28<br>1st Trimester<br>28-32<br>20-32<br>1st Trimester<br>28-32<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20-32<br>20<br>20<br>20-32<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20   | in weeks<br>postpartum<br>4<br>4<br>4<br>24<br>4<br>4<br>12<br>0<br>NR<br>4<br>12<br>0<br>NR<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>0<br>NR<br>8<br>4<br>4<br>12<br>NR<br>NR<br>28<br>3:44<br>NR<br>NR<br>NR<br>8<br>4<br>4<br>NR<br>NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  |             |   | ╴┤╡╦ <sub>╋</sub> ╏╺╬╬╶╢╖╗╗╗<br>╴┤╡╦╦┥╫╝╝╌╶ <del>╲</del> ╦╡╫╎╝╫┝╦╦┝┝╶╴ |          |          | OR (95%)<br>0.33 (0.0<br>0.07 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.06 (0.0) (0.06 (0.0   | 6 CI)<br>33, 3.19)<br>55, 1.41)<br>50, 0, 1.21)<br>51, 0.46)<br>50, 0, 1.21)<br>51, 0.46)<br>51, 0.26)<br>51, 0.26)<br>51, 0.26)<br>52, 0.26)<br>53, 0.26)<br>54, 0.26)<br>55, 0.26)   | Events,<br>Treatment<br>1/100<br>2/28<br>0/40<br>1/50<br>0/34<br>1/30<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/51<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46          | Events, Control<br>3/100 6/26 6/40 13/50 9/34 8/30 9/54 58/374 7/40 6/32 11/44 7/40 6/32 11/49 12/46 4/75 6/60 9/36 9/51 3/22 8/86 4/34 5/40  |
|--|---|---|--|-------------|---|--|----------|----------|---|--|--|---|
| Author         Year           Randomised controlled<br>Fu PX         2016           Guo HJ         2011           Yang HW         2015           Zhang Y         2018           Zhan DB         2010           Zhao DB         2010           Zhao Y         2017           Subtotal (I-squared = 0           Non-randomised contro<br>Chen CY         2015           Chen F         2016           Chen WJ         2017           Chen RZ         2017           Chen RZ         2017           Ge YL         2015           Fan LY         2015           Feng XM         2017           Gao P         2016           Ge YL         2015           Han GR         2015           Han GR         2015           Han GR         2016           Hu W         2016           Hu Y         2018           Jiang S         2017           Li X         2016           Li X         2017           Li X         2016           Peng BA         2012           Qiu B         2016           Peng BA         2012   | Country<br>d trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | gestation<br>24-28<br>28<br>12-14<br>28<br>12-28<br>12<br>28<br>28<br>28<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>20-32<br>1st 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<b>╲╔┥┍┝╸╴╶╲┙╡╓╷┝╷┝╶╶╶┤┤</b> ╼╦╎┍╗┙                               |          |          | OR (95°<br>0.33 (0.0<br>0.26 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.05 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.09 (0.0) (0.0) (0.0<br>0.09 (0.0)                           | <pre>% CI) 33, 3.19) 55, 1.41) 30, 1.21) 31, 0.46) 30, 0.70) 31, 0.82) 31, 1.92) 31, 0.68) 35, 0.26) 30, 0.31) 31, 0.63) 31, 0.43) 31, 0.43) 31, 0.43) 31, 0.22) 30, 0.77) 31, 1, 2.02) 30, 0.231 31, 2.02) 30, 1.30) 31, 2.02) 30, 1.30) 31, 2.02) 30, 1.30) 31, 2.02) 30, 1.30) 31, 4.81)</pre>  | Treatment 1/100 2/28 0/40 1/50 0/34 1/30 0/40 1/60 6/382 0/42 0/31 1/79 1/41 1/50 0/82 0/58 1/36 0/51 0/20 0/358 0/32 0/358 0/32 0/46  | Control<br>3/100<br>6/26<br>6/40<br>13/50<br>9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>12/26<br>8/86<br>4/34                     |
| Randomised controlled           Fu PX         2016           Guo HJ         2011           Wang HY         2018           Yang HW         2015           Zhang Y         2018           Zhao DB         2010           Zhao Y         2017           Subtotal (I-squared = 0           Non-randomised contro           Chen CY         2015           Chen F         2016           Chen WJ         2017           Chen ZX         2017           Cui ZL         2015           Deng Y         2015           Fan LY         2013           Feng XM         2017           Gao P         2016           Ge YL         2015           Han GR         2015           Han GR         2015           Han GR         2016           Hu W         2016           Hu Y         2018           Jiang S         2017           Li CM         2016           Hu ZY         2018           Liu Z         2016           Peng BA         2012           Qiu B         2016           Peng BA         201   | trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 24-28<br>28<br>12-14<br>28<br>12-14<br>28<br>12<br>28<br>28<br>3888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>20-32<br>1st Trimester<br>28-32<br>28-32<br>28<br>20-32<br>28<br>20-32<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>29<br>28<br>29<br>20<br>20<br>28<br>29<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20  | 4<br>4<br>24<br>4<br>12<br>0<br>NR<br>NR<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>12<br>NR<br>NR<br>8<br>3-4<br>NR<br>NR<br>9<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | -<br>-<br>- |   | ┍╴┫┥ <b>╼╓╧╶╌┊╧╝┿</b> ╆╫╣╧┷╬╶╶ <del>┝</del> ╫╪╫╞╫╦┝┠╶                  |          |          | 0.33 (0.0<br>0.26 (0.0<br>0.07 (0.0<br>0.06 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.01 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.07 (0.0<br>0.01 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.0<br>0.01 (0.0<br>0.01 (0.0) (0.   | 33, 3.19)<br>35, 1.41)<br>30, 1.21)<br>11, 0.46)<br>30, 0.70)<br>11, 0.82)<br>11, 1.92)<br>11, 0.68)<br>35, 0.26)<br>30, 0.35)<br>30, 0.31)<br>31, 0.47)<br>31, 0.47)<br>31, 0.47)<br>31, 0.47)<br>31, 0.47)<br>31, 0.22)<br>30, 0.77)<br>31, 2.22)<br>30, 0.33)<br>31, 2.22)<br>30, 0.33)<br>31, 0.23)<br>31, 0.23)<br>31, 2.22)<br>30, 1.30)<br>31, 2.20)<br>30, 1.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 2.30)<br>31, 30)<br>31, 40)<br>31, | 1/100<br>2/28<br>0/40<br>1/50<br>0/34<br>1/30<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46                          | 3/100<br>6/26<br>6/40<br>13/50<br>9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/36<br>9/36<br>9/36<br>9/36<br>9/36<br>9/36<br>9/36 |
| Fu PX         2016           Guo HJ         2011           Wang HW         2018           Zhang Y         2018           Zhang Y         2017           Zhang Y         2017           Subtotal (I-squared = 0           Ono-randomised contro           Chen CY         2017           Subtotal (I-squared = 0           Ono-randomised contro           Chen CY         2015           Fan JY         2017           Chen CY         2017           Chen CY         2017           Chen Z         2017           Gao P         2016           Ge YL         2015           Han GR         2017           Li M         2016           Li ZY         2018           Jiang S         2017           Li XB         2016           Li Y         2018           Uia XB         2016 <td>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China</td> <td>24-28<br/>28<br/>12-14<br/>28<br/>Pre-pregnancy<br/>28<br/>12<br/>28<br/>888)<br/>1st Trimester<br/>Pre-pregnancy<br/>28<br/>13-32<br/>28<br/>24-36<br/>28<br/>24-36<br/>28<br/>24-36<br/>28<br/>24-36<br/>28<br/>24-36<br/>28<br/>20-32<br/>20-32<br/>21st Trimester<br/>28-30<br/>20-32<br/>28<br/>28-32<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>29<br/>20-32<br/>28<br/>28<br/>29<br/>20-32<br/>28<br/>28<br/>29<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20</td> 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<td>-<br/>-<br/></td> <td></td> <td>┥┥<b>ᇾ</b><sub>╋╡</sub>┉쀠╪┵╴╴<sub>┪</sub>┱╕╝┫┿╪╫╡┇╴╧┿╴┨╣╴</td> <td></td> <td></td> <td>0.33 (0.1<br/>0.28 (0.1)<br/>0.07 (0.1)<br/>0.06 (0.1)<br/>0.06 (0.1)<br/>0.09 (0.1)<br/>0.09 (0.1)<br/>0.08 (0.1)<br/>0.08 (0.1)<br/>0.08 (0.1)<br/>0.08 (0.1)<br/>0.06 (0.1)<br/>0.06 (0.1)<br/>0.06 (0.1)<br/>0.06 (0.1)<br/>0.07 (0.1)<br/>0.01 (0.1)</td> <td>33, 3, 19)           35, 1, 41)           05, 1, 41)           05, 0, 1, 21)           11, 0, 46)           00, 0, 70)           11, 1, 0, 46)           00, 0, 0, 70)           11, 1, 0, 46)           00, 0, 0, 70)           11, 1, 0, 20)           00, 0, 0, 55)           00, 0, 0, 55)           00, 0, 0, 31)           11, 0, 40)           11, 0, 40)           11, 0, 43)           11, 0, 72)           00, 0, 0, 77)           11, 2, 21)           00, 0, 0, 23)           11, 2, 202)           00, 1, 2, 30)           11, 2, 202)           10, 1, 2, 30)           11, 2, 43)</td> 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 | 24-28<br>28<br>12-14<br>28<br>Pre-pregnancy<br>28<br>12<br>28<br>888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>20-32<br>20-32<br>21st Trimester<br>28-30<br>20-32<br>28<br>28-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>20-32<br>28<br>28<br>29<br>20-32<br>28<br>28<br>29<br>20-32<br>28<br>28<br>29<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20   | 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| -<br>-<br>  |   | ┥┥ <b>ᇾ</b> <sub>╋╡</sub> ┉쀠╪┵╴╴ <sub>┪</sub> ┱╕╝┫┿╪╫╡┇╴╧┿╴┨╣╴         |          |          | 0.33 (0.1<br>0.28 (0.1)<br>0.07 (0.1)<br>0.06 (0.1)<br>0.06 (0.1)<br>0.09 (0.1)<br>0.09 (0.1)<br>0.08 (0.1)<br>0.08 (0.1)<br>0.08 (0.1)<br>0.08 (0.1)<br>0.06 (0.1)<br>0.06 (0.1)<br>0.06 (0.1)<br>0.06 (0.1)<br>0.07 (0.1)<br>0.01 (0.1) | 33, 3, 19)           35, 1, 41)           05, 1, 41)           05, 0, 1, 21)           11, 0, 46)           00, 0, 70)           11, 1, 0, 46)           00, 0, 0, 70)           11, 1, 0, 46)           00, 0, 0, 70)           11, 1, 0, 20)           00, 0, 0, 55)           00, 0, 0, 55)           00, 0, 0, 31)           11, 0, 40)           11, 0, 40)           11, 0, 43)           11, 0, 72)           00, 0, 0, 77)           11, 2, 21)           00, 0, 0, 23)           11, 2, 202)           00, 1, 2, 30)           11, 2, 202)           10, 1, 2, 30)           11, 2, 43)   | 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| Guo HJ         2011           Wang HW         2018           Wang HW         2018           Yang HW         2018           Zhang HZ         2015           Zhang HW         2017           Zhao DB         2010           Zhao Y         2017           Zhu J         2017           Zhu J         2017           Chen CY         2015           Chen F         2016           Chen WJ         2017           Chen ZX         2017           Gao P         2016           Gay L         2015           Fan LY         2018           Hu W1         2016           Gay L         2017           Li CM         2017           Li CM         2017           Li CM         2017           Li W1         2016           Li W1         2016           Li W1         2016           Li W2         2017           Li W3         2017           Li W1 </td 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<td>28<br/>12-14<br/>28<br/>Pre-pregnancy<br/>28<br/>12<br/>28<br/>888)<br/>1st Trimester<br/>Pre-pregnancy<br/>28<br/>13-32<br/>28<br/>24-36<br/>28<br/>24-36<br/>28<br/>1st Trimester<br/>28-30<br/>20-32<br/>1st Trimester<br/>28-30<br/>20-32<br/>1st Trimester<br/>28-30<br/>20-32<br/>1st Trimester<br/>28-30<br/>20-32<br/>28<br/>28<br/>28<br/>20-32<br/>28<br/>28<br/>28<br/>28<br/>29<br/>20-32<br/>28<br/>28<br/>28<br/>29<br/>20<br/>30<br/>20-32<br/>28<br/>28<br/>28<br/>28<br/>29<br/>20<br/>30<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20<br/>20</td> <td>4<br/>24<br/>NR<br/>4<br/>12<br/>0<br/>NR<br/>0<br/>NR<br/>4<br/>4<br/>24<br/>4<br/>0<br/>12<br/>NR<br/>28<br/>34<br/>NR<br/>28<br/>34<br/>NR<br/>NR<br/>4<br/>NR<br/>4<br/>4<br/>4<br/>4</td> <td>-<br/>-<br/></td> <td></td> <td>┤╦╧╡┉╩┍╶╶╦╦╡╩╝╬╋╖╝╕</td> <td></td> <td></td> <td>0.28 (0.0<br/>0.07 (0.0<br/>0.06 (0.0<br/>0.09 (0.0<br/>0.09 (0.0<br/>0.08 (0.0<br/>0.08 (0.0<br/>0.08 (0.0<br/>0.06 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  | 28<br>12-14<br>28<br>Pre-pregnancy<br>28<br>12<br>28<br>888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>28<br>28<br>28<br>20-32<br>28<br>28<br>28<br>28<br>29<br>20-32<br>28<br>28<br>28<br>29<br>20<br>30<br>20-32<br>28<br>28<br>28<br>28<br>29<br>20<br>30<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20<br>20  | 4<br>24<br>NR<br>4<br>12<br>0<br>NR<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>12<br>NR<br>28<br>34<br>NR<br>28<br>34<br>NR<br>NR<br>4<br>NR<br>4<br>4<br>4<br>4  | -<br>-<br>  |   | ┤╦╧╡┉╩┍╶╶╦╦╡╩╝╬╋╖╝╕  |          |          | 0.28 (0.0<br>0.07 (0.0<br>0.06 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.09 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6/26<br>6/40<br>13/50<br>9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/36<br>9/36<br>9/32<br>8/86<br>4/34<br>5/40                  |
| Wang HY         2018           Yang HW         2015           Zhang Y         2018           Zhao DB         2010           Zhao Y         2017           Subtotal         (I-squared e)           Von-randomised contra           Chen CY         2017           Subtotal         (I-squared e)           Chen CY         2017           Chen F         2016           Chen F         2016           Chen XJ         2017           Chen F         2016           Chen F         2016           Chen F         2017           Chen F         2016           Chen F         2016           Gae YL         2015           Han GR         2015           Han GR         2016           Gae YL         2018           Jiang S         2017           Li N         2016           Li Y         2018           Li GM         2017           Li XB         2016           Li Y         2018           Li XB         2017           Li XB         2016           QUB         2017 <t< td=""><td>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>China<br/>Olo%, <math>p = 0</math><br/>olled 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Trimester<br/>28-32<br/>28-32<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28-32<br/>28<br/>28<br/>28-32<br/>28<br/>28<br/>28-32<br/>28<br/>28<br/>28-32<br/>28<br/>28<br/>28<br/>28-32<br/>28<br/>28<br/>28<br/>28<br/>28<br/>28<br/>28<br/>28<br/>28<br/>2</td><td>24<br/>4<br/>NR<br/>4<br/>12<br/>0<br/>NR<br/>0<br/>NR<br/>4<br/>4<br/>24<br/>0<br/>12<br/>NR<br/>NR<br/>8<br/>3-4<br/>NR<br/>NR<br/>NR<br/>NR<br/>8<br/>3-4<br/>NR<br/>NR<br/>4<br/>NR<br/>4<br/>4<br/>4<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12<br/>12</td><td>-<br/>-<br/></td><td></td><td>┙╗╡┉╖╘╌╶╧┿╪╺╞╧╛┶┶┿<br/>┙</td><td></td><td></td><td>0.07 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 | 24<br>4<br>NR<br>4<br>12<br>0<br>NR<br>0<br>NR<br>4<br>4<br>24<br>0<br>12<br>NR<br>NR<br>8<br>3-4<br>NR<br>NR<br>NR<br>NR<br>8<br>3-4<br>NR<br>NR<br>4<br>NR<br>4<br>4<br>4<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12  | -<br>-<br>  |   | ┙╗╡┉╖╘╌╶╧┿╪╺╞╧╛┶┶┿<br>┙  |          |          | 0.07 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.09 (0.0<br>0.04 (0.04                                 | 00, 1.21)<br>11, 0.46)<br>00, 0.70)<br>11, 0.82)<br>11, 1.92)<br>11, 0.69)<br>15, 0.26)<br>10, 0.69)<br>15, 0.26)<br>10, 0.69)<br>15, 0.26)<br>10, 0.47)<br>11, 1.82)<br>10, 0.47)<br>11, 0.83)<br>11, 0.72)<br>10, 0.77)<br>11, 2.81)<br>10, 0.23)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>11, 2.81)<br>12, 2.81)<br>13, 2.81)<br>14, 2.81)<br>14, 2.81)<br>14, 2.81)<br>14, 2.81)<br>14, 2.81)<br>14, 2.81)<br>15, 0.26)<br>15, 0.26)<br>16, 0.95)<br>16, 0.95)<br>17, 0.82)<br>17, 0.82)<br>18, 0.85)<br>19, 0.85)   | 0/40<br>1/50<br>0/34<br>1/30<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/35<br>0/32<br>0/46                                   | 6/40<br>13/50<br>9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34  |
| Yang HW         2015           Yang HW         2015           Zhang Y         2018           Zhao DB         2017           Subtotal (I-squared = I           Von-randomised contro           Chen CY         2017           Subtotal (I-squared = I           Von-randomised contro           Chen CY         2017           Subtotal (I-squared = I           Onen XU         2017           Chen WJ         2018           Cao P         2016           Cae YL         2016           Cae YL         2016           Cae YL         2018           UWH         2016           Li W         2016           Li W         2016           Li W         2016           Chen N         2015           Sheng Q         2018b           Sun W         2017           Sheng Q         2018b<   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>Pre-pregnancy<br>28<br>12<br>28<br>888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2   | 4<br>NR<br>12<br>0<br>NR<br>4<br>24<br>0<br>12<br>NR<br>8<br>4<br>4<br>24<br>0<br>12<br>NR<br>8<br>34<br>4<br>NR<br>8<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>8<br>4<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8   | -<br>-<br>- |   | ╺╴╡╫╼╶┝╴╴╶┰╼╞╎╝╣┝╝   |          |          | 0.06 (0.0<br>0.04 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.010 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.05 (0.0<br>0.04 (0.0<br>0.05 (0.0) (0.05 (0.0) (0.05                               | 11, 0.46)           10, 0.46)           10, 0.70)           11, 0.82)           11, 1.92)           11, 1.92)           11, 0.68)           15, 0.26)           00, 0.95)           10, 1.20)           00, 0.31)           11, 0.83)           11, 0.83)           11, 0.83)           11, 0.83)           11, 0.72)           00, 0.77)           11, 2.81)           00, 0.23)           11, 2.81)           00, 0.23)           11, 2.81)           00, 0.23)           11, 2.81)           01, 0.23)           11, 2.81)           01, 0.23)           11, 2.81)           01, 0.23)           11, 2.81)           01, 0.23)           11, 2.81)           01, 0.23)           11, 2.81)           02, 0.33)           11, 2.81)           03, 0.33)           11, 2.81)           03, 0.33)           11, 3.81)           03, 1.30)           11, 4.81)  | 1/50<br>0/34<br>1/30<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/358<br>0/32<br>0/46                                  | 13/50<br>9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>13/22<br>8/86<br>4/34<br>5/40   |
| Zhang Y         2018           Zhao Y         2017           Zhao Y         2017           Zhu J         2017           Zhu J         2017           Subtotal (L-squared = 1)         2017           Non-randomised control         2016           Chen CY         2015           Dong Y         2017           Chen ZX         2017           Cui ZL         2015           Deng Y         2015           Deng XM         2017           Gao P         2016           Ge YL         2015           Han GR         2015           Han GR         2018           Hu W         2018           Liang S         2017           Li M         2016           Li L Q         2018           Li L Q         2017           Li M         2016           Liang S         2017           Li M         2016           Diu B         2016           Peng BA         2012           Diu B         2016           Ren N         2018           Sheng Q         2018a           Sheng Q         2018b  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | Pre-pregnancy<br>28<br>12<br>28<br>.888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>22<br>1st Trimester<br>28<br>29<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28<br>28<br>28<br>20-32<br>1st Trimester<br>28<br>28<br>28<br>29<br>20-32<br>1st Trimester<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | NR<br>4<br>12<br>0<br>NR<br>NR<br>0<br>NR<br>4<br>4<br>4<br>4<br>4<br>24<br>4<br>0<br>12<br>NR<br>NR<br>28<br>34<br>NR<br>NR<br>NR<br>28<br>34<br>NR<br>NR<br>4<br>4<br>NR   | -<br>-<br>  |   | ╷ <sub>┥</sub> ╫╬╟╱╶╶╦┰┨╜┪╬╗╬┥┨╴┦╅╸╗╣╴                                 |          |          | 0.04 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.07 (0.0) (0.07 (0.0) (0.07 (0.0) (0.07 (0.0) (0.07 (0.0) (0.07 (0.0) (0.07 (0.0) (0.07   | 00, 0.70)           01, 0.82)           01, 1.92)           01, 1.92)           01, 0.82)           01, 0.82)           05, 0.26)           00, 0.95)           00, 0.95)           00, 0.31)           11, 0.83)           01, 0.47)           01, 1.82)           00, 0.130)           01, 0.72)           00, 0.33)           01, 2.81)           01, 2.81)           01, 2.83)           01, 2.83)           01, 2.83)           01, 2.83)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 2.81)           01, 3.01)           01, 4.81)   | 0/34<br>1/30<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/32<br>0/46   | 9/34<br>8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34   |
| Lands         Control           Chao DB         2010           Chao DY         2017           Subtotal         (I-squared = 0           Non-randomised contro         2015           Subtotal         (I-squared = 0           Non-randomised contro         2017           Chen F         2016           Chen WJ         2017           Chen WJ         2017           Chen WJ         2017           Chen WJ         2017           Chen WJ         2015           Gan QY         2015           Gan CP         2016           Gan GR         2017           Gan GR         2015           Han GR         2015           Han GR         2016           Gan YL         2018           Gu WH         2018           Gu WH         2017           Li W         2018           Li CY         2018           Li W Z         2017           Li W Z         2017           Li W Z         2017           Li W Z         2017           Li W Z         2018           Diu W Z         2018           Diu W Z   | China<br>China<br>China<br>China<br>O.0%, p = 0<br>olled trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 1st Trimester           Pre-pregnancy           28           18t Trimester           Pre-pregnancy           28           13-32           28           24-36           28           24-36           28           20-32           1st Trimester           28-30           20-32           28           28-32           28           28           28-32           28           28           28           28           29-32           28           28           28           29-32           28           28           28           29           28           29           28           28           29           28           29           28           29           28           29           28           29           28           29           28      2   | 4<br>12<br>0<br>NR<br>0<br>NR<br>0<br>NR<br>4<br>24<br>0<br>2<br>NR<br>NR<br>4<br>24<br>0<br>2<br>NR<br>NR<br>8<br>3-4<br>NR<br>NR<br>0<br>2<br>NR<br>NR<br>4<br>24<br>4<br>0<br>2<br>NR<br>8<br>3-4<br>NR<br>8<br>3-4<br>NR<br>8<br>4<br>4<br>2<br>4<br>0<br>2<br>8<br>4<br>4<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>4<br>8<br>8<br>8<br>8<br>8<br>8<br>8   | -<br>-<br>  |   | ┙┙┿┿ <u>┝╶╶</u> ┿╦╕╝╅┿╬┇╶╴┿╦╴╴╡╝╴                                      |          |          | 0.09 (0.1<br>0.08 (0.1<br>0.08 (0.0<br>0.08 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.07 (0.0<br>0.01 (0.0<br>0.04 (0.0) (0.04 (0.0) (0.04 (0.0) (0.04 (0.0) (0.04 (  | D1, 0.82)           D1, 0.82)           D1, 0.69)           D5, 0.26)           D0, 0.95)           D0, 0.31)           D1, 0.83)           D1, 0.83)           D1, 0.83)           D1, 1.20)           D0, 0.31)           D1, 0.83)           D1, 1.20)           D0, 0.31)           D1, 1.20)           D0, 0.23)           D1, 2.81)           D0, 0.23)           D1, 2.83)           D1, 2.81)           D0, 0.30)           D1, 2.81)           D0, 1.30)           D1, 4.81)  | 0/42<br>0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/58<br>1/36<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/358<br>0/32<br>0/46  | 8/30<br>4/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Instruct         Construct           Chao Y         2017           Subtotal         (I-squared = (           Non-randomised contr         Construct           Subtotal         (I-squared = (           Subtotal         (I-squared = (           Chen CY         2015           Chen F         2016           Deng Y         2017           Chen ZX         2017           Chen ZX         2017           Care X         2018           Care X         2018           Hu W         2016           Care X         2017           Li W         2018           Li CM         2017           Li N         2016           Care X         2017           Li N         2016           Care X         2017           Li N         2016           Care X         2017           Li N         <   | China<br>China<br>O.0%, p = 0<br>olled trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 12<br>12<br>28<br>.888)<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>28<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2  | 12<br>0<br>NR<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>12<br>NR<br>28<br>34<br>NR<br>28<br>34<br>NR<br>8<br>34<br>NR<br>4<br>NR<br>4<br>8<br>4<br>8<br>4  | -<br>       |   | ┉┉┝╌╶╁╖┧┉╓┿┑┙┙┙  |          |          | 0.00 (0.0<br>0.08 (0.0<br>0.08 (0.0<br>0.01 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.09 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.01 (0.0) (0.01   | 11, 1.92)           11, 1.92)           11, 0.69)           15, 0.26)           00, 0.95)           00, 0.31)           11, 0.83)           11, 0.83)           11, 0.72)           00, 1.20)           11, 0.72)           00, 0.31)           11, 0.72)           00, 0.23)           11, 2.81)           00, 0.23)           11, 2.81)           00, 0.33)           11, 2.82)           00, 0.33)           11, 2.81)           00, 0.33)           11, 4.81)  | 0/40<br>1/60<br>6/382<br>0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46   | 7/40<br>9/54<br>58/374<br>7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Linux /         2017           Subtotal         (I-squared e)           Non-randomised contra           Chen CY         2015           Chen F         2016           Chen F         2016           Chen F         2017           Chen F         2016           Chen F         2017           Chu Z         2017           Chu Z         2017           Chu Z         2015           Fan LY         2013           Feng XM         2017           Gao P         2016           Ga YL         2015           Hat GR         2015           Hat GR         2015           Hat GR         2015           Hat GR         2015           Lian GR         2017           Li N         2016           Li Y         2018           Li LY         2018           Li LY         2016           Peng BA         2012           Qiu B         2016           Ren N         2015           Sheng Q         2018           Sun W         2017           Fan Z         2018      Sheng Q         2   | China<br>O.0%, p = 0<br>olled trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>24-36<br>28<br>20-32<br>1st Trimester<br>28-32<br>28-32<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28<br>28-32<br>28<br>28-32<br>28<br>28-32<br>28<br>28-32<br>28<br>28-32<br>28<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32<br>39-32 | 0<br>NR<br>NR<br>0<br>NR<br>4<br>4<br>24<br>0<br>NR<br>NR<br>8<br>34<br>NR<br>NR<br>NR<br>NR<br>NR<br>NR<br>NR<br>NR<br>4<br>NR<br>NR<br>4<br>NR<br>12<br>NR<br>NR<br>0<br>NR<br>0<br>NR<br>0<br>NR<br>0<br>NR<br>0<br>NR<br>0<br>NR<br>0  | -<br>       |   | ┍╏┇╏┾┟┠┠╣ <b>╩╁╟┇┸┦╶╶</b> Ѧ┥   | ><br>    |          | 0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.01 (0.0) (0.01 (0.0) (0.01 (0.   | b1, 1.62/           b1, 0.68)           b5, 0.26)           b5, 0.26)           b0, 0.95)           b0, 1.20)           b0, 0.31)           b1, 0.43)           b1, 0.43)           b1, 0.43)           b1, 0.47)           b1, 1.82)           b0, 1.30)           b1, 0.72)           b0, 0.77)           b1, 2.81)           b0, 0.23)           b1, 2.81)           b0, 0.23)           b1, 2.81)           b0, 1.30)           b1, 4.81)  | 0/42<br>0/31<br>1/79<br>1/41<br>1/79<br>1/41<br>1/50<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/358<br>0/32<br>0/46   | 7/40<br>6/32<br>11/44<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Linu G         Linu G           Abbotal         [H-quared = 1]           Non-randomised contro         Chen CY         2015           Chen CY         2015         Chen WJ         2017           Chen ZX         2017         Chen ZX         2017           Chen ZX         2017         Chen ZX         2017           Chen ZX         2017         Chen ZX         2017           Gao P         2016         Cae YL         2016           Ger YL         2016         Cae YL         2016           Ger YL         2018         Cae YL         2018           Han GR         2017         Cae YL         2018           Jiang S         2017         Cae YL         2018           Li X         2018         2016         Cae YL           Li X         2018         2017         Cae YL           Li X         2018         2016         Cae YL           QUB<   | Ohina<br>Ohina<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | 1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28<br>28<br>28<br>29<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | NR<br>NR<br>0<br>NR<br>4<br>24<br>0<br>12<br>NR<br>8<br>3-4<br>NR<br>NR<br>23-4<br>NR<br>NR<br>8<br>3-4<br>NR<br>NR<br>8<br>4<br>NR<br>4<br>NR<br>9<br>4<br>NR<br>9<br>12<br>10<br>12<br>10<br>12<br>10<br>12<br>10<br>10<br>12<br>10<br>10<br>12<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10  | -<br>       |   | ·Ŷ╴╴╁┱┧╙╫┿╫╫┆╌╴┽┱╴╴┙   | ><br>    |          | 0.05 (0.0<br>0.05 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.07 (0.0) (   | b1, 0.00         b1, 0.00           b5, 0.26)         b2, 0.26)           b0, 0.95)         b0, 0.31)           b1, 0.83)         b1, 0.47)           b1, 1.82)         b0, 1.30)           b1, 0.77)         b1, 2.81)           b0, 0.23)         b1, 2.02)           b1, 2.02)         b0, 0.130)           b1, 2.02)         b0, 0.23)           b1, 2.02)         b0, 1.30)           b1, 4.81)         b1, 4.81)   | 0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/358<br>0/32<br>0/46   | 7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Non-randomised contrr           Chen CY         2015           Chen CY         2015           Chen WJ         2017           Chen WJ         2017           Chen ZX         2017           Chen ZX         2017           Cui ZL         2015           Fan LY         2013           Feng XM         2017           Gao P         2016           Ge YL         2018           Han GR         2018           Hu W         2016           Li W         2018           Liang S         2017           Li CM         2016           Li ZY         2018           Liang S         2017           Liang S         2016           Ren N         2016           Sheng Q         2018      Sheng Q  | olled trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28<br>28-32<br>28<br>28<br><0-28<br>28<br>30<br>20-36  | NR<br>NR<br>0<br>NR<br>4<br>24<br>4<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>4<br>NR   | -<br>       |   |  |          |          | 0.05 (0.0<br>0.06 (0.0<br>0.04 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.07 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.110 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.023 (0.0)   | 00, 0.95)<br>00, 1.20)<br>01, 0.31)<br>01, 0.47)<br>01, 0.47)<br>01, 0.47)<br>01, 0.77)<br>01, 0.72)<br>00, 0.77)<br>01, 0.23)<br>01, 2.20)<br>00, 0.33)<br>01, 2.20)<br>00, 0.33)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 2.31)<br>01, 0.43)<br>01, 0.43)   | 0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/82<br>0/58<br>1/36<br>0/51<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Non-Failloonised Colinit           Non-Failloonised Colinit           Chen F         2015           Chen ZX         2017           Gao P         2013           Fen XM         2017           Gao P         2016           Ge YL         2015           Hen GR         2015           He T         2018           Jiang S         2017           Li CM         2016           Li ZY         2018           Jiang S         2017           Li M         2016           Li ZY         2018           Li Li Q         2017           Li X         2016           Ren N         2016           Sheng Q         2018           Sun W         2017           Sheng Q         2018           Sun W         2017           Fan X         2016           Gen N         2015           Sheng Q   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 1st Trimester<br>Pre-pregnancy<br>28<br>13-32<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28-32<br>28<br><0-28<br>28<br>28<br>30<br>20-32<br>28<br>30<br>20-32<br>28<br>30<br>28-36  | NR<br>NR<br>0<br>NR<br>4<br>24<br>4<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>4<br>NR   | -<br>       |   | ┍ <u>┍</u> ┍┍┍┍┍┍┍┍┍   | -        |          | 0.05 (0.0<br>0.04 (0.0<br>0.11 (0.0<br>0.06 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.10 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.023 (0.0)   | 00, 0.95)           00, 1.20)           00, 0.31)           01, 0.83)           01, 0.47)           01, 1.82)           00, 1.30)           01, 0.72)           00, 0.31)           01, 0.72)           00, 0.77)           01, 2.81)           01, 2.23)           01, 2.02)           01, 3.00)           01, 4.81)  | 0/42<br>0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 7/40<br>6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/36<br>9/36<br>9/36<br>3/22<br>8/86<br>4/34<br>5/40   |
| Abel O         2016           Chen F         2016           Chen ZX         2017           Cui ZL         2015           Deng Y         2015           Deng XM         2017           Cui ZL         2015           Deng XM         2017           Jan P         2016           Bay N         2017           Jan GR         2015           Hu Y         2018           Ju WH         2016           Ju Y         2018           Ju CY         2014           Ju Y         2018           Ju CY         2014           Ju Y         2016           Pang BA         2012           Ju B         2016           Pang BA         2012           Ju B         2016           Pang BA         2012           Sheng Q         2018           Sun W         2017           Fan Z         2018           Sun W         2017           Tan Z         2016           Tan Z         2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 13     -1000       Pre-pregnancy       28       13-32       28       24-36       28       28       28       20-32       1st Trimester       28-32       28       28-32       28       29    <   | NR<br>0<br>NR<br>4<br>4<br>24<br>4<br>0<br>12<br>NR<br>NR<br>28<br>3-4<br>NR<br>28<br>3-4<br>NR<br>NR<br>4<br>NR<br>NR<br>4<br>4<br>NR   |             |   | ╵╡┇╹╺┝╺┝╶┝╹╕╝┝┙┙   |          |          | 0.06 (0.0<br>0.04 (0.0<br>0.11 (0.0<br>0.06 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.23 (0.0)<br>0.02 (0.0<br>0.02 (0.0)   | x0, 0.303           x0, 0.303           y00, 1.20           y00, 0.31           y1, 0.83           y1, 0.83           y1, 0.47           y01, 1.82           y00, 1.30           y1, 0.72           y00, 0.77           y01, 2.81           y00, 0.23           y01, 2.02           y00, 1.30           y1, 2.02           y00, 1.30           y1, 4.81  | 0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/32<br>0/46  | 6/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Julei F         2016           Johen WJ         2017           Chen XZ         2017           Cui ZL         2017           Cui ZL         2015           Fan LY         2013           Fan LY         2013           Fan LY         2015           Fan LY         2016           Gao P         2016           Hu WH         2016           Hu WH         2016           Li CM         2017           Li CM         2017           Li CM         2016           Li ZY         2018           Suic Y         2016           Li U         2016           Li W Z         2016           Di W         2016           Di W         2016           Sheng Q         2018           Sun W         2017           Tar Z         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | Prepagnaticy<br>28<br>13-32<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28-32<br>28<br><0-28<br>28<br><0-28<br>28<br>30<br><0-28<br>28<br>30<br>28-36<br>28<br>30<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-36<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-3               | NN<br>NR<br>4<br>24<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4   | -           |   | ╺ <u>┍</u> ╒╹╘┶┟╘┎┾┉┶┟╹ <b>┙</b>                                       |          |          | 0.05 (0.0<br>0.04 (0.0<br>0.11 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.14 (0.0<br>0.10 (0.0<br>0.01 (0.0<br>0.07 (0.0))   | x0, 1.20)           x0, 0.31)           x0, 0.83)           x1, 0.47)           x1, 1.82)           x0, 1.30)           x1, 1.30)           x1, 2.30)           x1, 2.81)           x0, 0.23)           x1, 2.02)           x0, 1.30)           x1, 2.02)           x1, 2.02)           x1, 2.02)           x1, 4.81)  | 0/31<br>1/79<br>1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/32<br>0/46  | 0/32<br>11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Inter Wo         2017           Deng Y         2015           Jan LY         2013           Feng XM         2017           Jac Z         2015           Fan LY         2013           Feng XM         2017           Jac AR         2015           Jan GR         2016           Ju WH         2016           Ju Y         2018           Liu CY         2014           Liu J         2017           Li X         2016           Ju J         2017           Liu S         2016           Ju J         2017           Liu S         2016           Ju B         2016           Pang BA         2012           Ju B         2016           Ren N         2015           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Fan J         2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>13-32<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28<br>28-32<br>28<br><0-28<br>28<br>30<br><0-28<br>28<br>30<br>28-36<br>28<br>30<br>28-36<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 0<br>NR<br>4<br>24<br>4<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR  | _<br>       |   | ╶╏╡╶┉╶╴╴╴  | *        |          | 0.04 (0.0<br>0.11 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.14 (0.0<br>0.14 (0.0<br>0.14 (0.0<br>0.10 (0.0<br>0.10 (0.0<br>0.23 (0.0<br>0.23 (0.0)   | 00, 0.31)<br>01, 0.83)<br>01, 0.47)<br>01, 1.82)<br>00, 1.30)<br>01, 0.72)<br>00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)   | 1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 11/44<br>17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Jhen ZX         2017           Qil ZL         2015           Deng Y         2015           Fan LY         2013           Feng XM         2017           Bao P         2016           Ger YL         2015           Han GR         2015           Han GR         2015           Han GR         2016           Hu WH         2016           Li W         2017           Li M         2016           Li CY         2018           Liu CY         2014           Liu J         2017           Li W         2016           Pang BA         2012           Qiu B         2016           Pang BA         2015           Sheng Q         2018           Sun W         2017           Fan Z         2018           Sun W         2017   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 13-32<br>28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28-32<br>28<br><0-28<br>28<br>28<br>30<br>28-36<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>30<br>28<br>28<br>30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | NH<br>4<br>24<br>0<br>12<br>NR<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR  |             |   | ╶ <b>╹</b> ╘╹╘╺╘╵ <mark>╞</mark> ╗┡ <sub>┝</sub> ┡╷                    | -        |          | 0.11 (0.0<br>0.06 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.14 (0.0<br>0.10 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.23 (0.0<br>0.0 25 (0.0  | 01, 0.83)         01, 0.47)         01, 1.82)         00, 1.30)         01, 0.72)         00, 0.77)         01, 2.81)         00, 0.23)         01, 2.02)         00, 1.30)         01, 2.02)         00, 1.30)         01, 4.81)  | 1/41<br>1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 17/89<br>12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Jui ZL         2015           Jong Y         2013           Feng XM         2017           Jao P         2016           Jao R         2015           He T         2018           Hu W         2016           Ju Y         2018           Lin GM         2017           Ji N         2016           Ju Y         2018           Ju GY         2014           Ju J         2017           Ju X         2016           Peng BA         2012           Ju B         2016           Peng NA         2015           Sheng Q         2018           Sun W         2017           Tar Z         2018           Sun W         2017   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>24-36<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br><0-28<br>28<br><0-28<br>28<br>28<br>28<br>30<br>28-36   | 4<br>24<br>4<br>0<br>12<br>NR<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR   | -           |   |  | -        |          | 0.06 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.23 (0.0   | 01, 0.47)<br>01, 1.82)<br>00, 1.30)<br>01, 0.72)<br>00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)   | 1/50<br>0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 12/46<br>4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40   |
| Jeng Y         2015           Feng XM         2017           Jaao P         2016           Jaar P         2016           Jaar R         2015           Han GR         2015           Han GR         2015           Han GR         2016           Hu Y         2018           Ju WH         2017           Li K         2017           Li K         2017           Li K         2017           Li K         2016           Ju CY         2018           Ju CY         2016           Pang BA         2012           Qui B         2016           Pang BA         2015           Sheng Q         2018a           Sheng Q         2018a           Sun W         2017           Fan Z         2016           Tan Z         2016  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 24-36<br>28<br>28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28<br><0-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 4<br>24<br>4<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>NR<br>4<br>NR<br>4<br>NR  | -<br>       | - |  | *        |          | 0.10 (0.0<br>0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.01 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.23 (0.0   | 01, 1.82)<br>00, 1.30)<br>01, 0.72)<br>00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)  | 0/82<br>0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 4/75<br>6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Fan LY         2013           Feng XM         2017           Jaao P         2016           Jaa P         2016           Jaa P         2015           Han GR         2015           Har GR         2018           Ju WH         2018           Jiang S         2017           Ji M         2016           Ji TY         2018           Jiang S         2017           Ji N         2016           Ji ZY         2018           Jiu Y         2016           Peng BA         2012           Qiu B         2016           Peng NA         2015           Sheng Q         2018           Sun W         2017           Fan X         2018           Sun W         2017           Fan Z         2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28-32<br>28<br>28<br>40-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 24<br>4<br>0<br>12<br>NR<br>8<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>8  | -<br>       | * |  | -        |          | 0.07 (0.0<br>0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.11 (0.0<br>0.10 (0.0<br>0.23 (0.0<br>0.23 (0.0  | 00, 1.30)<br>01, 0.72)<br>00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)   | 0/58<br>1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 6/60<br>9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Feng XM         2017           Sao P         2016           Sao YL         2015           San GR         2015           Han GR         2015           Han GR         2015           He T         2018           Hu YH         2018           Biang S         2017           Li CM         2017           Li N         2018           Liu CY         2014           Liu J         2017           Liu XB         2016           Pang BA         2012           Diu B         2016           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Fan Z         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br><0-28<br>28<br><0-28<br>28<br>30<br>28-36  | 4<br>0<br>12<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4  | -<br>       | - |  | <u> </u> |          | 0.09 (0.0<br>0.04 (0.0<br>0.14 (0.0<br>0.01 (0.0<br>0.01 (0.0<br>0.07 (0.0<br>0.23 (0.0   | 01, 0.72)<br>00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)  | 1/36<br>0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 9/36<br>9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Gao P         2016           Ge YL         2015           Jan GR         2015           Ha T         2018           Ju WH         2018           Juang S         2017           Li M         2018           Jiang S         2017           Li N         2018           Jiu Y         2018           Jiu ZY         2018           Jiu XB         2016           Pang BA         2012           Qiu B         2016           Sheng Q         2018           Sun W         2017           Fan Z         2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 1st Trimester<br>28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br><0-28<br>28<br><0-28<br>28<br>28<br>30<br>28-36  | 0<br>12<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4   | -<br>       | - |  | -        |          | 0.04 (0.0<br>0.14 (0.0<br>0.01 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.23 (0.0  | 00, 0.77)<br>01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)   | 0/51<br>0/20<br>0/358<br>0/32<br>0/46  | 9/51<br>3/22<br>8/86<br>4/34<br>5/40  |
| Ge YL         2015           Han GR         2015           Han GR         2015           He T         2018           Hu WH         2018           Hu WH         2018           Hu WH         2017           Li CM         2017           Li CM         2016           Li ZY         2018           Liu J         2017           Liu XB         2016           Liu Y         2016           Liu Z         2016           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Fan Z         2016           Tan Z         2016   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-30<br>20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28<br><0-28<br>28<br>28<br>28<br>30<br>28-36  | 12<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR  | •           |   |  | -        |          | 0.14 (0.0<br>0.01 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.23 (0.0   | 01, 2.81)<br>00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)  | 0/20<br>0/358<br>0/32<br>0/46  | 3/22<br>8/86<br>4/34<br>5/40  |
| tan GR         2015           te T         2018           tu WH         2016           tu Y         2018           tiang S         2017           i CM         2016           tu Y         2018           i I CY         2018           i U CY         2014           ti J 2017         2016           i u XP         2016           Pang BA         2012           2018         2016           Scheng Q         2018a           Sheng Q         2018b           Sun W         2017           fan Z         2016           fan Z         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 20-32<br>1st Trimester<br>28<br>28-32<br>28<br>28<br><0-28<br>28<br>28<br>28<br>30<br>28-36   | NR<br>NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4  | •           | _ |  |          |          | 0.01 (0.0<br>0.10 (0.0<br>0.07 (0.0<br>0.23 (0.0  | 00, 0.23)<br>01, 2.02)<br>00, 1.30)<br>01, 4.81)   | 0/358<br>0/32<br>0/46  | 8/86<br>4/34<br>5/40  |
| He T         2018           Hu WH         2016           Hu Y         2018           Iiang S         2017           i CM         2016           i ZY         2018           iu GY         2018           iu Q         2017           i N         2016           iu Y         2014           iu J         2017           iu XB         2016           Pang BA         2012           Diu B         2016           Pang Q         2018           Sheng Q         2018           Sun W         2017           fan Z         2018           Sun W         2017           fan Z         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 1st Trimester<br>28<br>28-32<br>28<br>28<br><-0-28<br>28<br>28<br>30<br>28-36   | NR<br>28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4  |             |   |  | *        |          | 0.10 (0.0<br>0.07 (0.0<br>0.23 (0.0   | 01, 2.02)<br>00, 1.30)<br>01, 4.81)  | 0/32<br>0/46   | 4/34<br>5/40  |
| łu WH         2016           łu Y         2018           łang S         2017           i CM         2017           i CM         2017           i V         2018           ju U         2017           ju J         2017           ju J         2017           ju J         2017           ju J         2017           ju XB         2016           heng Q         2018a           heng Q         2018b           Jun W         2017           'an Z         2016           ian JH         2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28-32<br>28<br>28<br><0-28<br>28<br>28<br>30<br>28-36   | 28<br>3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4  |             | _ |  | *        | <b> </b> | 0.07 (0.0   | 00, 1.30)<br>01, 4.81)   | 0/46   | 5/40  |
| u Y         2018           u Y         2017           i CM         2017           i N         2016           i ZY         2018           iu CY         2014           iu J         2017           iu XB         2016           iu Y         2016           Pang BA         2016           Ren N         2015           Sheng Q         2018b           Sun W         2017           an Z         2018           Sun W         2017           an JH         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28-32<br>28<br>28<br><0-28<br>28<br>28<br>28<br>30<br>28-36   | 3-4<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4  |             |   |  | *        | <u> </u> | 0.23 (0.0   | 01, 4.81)  |  |   |
| iang S         2017           i CM         2017           i N         2016           i ZY         2018           iu CY         2014           iu J         2017           iu XB         2016           iu Y         2016           iu Y         2016           ibu B         2016           bin B         2015           sheng Q         2018a           byon W         2017           an Z         2016           ian H         2018  | China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br><0-28<br>28<br>28<br>30<br>28-36  | NR<br>4<br>NR<br>4<br>NR<br>4<br>NR<br>4   | •           |   |  |          |          | 0.05 (0.0   | .,   | 0/105  | 2/122   |
| Ling G         2017           i M         2016           i ZY         2018           iu CY         2014           iu J         2017           ju XB         2016           ian M         2015           jun V         2018           jun Z         2016           jan JL         2017  | China<br>China<br>China<br>China<br>China<br>China  | 28<br><0-28<br>28<br>28<br>28<br>30<br>28-36  | 4<br>NR<br>NR<br>4<br>NR<br>4  |             |   |  |          |          |   | 0 4 0 1 0 4 0  | 1/44   | 14/44   |
| Juni         2016           iN         2016           iZY         2018           juCY         2014           ju GY         2017           ju XB         2016           vange         2016           vange         2016           vange         2016           vange         2015           sheng Q         2018           Sun W         2017           an Z         2016           ian JH         2018   | China<br>China<br>China<br>China<br>China<br>China  | <0-28<br>28<br>28<br>30<br>28-36  | +<br>NR<br>NR<br>4<br>NR<br>4  |             |   |  |          |          | 0.11 (0.0   |  | 1/30   | 7/30  |
| IV         2018           jiz ZY         2018           ju GY         2017           ju J         2017           ju XB         2016           ju Y         2016           ju B         2016           ju B         2016           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           fan Z         2016           fan JH         2018  | China<br>China<br>China<br>China<br>China   | <0-20<br>28<br>28<br>30<br>28-36  | NR<br>4<br>NR<br>4   | _           |   |  |          |          | 0.01 (0.0   | (0.00)   | 1/65   | 0/05  |
| L1         2018           Lic CY         2014           Liu J         2017           Jiu XB         2016           Ju Y         2016           Pang BA         2012           Ju B         2016           Join B         2015           Sheng Q         2018           Sun W         2017           Fan Z         2016           Tan Z         2016           Tan JH         2018  | China<br>China<br>China<br>China  | 28<br>30<br>28-36   | 4<br>NR<br>4   | _           |   |  |          |          | 0.03 (0.0   | JO, 0.24)  | 0/41   | 9/25  |
| Li UY 2014<br>Li U 2017<br>Li UXB 2016<br>Li UY 2016<br>Peng BA 2012<br>Qiu B 2016<br>Ren N 2015<br>Sheng Q 2018a<br>Sheng Q 2018b<br>Sun W 2017<br>Fan Z 2016<br>Tian JH 2018   | China<br>China<br>China   | 28<br>30<br>28-36   | 4<br>NR<br>4   |             |   |  |          |          | 0.24 (0.0   | JO, U.97)  | 3/41   | 70/41   |
| Liu J 2017<br>Liu XB 2016<br>Jui XB 2016<br>Peng BA 2012<br>Qiu B 2016<br>Ren N 2015<br>Sheng Q 2018a<br>Sheng Q 2018b<br>Sun W 2017<br>Fan Z 2016<br>Tian JH 2018   | China<br>China  | 30<br>28-36   | NR<br>4  |             |   |  |          |          | 0.12 (0.0   | J1, 1.01)  | 1/34   | 7/34  |
| Liu XB 2016<br>2019 2016<br>Peng BA 2012<br>2010 B 2016<br>Ren N 2015<br>Sheng Q 2018a<br>Sheng Q 2018b<br>Sun W 2017<br>Fan Z 2016<br>Tian JH 2018  | China   | 28-36   | 4  |             |   |  |          | Г        | 0.05 (0.0   | 0, 1.17)   | 0/97   | 2/28  |
| Liu Y 2016<br>Peng BA 2012<br>Diu B 2016<br>Ren N 2015<br>Sheng Q 2018a<br>Sheng Q 2018b<br>Sun W 2017<br>Fan Z 2016<br>Fian JH 2018   |   | L0 00   |  |             |   | _  |          |          | 0.09 (0.0   | 0, 1.78)   | 0/20   | 4/20  |
| Peng BA         2012           Qiu B         2016           Ren N         2015           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Fan Z         2016           Gan Z         2018  | China   | 4 <b>-</b> 32   | 4  |             |   |  | _        |          | 0.03 (0.0   | 0, 0.50)   | 0/82   | 13/78   |
| Qiu B         2016           Ren N         2015           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Tan Z         2016           Finan JH         2018  | China   | 28  | 0  |             |   | _  | •        |          | 0.23 (0.0   | 02, 2.16)  | 1/40   | 4/40  |
| Ren N         2015           Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Fan Z         2016           Fian JH         2018  | China   | <0 <b>-</b> 24  | 0  |             | - | •  |          |          | 0.08 (0.0   | 02, 0.35)  | 2/120  | 11/60   |
| Sheng Q         2018a           Sheng Q         2018b           Sun W         2017           Tan Z         2016           Fian JH         2018   | China   | 28  | 24   |             |   |  |          |          | 0.08 (0.0   | 01, 0.65)  | 1/46   | 10/46   |
| Sheng Q         2018b           Sun W         2017           Fan Z         2016           Fian JH         2018   | China   | 24-32   | 0  | -           |   |  |          | ł        | 0.05 (0.0   | 00, 1.06)  | 0/79   | 2/21  |
| Sun W 2017<br>Fan Z 2016<br>Fian JH 2018   | China   | 24-28   | 0  |             |   |  |          | 4        | 0.06 (0.0   | 00, 1.05)  | 0/66   | 5/46  |
| Fan Z 2016<br>Fian JH 2018   | China   | 12-28   | 12   |             |   |  | _        |          | 0.02 (0.0   | 0. 0.30)   | 0/123  | 12/65   |
| Fian JH 2018   | China   | <14-28  | NB   |             |   |  |          |          | 0.06 (0.0   | 0.0.97)  | 0/171  | 15/320  |
| 2010   | China   | Anvtime   | NB   |             |   |  |          |          | 0 11 (0 0   | 01 2 01)   | 0/135  | 6/203   |
| Vano B 2016  | China   | 28  | 4  | -           |   |  |          |          | 0.05 (0.0   | 0.079  | 0/110  | 16/187  |
| Vang DM 2016   | China   | 28-30   | 12   |             | _ |  |          |          | 0.00 (0.0   | 1 0 80   | 1/36   | 5/20  |
| Vang UR 2010   | China   | 20-36   |  |             |   |  |          |          | 0.03 (0.0   | 0.000)   | 0/100  | 3/20  |
| Vang L 2015  | Chin-   | 20-30   |  |             |   |  |          |          | 0.04 (0.0   |  | 1/200  | 2/20  |
| vang J 2017  | Unina   | 24-28   | NK   | _           |   | le.  | •        |          | 0.02 (0.0   | JU, U.15)  | 1/329  | 9/65  |
| vang WP 2012   | China   | <27-28  | U  |             |   |  |          | Г        | 0.09 (0.0   | ת, 1.54)   | 0/47   | 20/198  |
| Vu Q 2015  | China   | 24-32   | 0 or 4   | <b>—</b>    |   | -  | _        |          | 0.01 (0.0   | 0, 0.23)   | 0/204  | 14/95   |
| iao XH 2017  | China   | 28  | 0 or 4   |             |   |  |          | <u> </u> | 0.19 (0.0   | 01, 4.05)  | 0/62   | 2/61  |
| hang BF 2018   | China   | 24-28   | 0  |             |   |  |          | ŧ        | 0.06 (0.0   | 00, 1.10)  | 0/36   | 13/75   |
| hang GH 2018   | China   | 28  | 4  |             |   |  | -        | <u> </u> | 0.13 (0.0   | 01, 2.65)  | 0/40   | 3/40  |
| hang H 2014  | China   | 28-30   | 4  |             |   |  |          | ł        | 0.06 (0.0   | 00, 1.09)  | 0/257  | 10/352  |
| hang X 2015  | China   | 28  | 12   |             | _ | ÷  |          | ┢        | 0.08 (0.0   | 00, 1,48)  | 0/48   | 5/47  |
| hang YF 2010b  | China   | 28  | 4  |             |   |  |          |          | 0.05 (0 (   | 01. 0.40)  | 1/60   | 15/60   |
| 'hao I 2013  | China   | 20  | 0  |             |   |  |          | L        | 0.09.00   | 01 1 55)   | 0/41   | 23/202  |
| heng IC 2019   | China   | 28  | 4  |             | _ |  |          |          | 0 10 (0.0   | 1 1 92   | 0/23   | 6/37  |
| Subtotal (I-squared = (  | 0.0%, p = 1   | .000)   | +  |             |   | $\diamond$   |          |          | 0.07 (0.0   | ), 1. <u>52</u> )<br>)5, 0.10)   | 18/3617  | 377/333   |
| werall (Lequared - 0   | 0% n = 1 (  | 2001  |  |             |   | -  |          |          | 0.08.00   | 06.0.11  | 24/2000  | 195/971   |
| Jverall (I-Squared = 0.  | .0 /0, p = 1.0  | 500)  |  |             |   | Ý  |          |          | 0.08 (0.0   | 50, 0.11)  | 24/3333  | 400/071   |

|    | Author              |           |                           | Charac                                | teristics of            | mothers                          |                                       | Peripart<br>proj              | um antiviral<br>phylaxis  |                  | Characteristi    | cs of infants    | 3                             |
|----|---------------------|-----------|---------------------------|---------------------------------------|-------------------------|----------------------------------|---------------------------------------|-------------------------------|---------------------------|------------------|------------------|------------------|-------------------------------|
| ID | year                | Country   | Age at baseline           | HBV DNA<br>at baseline<br>(log IU/mL) | HBeAg<br>at<br>baseline | Other (e.g.<br>HIV, HDV,<br>etc) | HBV DNA<br>at delivery<br>(log IU/mL) | Treatment<br>start            | Treatment discontinuation | Mode of delivery | HepB-BD          | HBIG             | Infant<br>vaccines<br>(HepB3) |
| 1  | Liu MH,<br>2017     | China     | Between<br>20-40<br>years | ≥5.3                                  | Positive                | No<br>HCV/HIV                    | >6.0                                  | Between<br>weeks 28<br>and 30 | At delivery               | N/R              | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6                   |
| 2  | Chen HL,<br>2015    | Taiwan    | N/R                       | 8.2                                   | Positive                | No<br>HCV/HIV                    | 4.2                                   | Between<br>weeks 30<br>and 32 | 1 month<br>postpartum     | N/R              | Yes,<br>NR       | Yes,<br><24hr    | Yes,<br>1/6                   |
| 3  | Chen WJ,<br>2017    | China     | N/R                       | ≥6.0                                  | Positive                | No<br>HCV/HIV                    | N/R                                   | 28                            | At delivery               | N/R              | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6                   |
| 4  | Gong Q,<br>2017     | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | Between<br>weeks 1<br>and 6   | N/R                       | N/R              | Yes,<br><24hr    | Yes,<br><24hr    | Yes,<br>1/6                   |
| 5  | Greenup<br>AJ, 2014 | Australia | N/R                       | N/R                                   | Positive                | N/R                              | 4.4                                   | 32                            | 12 weeks<br>postpartum    | Vaginal          | Yes,<br>At birth | Yes,<br>NR       | Yes,<br>2/4/6                 |
| 6  | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 7  | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 8  | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 9  | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 10 | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 11 | He LL,<br>2018      | China     | Between<br>22-36<br>years | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6                   |
| 12 | He LL,              | China     | Between                   | N/R                                   | N/R                     | N/R                              | N/R                                   | 28                            | N/R                       | N/R              | Yes,             | Yes,             | Yes,                          |

# Appendix I: Characteristics of infants with MTCT despite maternal TDF 300 mg prophylaxis

|    | 2018            |       | 22-36                     |      |     |               |     |    |             |     | <12hr            | <12hr            | 1/6         |
|----|-----------------|-------|---------------------------|------|-----|---------------|-----|----|-------------|-----|------------------|------------------|-------------|
|    |                 |       | years                     |      |     |               |     |    |             |     |                  |                  |             |
| 13 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 14 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 15 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 16 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 17 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 18 | He LL,<br>2018  | China | Between<br>22-36<br>years | N/R  | N/R | N/R           | N/R | 28 | N/R         | N/R | Yes,<br><12hr    | Yes,<br><12hr    | Yes,<br>1/6 |
| 19 | Wan JY,<br>2017 | China | N/R                       | ≥5.3 | N/R | No<br>HCV/HIV | N/R | 28 | At delivery | N/R | N/R              | N/R              | N/R         |
| 20 | Wan JY,<br>2017 | China | N/R                       | ≥5.3 | N/R | No<br>HCV/HIV | N/R | 28 | At delivery | N/R | N/R              | N/R              | N/R         |
| 21 | Wan JY,<br>2017 | China | N/R                       | ≥5.3 | N/R | No<br>HCV/HIV | N/R | 28 | At delivery | N/R | N/R              | N/R              | N/R         |
| 22 | Hu MF,<br>2018  | China | N/R                       | ≥6.0 | N/R | No<br>HCV/HIV | N/R | 28 | N/R         | N/R | Yes,<br>At birth | Yes,<br>At birth | Yes,<br>1/6 |

Abbreviations: N/R, not reported Sex of infant was not reported in any of the MTCT cases.

## Appendix J: Efficacy by timing of PAP initiation

### • TDF 300 mg by timing of PAP initiation

- <28 weeks gestation (n=10): pooled OR= 0.10 (95% CI: 0.04-0.25), p<0.001,  $I^2=0\%$
- 28 weeks gestation (n=7): pooled OR=0.25 (95%CI: 0.13-0.48), p<0.001, I<sup>2</sup>=0%
- >28 weeks gestation (n=5): pooled OR=0.10 (95%CI: 0.03-0.29), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.15

|               |         |              | Tx start<br>in weeks | Tx end<br>in weeks | Events,   | Events, |            |                    |
|---------------|---------|--------------|----------------------|--------------------|-----------|---------|------------|--------------------|
| Author        | Year    | Country      | gestation            | postpartum         | Treatment | Control |            | OR (95% CI)        |
| Median <28    | weeks   | of gestatior | <br>ו                |                    |           |         |            |                    |
| Celen MK      | 2013    | Turkey       | 18-27                | 4                  | 0/21      | 2/23    |            | 0.20 (0.01, 4.42   |
| Gong Q        | 2017    | China        | 1-6                  | NR                 | 1/44      | 7/44    |            | 0.12 (0.01, 1.05   |
| Hu MF         | 2018    | China        | 14                   | NR                 | 0/30      | 3/30    | •          | 0.13 (0.01, 2.61   |
| Huang Q       | 2017    | China        | 24-28                | 12                 | 0/20      | 3/20    |            | 0.12 (0.01, 2.53   |
| Lin Y         | 2018    | China        | 24                   | 4                  | 0/58      | 4/52    |            | 0.09 (0.00, 1.75   |
| Wakano Y      | 2018    | Japan        | 22-28                | 4-8                | 0/2       | 2/3     |            | 0.12 (0.00, 4.61   |
| Wang HB       | 2018    | China        | 20-24                | NR                 | 0/40      | 2/20    |            | 0.09 (0.00, 2.00   |
| Yu CY         | 2018    | China        | 24                   | 4                  | 0/30      | 4/30    |            | 0.10 (0.00, 1.88   |
| Zhang BF      | 2018    | China        | 24-28                | 0                  | 0/39      | 15/75   |            | 0.05 (0.00, 0.85   |
| Zhou Y        | 2018    | China        | 24-28                | 0                  | 0/60      | 5/36    |            | 0.05 (0.00, 0.88   |
| Subtotal (I-s | squared | = 0.0%, p    | = 1.000)             |                    |           |         | $\diamond$ | 0.10 (0.04, 0.25   |
| Median 28 w   | eeks of | gestation    |                      |                    |           |         |            |                    |
| Chen WJ       | 2017    | China        | 28                   | 0                  | 1/30      | 16/44   |            | 0.06 (0.01, 0.49   |
| He LL         | 2018    | China        | 28                   | NR                 | 13/50     | 17/35   |            | 0.37 (0.15, 0.93   |
| Hu MF         | 2018    | China        | 28                   | NR                 | 1/30      | 3/30    |            | 0.31 (0.03, 3.17   |
| Jourdain G    | 2018    | Thailand     | 26-29                | 8                  | 0/149     | 3/147   |            | 0.14 (0.01, 2.70   |
| Wan JY        | 2017    | China        | 28                   | 0                  | 3/74      | 7/42    |            | 0.21 (0.05, 0.87   |
| Wang HB       | 2018    | China        | 28                   | NR                 | 0/20      | 2/20    |            | 0.18 (0.01, 4.01   |
| Xiao XH       | 2017    | China        | 28                   | 0 or 4             | 0/60      | 1/61    |            | 0.33 (0.01, 8.35   |
| Subtotal (I-s | quared  | = 0.0%, p    | = 0.815)             |                    |           |         | $\diamond$ | • 0.25 (0.13, 0.48 |
| Median >28    | weeks   | of gestatior | ı                    |                    |           |         |            |                    |
| Chen HL       | 2015    | Taiwan       | 30-32                | 4                  | 1/65      | 6/56    |            | 0.13 (0.02, 1.12   |
| Greenup AJ    | 2014    | Australia    | 32                   | 12                 | 1/69      | 2/10    |            | 0.06 (0.00, 0.72   |
| Liu MH        | 2017    | China        | 28-30                | 0                  | 1/20      | 6/20    |            | 0.12 (0.01, 1.14   |
| Pan CQ        | 2016    | China        | 30-32                | 4                  | 0/92      | 6/88    |            | 0.07 (0.00, 1.24   |
| Wang HB       | 2018    | China        | 32-36                | NR                 | 0/40      | 2/20    |            | 0.09 (0.00, 2.00   |
| Subtotal (I-s | quared  | = 0.0%, p    | = 0.988)             |                    |           |         | $\sim$     | 0.10 (0.03, 0.29   |
|               |         | 7 F          | ,                    |                    |           |         |            |                    |
|               |         |              |                      |                    |           |         |            |                    |
|               |         |              |                      |                    |           | .001    | 01 1       | 1 10               |

## • LAM 100-150 mg by timing of PAP initiation

- <28 weeks gestation (n=7): pooled OR= 0.10 (95% CI: 0.04-0.26), p<0.001, I<sup>2</sup>=0%
- 28 weeks gestation (n=20): pooled OR=0.16 (95% CI: 0.11-0.22), p<0.001,  $I^2=0\%$
- >28 weeks gestation (n=11): pooled OR=0.31 (95%CI: 0.16-0.57), p<0.001,  $I^2=0\%$
- The p-value for heterogeneity between subgroups was 0.06

|                |            |                    | TX<br>start in weeks | in weeks   | Events    | Events     |               |
|----------------|------------|--------------------|----------------------|------------|-----------|------------|---------------|
| Author         | Year       | Country            | gestation            | postpartum | Treatment | Control    | OR (95% CI)   |
| Median <28 w   | veeks of c | estation           |                      |            |           |            |               |
| He T           | 2018       | China              | 1st Trimester        | NR         | 0/29      | 4/34       | 0.11 (0.01, 2 |
| Li WF          | 2006       | China              | 24                   | 0          | 1/36      | 7/44       | 0.15 (0.02, 1 |
| Pan CQ         | 2017       | China              | 13-26                | 4          | 0/66      | 5/89       | 0.12 (0.01, 2 |
| Shen ML        | 2016       | China              | 26                   | 4          | 0/60      | 11/28      | 0.01 (0.00, 0 |
| Yuan QF        | 2012       | China              | 27                   | 4          | 1/32      | 3/32       | 0.31 (0.03, 3 |
| Zhou DS        | 2013       | China              | 20                   | NB         | 0/49      | 28/95      | 0.02 (0.00, 0 |
| Zhu M          | 2014       | China              | 26                   | 0          | 2/24      | 9/24       | 0 15 (0 03 0  |
| Subtotal (I-sq | uared = (  | 0.0%, p = 0.583)   |                      | •          |           |            | 0.10 (0.04, 0 |
|                |            | ., ,               |                      |            |           |            | •             |
| Median 28 we   | eks of ge  | station            |                      |            |           | _          |               |
| Bai XW         | 2011       | China              | 28                   | 4          | 3/30      | 8/25       | 0.24 (0.05, 1 |
| Chen QR        | 2018       | China              | 28                   | 4          | 1/33      | 5/28       | 0.14 (0.02, 1 |
| Chen SM        | 2017       | China              | 28                   | NR         | 1/30      | 10/30      | 0.07 (0.01, 0 |
| Feng HF        | 2007       | China              | 28                   | 4          | 7/48      | 16/42      | 0.28 (0.10, 0 |
| Guo YZ         | 2008       | China              | 28                   | 0          | 3/70      | 13/40      | 0.09 (0.02, 0 |
| Han YP         | 2014       | China              | 28                   | 6          | 1/30      | 4/30       | 0.22 (0.02, 2 |
| Han ZH         | 2005       | China              | 28                   | 0          | 0/43      | 5/35       | 0.06 (0.00, 1 |
| li YY          | 2015       | China              | 28                   | 4          | 2/65      | 12/65      | 0 14 (0 03 0  |
| LIG            | 2006       | China              | 28                   | 0          | 1/35      | 7/32       | 0.11 (0.01, 0 |
|                | 2000       | China              | 28                   | 4          | 1/33      | 8/27       | 0.07 (0.01, 0 |
|                | 2017       | China              | 20                   | 4          | 1/05      | 4/05       | 0.07 (0.01, 0 |
|                | 2015       | China              | 20                   | 0          | 1/25      | 4/25       | 0.22 (0.02, 2 |
| Ren CJ         | 2016       | China              | 28                   | 0          | 2/67      | 10/72      | 0.19 (0.04, 0 |
| Ren YJ         | 2011       | China              | 28                   | 0          | 1/30      | 13/155     | 0.38 (0.05, 2 |
| Tian XQ        | 2015       | China              | 28                   | 0          | 11/110    | 49/110     | 0.14 (0.07, 0 |
| Wang EJ        | 2012       | China              | 28                   | 4          | 1/32      | 5/27       | 0.14 (0.02, 1 |
| Wang W         | 2014       | China              | 28                   | 4          | 0/35      | 2/28       | 0.15 (0.01, 3 |
| Yang HW        | 2014       | China              | 28                   | 4          | 1/53      | 4/53 *     | 0.24 (0.03, 2 |
| Zeng YM        | 2013       | China              | 28                   | 0-6        | 0/90      | 3/30       | 0.04 (0.00, 0 |
| Zhang YF       | 2010a      | China              | 28                   | 4          | 3/50      | 16/50      | 0.14 (0.04, 0 |
| Zhou DS        | 2013       | China              | 28                   | NR         | 5/64      | 28/95      | 0.20 (0.07, 0 |
| Subtotal (I-sq | uared = 0  | 0.0%, p = 0.998)   |                      |            |           | $\diamond$ | 0.16 (0.11, 0 |
| Madian - 00 u  | ooko of c  | entation           |                      |            |           | _          |               |
| Chopa VC       | 2011       | China              | 22                   | 4          | 9/20      | 6/26       | 1 21 (0 26 /  |
|                | 2011       | China              | 20 20                | 10         | 0/16      | 2/00       | 0.17 (0.30, 4 |
|                | 2015       | Australia          | 20-30                | 12         | 0/10      |            | 0.17 (0.01, 3 |
| Greenup AJ     | 2014       | Australia          | 32<br>00             | ~          | 0/43      | 2/10       | 0.04 (0.00, 0 |
| Jackson v      | 2015       | ireiand            | 32                   | 0          | 0/21      | 1/0        | 0.09 (0.00, 2 |
| Pan CQ         | 2017       | China              | 28-30                | 4          | 0/94      | 5/89       | 0.08 (0.00, 1 |
| SUIB           | 2009       | China              | 32                   | U          | 5/128     | 13/120     | 0.33 (0.12, 0 |
| Tang X         | 2009       | China              | 33                   | 4          | 0/17      | 4/24       | 0.13 (0.01, 2 |
| Wakano Y       | 2018       | Japan              | 28-32                | 4-8        | 0/3       | 2/3        | 0.09 (0.00, 3 |
| Wang DM        | 2016       | China              | 28-30                | 12         | 1/42      | 5/20       | 0.07 (0.01, 0 |
| Xu WM          | 2009       | China, Philippines | 30-34                | 4          | 3/49      | 5/41       | 0.47 (0.11, 2 |
| Zhang H        | 2014       | China              | 28-30                | 4          | 0/52      | 10/352 +   | 0.31 (0.02, 5 |
| Subtotal (I-sq | uared = 1  | 7.7%, p = 0.371)   |                      |            |           | $\diamond$ | 0.31 (0.16, 0 |
| •              |            |                    |                      |            |           |            |               |
|                |            |                    |                      |            |           | <u> </u>   |               |
|                |            |                    |                      |            |           | 001 01 1   | 1 10          |

## • LdT 600 mg by timing of PAP initiation

- <28 weeks gestation (n=24): pooled OR=0.08 (95% CI: 0.05-0.13), p<0.001,  $I^2=0\%$
- 28 weeks gestation (n=44): pooled OR=0.13 (95%CI: 0.10-0.18), p<0.001, I<sup>2</sup>=0%
- >28 weeks gestation (n=13): pooled OR=0.09 (95%CI: 0.04-0.20), p<0.001,  $I^2=0\%$
- The p-value for heterogeneity between subgroups was 0.20

| Author   | Year   | Country  | Tx<br>start in weeks<br>gestation   | Tx end<br>in weeks<br>postpartum  | Events,<br>Treatment   | Events,<br>Control   |                    |          | _    | OR (95% CI)   | Events,<br>Treatment   | Events,<br>Control   |
|--|--|--|---|---|--|--|--------------------|----------|------|---|--|--|
| Median -22<br>Chen CY<br>Fu PX<br>Gao P<br>Guan ZF<br>Han GR<br>He T<br>Huang HY<br>Huang Q<br>Liu Y<br>Oiu B<br>Shen ML<br>Sheng Q<br>Shi OW<br>Sun WH<br>Sun WH<br>Tan Z<br>Wang HY<br>Wang J<br>Wang WP<br>Zhao J<br>Zhao J<br>Subtotal (   | 8 weeks<br>2015<br>2016<br>2016<br>2017<br>2015<br>2018<br>2016<br>2017<br>2016<br>2016<br>2016<br>2016<br>2016<br>2016<br>2016<br>2016              | of gestatio<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | n<br>1st Trimester<br>24-28<br>1st Trimester<br>20-27<br>1st Trimester<br>20-24<br>24-28<br>4-27<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24<br>24  | NR<br>4<br>0<br>12<br>NNR<br>0<br>12<br>4<br>0<br>4<br>0<br>12<br>12<br>NR<br>NR<br>0<br>12<br>12<br>NR<br>NR<br>0<br>12<br>12<br>NR<br>0<br>12<br>12<br>NR<br>0<br>12<br>12<br>NR<br>0<br>12<br>12<br>NR<br>0<br>12<br>14<br>0<br>12<br>14<br>0<br>12<br>14<br>0<br>12<br>14<br>0<br>12<br>14<br>0<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>14<br>10<br>12<br>12<br>14<br>10<br>12<br>12<br>14<br>10<br>12<br>12<br>14<br>10<br>12<br>12<br>14<br>10<br>12<br>12<br>14<br>10<br>12<br>12<br>11<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12 | 1/42<br>1/100<br>1/51<br>0/256<br>0/256<br>0/250<br>0/50<br>0/50<br>0/66<br>3/100<br>0/66<br>3/100<br>0/66<br>0/123<br>0/64<br>0/123<br>0/64<br>0/123<br>0/40<br>1/329<br>0/22<br>0/36<br>0/22<br>0/26<br>0/22<br>0/26<br>0/21<br>0/40<br>0/22<br>0/22<br>0/26<br>0/22<br>0/26<br>0/20<br>0/20<br>0/2          | 7/40<br>3/100<br>9/51<br>14/122<br>8/86<br>23/30<br>19/78<br>12/60<br>11/28<br>5/46<br>12/100<br>11/28<br>8/46<br>12/100<br>12/65<br>8/46<br>6/40<br>9/65<br>20/198<br>15/75<br>23/202<br>5/40<br>6/34   | , 1444 - 41164 III |          |      | $\begin{array}{c} 0.11 \ (0.01, 0.98)\\ 0.33 \ (0.03, 3.19)\\ 0.09 \ (0.01, 0.77)\\ 0.03 \ (0.00, 0.52)\\ 0.02 \ (0.00, 0.32)\\ 0.10 \ (0.01, 2.02)\\ 0.12 \ (0.01, 2.53)\\ 0.29 \ (0.09, 0.54)\\ 0.11 \ (0.00, 0.22)\\ 0.06 \ (0.00, 1.05)\\ 0.06 \ (0.00, 1.05)\\ 0.02 \ (0.00, 0.30)\\ 0.05 \ (0.00, 0.30)\\ 0.05 \ (0.00, 0.37)\\ 0.06 \ (0.00, 0.37)\\ 0.06 \ (0.00, 0.37)\\ 0.06 \ (0.00, 0.37)\\ 0.06 \ (0.00, 0.121)\\ 0.07 \ (0.00, 0.123)\\ 0.09 \ (0.01, 1.55)\\ 0.08 \ (0.00, 1.47)\\ 0.09 \ (0.01, 1.55)\\ 0.08 \ (0.00, 1.47)\\ 0.09 \ (0.01, 1.57)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.08 \ (0.05, 0.13)\\ 0.09 \ (0.01, 0.78)\\ 0.08 \ (0.05, 0.13)\\ $ | 1/42<br>1/100<br>1/51<br>0/123<br>0/256<br>6/60<br>0/20<br>0/50<br>0/60<br>0/61<br>3/100<br>0/61<br>3/100<br>0/123<br>0/64<br>0/123<br>0/64<br>0/171<br>0/40<br>0/171<br>0/40<br>0/171<br>0/40<br>0/122<br>0/36<br>1/53<br>18/2000   | 7/40<br>3/100<br>9/61<br>14/122<br>8/86<br>4/86<br>4/34<br>23/30<br>19/78<br>12/60<br>11/28<br>5/46<br>12/100<br>12/65<br>8/46<br>6/40<br>9/65<br>2/20<br>2/20<br>2/0198<br>15/75<br>2/02<br>2/0198<br>15/75<br>2/02<br>2/0198<br>15/75<br>2/02<br>2/0198<br>15/75<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/05<br>8/46<br>6/44<br>2/04<br>2/05<br>8/46<br>6/40<br>2/04<br>2/05<br>8/46<br>6/40<br>2/04<br>2/05<br>8/46<br>6/40<br>9/05<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/04<br>2/   |
| Median 28<br>Mendon QR<br>Chen SM<br>Chen WJ<br>Cui ZL<br>Ding XP<br>Fang YM<br>Guo HJ<br>Han YP<br>Hu WH<br>Hu WH<br>Hu WH<br>Hu WH<br>Hu WH<br>Li QY<br>Jiang XN<br>Li NF<br>Li YH<br>Li QY<br>Lou JJ<br>Lu QJ<br>Lu QJ<br>Lu QJ<br>Lu QJ<br>Lu QJ<br>Ren N<br>Tian RH<br>Wang EB<br>Wang BA<br>Wang BB<br>Wang BB<br>Wang WP<br>Xiao XH<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Xing Y<br>Zhang SA<br>Zhang X<br>Zhang X<br>Zhang Y<br>Zhu J<br>Zhu LP<br>Subtotal ( | weeks 2017<br>2018<br>2017<br>2015<br>2017<br>2017<br>2017<br>2011<br>2011<br>2011<br>2011<br>2011   | f 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| Median >2<br>Bai HL<br>Ge YL<br>Han GR<br>Hu Y<br>Liu XB<br>Liu XB<br>Liu X<br>Pan YC<br>Wang DM<br>Wang DM<br>Yao LF<br>Zhang H<br>Zhang LJ<br>Subtotal (   | 8 weeks<br>2013<br>2015<br>2015<br>2018<br>2017<br>2016<br>2016<br>2016<br>2017<br>2016<br>2017<br>2016<br>2014<br>2014<br>2014<br>2009<br>I-squared | of gestatio<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | n<br>28-32<br>28-32<br>28-32<br>28-32<br>28-36<br>28-36<br>28-32<br>28-30<br>32-36<br>28-30<br>28-32<br>28-30<br>28-32<br>28-30<br>28-32<br>28-32<br>28-30<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-32<br>28-3 | 4<br>NR<br>3-4<br>NR<br>4<br>4<br>0<br>12<br>NR<br>6<br>4<br>4  | 0/27<br>0/20<br>0/102<br>0/105<br>0/97<br>0/20<br>1/32<br>0/81<br>1/36<br>0/40<br>0/30<br>0/257<br>0/30  | 4/30<br>3/22<br>8/86<br>2/122<br>2/28<br>5/20<br>19/78<br>21/370<br>5/20<br>2/20<br>2/30<br>10/352<br>4/30   |                    | <b>A</b> |      | $\begin{array}{c} 0.11 \ (0.01, 2.09) \\ 0.14 \ (0.01, 2.81) \\ 0.05 \ (0.00, 0.79) \\ 0.23 \ (0.01, 4.81) \\ 0.05 \ (0.00, 1.37) \\ 0.05 \ (0.00, 1.37) \\ 0.07 \ (0.00, 1.34) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.01, 0.78) \\ 0.10 \ (0.00, 1.08) \\ 0.10 \ (0.00, 1.08) \\ 0.06 \ (0.00, 1.08) \\ 0.06 \ (0.00, 1.08) \\ 0.09 \ (0.04, 0.20) \\ 0.00 \ (0.04, 0$      | 0/27<br>0/20<br>0/102<br>0/97<br>0/20<br>1/32<br>0/81<br>1/36<br>0/40<br>0/30<br>0/257<br>0/30<br>2/877  | 4/30<br>3/22<br>8/86<br>2/122<br>2/28<br>5/20<br>19/78<br>21/370<br>5/20<br>2/30<br>2/30<br>10/352<br>4/30<br>87/1208  |
|  |  |  |   |   |  | .001   | .01                | .1       | 1 10 |   |  |  |

## **Appendix K: Efficacy by timing of PAP discontinuation**

- TDF 300 mg by timing of PAP discontinuation
  - At delivery (n=5): pooled OR= 0.11 (95% CI: 0.04-0.28), p<0.001, I<sup>2</sup>=0%
  - 4-8 weeks after delivery (n=7): pooled OR=0.12 (95%CI: 0.04-0.34), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.96

|               |          |               | Tx start  | Tx end     |           |         |     |        |   |    |                   |
|---------------|----------|---------------|-----------|------------|-----------|---------|-----|--------|---|----|-------------------|
|               |          |               | in weeks  | in weeks   | Events,   | Events, |     |        |   |    |                   |
| Author        | Year     | Country       | gestation | postpartum | Treatment | Control |     |        |   |    | OR (95% CI)       |
|               |          |               |           |            |           |         |     |        |   |    |                   |
| At delivery   |          |               |           |            |           |         |     |        |   |    |                   |
| Chen WJ       | 2017     | China         | 28        | 0          | 1/30      | 16/44   |     |        | _ |    | 0.06 (0.01, 0.49) |
| Liu MH        | 2017     | China         | 28        | 0          | 1/20      | 6/20    |     |        |   |    | 0.12 (0.01, 1.14) |
| Wan JY        | 2017     | China         | 28        | 0          | 3/74      | 7/42    |     |        |   |    | 0.21 (0.05, 0.87) |
| Zhang BF      | 2018     | China         | 24-28     | 0          | 0/39      | 15/75   |     | -      |   |    | 0.05 (0.00, 0.85) |
| Zhou Y        | 2018     | China         | 24-28     | 0          | 0/60      | 5/36    |     |        |   |    | 0.05 (0.00, 0.88) |
| Subtotal (I-s | quared = | = 0.0%, p = 0 | 0.751)    |            |           |         |     | $\sim$ | > |    | 0.11 (0.04, 0.28) |
|               |          |               |           |            |           |         |     |        |   |    |                   |
| 4 to 8 weeks  | post-de  | livery        |           |            |           |         |     |        |   |    |                   |
| Celen MK      | 2013     | Turkey        | 18-27     | 4          | 0/21      | 2/23    |     | 3      | - |    | 0.20 (0.01, 4.42) |
| Chen HL       | 2015     | Taiwan        | 30-32     | 4          | 1/65      | 6/56    |     |        |   |    | 0.13 (0.02, 1.12) |
| Jourdain G    | 2018     | Thailand      | 26-29     | 8          | 0/149     | 3/147   |     |        |   | _  | 0.14 (0.01, 2.70) |
| Lin Y         | 2018     | China         | 24        | 4          | 0/58      | 4/52    |     |        |   | -  | 0.09 (0.00, 1.75) |
| Pan CQ        | 2016     | China         | 30-32     | 4          | 0/92      | 6/88    |     |        |   |    | 0.07 (0.00, 1.24) |
| Wakano Y      | 2018     | Japan         | 22-28     | 4-8        | 0/2       | 2/3     |     | *      |   |    | 0.12 (0.00, 4.61) |
| Yu CY         | 2018     | China         | 24        | 4          | 0/30      | 4/30    |     |        |   | -  | 0.10 (0.00, 1.88) |
| Subtotal (I-s | quared = | = 0.0%, p = 0 | 0.999)    |            |           |         |     | $\sim$ | > |    | 0.12 (0.04, 0.34) |
|               |          |               |           |            |           |         |     | •      |   |    |                   |
|               |          |               |           |            |           |         |     |        |   |    |                   |
|               |          |               |           |            |           |         |     |        |   | r  |                   |
|               |          |               |           |            |           | .001    | .01 | .1     | 1 | 10 | )                 |
|               |          |               |           |            |           |         |     |        |   |    |                   |

## • LAM 100-150 mg by timing of PAP discontinuation

- At delivery (n=13): pooled OR = 0.15 (95% CI: 0.10-0.23), p<0.001, I<sup>2</sup>=0%
- 4-8 weeks after delivery (n=21): pooled OR=0.23 (95%CI: 0.15-0.34), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.19

| Author       | Year      | Country               | start in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control | OR (95% C       |
|--------------|-----------|-----------------------|-----------------------------|------------------------|----------------------|--------------------|-----------------|
| At delivery  |           |                       |                             |                        |                      | _                  |                 |
| Guo YZ       | 2008      | China                 | 28                          | 0                      | 3/70                 | 13/40              | - 0.09 (0.02,   |
| Han ZH       | 2005      | China                 | 28                          | 0                      | 0/43                 | 5/35               | 0.06 (0.00,     |
| Jackson V    | 2015      | reland                | 32                          | 0                      | 0/21                 | 1/6                | 0.09 (0.00, 3   |
| Jiang HX     | 2012      | China                 | 20-34                       | 0                      | 0/164                | 8/92 *             | 0.03 (0.00, 0   |
| Li G         | 2006      | China                 | 28                          | 0                      | 1/35                 | 7/32 +             | 0.11 (0.01, 0   |
| Li WF        | 2006      | China                 | 24                          | 0                      | 1/36                 | 7/44               | 0.15 (0.02,     |
| Ren CJ       | 2016      | China                 | 28                          | 0                      | 2/67                 | 10/72              | 0.19 (0.04,     |
| Ren YJ       | 2011      | China                 | 28                          | 0                      | 1/30                 | 13/155             | 0.38 (0.05, 1   |
| Su TB        | 2009      | China                 | 32                          | 0                      | 5/128                | 13/120             | 0.33 (0.12,     |
| Tian XQ      | 2015      | China                 | 28                          | 0                      | 11/110               | 49/110             | 0.14 (0.07,     |
| Wang TM      | 2005      | China                 | Pre-pregnancy               | 0                      | 0/32                 | 8/32               | 0.04 (0.00.     |
| Zena YM      | 2013      | China                 | 28                          | 0                      | 0/30                 | 3/30               | 0.13 (0.01      |
| Zhu M        | 2014      | China                 | 26                          | 0                      | 2/24                 | 9/24               | 0.15 (0.03.     |
| Subtotal (I- | squared   | = 0.0% n $= 0.913$ )  | 20                          | Ū.                     |                      |                    | 0 15 (0 10      |
|              | oqualou   | - 010 /01 p = 010 /07 |                             |                        |                      | •                  | 0110 (0110,     |
| 4 to 8 week  | s post-de | livery                |                             |                        |                      |                    |                 |
| Bai XW       | 2011      | China                 | 28                          | 4                      | 3/30                 | 8/25               | 0.24 (0.05,     |
| Chen QR      | 2018      | China                 | 28                          | 4                      | 1/33                 | 5/28               | 0.14 (0.02,     |
| Cheng YC     | 2011      | China                 | 32                          | 4                      | 8/30                 | 6/26               | 1.21 (0.36,     |
| Feng HF      | 2007      | China                 | 28                          | 4                      | 7/48                 | 16/42              | • 0.28 (0.10, e |
| Han YP       | 2014      | China                 | 28                          | 6                      | 1/30                 | 4/30               | 0.22 (0.02, 3   |
| Ji YY        | 2015      | China                 | 28                          | 4                      | 2/65                 | 12/65              | 0.14 (0.03,     |
| Li JH        | 2017      | China                 | 28                          | 4                      | 1/33                 | 8/27               | 0.07 (0.01,     |
| Li ZG        | 2015      | China                 | 28                          | 6                      | 1/25                 | 4/25               | 0.22 (0.02, 3   |
| Pan CQ       | 2017      | China                 | 13-26                       | 4                      | 0/66                 | 5/89               | 0.12 (0.01, 3   |
| Pan CQ       | 2017      | China                 | 28-30                       | 4                      | 0/94                 | 5/89               | 0.08 (0.00,     |
| Shen ML      | 2016      | China                 | 26                          | 4                      | 0/60                 | 11/28 🗲 🔹          | 0.01 (0.00,     |
| Tang X       | 2009      | China                 | 33                          | 4                      | 0/17                 | 4/24               | 0.13 (0.01,     |
| Wakano Y     | 2018      | Japan                 | 28-32                       | 4-8                    | 0/3                  | 2/3                | 0.09 (0.00, 3   |
| Wang EJ      | 2012      | China                 | 28                          | 4                      | 1/32                 | 5/27 +             | 0.14 (0.02.     |
| Wang W       | 2014      | China                 | 28                          | 4                      | 0/35                 | 2/28               | 0.15 (0.01.     |
| Xu WM        | 2009      | China, Philippines    | 30-34                       | 4                      | 3/49                 | 5/41               | 0.47 (0.11.     |
| Yang HW      | 2014      | China                 | 28                          | 4                      | 1/53                 | 4/53               | 0.24 (0.03      |
| Yuan QF      | 2012      | China                 | 27                          | 4                      | 1/32                 | 3/32               | 0.31 (0.03      |
| Zena YM      | 2013      | China                 | 28                          | 4-6                    | 0/60                 | 3/30               |                 |
| Zhang H      | 2014      | China                 | 28-30                       | 4                      | 0/52                 | 10/352             | 0.31 (0.02)     |
| Zhang VE     | 2010-     | China                 | 28                          | 4                      | 3/50                 | 16/50              | 0.14 (0.02,     |
| Subtotal (L  | squarod   | - 0.0% p = 0.665)     | 20                          | -                      | 0/00                 | 10/00              | 0.14 (0.04,     |
|              | squared   | – 0.0%, µ = 0.000)    |                             |                        |                      |                    | 0.23 (0.15,     |
|              |           |                       |                             |                        |                      |                    |                 |
|              |           |                       |                             |                        |                      |                    |                 |

### • LdT 600 mg by timing of PAP discontinuation

- At delivery (n=16): pooled OR=0.10 (95% CI: 0.06-0.16), p<0.001,  $I^2=0\%$
- 4-8 weeks after delivery (n=33): pooled OR=0.13 (95%CI: 0.09-0.19), p<0.001,  $I^2=0\%$
- 12 weeks after delivery (n=8): pooled OR=0.06 (95%CI: 0.02-0.16), p<0.001, I<sup>2</sup>=0%
- 24+ weeks after delivery (n=6): pooled OR=0.11 (95%CI: 0.04-0.29), p<0.001,  $I^2=0\%$
- The p-value for heterogeneity between subgroups was 0.49

|                 |                 |            | Tx             | Tx end     |           |         |            |                                       |
|-----------------|-----------------|------------|----------------|------------|-----------|---------|------------|---------------------------------------|
|                 |                 |            | start in weeks | in weeks   | Events,   | Events, |            |                                       |
| Author          | Year            | Country    | gestation      | postpartum | Treatment | Control |            | OR (95% CI)                           |
|                 |                 |            |                |            |           |         |            |                                       |
| At delivery     |                 |            |                |            |           |         |            |                                       |
| Chen WJ         | 2017            | China      | 28             | 0          | 4/79      | 16/44   |            | 0.09 (0.03, 0.30)                     |
| Geo P           | 2016            | China      | 1et Trimester  | 0          | 1/51      | 0/51    |            | 0.09 (0.01 0.77)                      |
| Livere LIV      | 2010            | China      | 00.00          | ő          | 16/00     | 0000    |            | 0.03 (0.01, 0.17)                     |
| Huang HT        | 2016            | onna       | 20-20          | 0          | 16/90     | 23/30   |            | 0.07 (0.02, 0.18)                     |
| Lu QY           | 2016            | China      | 28             | 0          | 2/152     | 12/132  |            | 0.13 (0.03, 0.61)                     |
| Pan YC          | 2017            | China      | 32             | 0          | 0/81      | 21/370  |            | 0.10 (0.01, 1.66)                     |
| Peng BA         | 2012            | China      | 28             | 0          | 1/40      | 10/40   |            | 0.08 (0.01, 0.63)                     |
| Qiu B           | 2016            | China      | <0-24          | 0          | 4/120     | 12/60   |            | 0.14 (0.04, 0.45)                     |
| Sheng Q         | 2018a           | China      | 24-32          | 0          | 0/79      | 2/21    |            | 0.05 (0.00, 1.06)                     |
| Sheng Q         | 2018b           | China      | 24-28          | 0          | 0/66      | 5/46    |            | 0.06 (0.00, 1.05)                     |
| Shi OW          | 2017            | China      | 24             | 0          | 3/100     | 12/100  |            | 0.23 (0.06, 0.83)                     |
| Ten I           | 2017            | China      | 24             | 0          | 0/100     | 000     |            | 0.10 (0.00, 0.00)                     |
| Tan J           | 2019            | China      | 20             | 0          | 0/41      | 0/59    |            | 0.10 (0.01, 1.81)                     |
| Wang WP         | 2012            | China      | 0-28           | 0          | 0/47      | 20/198  | -          | 0.09 (0.01, 1.54)                     |
| Zhang BF        | 2018            | China      | 24-28          | 0          | 0/36      | 15/75   |            | 0.05 (0.00, 0.92)                     |
| Zhao J          | 2013            | China      | 20             | 0          | 0/41      | 23/202  |            | 0.09 (0.01, 1.55)                     |
| Zhou YJ         | 2014            | China      | 1st Trimester  | 0          | 1/53      | 6/34    |            | 0.09 (0.01, 0.78)                     |
| Zhu J           | 2017            | China      | 28             | 0          | 1/60      | 8/54    |            | 0.10 (0.01, 0.81)                     |
| Subtotol /Logu  | uprod - 0.0%    | - 0.000)   | 20             | Ŭ.         |           | 0.01    |            | 0.10 (0.08, 0.16)                     |
| Subtotal (I-squ | aieu = 0.0%, p  | 0.999)     |                |            |           |         | $\sim$     | 0.10 (0.06, 0.16)                     |
| •               |                 |            |                |            |           |         |            |                                       |
| 4 to 8 weeks po | ost-delivery    |            |                |            |           |         |            |                                       |
| Bai HL          | 2013            | China      | 28-32          | 4          | 0/27      | 4/30    |            | 0.11 (0.01, 2.09)                     |
| Chen QB         | 2018            | China      | 28             | 4          | 0/29      | 5/28    |            | 0.07 (0.00, 1.38)                     |
| Cui 7!          | 2015            | Chine      | 28             | 4          | 1/50      | 13/46   |            | 0.05 (0.01 0.42)                      |
| Dana V          | 2015            | China      | 04.00          | -          | 0/80      | 10/40   |            | 0.10 (0.01, 1.00)                     |
| Deng Y          | 2015            | China      | 24-30          | 4          | 0/82      | 4//5    |            | 0.10 (0.01, 1.82)                     |
| Ding XP         | 2018            | China      | 28             | 4          | 0/38      | 4/38    |            | 0.10 (0.01, 1.92)                     |
| Feng XM         | 2017            | China      | 28             | 4          | 1/36      | 7/36    |            | 0.12 (0.01, 1.02)                     |
| Fu PX           | 2016            | China      | 24-28          | 4          | 1/100     | 3/100   |            | 0.33 (0.03, 3.19)                     |
| Guo H.I         | 2011            | China      | 28             | 4          | 6/28      | 6/26    |            | 0.91 (0.25. 3.28)                     |
| Han VP          | 2014            | China      | 28             | 6          | 0/30      | 4/30    |            | 0.10 (0.00, 1.88)                     |
| THE Y           | 2014            | China      | 20 00          |            | 0/00      |         |            |                                       |
| HUY             | 2018            | China      | 28-32          | 3-4        | 0/105     | 2/122   |            | <ul> <li>0.23 (0.01, 4.81)</li> </ul> |
| Ji YY           | 2015            | China      | 28             | 4          | 3/65      | 12/65   |            | 0.21 (0.06, 0.80)                     |
| Li CM           | 2017            | China      | 28             | 4          | 1/30      | 8/30    |            | 0.09 (0.01, 0.82)                     |
| Liu CY          | 2014            | China      | 28             | 4          | 1/34      | 8/34    |            | 0.10 (0.01, 0.84)                     |
| Liu XB          | 2016            | China      | 28-36          | 4          | 0/20      | 5/20    |            | 0.07 (0.00 1.34)                      |
| Lin X           | 2016            | China      | 4 99           | 4          | 1/80      | 10/79   |            | 0.04 (0.00, 0.29)                     |
| LIUT            | 2016            | onna       | 4-32           | +          | 1/62      | 19/76   |            | 0.04 (0.00, 0.29)                     |
| Lou JJ          | 2015            | China      | 28             | 4          | 0/125     | 3/58    |            | 0.06 (0.00, 1.24)                     |
| Shen ML         | 2016            | China      | 26             | 4          | 0/61      | 11/28   | +          | 0.01 (0.00, 0.22)                     |
| Tian RH         | 2016            | China      | 28             | 4          | 3/318     | 17/374  |            | 0.20 (0.06, 0.69)                     |
| Wang B          | 2016            | China      | 28             | 4          | 0/110     | 16/187  |            | 0.05 (0.00, 0.79)                     |
| Wang E.I        | 2012            | China      | 28             | 4          | 0/28      | 5/27    | -          | 0.07 (0.00, 1.37)                     |
| Wang TD         | 2015            | China      | 20             | Å          | 0/52      | 9/60    |            | 0.05 (0.00, 0.97)                     |
| wang TD         | 2015            | China      | 20             | 4          | 0/53      | 0/02    |            | 0.05 (0.00, 0.87)                     |
| Xie PY          | 2016            | China      | 28             | 4          | 1/60      | 4/60    |            | 0.24 (0.03, 2.19)                     |
| Xing Y          | 2018            | China      | 28             | 4          | 0/30      | 7/30    |            | 0.05 (0.00, 0.95)                     |
| Yang HW         | 2015            | China      | 28             | 4          | 1/50      | 12/50   |            | 0.06 (0.01, 0.52)                     |
| Yao LF          | 2014            | China      | 28-32          | 6          | 0/30      | 2/30    |            | 0.19 (0.01, 4.06)                     |
| Yao ZC          | 2011            | China      | 28             | 4          | 0/28      | 4/30    |            | 0.10 (0.01, 2.01)                     |
| Zhano GH        | 2018            | China      | 28             | 4          | 0/40      | 3/40    |            | 0.13 (0.01, 2.65)                     |
| Zhang GH        | 2018            | China      | 20             | 4          | 0/40      | 3/40    |            | 0.13 (0.01, 2.05)                     |
| Zhang H         | 2014            | China      | 26-30          | 4          | 0/257     | 10/352  |            | 0.06 (0.00, 1.09)                     |
| Zhang LJ        | 2009            | China      | 28-32          | 4          | 0/30      | 4/30    |            | 0.10 (0.00, 1.88)                     |
| Zhang YF        | 2010b           | China      | 28             | 4          | 1/60      | 16/60   |            | 0.05 (0.01, 0.36)                     |
| Zhao DB         | 2010            | China      | 28             | 4          | 1/30      | 3/30    |            | 0.31 (0.03, 3.17)                     |
| Zhena JC        | 2018            | China      | 28             | 4          | 0/23      | 8/37    |            | 0.07 (0.00, 1.35)                     |
| ZhulP           | 2014            | China      | 28             | 4          | 0/30      | 3/30    |            | 0.13 (0.01, 2.61)                     |
| Cubtotal (Lagu  |                 | 0.020)     | 20             | -          | 0,00      | 0.00    | ~          | 0.10 (0.00, 0.10)                     |
| Guororai (i-squ |                 | - 0.002)   |                |            |           |         | $\sim$     | 0.10 (0.08, 0.18)                     |
| •               |                 |            |                |            |           |         |            |                                       |
| 12 weeks post-  | -delivery       |            |                |            |           |         |            |                                       |
| Ge YL           | 2015            | China      | 28-30          | 12         | 0/20      | 3/22    |            | 0.14 (0.01, 2.81)                     |
| Guan ZF         | 2017            | China      | 24             | 12         | 0/123     | 14/122  |            | 0.03 (0.00, 0.51)                     |
| Huano O         | 2017            | China      | 24-28          | 12         | 0/20      | 3/20    |            | 0.12 (0.01 2 53)                      |
| Sup W           | 2017            | China      | 10.09          | 10         | 0/109     | 10/65   |            | 0.02 (0.00, 0.20)                     |
| Gun W           | 2017            | Chin       | 10.00          | 14         | 0/123     | 0/10    |            | 0.02 (0.00, 0.30)                     |
| Sun WH          | 2015            | China      | 12-28          | 12         | 0/84      | 8/46    |            | 0.03 (0.00, 0.48)                     |
| Wang DM         | 2016            | China      | 28-30          | 12         | 1/36      | 5/20    |            | 0.09 (0.01, 0.80)                     |
| Zhang X         | 2015            | China      | 28             | 12         | 0/48      | 5/47    |            | 0.08 (0.00, 1.48)                     |
| Zhao Y          | 2017            | China      | 12             | 12         | 0/40      | 5/40    |            | 0.08 (0.00, 1.49)                     |
| Subtotal (Leon  | uared = 0.0%    | 0 = 0.960  |                |            |           |         |            | 0.06 (0.02, 0.16)                     |
| Castoter (1-540 |                 |            |                |            |           |         |            | 0.00 (0.02, 0.10)                     |
| •               |                 |            |                |            |           |         |            |                                       |
| 24+ weeks pos   | st-delivery     |            |                |            |           |         |            |                                       |
| Fan LY          | 2013            | China      | 28             | 24         | 0/58      | 6/60    |            | 0.07 (0.00, 1.30)                     |
| Hu WH           | 2016            | China      | 28             | 28         | 0/46      | 5/40    | ÷          | 0.07 (0.00, 1.30)                     |
| Li SF           | 2015            | China      | 28             | 24         | 0/60      | 6/60    |            | 0.07 (0.00, 1.26)                     |
| LIYH            | 2017            | Chine      | 28             | ~36        | 1/30      | 5/32    |            | 0 19 (0 02 1 70)                      |
| Bop N           | 2015            | China      | 20             |            | 2/46      | 11/46   |            | 0.14 (0.02, 0.70)                     |
| Maria 107       | 2013            | Ohina      | 20             | 24         | 2/40      | 11/40   |            | 0.14 (0.03, 0.70)                     |
| Wang HY         | 2018            | China      | 12-14          | 24         | 0/40      | 6/40    |            | 0.07 (0.00, 1.21)                     |
| Subtotal (I-squ | uared = 0.0%, p | o = 0.980) |                |            |           |         | $\sim$     | 0.11 (0.04, 0.29)                     |
| •               |                 |            |                |            |           |         |            |                                       |
|                 |                 |            |                |            |           |         |            |                                       |
|                 |                 |            |                |            |           |         |            |                                       |
|                 |                 |            |                |            |           |         |            | I                                     |
|                 |                 |            |                |            |           |         | 001 01 1 1 | 10                                    |
|                 |                 |            |                |            |           |         | 1991 - 1 I |                                       |

## Appendix L: Efficacy by mean maternal viral load at baseline

- TDF 300 mg by mean maternal viral load at baseline
  - 7.0-7.9 log10 IU/mL (n=3): pooled OR= 0.10 (95% CI: 0.03-0.41), p=0.001,  $I^2=0\%$
  - 8.0-8.9 log10 IU/mL (n=3): pooled OR= 0.11 (95%CI: 0.02-0.51), p<0.001,  $I^2=0\%$
  - The p-value for heterogeneity between subgroups was 0.96
  - Note: Studies were only included in this analysis if the standard deviation for the mean viral load at baseline was less than or equal to 1

| Author     | Year   | Country    | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |     |   |   |     | OR (95% CI)       |
|------------|--------|------------|-----------------------------------|----------------------------------|----------------------|--------------------|-----|---|---|-----|-------------------|
| 7 log10 IU | /mL    |            |                                   |                                  |                      |                    |     |   |   |     |                   |
| Hu MF      | 2018   | China      | <0-28                             | NR                               | 1/89                 | 3/30               | _   |   |   | _   | 0.10 (0.01, 1.02) |
| Chen WJ    | 2017   | China      | 28                                | 0                                | 1/30                 | 16/44              |     |   |   |     | 0.06 (0.01, 0.49) |
| Xiao XH    | 2017   | China      | 28                                | 0 or 4                           | 0/60                 | 1/61               | -   |   | * |     | 0.33 (0.01, 8.35) |
| Subtotal ( | I-squa | red = 0.0% | %, p = 0.678                      | 3)                               |                      |                    |     | < | > |     | 0.10 (0.03, 0.41) |
|            |        |            |                                   |                                  |                      |                    |     |   |   |     |                   |
| 8 log10 IU | /mL    |            |                                   |                                  |                      |                    |     |   |   |     |                   |
| Chen HL    | 2015   | Taiwan     | 30-32                             | 4                                | 1/65                 | 6/56               |     |   |   | +   | 0.13 (0.02, 1.12) |
| Pan CQ     | 2016   | China      | 30-32                             | 4                                | 0/92                 | 6/88               |     | - |   | +   | 0.07 (0.00, 1.24) |
| Wakano Y   | 2018   | Japan      | 22-28                             | 4-8                              | 0/2                  | 2/3                |     |   |   |     | 0.12 (0.00, 4.61) |
| Subtotal ( | I-squa | red = 0.0% | %, p = 0.937                      | 7)                               |                      |                    |     | < | > |     | 0.11 (0.02, 0.51) |
|            |        |            |                                   |                                  |                      |                    |     |   |   |     |                   |
|            |        |            |                                   |                                  |                      |                    |     |   |   |     |                   |
|            |        |            |                                   |                                  |                      | .001               | .01 |   | 1 | 1 1 | 0                 |

LAM 100-150 mg by mean maternal viral load at baseline
6.0-6.9 log10 IU/mL (n=4): pooled OR= 0.15 (95% CI: 0.06-0.37), p=0.001, I<sup>2</sup>=0%

|              |           |             | Tx start  | Tx end     |           |         |     |            |                   |
|--------------|-----------|-------------|-----------|------------|-----------|---------|-----|------------|-------------------|
|              |           |             | in weeks  | in weeks   | Events,   | Events, |     |            |                   |
| Author       | Year      | Country     | gestation | postpartum | Treatment | Control |     |            | OR (95% CI)       |
| 6 log10 lU/r | nL        |             |           |            |           |         |     |            |                   |
| Ren CJ       | 2016      | China       | 28        | 0          | 2/67      | 10/72   |     |            | 0.19 (0.04, 0.91) |
| Zeng YM      | 2013      | China       | 28        | 0-6        | 0/90      | 3/30    |     |            | 0.04 (0.00, 0.87) |
| Zhang H      | 2014      | China       | 28-30     | 4          | 0/52      | 10/352  | _   |            | 0.31 (0.02, 5.38) |
| Zhang YF     | 2010a     | China       | 28        | 4          | 3/50      | 16/50   |     |            | 0.14 (0.04, 0.50) |
| Subtotal (I- | squared = | 0.0%, p = 0 | 0.795)    |            |           |         |     | $\diamond$ | 0.15 (0.06, 0.37) |
| •            |           |             |           |            |           |         |     |            |                   |
|              |           |             |           |            |           |         |     |            |                   |
|              |           |             |           |            |           | .001    | .01 | .1         | 1 10              |

## • LdT 600 mg by mean maternal viral load at baseline

- 6.0-6.9 log10 IU/mL (n=10): pooled OR= 0.13 (95% CI: 0.07-0.23), p<0.001,  $I^2=0\%$
- 7.0-7.9 log10 IU/mL (n=13): pooled OR= 0.06 (95% CI: 0.03-0.13), p<0.001,  $I^2=0\%$
- The p-value for heterogeneity between subgroups was 0.14

| Author     | Year     | Country   | Tx<br>start in weeks<br>gestation | Tx end<br>in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |            |      | OR (95% Cl)       |
|------------|----------|-----------|-----------------------------------|----------------------------------|----------------------|--------------------|------------|------|-------------------|
| 6 log10 Il | J/mL     |           |                                   |                                  |                      |                    |            |      |                   |
| Jiang S    | 2017     | China     | 28                                | NR                               | 1/44                 | 15/44              |            | -    | 0.04 (0.01, 0.36) |
| Li CM      | 2017     | China     | 28                                | 4                                | 1/30                 | 8/30               | •          |      | 0.09 (0.01, 0.82) |
| Li SF      | 2015     | China     | 28                                | 24                               | 0/60                 | 6/60               | *          |      | 0.07 (0.00, 1.26) |
| Li ZY      | 2018     | China     | 28                                | NR                               | 4/41                 | 9/41               |            | •    | 0.38 (0.11, 1.37) |
| Peng BA    | 2012     | China     | 28                                | 0                                | 1/40                 | 10/40              | •          | —    | 0.08 (0.01, 0.63) |
| PengML     | 2014     | China     | 28                                | NR                               | 1/30                 | 8/30               |            |      | 0.09 (0.01, 0.82) |
| Tian RH    | 2016     | China     | 28                                | 4                                | 3/318                | 17/374             |            |      | 0.20 (0.06, 0.69) |
| Yang HW    | 2015     | China     | 28                                | 4                                | 1/50                 | 12/50              |            | -    | 0.06 (0.01, 0.52) |
| Zhang H    | 2014     | China     | 28-30                             | 4                                | 0/257                | 10/352             | 2          |      | 0.06 (0.00, 1.09) |
| Zhang YF   | 2010b    | China     | 28                                | 4                                | 1/60                 | 16/60              | •          | -    | 0.05 (0.01, 0.36) |
| Subtotal   | (I-squar | ed = 0.0% | %, p = 0.671)                     |                                  |                      |                    | $\diamond$ |      | 0.13 (0.07, 0.23) |
|            |          |           |                                   |                                  |                      |                    |            |      |                   |
| 7 log10 Il | J/mL     |           |                                   |                                  |                      |                    |            |      |                   |
| Chen CY    | 2015     | China     | 1st Trimester                     | NR                               | 1/42                 | 7/40               | •          |      | 0.11 (0.01, 0.98) |
| Ding XP    | 2018     | China     | 28                                | 4                                | 0/38                 | 4/38               |            |      | 0 10 (0 01, 1 92) |
| Gao P      | 2016     | China     | 1st Trimester                     | 0                                | 1/51                 | 9/51               | •          |      | 0.09 (0.01, 0.77) |
| Guan ZF    | 2017     | China     | 24                                | 12                               | 0/123                | 14/122             |            | -    | 0.03 (0.00, 0.51) |
| Sun W      | 2017     | China     | 12-28                             | 12                               | 0/123                | 12/65              |            |      | 0.02 (0.00, 0.30) |
| Sun WH     | 2015     | China     | 12-28                             | 12                               | 0/84                 | 8/46               | *          | _    | 0.03 (0.00, 0.48) |
| Tan J      | 2019     | China     | 28                                | 0                                | 0/41                 | 6/59               |            |      | 0.10 (0.01, 1.81) |
| Wang B     | 2016     | China     | 28                                | 4                                | 0/110                | 16/187 -           | •          |      | 0.05 (0.00, 0.79) |
| Wang DN    | 1 2016   | China     | 28-30                             | 12                               | 1/36                 | 5/20               | •          |      | 0.09 (0.01, 0.80) |
| Wang TD    | 2015     | China     | 28                                | 4                                | 0/53                 | 8/52 -             |            |      | 0.05 (0.00, 0.87) |
| Wu Q       | 2015     | China     | 24-32                             | 0 or 4                           | 0/204                | 14/95 🗲 🗕          |            |      | 0.01 (0.00, 0.23) |
| Xiao XH    | 2017     | China     | 28                                | 0 or 4                           | 0/62                 | 1/61               |            |      | 0.32 (0.01, 8.08) |
| Zhang X    | 2015     | China     | 28                                | 12                               | 0/48                 | 5/47               |            |      | 0.08 (0.00, 1.48) |
| Subtotal   | (I-squar | ed = 0.0% | %, p = 0.974)                     |                                  |                      |                    | $\diamond$ |      | 0.06 (0.03, 0.13) |
|            |          |           | . ,                               |                                  |                      |                    | •          |      |                   |
|            |          |           |                                   |                                  |                      |                    |            |      |                   |
|            |          |           |                                   |                                  |                      | 1                  |            |      |                   |
|            |          |           |                                   |                                  |                      | .001               | 01 1       | 1 10 | I                 |
|            |          |           |                                   |                                  |                      |                    |            |      |                   |

## Appendix M: Efficacy by maternal HBeAg status at baseline

TDF 300 mg by maternal HBeAg status at baseline
HBeAg positive only (n=11): pooled OR= 0.09 (95% CI: 0.04-0.21), p<0.001, I<sup>2</sup>=0%

|                |         |                   | Tx start  | Tx end     |           |         |     |            |    |                   |
|----------------|---------|-------------------|-----------|------------|-----------|---------|-----|------------|----|-------------------|
|                |         |                   | in weeks  | in weeks   | Events,   | Events, |     |            |    |                   |
| Author         | Year    | Country           | gestation | postpartum | Treatment | Control |     |            |    | OR (95% CI)       |
|                |         |                   |           |            |           |         |     |            |    |                   |
| All HBeAg po   | sitive  |                   |           |            |           |         |     |            |    |                   |
| Celen MK       | 2013    | Turkey            | 18-27     | 4          | 0/21      | 2/23    |     | =          |    | 0.20 (0.01, 4.42) |
| Chen HL        | 2015    | Taiwan            | 30-32     | 4          | 1/65      | 6/56    |     |            |    | 0.13 (0.02, 1.12) |
| Chen WJ        | 2017    | China             | 28        | 0          | 1/30      | 16/44   |     |            |    | 0.06 (0.01, 0.49) |
| Huang Q        | 2017    | China             | 24-28     | 12         | 0/20      | 3/20    |     |            |    | 0.12 (0.01, 2.53) |
| Jourdain G     | 2018    | Thai <b>l</b> and | 26-29     | 8          | 0/149     | 3/147   |     |            |    | 0.14 (0.01, 2.70) |
| Lin Y          | 2018    | China             | 24        | 4          | 0/58      | 4/52    |     |            | _  | 0.09 (0.00, 1.75) |
| Liu MH         | 2017    | China             | 28-30     | 0          | 1/20      | 6/20    |     |            |    | 0.12 (0.01, 1.14) |
| Pan CQ         | 2016    | China             | 30-32     | 4          | 0/92      | 6/88    |     | -          | •  | 0.07 (0.00, 1.24) |
| Wakano Y       | 2018    | Japan             | 22-28     | 4-8        | 0/2       | 2/3     |     |            |    | 0.12 (0.00, 4.61) |
| Zhang BF       | 2018    | China             | 24-28     | 0          | 0/39      | 15/75   |     |            |    | 0.05 (0.00, 0.85) |
| Zhou Y         | 2018    | China             | 24-28     | 0          | 0/60      | 5/36    |     | -          |    | 0.05 (0.00, 0.88) |
| Subtotal (I-sc | uared = | 0.0%, p = 1.0     | 000)      |            |           |         |     | $\diamond$ |    | 0.09 (0.04, 0.21) |
|                |         |                   |           |            |           |         |     |            |    |                   |
|                |         |                   |           |            |           |         |     |            |    |                   |
|                |         |                   |           |            |           | 1       | 1   | <u> </u>   |    |                   |
|                |         |                   |           |            |           | .001    | .01 | .1 1       | 10 | 1                 |

## • LAM 100-150 mg by maternal HBeAg status at baseline

- HBeAg positive only (n=30): pooled OR= 0.16 (95% CI: 0.12-0.23), p<0.001,  $I^2=0\%$
- Mixed HBeAg positivity (n=4): pooled OR=0.26 (95%CI: 0.08-0.82), p=0.022, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.45

| Author         Year         Country         gestation         postpartum         Treatment         Control         OR (95% Cl)           All HeAg positive   |
|--|
| Author         Year         Country         gestation         postpartum         Treatment         Control         OR (95% CI)           All HBeAg positive         Chen QR         2018         China         28         4         1/33         5/28         0.14 (0.02, 1.31)         0.07 (0.01, 0.58)           Chen SM         2017         China         28         NR         1/30         10/30         0.07 (0.01, 0.58)         0.22 (0.02, 2.13)         0.22 (0.10, 0.77)         0.22 (0.02, 2.43)         0.22 (0.02, 2.43)         0.22 (0.02, 2.43)         0.22 (0.02, 2.43)         0.22 (0.02, 2.43)         0.22 (0.02, 2.43)         0.06 (0.00, 1.20)         0.06 (0.00, 0.23)         0.14 (0.02, 0.33)         0.22 (0.02, 2.44)         0.09 (0.00, 0.23)         0.14 (0.03, 0.65)         0.02 (0.00, 0.23)         0.14 (0.03, 0.65)         0.02 (0.00, 0.23)         0.14 (0.03, 0.65)         0.03 (0.00, 0.53)         0.14 (0.03, 0.65)         0.03 (0.00, 0.53)         0.14 (0.03, 0.65)         0.03 (0.00, 0.53)         0.14 (0.03, 0.65)         0.03 (0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.02, 0.20)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.03, 0.00, 0.53)         0.14 (0.04, 0.51)         0.14 (0.02, 0.2  |
| All HBeAg positive       Chen QR       2018       China       28       4       1/33       5/28       0.14 (0.02, 1.31)         Chen SM       2017       China       28       NR       1/30       10/30       0.7 (0.01, 0.58)         Cheng VC       2015       China       28       4       8/30       6/26       0.14 (0.02, 1.31)         Ge YL       2015       China       28       4       7/48       16/42       0.14 (0.02, 0.35)         Gu VZ       2008       China       28       0       3/70       13/40       0.28 (0.10, 0.77)         Jackson V       2015       China       28       0       0/43       5/35       0.22 (0.02, 2.14)         Jackson V       2015       China       28       0       0/43       5/35       0.09 (0.02, 0.85)         Jiang HX       2015       China       28       0       1/36       7/44       0.00 (0.0, 0.53)       0.11 (0.01, 0.91)         Li WE       2006       China       28       6       1/25       0.13 (3.13/155       0.33 (0.00, 0.53)       0.19 (0.04, 0.91)       0.28 (0.00, 0.41)       0.28 (0.03, 0.00)       0.29 (0.02, 2.19)       0.28 (0.03, 0.00)       0.31 (0.01, 2.99)       0.28 (0.03, 0.00)       0.31  |
| Chen QR       2018       China       28       4       1/33       5/28       0.14 (0.02, 1.31)         Chen SM       2017       China       28       NR       1/30       10/30       0.07 (0.01) 0.58)         Cheng YC       2011       China       28       4       7/48       16/42       0.28 (0.10, 0.77)         Ge YL       2015       China       28-30       12       0/16       3/22       0.17 (0.01, 0.58)         Guo YZ       2008       China       28       0       3/70       13/40       0.09 (0.02, 0.35)         Guo YZ       2005       China       28       0       0/43       5/35       0.06 (0.00, 1.20)         Jackson VZ       China       28       0       0/43       5/35       0.09 (0.00, 2.39)         Ji YY       2015       China       28       0       1/35       7/32       0.14 (0.03, 0.66)         Li G       2006       China       28       0       1/35       7/32       0.13 (0.00, 0.53)         Li ZG       2015       China       28       6       1/25       4/25       0.22 (0.02, 2.14)         Jackson V       2016       China       28       0       1/36       7/3   |
| Chen SM       2017       China       28       NR       1/30       10/30       Image: Constraint of the constraint of   |
| Cheng YC       2011       China       32       4       8/30       6/26       121 (0.36, 4.10)         Feng HF       2007       China       28       4       7/48       16/42       0.28 (0.10, 0.77)         Ge YL       2015       China       28-30       12       0/16       3/22       0.28 (0.10, 0.77)         Gu YZ       2008       China       28       0       3/70       13/40       0.28 (0.10, 0.77)         Han YP       2014       China       28       0       3/70       13/40       0.09 (0.02, 0.35)         Jackson V       2005       China       28       0       0/43       5/35       0.09 (0.00, 2.39)         Jarkson V       2015       China       28       0       0/43       5/35       0.09 (0.00, 0.30)         Jiang HX       2012       China       20-34       0       1/36       7/44       0.11 (0.01, 0.91)         Li WF       2006       China       24       0       1/36       7/44       0.15 (0.02, 1.29)         Li ZG       2015       China       28       0       1/25       0.22 (0.02, 2.11)         Ma J       2006       China       28       0       1/26       0.0   |
| Feng HF       2007       China       28       4       7/48       16/42       0.28 (0.10, 0.77)         Ge YL       2015       China       28.00       12       0/16       3/22       0.00       0.00       0.00 (0.02, 0.35)       0.00 (0.02, 0.35)       0.00 (0.02, 0.35)       0.00 (0.02, 0.35)       0.00 (0.02, 0.35)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.00 (0.00, 0.02)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.03 (0.00, 0.02)       0.03 (0.00, 0.02)       0.01 (0.01, 0.01)       0.03 (0.00, 0.02)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.01 (0.01, 0.01)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)       0.02 (0.00, 0.04)   |
| Ge YL       2015       China       28-30       12       0/16       3/22       0.17 (0.01, 3.51)         Gu YZ       2008       China       28       0       3/70       13/40       0.09 (0.02, 0.36)         Han YP       2014       China       28       6       1/30       4/30       0.09 (0.02, 0.36)         Jackson V       2015       China       28       0       0/43       5/35       0.06 (0.00, 1.20)         Jackson V       2015       China       28       4       2/65       0.02 (0.02, 2.38)         Jiarg HX       2012       China       28       0       0/164       8/92       0.03 (0.00, 0.53)         Li G       2006       China       28       0       1/35       7/32       0.01 (10.01, 0.91)         Li WF       2006       China       28       6       1/25       4/25       0.03 (0.00, 0.53)         Li WF       2016       China       28       0       1/36       7/44       0.13 (0.01, 2.59)         Li ZG       2016       China       28       0       1/170       0.90 (0.00, 2.19)         Jackson Y       2011       China       28       0       1/1710       4/175       0.   |
| Guo YZ       2008       China       28       0       3/70       13/40       Image: Constraint of the second sec   |
| Han YP 2014 China 28 6 1/30 4/30 0.22 (0.02, 2.14)<br>Han ZH 2005 China 28 0 0/43 5/35<br>Jiackson V 2015 Ireland 32 0 0/21 1/6<br>Jiang HX 2012 China 28 4 2/65 12/65<br>Jiang HX 2012 China 28 0 1/35 7/32<br>Li G 2006 China 28 0 1/35 7/32<br>Li ZG 2015 China 28 6 1/25 4/25 0.05 (0.00, 0.23)<br>Li ZG 2015 China 28 6 1/25 4/25 0.05 (0.00, 0.23)<br>Li ZG 2015 China 28 6 1/25 4/25 0.05 (0.00, 0.23)<br>Li ZG 2015 China 28 6 1/25 4/25 0.05 (0.00, 0.23)<br>Li ZG 2015 China 28 6 1/25 4/25 0.05 (0.00, 0.23)<br>Li ZG 2016 China 28 0 1/36 7/44 0.016 0.00 (0.00, 0.23)<br>Li ZG 2017 China 13-30 4 0/16 5/89<br>Pan CQ 2017 China 13-30 4 0/16 5/89<br>Tang X 2009 China 28 0 1/30 13/155 0.03 (0.00, 0.53)<br>Tang X 2009 China 28 0 1/30 13/155 0.03 (0.00, 0.53)<br>Tang X 2019 China 28 0 1/1/10 49/110 0.05 (0.00, 0.88)<br>Wang EJ 2012 China 28 0 11/110 49/110 0.05 (0.00, 0.88)<br>Wang EJ 2012 China 28 0 11/110 49/110 0.014 (0.07, 0.29)<br>Wakano Y 2018 Japan 28-32 4-8 0/3 2/3 0.014 (0.07, 0.29)<br>Wakano Y 2018 Japan 28-30 12 1/42 5/27 0.014 (0.07, 0.28)<br>Wang TM 2005 China 28 4 1/32 3/32 0.014 (0.02, 1.30)<br>Wang TM 2005 China 28 4 1/32 3/30 0.04 (0.00, 0.81)<br>Yan QF 2012 China 28 4 1/32 3/30 0.014 (0.02, 1.30)<br>Wang TM 2013 China 28 4 1/32 3/30 0.014 (0.02, 1.30)<br>O.04 (0.00, 0.81)<br>Yan QF 2013 China 28 4 1/32 3/30 0.014 (0.02, 1.30)<br>China 28 4 3/50 16/50 0.013 0.013 (0.02, 5.38)<br>China 28 4 3/50 16/50 0.014 0.023 0.013 (0.02, 5.38)<br>China 0.04 (0.00, 0.87)<br>D.04 (0.00, 0.87)<br>D.05 (0.03, 0.80)<br>D.05 (0.03, 0.80)<br>D.04 (0.00, 0.87)<br>D.04 (0.00, 0.87)<br>D.05 (0.03, 0.80)<br>D.05 |
| Han ZH       2005       China       28       0       0/43       5/35       0.06 (0.00, 1.20)         Jackson V       2015       Ireland       32       0       0/21       1/6       0.09 (0.00, 2.39)         Ji YY       2015       China       28       4       2/65       0.14 (0.03, 0.66)         Jang HX       2012       China       28       0       1/35       7/32       0.14 (0.03, 0.65)         Li G       2006       China       28       0       1/35       7/32       0.11 (0.01, 0.91)         Li XG       2015       China       28       6       1/25       4/25       0.22 (0.02, 2.11)         Ma J       2006       China       28       0       1/36       7/44       0.15 (0.02, 1.29)         Li ZG       2017       China       13-30       4       0/160       5/89       0.22 (0.02, 2.11)         Pan CQ       2017       China       28       0       1/30       13/155       0.38 (0.05, 2.99)         Tan X       2009       China       33       4       0/17       4/24       0.13 (0.01, 2.59)         Wang EU       2012       China       28       0       1/30       13/155  |
| Jackson V 2015 Ireland 32 0 0/21 1/6 0.09 (0.00, 2.39)<br>Ji YY 2015 China 28 4 2/65 12/65 0.03 (0.00, 0.53)<br>Li G 2006 China 28 0 1/35 7/32 0.01 (0.01, 0.91)<br>Li WF 2006 China 24 0 1/36 7/44 0.15 (0.02, 1.29)<br>Li ZG 2015 China 28 6 1/25 4/25 0.22 (0.02, 2.11)<br>Ma J 2006 China 28 0 2/67 10/72 0.02 (0.00, 0.41)<br>Pan CQ 2017 China 28 0 2/67 10/72 0.02 (0.00, 0.41)<br>Pan CQ 2015 China 28 0 1/30 13/155 0.03 (0.00, 0.53)<br>Tan XQ 2015 China 28 0 1/30 13/155 0.03 (0.00, 0.88)<br>Ren CJ 2016 China 28 0 1/30 13/155 0.03 (0.00, 0.88)<br>Ren CJ 2016 China 28 0 1/30 13/155 0.03 (0.00, 0.88)<br>Ren CJ 2016 China 28 0 1/30 13/155 0.03 (0.00, 0.88)<br>Ren CJ 2015 China 28 0 11/10 49/110 0.19 (0.04, 0.91)<br>Mang DM 2016 China 28 0 11/110 49/110 0.13 (0.01, 0.59)<br>Wang DM 2016 China 28 4 1/53 4/53 0.02 (0.00, 0.81)<br>Wang TM 2005 China Pre-pregnancy 0 0/32 8/32 0.00 (0.00, 3.10)<br>Wang TM 2005 China Pre-pregnancy 0 0/32 8/32 0.00 (0.00, 0.81)<br>Yan QF 2012 China 28 0 12 1/42 5/20 0.00 (0.00, 0.81)<br>Yan QF 2012 China 28 4 1/53 4/53 0.02 (0.00, 0.81)<br>Yan QF 2012 China 28 4 1/53 4/53 0.02 (0.00, 0.81)<br>Yan QF 2012 China 28 4 1/53 4/53 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.03 (0.00, 0.8   |
| Ji YY       2015       China       28       4       2/65       12/65       12/65       0.14 (0.03, 0.65)         Jiang HX       2012       China       20-34       0       0/164       8/92       0.11 (0.01, 0.91)         Li G       2006       China       28       0       1/35       7/32       0.11 (0.01, 0.91)         Li ZG       2015       China       28       6       1/25       4/25       0.22 (0.02, 2.11)         Ma J       2006       China       Pre-pregnancy       NR       0/160       5/89       0.05 (0.00, 0.88)         Ren CJ       2016       China       28       0       1/30       13/155       0.14 (0.07, 0.29)         Tang X       2009       China       38       4       0/17       4/24       0.13 (0.01, 2.59)         Tang X       2009       China       38       4       0/32       2/3       0.38 (0.05, 2.99)         Tang X       2009       China       28       0       11/110       4/10       0.14 (0.07, 0.29)         Wakano Y       2015       China       28       0       11/110       4/12       5/20       0.03 (0.00, 0.81)         Wang EJ       2012       China   |
| Jiang HX       2012       China       20-34       0       0/164       8/92       Image: Construction of the cons   |
| Li G 2006 China 28 0 1/35 7/32 0.11 (0.01, 0.91)<br>Li WF 2006 China 24 0 1/36 7/44 0.15 (0.02, 1.29)<br>Li ZG 2015 China 28 6 1/25 4/25 0.22 (0.02, 2.11)<br>Ma J 2006 China Pre-pregnancy NR 0/18 9/16 0.02 (0.00, 0.88)<br>Ren CJ 2016 China 28 0 2/67 10/72 0.19 0.038 (0.05, 2.99)<br>Tang X 2009 China 33 4 0/17 4/24 0.19 0.038 (0.05, 2.99)<br>Tang X 2009 China 28 0 11/31/155 0.13 (0.01, 2.59)<br>Tian XQ 2015 China 28 0 11/11/10 49/110 0.14 (0.07, 0.29)<br>Wakano Y 2018 Japan 28-32 4-8 0/3 2/3 0.14 (0.00, 0.81)<br>Wang DM 2016 China 28 4 1/32 5/27 0.007 (0.01, 0.68)<br>Wang EJ 2012 China 28 4 1/32 5/27 0.007 (0.01, 0.68)<br>Wang HW 2014 China 28 0 6.12 1/42 5/20 0.007 (0.01, 0.68)<br>Yuan QF 2012 China 28 4 1/53 4/53 0.04 (0.00, 0.81)<br>Yuan QF 2013 China 28 0.66 0/90 3/30 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 3/50 16/50 0.31 (0.02, 5.39)<br>Zhang YF 2010a China 28 4 3/50 16/50 0.31 (0.02, 5.39)<br>Zhang YF 2010 China 28 4 3/50 16/50 0.31 (0.02, 5.39)<br>Zhang YF 2010 China 28 4 3/50 16/50 0.31 (0.02, 5.39)<br>Zhang YF 2010 China 28 4 3/50 16/50 0.31 (0.02, 5.39)<br>Zhang YF 2010a China 28 4 3/50 16/50 0.14 (0.04, 0.50)<br>China 28 0 0.2/24 9/24 0.03 (0.14 (0.02, 1.30)<br>0.14 (0.02, 1.30)<br>0.14 (0.02, 2.18)<br>0.14 (0.02, 2.18)<br>0.14 (0.02, 0.83)<br>0.14 (0.04, 0.50)<br>0.16 (0.12, 0.23)<br><br>Wixed HBeAg positivity   |
| Li WF 2006 China 24 0 1/36 7/44 0.15 (0.02, 1.29)<br>Li ZG 2015 China 28 6 1/25 4/25 0.22 (0.02, 2.11)<br>Ma J 2006 China Pre-pregnancy NR 0/18 9/16 0.20 (0.00, 0.88)<br>Pan CQ 2017 China 13-30 4 0/160 5/89<br>Ren CJ 2016 China 28 0 2/67 10/72 0.038 (0.05, 2.99)<br>Tang X 2009 China 33 4 0/17 4/24 0.13 (0.01, 2.59)<br>Tian XQ 2015 China 28 0 11/110 49/110 0.13 (0.01, 2.59)<br>Tian XQ 2015 China 28 0 11/110 49/110 0.14 (0.07, 0.29)<br>Wang DM 2016 China 28 4 1/32 5/27 0.000 (0.81)<br>Wang TM 2005 China Pre-pregnancy 0 0/32 8/32 0.000 (0.81)<br>Yuan QF 2012 China 28 4 1/32 3/32 0.04 (0.00, 0.81)<br>Yuan QF 2012 China 28 4 1/32 3/32 0.04 (0.00, 0.81)<br>Yuan QF 2012 China 28 4 1/32 3/32 0.04 (0.00, 0.81)<br>Yuan QF 2012 China 28 4 1/32 3/32 0.04 (0.00, 0.81)<br>Yuan QF 2013 China 28 4 0/52 10/352 0.03 (0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 3/50 16/50 0.14 (0.02, 1.38)<br>China 28 4 0/52 10/352 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>Zhu M 2014 China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>Zhu M 2014 China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>Zhu M 2014 China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>Zhu M 2014 China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>Zhu M 2014 China 28 4 0/52 10/352 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.02, 2.38)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.04, 0.50)<br>China 28 0 0.01 (0.02, 0.38)<br>China 28 0 0.01 (   |
| Li ZG 2015 China 28 6 1/25 4/25 0.22 (0.02, 2.11)<br>Ma J 2006 China Pre-pregnancy NR 0/18 9/16 0.02 (0.00, 0.41)<br>Pan CQ 2017 China 13-30 4 0/160 5/89 0.05 (0.00, 0.88)<br>Ren CJ 2016 China 28 0 2/67 10/72 0.03 (0.04, 0.91)<br>Ren YJ 2011 China 28 0 1/30 13/155 0.19 (0.04, 0.91)<br>Tian XQ 2009 China 33 4 0/17 4/24 0.13 (0.01, 2.59)<br>Tian XQ 2015 China 28 0 11/110 49/110 0.03 (0.00, 0.80)<br>Wakano Y 2018 Japan 28-32 4.8 0/3 2/3 0.000 (0.00, 0.81)<br>Wang DM 2016 China 28 4 1/32 5/27 0.007 (0.01, 0.68)<br>Wang TM 2005 China Pre-pregnancy 0 0/32 8/32 0.007 (0.01, 0.68)<br>Wang TM 2005 China 27 4 1/32 3/32 0.04 (0.00, 0.81)<br>Yuan QF 2012 China 28 4 1/53 4/53 0.24 (0.03, 2.18)<br>Yuan QF 2012 China 28 4 1/53 4/53 0.34 (0.03, 3.17)<br>Zeng YM 2013 China 28 0-6 0/90 3/30 0.04 (0.00, 0.87)<br>Zhang YF 2010a China 28 4 3/50 16/50 0.14 (0.02, 5.38)<br>China 28 4 3/50 16/50 0.14 (0.02, 0.58)<br>Subtotal (I-squared = 0.0%, p = 0.847)<br><br>Mixed HBeAg positivity   |
| Ma J       2006       China       Pre-pregnancy       NR       0/18       9/16       0.02 (0.00, 0.41)         Pan CQ       2017       China       13-30       4       0/160       5/89       0.05 (0.00, 0.88)         Ren CJ       2016       China       28       0       1/30       13/155       0.19 (0.04, 0.91)         Tang X       2009       China       28       0       1/30       13/155       0.19 (0.04, 0.91)         Tang X       2009       China       28       0       1/110       49/110       0.38 (0.05, 2.99)         Wakano Y       2018       Japan       28-32       4-8       0/3       2/3       0.09 (0.00, 3.10)         Wakano Y       2018       Japan       28-30       12       1/42       5/20       0.07 (0.01, 0.68)         Wang DM       2016       China       28       4       1/32       5/27       0.04 (0.00, 0.81)         Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       0.31 (0.03, 3.17)         Yuan OF       2012       China       27       4       1/32       3/32       0.34 (0.03, 3.17)         Zhang YF       2014       China       28 </td  |
| Pan CQ       2017       China       13-30       4       0/160       5/89       0.05 (0.00, 0.88)         Ren CJ       2016       China       28       0       2/67       10/72       0.19 (0.04, 0.91)         Ren YJ       2011       China       28       0       1/30       13/155       0.38 (0.05, 2.99)         Tang X       2009       China       33       4       0/17       4/24       0.13 (0.01, 2.59)         Tian XQ       2015       China       28       0       11/110       49/110       0.13 (0.07, 0.29)         Wakano Y       2018       Japan       28-30       12       1/42       5/20       0.09 (0.00, 3.10)         Wang TM       2005       China       28       4       1/32       3/32       0.04 (0.00, 0.81)         Yang HW       2014       China       28       4       1/32       3/32       0.44 (0.03, 2.18)         Yuan QF       2012       China       27       4       1/32       3/32       0.31 (0.00, 0.81)         Yuan QF       2012       China       27       4       1/32       3/32       0.31 (0.02, 5.30)         Zhang YF       2013       China       28       0.6   |
| Ren CJ       2016       China       28       0       2/67       10/72       0.19 (0.04, 0.91)         Ren YJ       2011       China       28       0       1/30       13/155       0.38 (0.05, 2.99)         Tang X       2009       China       33       4       0/17       4/24       0.19 (0.04, 0.91)         Wakano Y       2015       China       28       0       11/110       49/110       0.14 (0.07, 0.29)         Wakano Y       2016       China       28-30       12       1/42       5/20       0.09 (0.00, 3.10)         Wang EJ       2012       China       28       4       1/32       5/27       0.14 (0.02, 1.30)         Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       0.04 (0.00, 0.81)         Yuan QF       2012       China       28       4       1/32       3/32       0.31 (0.03, 2.18)         Yuan QF       2013       China       28       0.6       0/90       3/30       0.34 (0.00, 0.87)       0.31 (0.02, 5.38)         Zhang YF       2010       China       28       4       3/50       16/50       0.14 (0.04, 0.50)       0.15 (0.03, 0.80)       0.14 (0.04, 0.50)   |
| Ren YJ       2011       China       28       0       1/30       13/155       0.38 (0.05, 2.99)         Tang X       2009       China       33       4       0/17       4/24       0.13 (0.01, 2.59)         Tian XQ       2015       China       28       0       11/110       4/24       0.13 (0.01, 2.59)         Wakano Y       2018       Japan       28-32       4.8       0/3       2/3       0.09 (0.00, 3.10)         Wang DM       2016       China       28-30       12       1/42       5/20       0.07 (0.01, 0.68)         Wang EJ       2012       China       28       4       1/32       5/27       0.14 (0.02, 1.30)         Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       0.04 (0.00, 0.81)         Yuan QF       2012       China       28       4       1/32       3/32       0.31 (0.03, 2.18)       0.31 (0.03, 3.17)         Zeng YM       2013       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)       0.31 (0.02, 5.38)       0.31 (0.02, 5.38)       0.31 (0.02, 5.38)       0.31 (0.02, 5.38)       0.31 (0.02, 5.38)       0.31 (0.02, 0.80)       0.15 (0.03, 0.80)       0.15 (0.03, 0.80)  |
| Tang X       2009       China       33       4       0/17       4/24       0.13 (0.01, 2.59)         Tian XQ       2015       China       28       0       11/110       49/110       0.14 (0.07, 0.29)         Wakano Y       2018       Japan       28-32       4-8       0/3       2/3       0.09 (0.00, 3.10)         Wang DM       2016       China       28-32       4-8       0/3       2/3       0.07 (0.01, 0.68)         Wang EJ       2012       China       28       4       1/32       5/27       0.14 (0.02, 1.30)         Wang TM       2005       China       28       4       1/33       4/53       0.44 (0.02, 1.30)         Yang HW       2014       China       28       4       1/32       3/30       0.04 (0.00, 0.81)         Yang HW       2014       China       28       4       1/32       3/30       0.31 (0.03, 3.17)         Zeng YM       2013       China       27       4       1/32       3/30       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       0.4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4  |
| Tian XQ       2015       China       28       0       11/110       49/110       0.14 (0.07, 0.29)         Wakano Y       2018       Japan       28-32       4-8       0/3       2/3       0.09 (0.00, 3.10)         Wang DM       2016       China       28-30       12       1/42       5/27       0.09 (0.00, 3.10)         Wang LJ       2012       China       28       4       1/32       5/27       0.14 (0.07, 0.29)         Wang TM       2005       China       28       4       1/32       5/27       0.14 (0.00, 0.81)         Yang HW       2014       China       28       4       1/32       3/32       0.04 (0.00, 0.81)         Yuan QF       2012       China       27       4       1/32       3/32       0.31 (0.03, 3.17)         Zeng YM       2013       China       28       0-6       0/90       3/30       0.34 (0.00, 0.87)         Zhang YF       2010       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010       China       28       0       10/352       0.31 (0.04, 0.50)       0.14 (0.04, 0.50)         Zhu M       2014       China       26  |
| Wakano Y       2018       Japan       28-32       4-8       0/3       2/3       0.09 (0.00, 3.10)         Wang DM       2016       China       28-30       12       1/42       5/20       0.07 (0.01, 0.68)         Wang EJ       2012       China       28       4       1/32       5/27       0.09 (0.00, 3.10)         Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       0.04 (0.00, 0.2, 1.8)         Yang HW       2014       China       28       4       1/32       3/32       0.04 (0.00, 0.2, 1.8)         Yuan QF       2013       China       27       4       1/32       3/32       0.31 (0.03, 3.17)         Zhang H       2014       China       28       0-6       0/90       3/30       0.04 (0.00, 0.87)         Zhang YF       2013       China       28       4       3/50       16/50       0.14 (0.04, 0.50)         Zhu M       2014       China       28       0       2/24       9/24       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)            0.16 (0.12, 0.23)         Mixed HBeAg positivity        <   |
| Wang DM       2016       China       28-30       12       1/42       5/20       Image: Construction of the constructing and the construction of the construction of the cons   |
| Wang EJ       2012       China       28       4       1/32       5/27       Image: China       0.14 (0.02, 1.30)         Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       Image: China       0.04 (0.00, 0.81)         Yang HW       2014       China       28       4       1/53       4/53       Image: China       0.24 (0.03, 2.18)         Yuan QF       2012       China       27       4       1/32       3/32       Image: China       0.31 (0.03, 3.17)         Zeng YM       2013       China       28       0-6       0/90       3/30       Image: China       0.31 (0.02, 5.38)         Zhang H       2014       China       28       4       3/50       16/50       Image: China       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4       3/50       16/50       Image: China       0.14 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       Image: China       0.16 (0.12, 0.23)         Subtotal (I-squared = 0.0%, p = 0.847)       Image: China       Image: China       Image: China       Image: China       Image: China       Image: China       Image: China <t< td=""></t<>   |
| Wang TM       2005       China       Pre-pregnancy       0       0/32       8/32       0.04 (0.00, 0.81)         Yang HW       2014       China       28       4       1/53       4/53       0.24 (0.03, 2.18)         Yuan QF       2012       China       27       4       1/32       3/32       0.04 (0.00, 0.81)         Zeng YM       2013       China       28       0-6       0/90       3/30       0.04 (0.00, 0.87)         Zhang H       2014       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4       3/50       16/50       0.14 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)               Mixed HBeAg positivity   |
| Yang HW       2014       China       28       4       1/53       4/53       0.24 (0.03, 2.18)         Yuan QF       2012       China       27       4       1/32       3/32       0.31 (0.03, 3.17)         Zeng YM       2013       China       28       0-6       0/90       3/30       0.04 (0.00, 0.87)         Zhang H       2014       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4       3/50       16/50       0.14 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)               Mixed HBeAg positivity  |
| Yuan QF       2012       China       27       4       1/32       3/32       3/32       0.31 (0.03, 3.17)         Zeng YM       2013       China       28       0-6       0/90       3/30       0.04 (0.00, 0.87)         Zhang H       2014       China       28-30       4       0/52       10/352       0.31 (0.03, 3.17)         Zhang YF       2010       China       28       4       3/50       16/50       0.31 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       0.14 (0.04, 0.50)       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)       .       .       .       .       .       .         .       .       .       .       .       .       .       .       .         .       .       .       .       .       .       .       .       .       .         .   |
| Zeng YM       2013       China       28       0-6       0/90       3/30       0.04 (0.00, 0.87)         Zhang H       2014       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4       3/50       16/50       0.14 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)              Mixed HBeAg positivity   |
| Zhang H       2014       China       28-30       4       0/52       10/352       0.31 (0.02, 5.38)         Zhang YF       2010a       China       28       4       3/50       16/50       0.14 (0.04, 0.50)         Zhu M       2014       China       26       0       2/24       9/24       0.15 (0.03, 0.80)         Subtotal (I-squared = 0.0%, p = 0.847)       .       .       .       .       .   |
| Zhang YF         2010a         China         28         4         3/50         16/50         1         0.14 (0.04, 0.50)           Zhu M         2014         China         26         0         2/24         9/24         0.15 (0.03, 0.80)           Subtotal (I-squared = 0.0%, p = 0.847)         .         .         .         .         .  |
| Zhu M         2014         China         26         0         2/24         9/24         0.15 (0.03, 0.80)         0.15 (0.03, 0.80)         0.16 (0.12, 0.23)  |
| Subtotal (I-squared = 0.0%, p = 0.847)         Image: Constraint of the squared sector of the square   |
| Mixed HBeAg positivity   |
| Mixed HBeAg positivity   |
| 51 5   |
| Foaud HM 2019 Egypt Anytime NR 0/29 1/30 - 0.33 (0.01, 8.52)   |
| Greenup AJ 2014 Australia 32 2 0/43 2/10 0.04 (0.00, 0.89)   |
| He T 2018 China 1st Trimester NR 0/29 4/34 - 0.11 (0.01, 2.23)   |
| Xu WM 2009 China, Philippines 30-34 4 3/49 5/41 - 0.47 (0.11, 2.10)  |
| Subtotal (I-squared = 0.0%, p = 0.504) 0.26 (0.08, 0.82)   |
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## • LdT 600 mg by maternal HBeAg status at baseline

- HBeAg positive only (n=52): pooled OR= 0.11 (95% CI: 0.08-0.14), p<0.001,  $I^2=0\%$
- Mixed HBeAg positivity (n=6): pooled OR=0.09 (95%CI: 0.04-0.21), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.65

| Author        | Year        | Country     | Tx<br>start in weeks<br>gestation | Tx end<br>in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control | OR (95% Cl)         |
|---------------|-------------|-------------|-----------------------------------|----------------------------------|----------------------|--------------------|---------------------|
| All HBeAa     | oositive    |             |                                   |                                  |                      |                    |                     |
| Chen CY       | 2015        | China       | 1st Trimester                     | NR                               | 1/42                 | 7/40               | 0.11 (0.01, 0.98)   |
| Chen F        | 2016        | China       | Pre-pregnancy                     | NR                               | 0/31                 | 6/32               | 0.06 (0.00, 1.20)   |
| Chen QR       | 2018        | China       | 28                                | 4                                | 0/29                 | 5/28               | 0.07 (0.00, 1.38)   |
| Chen SM       | 2017        | China       | 28                                | NR                               | 0/30                 | 10/30              | 0.03 (0.00, 0.58)   |
| Chen WJ       | 2017        | China       | 28                                | 0                                | 4/79                 | 16/44              | 0.09 (0.03, 0.30)   |
| Ding XP       | 2015        | China       | 20                                | 4                                | 0/38                 | //38               | 0.05 (0.01, 0.42)   |
| Fan I Y       | 2013        | China       | 28                                | 24                               | 0/58                 | 6/60               | 0.07 (0.00, 1.30)   |
| Feng XM       | 2017        | China       | 28                                | 4                                | 1/36                 | 7/36               | 0.12 (0.01, 1.02)   |
| Ge YL         | 2015        | China       | 28-30                             | 12                               | 0/20                 | 3/22               | 0.14 (0.01, 2.81)   |
| Guan ZF       | 2017        | China       | 24                                | 12                               | 0/123                | 14/122             | 0.03 (0.00, 0.51)   |
| Guo HJ        | 2011        | China       | 28                                | 4                                | 6/28                 | 6/26               | 0.91 (0.25, 3.28)   |
| Han GR        | 2015        | China       | 20-32                             | NR                               | 0/358                | 8/86               | 0.01 (0.00, 0.23)   |
| Han YP        | 2014        | China       | 28                                | 6                                | 0/30                 | 4/30               | 0.10 (0.00, 1.88)   |
| Huang HV      | 2016        | China       | 20-32                             | 3-4<br>0                         | 16/90                | 23/30              |                     |
| Huang O       | 2010        | China       | 24-28                             | 12                               | 0/20                 | 3/20               | - 0.12 (0.01, 2.53) |
| JiYY          | 2015        | China       | 28                                | 4                                | 3/65                 | 12/65              | 0.21 (0.06, 0.80)   |
| Jiang XN      | 2013        | China       | 26-30                             | NR                               | 1/65                 | 8/51               | 0.08 (0.01, 0.70)   |
| Li YH         | 2017        | China       | 28                                | ~36                              | 1/30                 | 5/32               | 0.19 (0.02, 1.70)   |
| Li ZY         | 2018        | China       | 28                                | NR                               | 4/41                 | 9/41               | 0.38 (0.11, 1.37)   |
| Liu CY        | 2014        | China       | 28                                | 4                                | 1/34                 | 8/34               | 0.10 (0.01, 0.84)   |
| Liu J         | 2017        | China       | 30                                | NR                               | 0/97                 | 2/28               | 0.05 (0.00, 1.17)   |
|               | 2016        | China       | 28-36                             | 4                                | 0/20                 | 5/20               | 0.07 (0.00, 1.34)   |
| Pan VC        | 2015        | China       | 20                                | 4                                | 0/125                | 21/370             | 0.00 (0.00, 1.24)   |
| Peng BA       | 2017        | China       | 28                                | 0                                | 1/40                 | 10/40              | 0.08 (0.01, 0.63)   |
| PenaML        | 2014        | China       | 28                                | ŇR                               | 1/30                 | 8/30               | 0.09 (0.01, 0.82)   |
| Ren N         | 2015        | China       | 28                                | 24                               | 2/46                 | 11/46              | 0.14 (0.03, 0.70)   |
| Sheng Q       | 2018a       | China       | 24-32                             | 0                                | 0/79                 | 2/21               | 0.05 (0.00, 1.06)   |
| Sun W         | 2017        | China       | 12-28                             | 12                               | 0/123                | 12/65              | 0.02 (0.00, 0.30)   |
| Sun WH        | 2015        | China       | 12-28                             | 12                               | 0/84                 | 8/46               | 0.03 (0.00, 0.48)   |
| Tian JH       | 2018        | China       | Anytime                           | NR                               | 0/135                | 7/203              | 0.10 (0.01, 1.71)   |
| Han HH        | 2016        | China       | 28                                | 4                                | 3/318                | 1//3/4             | 0.20 (0.06, 0.69)   |
| Wang DM       | 2016        | China       | 28-30                             | 4                                | 1/36                 | 5/20               | 0.05 (0.00, 0.79)   |
| Wang E.I      | 2012        | China       | 28                                | 4                                | 0/28                 | 5/27               | 0.07 (0.00, 1.37)   |
| Wang HY       | 2018        | China       | 12-14                             | 24                               | 0/40                 | 6/40               | 0.07 (0.00, 1.21)   |
| Wang TD       | 2015        | China       | 28                                | 4                                | 0/53                 | 8/52               | 0.05 (0.00, 0.87)   |
| Wang WP       | 2012        | China       | 0-28                              | 0                                | 0/47                 | 20/198             | 0.09 (0.01, 1.54)   |
| Wu Q          | 2015        | China       | 24-32                             | 0 or 4                           | 0/204                | 14/95              | 0.01 (0.00, 0.23)   |
| Yang HW       | 2015        | China       | 28                                | 4                                | 1/50                 | 12/50              | 0.06 (0.01, 0.52)   |
| Yao LF        | 2014        | China       | 28-32                             | 6                                | 0/30                 | 2/30               | 0.19 (0.01, 4.06)   |
| Zhang BF      | 2018        | China       | 24-28                             | 0                                | 0/36                 | 15//5              | 0.05 (0.00, 0.92)   |
| Zhang H       | 2010        | China       | 28-30                             | 4                                | 0/257                | 10/352             |                     |
| Zhang X       | 2015        | China       | 28                                | 12                               | 0/48                 | 5/47               | 0.08 (0.00, 1.48)   |
| Zhang YF      | 2010b       | China       | 28                                | 4                                | 1/60                 | 16/60              | 0.05 (0.01, 0.36)   |
| Zhao DB       | 2010        | China       | 28                                | 4                                | 1/30                 | 3/30               | 0.31 (0.03, 3.17)   |
| Zhao J        | 2013        | China       | 20                                | 0                                | 0/41                 | 23/202             | 0.09 (0.01, 1.55)   |
| Zhao Y        | 2017        | China       | 12                                | 12                               | 0/40                 | 5/40               | 0.08 (0.00, 1.49)   |
| Zheng JC      | 2018        | China       | 28                                | 4                                | 0/23                 | 8/37               | 0.07 (0.00, 1.35)   |
| Subtotal (I   | -squared =  | = 0.0%, p = | 0.985)                            |                                  |                      | <b>~</b>           | 0.11 (0.08, 0.14)   |
| Mixed HBe     | Ag positivi | ity         |                                   |                                  |                      |                    |                     |
| Chen ZX       | 2017        | China       | 13-32<br>Let Trimeeter            | NH                               | 1/41                 | 15/89              | 0.12 (0.02, 0.97)   |
| He I<br>Liu V | 2018        | China       | 1 St Trimester                    | 111H<br>4                        | 1/82                 | 4/34               | 0.10 (0.01, 2.02)   |
|               | 2010        | China       | 28                                | -<br>0                           | 2/152                | 12/132             | 0.04 (0.00, 0.29)   |
| Shena Q       | 2018b       | China       | 24-28                             | õ                                | 0/66                 | 5/46               | 0.06 (0.00, 1.05)   |
| Tan Z         | 2016        | China       | 0-28                              | NR                               | 0/171                | 15/320             | 0.06 (0.00, 0.97)   |
| Subtotal (I-  | -squared =  | = 0.0%, p = | 0.941)                            |                                  |                      | $\diamond$         | 0.09 (0.04, 0.21)   |
| •             |             |             |                                   |                                  |                      |                    |                     |
|               |             |             |                                   |                                  |                      |                    |                     |
|               |             |             |                                   |                                  |                      |                    |                     |
|               |             |             |                                   |                                  |                      | .001 .01 .1 1      | 10                  |
|               |             |             |                                   |                                  |                      |                    |                     |

## Appendix N: Efficacy by infant immunoprophylaxis regimen

- TDF 300 mg by infant immunoprophylaxis regimens
  - Timely HepB-BD & HBIG (n=14): pooled OR= 0.15 (95% CI: 0.09-0.27), p<0.001,  $I^2=0\%$
  - No or unclear timely HepB-BD/HBIG (n=5): pooled OR=0.16 (95%CI: 0.06-0.43), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.89

|                        |          |             | Events,   | Events, |                   |                            |
|------------------------|----------|-------------|-----------|---------|-------------------|----------------------------|
| Author                 | Year     | Country     | Treatment | Control |                   | OR (95% CI)                |
| Timely HBIG            | & Hep    | B-BD        |           |         |                   |                            |
| Chen WJ                | 2017     | China       | 1/30      | 16/44   |                   | 0.06 (0.01, 0.49)          |
| Gong Q                 | 2017     | China       | 1/44      | 7/44    |                   | 0.12 (0.01, 1.05)          |
| He LL                  | 2018     | China       | 13/50     | 17/35   |                   | 0.37 (0.15, 0.93)          |
| Hu MF                  | 2018     | China       | 1/89      | 3/30    |                   | 0.10 (0.01, 1.02)          |
| Huang Q                | 2017     | China       | 0/20      | 3/20    |                   | 0.12 (0.01, 2.53)          |
| Jourdain G             | 2018     | Thailand    | 0/149     | 3/147   |                   | 0.14 (0.01, 2.70)          |
| Lin Y                  | 2018     | China       | 0/58      | 4/52    |                   | 0.09 (0.00, 1.75)          |
| Liu MH                 | 2017     | China       | 1/20      | 6/20    |                   | 0.12 (0.01, 1.14)          |
| Pan CQ                 | 2016     | China       | 0/92      | 6/88    |                   | 0.07 (0.00, 1.24)          |
| Wakano Y               | 2018     | Japan       | 0/2       | 2/3     |                   | 0.12 (0.00, 4.61)          |
| Wang HB                | 2018     | China       | 0/100     | 2/20    |                   | 0.04 (0.00, 0.80)          |
| Yu CY                  | 2018     | China       | 0/30      | 4/30    |                   | 0.10 (0.00, 1.88)          |
| Zhang BF               | 2018     | China       | 0/39      | 15/75   |                   | 0.05 (0.00, 0.85)          |
| Zhou Y                 | 2018     | China       | 0/60      | 5/36    |                   | 0.05 (0.00, 0.88)          |
| Subtotal ( <b>I-</b> s | quared   | = 0.0%, p   | = 0.876)  |         | $\diamond$        | 0.15 (0.09, 0.27)          |
|                        |          |             |           |         |                   |                            |
| No or unclea           | r timely | HBIG/Hep    | DB-BD     |         | L                 |                            |
| Celen MK               | 2013     | Turkey      | 0/21      | 2/23    | ja                | 0.20 (0.01, 4.42)          |
| Chen HL                | 2015     | Taiwan      | 1/65      | 6/56    |                   | 0.13 (0.02, 1.12)          |
| Greenup AJ             | 2014     | Australia   | 1/69      | 2/10    |                   | 0.06 (0.00, 0.72)          |
| Wan JY                 | 2017     | China       | 3/74      | 7/42    |                   | 0.21 (0.05, 0.87)          |
| Xiao XH                | 2017     | China       | 0/60      | 1/61    |                   | <b>—</b> 0.33 (0.01, 8.35) |
| Subtotal (I-s          | quared   | = 0.0%, p   | = 0.907)  |         | $\langle \rangle$ | 0.16 (0.06, 0.43)          |
| Overall (I-sc          | uared :  | = 0.0%, p = | = 0.972)  |         | \$                | 0.16 (0.09, 0.25)          |
|                        |          |             |           | I       |                   | 1                          |
|                        |          |             |           | .00     | 1 .01 .1 1        | 10                         |

## • LAM 100-150 mg by infant immunoprophylaxis regimens

- Timely HepB-BD & HBIG (n=31): pooled OR= 0.18 (95% CI: 0.13-0.24), p<0.001,  $I^2=0\%$
- No or unclear timely HepB-BD/HBIG (n=9): pooled OR=0.13 (95%CI: 0.06-0.25), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.38

| Author             | Year      | Country           | Events,<br>Treatment | Events,<br>Control | OR (95% CI)        |
|--------------------|-----------|-------------------|----------------------|--------------------|--------------------|
| Timelv HBIG 8      | & HepB-Bl | D                 |                      |                    |                    |
| Bai XŴ             | 2011      | China             | 3/30                 | 8/25               | 0.24 (0.05, 1.02   |
| Chen QR            | 2018      | China             | 1/33                 | 5/28               | 0.14 (0.02, 1.31   |
| Chena YC           | 2011      | China             | 8/30                 | 6/26               | 1.21 (0.36, 4.10   |
| Fena HF            | 2007      | China             | 7/48                 | 16/42              | 0.28 (0.10, 0.77   |
| Foaud HM           | 2019      | Eavot             | 0/29                 | 1/30               | 0.33 (0.01, 8.52   |
| Go VI              | 2015      | China             | 0/16                 | 3/22               |                    |
|                    | 2013      | China             | 3/70                 | 13/40              | 0.09 (0.03, 0.35   |
|                    | 2000      | China             | 1/20                 | 1/20               | 0.09 (0.02, 0.33   |
| Hall IF<br>Ha T    | 2014      | China             | 0/20                 | 4/30               | 0.22 (0.02, 2.14   |
|                    | 2016      | Unina             | 0/29                 | 4/34               | 0.11 (0.01, 2.23)  |
| Jackson v          | 2015      | Ireland           | 0/21                 | 1/6                | 0.09 (0.00, 2.39   |
| JIYY               | 2015      | China             | 2/65                 | 12/65              | 0.14 (0.03, 0.65   |
| Jiang HX           | 2012      | China             | 0/164                | 8/92               | 0.03 (0.00, 0.53   |
| Li JH              | 2017      | China             | 1/33                 | 8/27               | 0.07 (0.01, 0.64   |
| Li ZG              | 2015      | China             | 1/25                 | 4/25               | 0.22 (0.02, 2.11)  |
| Ma J               | 2006      | China             | 0/18                 | 9/16               | 0.02 (0.00, 0.41   |
| Pan CQ             | 2017      | China             | 0/160                | 5/89               | 0.05 (0.00, 0.88   |
| Ren CJ             | 2016      | China             | 2/67                 | 10/72              | 0.19 (0.04, 0.91   |
| Ren YJ             | 2011      | China             | 1/30                 | 13/155             | 0.38 (0.05, 2.99   |
| Tang X             | 2009      | China             | 0/17                 | 4/24               | 0.13 (0.01, 2.59   |
| Tian XQ            | 2015      | China             | 11/110               | 49/110             | 0.14 (0.07, 0.29   |
| Wakano Y           | 2018      | Japan             | 0/3                  | 2/3                | 0.09 (0.00, 3.10   |
| Wang EJ            | 2012      | China             | 1/32                 | 5/27               | 0.14 (0.02, 1.30   |
| Wang W             | 2014      | China             | 0/35                 | 2/28               | 0 15 (0 01, 3 24   |
| XuWM               | 2009      | China Philippines | 3/49                 | 5/41               | 0.47 (0.11.2.10)   |
| Yang HW            | 2014      | China             | 1/53                 | 4/53               | 0.24 (0.03, 2, 18  |
| Yuan OF            | 2012      | China             | 1/32                 | 3/32               |                    |
| Tuan Qi<br>Zong VM | 2012      | China             | 0/90                 | 3/30               | 0.01 (0.00, 0.17   |
|                    | 2013      | China             | 0/50                 | 10/252             | 0.04 (0.00, 0.87   |
|                    | 2014      | Ohina             | 0/52                 | 10/332             | 0.31 (0.02, 5.38   |
| Zhang YF           | 2010a     | China             | 3/50                 | 16/50              | 0.14 (0.04, 0.50   |
| Zhou DS            | 2013      | China             | 5/113                | 28/95              | 0.11 (0.04, 0.30)  |
| Zhu M              | 2014      | China             | 2/24                 | 9/24               | 0.15 (0.03, 0.80   |
| Subtotal (I-sq     | uared = 0 | .0%, p = 0.851)   |                      |                    | 0.18 (0.13, 0.24   |
| No or unclear      | timely HB | IG/HepB-BD        |                      | _                  |                    |
| Chen SM            | 2017      | China             | 1/30                 | 10/30              | 0.07 (0.01, 0.58   |
| Greenup AJ         | 2014      | Australia         | 0/43                 | 2/10               | 0.04 (0.00, 0.89   |
| Han ZH             | 2005      | China             | 0/43                 | 5/35               | 0.06 (0.00, 1.20   |
| Li G               | 2006      | China             | 1/35                 | 7/32               | 0.11 (0.01, 0.91   |
| Li WF              | 2006      | China             | 1/36                 | 7/44               | 0.15 (0.02. 1.29   |
| Shen ML            | 2016      | China             | 0/60                 | 11/28              | 0.01 (0.00. 0.22   |
| Su TB              | 2009      | China             | 5/128                | 13/120             | 0.33 (0.12, 0.97   |
| Wang DM            | 2016      | China             | 1/42                 | 5/20               |                    |
| Wang TM            | 2005      | China             | 0/32                 | 8/32               |                    |
| Subtotal (I-sq     | uared = 0 | .0%, p = 0.458)   | 0/02                 |                    | > 0.13 (0.06, 0.25 |
|                    |           | )% n = 0.830)     |                      | (                  | 0.17 (0.13, 0.22   |
- LdT 100-150 mg by infant immunoprophylaxis regimens
  - Timely HepB-BD & HBIG (n=64): pooled OR= 0.10 (95% CI: 0.08-0.14), p<0.001,  $I^2=0\%$
  - No or unclear timely HepB-BD/HBIG (n=18): pooled OR=0.10 (95%CI: 0.06-0.16), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.83

| Author                 | Year          | Country    | Treatment | Control    | OH (95% CI)         |
|------------------------|---------------|------------|-----------|------------|---------------------|
| Timely HBIG &          | HepB-BD       |            |           | 1          |                     |
| Bai HL                 | 2013          | China      | 0/27      | 4/30       | 0.11 (0.01, 2.09)   |
| Chen QR                | 2018          | China      | 0/29      | 5/28       | 0.07 (0.00, 1.38)   |
| Chen WJ                | 2017          | China      | 4/79      | 16/44      | 0.09 (0.03, 0.30)   |
| Chen ZX                | 2017          | China      | 1/41      | 15/89      | 0.12 (0.02, 0.97)   |
|                        | 2015          | China      | 1/50      | 13/46      | 0.05 (0.01, 0.42)   |
| Deng Y                 | 2015          | China      | 0/82      | 4/75       | 0.10 (0.01, 1.82)   |
|                        | 2018          | China      | 0/38      | 4/38       | 0.10 (0.01, 1.92)   |
| Fan Li                 | 2013          | China      | 1/36      | 7/36       | 0.12 (0.01, 1.02)   |
|                        | 2017          | China      | 1/100     | 3/100      | 0.12 (0.01, 1.02)   |
| Ge YI                  | 2015          | China      | 0/20      | 3/22       | 0.14 (0.01, 2.81)   |
| Guan ZE                | 2017          | China      | 0/123     | 14/122     | 0.03 (0.00, 0.51)   |
| Guo HJ                 | 2011          | China      | 6/28      | 6/26       | 0.91 (0.25, 3.28)   |
| Han GB                 | 2015          | China      | 0/358     | 8/86       |                     |
| Han YP                 | 2014          | China      | 0/30      | 4/30       | 0.10 (0.00, 1.88)   |
| He T                   | 2018          | China      | 0/32      | 4/34       | 0.10 (0.01, 2.02)   |
| Hu WH                  | 2016          | China      | 0/46      | 5/40       | 0.07 (0.00, 1.30)   |
| Hu Y                   | 2018          | China      | 0/105     | 2/122      | 0.23 (0.01, 4.81)   |
| Huang Q                | 2017          | China      | 0/20      | 3/20       | 0.12 (0.01, 2.53)   |
| Ji YY                  | 2015          | China      | 3/65      | 12/65      | 0.21 (0.06, 0.80)   |
| Jiang S                | 2017          | China      | 1/44      | 15/44      | 0.04 (0.01, 0.36)   |
| LICM                   | 2017          | China      | 1/30      | 8/30 +     | 0.09 (0.01, 0.82)   |
| Li N                   | 2016          | China      | 1/65      | 9/25       | 0.03 (0.00, 0.24)   |
| Liu CY                 | 2014          | China      | 1/34      | 8/34       | 0.10 (0.01, 0.84)   |
| Liu XB                 | 2016          | China      | 0/20      | 5/20       | 0.07 (0.00, 1.34)   |
| Lou JJ                 | 2015          | China      | 0/125     | 3/58       | 0.06 (0.00, 1.24)   |
| Lu QY                  | 2016          | China      | 2/152     | 12/132     | 0.13 (0.03, 0.61)   |
| Pan YC                 | 2017          | China      | 0/81      | 21/370     | 0.10 (0.01, 1.66)   |
| Peng BA                | 2012          | China      | 1/40      | 10/40      | 0.08 (0.01, 0.63)   |
| PengML                 | 2014          | China      | 1/30      | 8/30       | 0.09 (0.01, 0.82)   |
| Qiu B                  | 2016          | China      | 4/120     | 12/60      | 0.14 (0.04, 0.45)   |
| Ren N                  | 2015          | China      | 2/46      | 11/46      | 0.14 (0.03, 0.70)   |
| Sheng Q                | 2018a         | China      | 0/79      | 2/21       | 0.05 (0.00, 1.06)   |
| Sheng Q                | 2018b         | China      | 0/66      | 5/46       | 0.06 (0.00, 1.05)   |
| Shi QW                 | 2017          | China      | 3/100     | 12/100     | 0.23 (0.06, 0.83)   |
| Sun W                  | 2017          | China      | 0/123     | 12/65      | - 0.02 (0.00, 0.30) |
| Sun WH                 | 2015          | China      | 0/84      | 8/46       | 0.03 (0.00, 0.48)   |
| Tan J                  | 2019          | China      | 0/41      | 6/59       | 0.10 (0.01, 1.81)   |
| lan∠                   | 2016          | China      | 0/171     | 15/320     | 0.06 (0.00, 0.97)   |
| Tian JH                | 2018          | China      | 0/135     | 7/203      | 0.10 (0.01, 1.71)   |
| lian HH                | 2016          | China      | 3/318     | 17/374     | 0.20 (0.06, 0.69)   |
| Nang B                 | 2016          | China      | 0/110     | 16/187     | 0.05 (0.00, 0.79)   |
| Wang EJ                | 2012          | China      | 0/28      | 5/27       | 0.07 (0.00, 1.37)   |
| Wang HB                | 2016          | China      | 0/100     | 2/20       | 0.04 (0.00, 0.80)   |
| Wang HY                | 2018          | China      | 0/40      | 6/40       | 0.07 (0.00, 1.21)   |
| wang J                 | 2017          | China      | 1/329     | 9/65       | 0.02 (0.00, 0.15)   |
| wang TD                | 2015          | China      | 0/53      | 8/52       | 0.05 (0.00, 0.87)   |
| wang wP                | 2012          | China      | 0/47      | 20/198     | 0.09 (0.01, 1.54)   |
| Wu Q<br>Ving V         | 2015          | China      | 0/204     | 7/20       | 0.01 (0.00, 0.23)   |
|                        | 2018          | China      | 0/30      | 10/50      | 0.05 (0.00, 0.95)   |
|                        | 2015          | China      | 0/09      | 1/20       | 0.06 (0.01, 0.52)   |
| 7a0 20<br>7hong (2)    | 2015          | China      | 0/28      | 5/47       | 0.08 (0.00, 1.48)   |
| Zhang (!)              | 2015          | China      | 0/46      | 15/75      | 0.05 (0.00, 1.48)   |
| Zhang GH               | 2018          | China      | 0/40      | 3/40       | 0.13 (0.01, 2.65)   |
| Zhang H                | 2010          | China      | 0/257     | 10/352     | 0.06 (0.00, 1.09)   |
| Zhang L I              | 2009          | China      | 0/30      | 4/30       | 0.10 (0.00, 1.88)   |
| Zhang VE               | 2000<br>2010b | China      | 1/60      | 16/60      | 0.05 (0.01, 0.36)   |
| Zhao DB                | 2010          | China      | 1/30      | 3/30       | 0.31 (0.03, 3.17)   |
| Zhao J                 | 2013          | China      | 0/41      | 23/202     | 0.09 (0.01, 1.55)   |
| Zhao Y                 | 2017          | China      | 0/40      | 5/40       | 0.08 (0.00, 1.49)   |
| Zhena JC               | 2018          | China      | 0/23      | 8/37       | 0.07 (0.00, 1.35)   |
| Zhu J                  | 2017          | China      | 1/60      | 8/54       | 0.10 (0.01, 0.81)   |
| Zhu LP                 | 2014          | China      | 0/30      | 3/30       | 0.13 (0.01, 2.61)   |
| Yue X                  | 2014          | China      | 0/31      | 0/30       | (Excluded)          |
| Subtotal (I-sou        | ared = 0.0%.  | p = 0.999) |           | <b>.</b>   | 0.10 (0.08. 0.14)   |
| 1 44                   | ,             | · · · ·    |           | Ť          | ·····,              |
| No or unclear ti       | mely HBIG/H   | epB-BD     |           |            |                     |
| Chen CY                | 2015          | China      | 1/42      | 7/40       | 0.11 (0.01, 0.98)   |
| Chen F                 | 2016          | China      | 0/31      | 6/32       | 0.06 (0.00, 1.20)   |
| Chen SM                | 2017          | China      | 0/30      | 10/30      | 0.03 (0.00, 0.58)   |
| Gao P                  | 2016          | China      | 1/51      | 9/51       | 0.09 (0.01, 0.77)   |
| Huang HY               | 2016          | China      | 16/90     | 23/30      | 0.07 (0.02, 0.18)   |
| Jiang XN               | 2013          | China      | 1/65      | 8/51       | 0.08 (0.01, 0.70)   |
| _i SF                  | 2015          | China      | 0/60      | 6/60       | 0.07 (0.00, 1.26)   |
| _i YH                  | 2017          | China      | 1/30      | 5/32       | 0.19 (0.02, 1.70)   |
| _i ZY                  | 2018          | China      | 4/41      | 9/41       | 0.38 (0.11, 1.37)   |
| _iu J                  | 2017          | China      | 0/97      | 2/28       | 0.05 (0.00, 1.17)   |
| _iu Y                  | 2016          | China      | 1/82      | 19/78      | 0.04 (0.00, 0.29)   |
| Shen ML                | 2016          | China      | 0/61      | 11/28      | 0.01 (0.00, 0.22)   |
| Wang DM                | 2016          | China      | 1/36      | 5/20       | 0.09 (0.01, 0.80)   |
| Xiao XH                | 2017          | China      | 0/62      | 1/61       | 0.32 (0.01, 8.08)   |
| Xie PY                 | 2016          | China      | 1/60      | 4/60       | 0.24 (0.03, 2.19)   |
| Yao LF                 | 2014          | China      | 0/30      | 2/30       | 0.19 (0.01, 4.06)   |
| Zhang Y                | 2018          | China      | 0/34      | 13/34      | 0.02 (0.00, 0.41)   |
| Zhou YJ                | 2014          | China      | 1/53      | 6/34       | 0.09 (0.01, 0.78)   |
| Subtotal (I-squ        | ared = 0.0%,  | p = 0.823) |           | $\diamond$ | 0.10 (0.06, 0.16)   |
|                        |               |            |           |            |                     |
|                        |               | 1.005      |           | 🔺          |                     |
| Overa <b>l</b> (I-squa | red = 0.0%, p | = 1.000)   |           | <b>\$</b>  | 0.10 (0.08, 0.13)   |

# **Appendix O: Efficacy by language used for reporting (Chinese versus English)**

- TDF 300 mg by language used for reporting (Chinese versus English)
  - Chinese language (n=12): pooled OR= 0.17 (95% CI: 0.10-0.30), p<0.001, I<sup>2</sup>=0%
  - English language (n=7): pooled OR=0.10 (95%CI: 0.04-0.30), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.40

| Author         | Year      | Country       | in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |            | OR (95% CI)        |
|----------------|-----------|---------------|-----------------------|------------------------|----------------------|--------------------|------------|--------------------|
| Chinese        |           |               |                       |                        |                      |                    |            |                    |
| Chen WJ        | 2017      | China         | 28                    | 0                      | 1/30                 | 16/44              | · · · ·    | - 0.06 (0.01, 0.49 |
| Gong Q         | 2017      | China         | 1-6                   | NR                     | 1/44                 | 7/44               |            | 0.12 (0.01, 1.05   |
| He LL          | 2018      | China         | 28                    | NR                     | 13/50                | 17/35              |            | • 0.37 (0.15, 0.93 |
| Hu MF          | 2018      | China         | 14                    | NR                     | 1/89                 | 3/30               |            | 0.10 (0.01, 1.02   |
| Huang Q        | 2017      | China         | 24-28                 | 12                     | 0/20                 | 3/20               |            | 0.12 (0.01, 2.53   |
| Liu MH         | 2017      | China         | 28                    | 0                      | 1/20                 | 6/20               |            | 0.12 (0.01, 1.14   |
| Wan JY         | 2017      | China         | 28                    | 0                      | 3/74                 | 7/42               | +          | 0.21 (0.05, 0.87   |
| Wang HB        | 2018      | China         | 24                    | NR                     | 0/100                | 2/20               |            |                    |
| Xiao XH        | 2017      | China         | 28                    | 0 or 4                 | 0/60                 | 1/61               |            | 0.33 (0.01, 8.35   |
| Yu CY          | 2018      | China         | 24                    | 4                      | 0/30                 | 4/30               |            | 0.10 (0.00, 1.88   |
| Zhang BF       | 2018      | China         | 24-28                 | 0                      | 0/39                 | 15/75              |            | 0.05 (0.00, 0.85   |
| Zhou Y         | 2018      | China         | 24-28                 | 0                      | 0/60                 | 5/36               |            | 0.05 (0.00, 0.88   |
| Subtotal (I-so | quared =  | 0.0%, p = 0   | .776)                 |                        |                      |                    | $\diamond$ | 0.17 (0.10, 0.30   |
|                |           |               |                       |                        |                      |                    | ۳ .<br>ا   |                    |
| English        |           |               |                       |                        |                      |                    |            |                    |
| Celen MK       | 2013      | Turkey        | 18-27                 | 4                      | 0/21                 | 2/23               |            | 0.20 (0.01, 4.42   |
| Chen HL        | 2015      | Taiwan        | 30-32                 | 4                      | 1/65                 | 6/56               |            | 0.13 (0.02, 1.12   |
| Greenup AJ     | 2014      | Australia     | 32                    | 12                     | 1/69                 | 2/10               |            | 0.06 (0.00, 0.72   |
| Jourdain G     | 2018      | Thailand      | 26-29                 | 8                      | 0/149                | 3/147              |            | 0.14 (0.01, 2.70   |
| Lin Y          | 2018      | China         | 24                    | 4                      | 0/58                 | 4/52               |            | 0.09 (0.00, 1.75   |
| Pan CQ         | 2016      | China         | 30-32                 | 4                      | 0/92                 | 6/88               |            | 0.07 (0.00, 1.24   |
| Wakano Y       | 2018      | Japan         | 22-28                 | 4-8                    | 0/2                  | 2/3                |            | 0.12 (0.00, 4.61   |
| Subtotal (I-so | quared =  | 0.0%, p = 0   | .997)                 |                        |                      |                    | $\diamond$ | 0.10 (0.04, 0.30   |
|                |           |               |                       |                        |                      |                    |            |                    |
| Overall (I-squ | uared = ( | 0.0%, p = 0.9 | 972)                  |                        |                      |                    | $\diamond$ | 0.16 (0.09, 0.25   |
|                |           |               |                       |                        |                      |                    | Ĭ          |                    |
|                |           |               |                       |                        |                      |                    |            |                    |

- LAM 100-150 mg by language used for reporting (Chinese versus English)
  - Chinese language (n=32): pooled OR= 0.17 (95% CI: 0.12-0.22), p<0.001,  $I^2=0\%$
  - English language (n=8): pooled OR=0.19 (95% CI: 0.08-0.48), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.78

| Author N<br>Chinese<br>Bai XW 2<br>Chen QR 2   | Year     | Country            | start in weeks<br>gestation | Tx end in<br>weeks postpartum | Events,<br>Treatment | Events,<br>Control |        | OR (95% Cl)      |
|--|----------|--------------------|-----------------------------|-------------------------------|----------------------|--------------------|--------|------------------|
| Author Au | Year     | Country            | gestation                   | weeks postpartum              | Treatment            | Control            |        | OR (95% CI)      |
| Chinese<br>Bai XW 2<br>Chen QR 2   |          |                    |                             |                               |                      |                    |        |                  |
| ai XW 2<br>Chen QR 2   |          |                    |                             |                               |                      |                    |        |                  |
| Chen QR 2  | 2011     | China              | 28                          | 4                             | 3/30                 | 8/25               |        | 0.24 (0.05, 1.   |
| Chan CM  | 2018     | China              | 28                          | 4                             | 1/33                 | 5/28               |        | 0.14 (0.02, 1.   |
| men Sivi Z   | 2017     | China              | 28                          | NR                            | 1/30                 | 10/30              |        | - 0.07 (0.01, 0. |
| heng YC 2  | 2011     | China              | 32                          | 4                             | 8/30                 | 6/26               |        | 1.21 (0.36, 4.   |
| eng HF 2   | 2007     | China              | 28                          | 4                             | 7/48                 | 16/42              |        | 0.28 (0.10, 0.   |
| aeYL 2   | 2015     | China              | 28-30                       | 12                            | 0/16                 | 3/22               |        | 0.17 (0.01, 3    |
| auo YZ 2   | 2008     | China              | 28                          | 0                             | 3/70                 | 13/40              |        | 0.09 (0.02, 0.   |
| lan YP 2   | 2014     | China              | 28                          | 6                             | 1/30                 | 4/30               |        | 0.22 (0.02, 2.   |
| lan ZH 2   | 2005     | China              | 28                          | 0                             | 0/43                 | 5/35               |        | 0.06 (0.00, 1.   |
| iyy 2  | 2015     | China              | 28                          | 4                             | 2/65                 | 12/65              |        | - 0.14 (0.03, 0, |
| iang HX 2  | 2012     | China              | 20-34                       | 0                             | 0/164                | 8/92               |        | - 0.03 (0.00, 0. |
| i G 2  | 2006     | China              | 28                          | 0                             | 1/35                 | 7/32               |        | 0.11 (0.01, 0.1  |
| iJH 2  | 2017     | China              | 28                          | 4                             | 1/33                 | 8/27               |        | - 0.07 (0.01, 0. |
| iWF 2  | 2006     | China              | 24                          | 0                             | 1/36                 | 7/44               |        | 0.15 (0.02, 1,   |
| iZG 2  | 2015     | China              | 28                          | 6                             | 1/25                 | 4/25               |        | 0.22 (0.02, 2,   |
| MaJ 2  | 2006     | China              | Pre-pregnancy               | NR                            | 0/18                 | 9/16               |        | - 0.02 (0.00, 0. |
| Ren C.I 2  | 2016     | China              | 28                          | 0                             | 2/67                 | 10/72              |        | 0.19 (0.04, 0    |
| Ren V.I 2  | 2011     | China              | 28                          | 0                             | 1/30                 | 13/155             |        | 0.38 (0.05, 2    |
| Shen MI 2  | 2016     | China              | 26                          | 4                             | 0/60                 | 11/28              |        | 0.01 (0.00, 2.   |
| UTR 2  | 2010     | China              | 32                          | 4<br>0                        | 5/128                | 13/120             | _      | 0.33 (0.12.0     |
| ang Y S  | 2003     | China              | 33                          | 4                             | 0/17                 | 10/120             |        | 0.03 (0.12, 0.   |
| any A 2  | 2009     | China              | 22                          | 4                             | 11/110               | 4/24               |        | 0.13 (0.01, 2.   |
| Vana DM 2  | 2015     | China              | 20 20                       | 12                            | 1/42                 | 49/110<br>E/20     |        | 0.14 (0.07, 0.   |
| Vang Divi 2  | 2010     | China              | 20-30                       | 12                            | 1/42                 | 5/20               |        |                  |
| Vang EJ 2  | 2012     | China              | 20<br>Dro prognopou         | 4                             | 0/22                 | 9/20               |        | 0.14 (0.02, 1.   |
| vang ivi 2   | 2005     | China              | Pre-pregnancy               | 0                             | 0/32                 | 8/32               |        | 0.04 (0.00, 0.   |
| vang w 2   | 2014     | China              | 28                          | 4                             | 0/35                 | 2/28               |        | 0.15 (0.01, 3.   |
| ang Hw 2   | 2014     | China              | 28                          | 4                             | 1/53                 | 4/53               |        | 0.24 (0.03, 2.   |
| uanQ⊢ 2  | 2012     | China              | 27                          | 4                             | 1/32                 | 3/32               |        | 0.31 (0.03, 3.   |
| eng Yivi 2   | 2013     | China              | 28                          | variable (0,4,6)              | 0/90                 | 3/30               |        | 0.04 (0.00, 0.   |
| hang YF 2  | 2010a    | China              | 28                          | 4                             | 3/50                 | 16/50              |        | - 0.14 (0.04, 0. |
| hou DS 2   | 2013     | China              | 28                          | NR                            | 5/113                | 28/95              |        | 0.11 (0.04, 0.   |
| hu M 2   | 2014     | China              | 26                          | 0                             | 2/24                 | 9/24               |        | - 0.15 (0.03, 0. |
| iubtotal (I-squ  | uared =  | 0.0%, p = 0.698)   |                             |                               |                      |                    | Ŷ      | 0.17 (0.12, 0.   |
| inglish  |          |                    |                             |                               |                      |                    | i i    |                  |
| oaud HM 2  | 2019     | Egypt              | Anytime                     | NR                            | 0/29                 | 1/30               |        | 0.33 (0.01, 8.   |
| ireenup AJ 2   | 2014     | Australia          | 32                          | 2                             | 0/43                 | 2/10               |        | 0.04 (0.00, 0.   |
| eT 2   | 2018     | China              | 1st Trimester               | NR                            | 0/29                 | 4/34               |        | 0.11 (0.01, 2.   |
| ackson V 2   | 2015     | Ireland            | 32                          | 0                             | 0/21                 | 1/6 -              |        | 0.09 (0.00, 2.   |
| an CQ 2  | 2017     | China              | 28-30                       | 4                             | 0/160                | 5/89               |        | 0.05 (0.00, 0.   |
| /akano Y 2   | 2018     | Japan              | 28-32                       | 4 <b>-</b> 8                  | 0/3                  | 2/3                |        | 0.09 (0.00, 3.   |
| u WM 2   | 2009     | China. Philippines | 30-34                       | 4                             | 3/49                 | 5/41               |        | 0.47 (0.11, 2,   |
| hang H 2   | 2014     | China              | 28-30                       | 4                             | 0/52                 | 10/352             |        | 0.31 (0.02.5     |
| ubtotal (I-squ   | uared =  | 0.0%, p = 0.776)   | 10 00                       |                               | 0.01                 | 10,001             | $\sim$ | • 0.19 (0.08, 0. |
| verall (I-squa   | ared = ( | 0.0%, p = 0.830)   |                             |                               |                      |                    | •      | 0.17 (0.13, 0.   |

- LdT 600 mg by language used for reporting (Chinese versus English)
  - Chinese language (n=72): pooled OR= 0.11 (95% CI: 0.08-0.14), p<0.001,  $I^2=0\%$
  - English language (n=11): pooled OR=0.05 (95%CI: 0.02-0.11), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.07

| Author                             | Year        | Country        | start in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |            | OR (95% CI)         |
|------------------------------------|-------------|----------------|-----------------------------|------------------------|----------------------|--------------------|------------|---------------------|
| Chinese                            | 00.17       | 01             | 20.00                       |                        | 0.07                 | 4/00               | i          |                     |
| Sai HL                             | 2013        | China          | 28-32                       | 4                      | 0/27                 | 4/30               |            | 0.11 (0.01, 2.09)   |
| hen Cr                             | 2015        | China          | Pro programov               | NR                     | 0/91                 | 6/22               |            | 0.06 (0.00, 1.20)   |
| hen OR                             | 2010        | China          | 29                          | 1                      | 0/20                 | 5/28               |            | 0.00 (0.00, 1.20)   |
| hen SM                             | 2010        | China          | 28                          | NR                     | 0/30                 | 10/30              |            | 0.03 (0.00, 0.58)   |
| then WJ                            | 2017        | China          | 28                          | 0                      | 4/79                 | 16/44              |            | 0.09 (0.03, 0.30)   |
| ui ZL                              | 2015        | China          | 28                          | 4                      | 1/50                 | 13/46              |            | 0.05 (0.01, 0.42)   |
| Deng Y                             | 2015        | China          | 24-36                       | 4                      | 0/82                 | 4/75               |            | 0.10 (0.01, 1.82)   |
| Ding XP                            | 2018        | China          | 28                          | 4                      | 0/38                 | 4/38               |            | 0.10 (0.01, 1.92)   |
| an LY                              | 2013        | China          | 28                          | 24                     | 0/58                 | 6/60               |            | 0.07 (0.00, 1.30)   |
| eng XM                             | 2017        | China          | 28                          | 4                      | 1/36                 | 7/36               |            | 0.12 (0.01, 1.02)   |
| <sup>-</sup> u PX                  | 2016        | China          | 24-28                       | 4                      | 1/100                | 3/100              |            | 0.33 (0.03, 3.19)   |
| Gao P                              | 2016        | China          | 1st Trimester               | 0                      | 1/51                 | 9/51               |            | 0.09 (0.01, 0.77)   |
| Ge YL                              | 2015        | China          | 28-30                       | 12                     | 0/20                 | 3/22               | 1.8        | 0.14 (0.01, 2.81)   |
| Guan ZF                            | 2017        | China          | 24                          | 12                     | 0/123                | 14/122             |            | 0.03 (0.00, 0.51)   |
| Guo HJ                             | 2011        | China          | 28                          | 4                      | 6/28                 | 6/26               |            | 0.91 (0.25, 3.28)   |
| lan YP                             | 2014        | China          | 28                          | 6                      | 0/30                 | 4/30               |            | 0.10 (0.00, 1.88)   |
| lu WH                              | 2016        | China          | 28                          | 28                     | 0/46                 | 5/40               |            | 0.07 (0.00, 1.30)   |
| Huang HY                           | 2016        | China          | 20                          | 0                      | 16/90                | 23/30              |            | 0.07 (0.02, 0.18)   |
| Huang Q                            | 2017        | China          | 24-28                       | 12                     | 0/20                 | 3/20               |            | 0.12 (0.01, 2.53)   |
| li YY                              | 2015        | China          | 28                          | 4                      | 3/65                 | 12/65              |            | 0.21 (0.06, 0.80)   |
| liang S                            | 2017        | China          | 28                          | NR                     | 1/44                 | 15/44              |            | 0.04 (0.01, 0.36)   |
| liang XN                           | 2013        | China          | 26-30                       | NR                     | 1/65                 | 8/51               |            | 0.08 (0.01, 0.70)   |
| .i CM                              | 2017        | China          | 28                          | 4                      | 1/30                 | 8/30               |            | 0.09 (0.01, 0.82)   |
| .IN                                | 2016        | China          | 28                          | NR                     | 1/65                 | 9/25               |            | 0.03 (0.00, 0.24)   |
| JSF                                | 2015        | China          | 28                          | 24                     | 0/60                 | 6/60               |            | 0.07 (0.00, 1.26)   |
| J YH                               | 2017        | China          | 28                          | ~36                    | 1/30                 | 5/32               |            | 0.19 (0.02, 1.70)   |
| J ZY                               | 2018        | China          | 28                          | NR                     | 4/41                 | 9/41               |            | 0.38 (0.11, 1.37)   |
| Liu CY                             | 2014        | China          | 28                          | 4<br>ND                | 1/34                 | 8/34               |            | 0.10 (0.01, 0.84)   |
| u J                                | 2017        | China          | 30                          | NH<br>4                | 0/97                 | 2/28               |            | 0.05 (0.00, 1.17)   |
| JU XB                              | 2016        | China          | 28-36                       | 4                      | 0/20                 | 5/20               |            | 0.07 (0.00, 1.34)   |
| UU JJ                              | 2015        | Ohina<br>Ohini | 28                          | 4                      | 0/125                | 3/58               |            | 0.06 (0.00, 1.24)   |
| .u QY                              | 2016        | China<br>China | 28                          | 0                      | 2/152                | 12/132             |            | 0.13 (0.03, 0.61)   |
| Pan YC                             | 2017        | China          | 32                          | 0                      | 0/81                 | 21/3/0             |            | 0.10 (0.01, 1.66)   |
| Peng BA                            | 2012        | China          | 28                          | 0                      | 1/40                 | 10/40              |            | 0.08 (0.01, 0.63)   |
| PengML                             | 2014        | China          | 28<br>Dec                   | NH                     | 1/30                 | 8/30               |            | 0.09 (0.01, 0.82)   |
| JIU B                              | 2016        | China          | Pre-pregnancy               | 0                      | 4/120                | 12/60              |            | 0.14 (0.04, 0.45)   |
|                                    | 2015        | China          | 28                          | 24                     | 2/40                 | 11/40              |            | 0.14 (0.03, 0.70)   |
|                                    | 2010        | China          | 26                          | 4                      | 0/61                 | 10/100             |            | 0.01 (0.00, 0.22)   |
| Shir QVV                           | 2017        | China          | 24                          | 10                     | 3/100                | 12/100             |            | 0.23 (0.00, 0.03)   |
| Sull VVIII                         | 2015        | China          | 12                          | 12                     | 0/64                 | 6/40               |            | 0.03 (0.00, 0.46)   |
| ian III                            | 2018        | China          | Anutimo                     | ND                     | 0/125                | 7/202              |            | 0.10 (0.01, 1.01)   |
| Fian RH                            | 2010        | China          | 28                          | 4                      | 3/218                | 17/374             |            | 0.20 (0.06, 0.69)   |
| Nana B                             | 2016        | China          | 28                          | 4                      | 0/110                | 16/187             |            | 0.05 (0.00, 0.03)   |
| Nang DM                            | 2016        | China          | 28-30                       | 12                     | 1/36                 | 5/20               |            | 0.09 (0.01, 0.80)   |
| Nang El                            | 2012        | China          | 28                          | 4                      | 0/28                 | 5/27               |            | 0.03 (0.01, 0.00)   |
| Nang HB                            | 2016        | China          | 32                          | NB                     | 0/100                | 2/20               |            | 0.04 (0.00, 0.80)   |
| Nang HV                            | 2018        | China          | 12-14                       | 24                     | 0/40                 | 6/40               |            | 0.07 (0.00, 1.21)   |
| Nang III<br>Nang I                 | 2010        | China          | 24.28                       | NB                     | 1/329                | 9/65               |            | 0.02 (0.00, 0.15)   |
| Nang TD                            | 2015        | China          | 28                          | 4                      | 0/53                 | 8/52               |            | 0.05 (0.00, 0.87)   |
| Vang WP                            | 2012        | China          | 28                          | 0                      | 0/47                 | 20/198             |            | 0.09 (0.01, 1.54)   |
| (iao XH                            | 2017        | China          | 28                          | 0 or 4                 | 0/62                 | 1/61               |            | - 0.32 (0.01, 8.08) |
| (ie PY                             | 2016        | China          | 28                          | 4                      | 1/60                 | 4/60               |            | 0.24 (0.03, 2.19)   |
| King Y                             | 2018        | China          | 28                          | 4                      | 0/30                 | 7/30               |            | 0.05 (0.00, 0.95)   |
| ang HW                             | 2015        | China          | 28                          | 4                      | 1/50                 | 12/50              |            | 0.06 (0.01, 0.52)   |
| /ao LF                             | 2014        | China          | 28-32                       | 6                      | 0/30                 | 2/30               |            | 0.19 (0.01, 4.06)   |
| íao ZC                             | 2011        | China          | 28                          | 4                      | 0/28                 | 4/30               |            | 0.10 (0.01, 2.01)   |
| hang BF                            | 2018        | China          | 24-28                       | 0                      | 0/36                 | 15/75              |            | 0.05 (0.00, 0.92)   |
| hang GH                            | 2018        | China          | 28                          | 4                      | 0/40                 | 3/40               |            | 0.13 (0.01, 2.65)   |
| hang LJ                            | 2009        | China          | 28-32                       | 4                      | 0/30                 | 4/30               |            | 0.10 (0.00, 1.88)   |
| hang X                             | 2015        | China          | 28                          | 12                     | 0/48                 | 5/47               |            | 0.08 (0.00, 1.48)   |
| hang Y                             | 2018        | China          | Pre-pregnancy               | NB                     | 0/34                 | 13/34              |            | 0.02 (0.00, 0.41)   |
| hang YF                            | 2010b       | China          | 28                          | 4                      | 1/60                 | 16/60              |            | 0.05 (0.01, 0.36)   |
| hao DB                             | 2010        | China          | 28                          | 4                      | 1/30                 | 3/30               |            | 0.31 (0.03, 3.17)   |
| 'hao J                             | 2013        | China          | 20                          | 0                      | 0/41                 | 23/202             |            | 0.09 (0.01, 1.55)   |
| hao Y                              | 2017        | China          | 12                          | 12                     | 0/40                 | 5/40               |            | 0.08 (0.00, 1.49)   |
| heng JC                            | 2018        | China          | 28                          | 4                      | 0/23                 | 8/37               |            | 0.07 (0.00, 1.35)   |
| hou YJ                             | 2014        | China          | 1st Trimester               | 0                      | 1/53                 | 6/34               | I          | 0.09 (0.01, 0.78)   |
| lhu J                              | 2017        | China          | 28                          | 0                      | 1/60                 | 8/54               |            | 0.10 (0.01, 0.81)   |
| thu LP                             | 2014        | China          | 28                          | 4                      | 0/30                 | 3/30               |            | 0.13 (0.01, 2.61)   |
| /ue X                              | 2014        | China          | Anytime                     | NR                     | 0/31                 | 0/30               | L L        | (Excluded)          |
| ubtotal (I-squa                    | ared = 0.0% | , p = 0.999)   |                             |                        |                      |                    | •          | 0.11 (0.08, 0.14)   |
| Inglish                            |             |                |                             |                        |                      |                    |            |                     |
| Chen ZX                            | 2017        | China          | 13-32                       | NR                     | 1/41                 | 15/89              |            | 0.12 (0.02, 0.97)   |
| lan GR                             | 2015        | China          | 28-32                       | NR                     | 0/358                | 8/86 🖛             |            | 0.01 (0.00, 0.23)   |
| le T                               | 2018        | China          | 1st Trimester               | NB                     | 0/32                 | 4/34               |            | 0.10 (0.01, 2.02)   |
| łu Y                               | 2018        | China          | 28-32                       | 3-4                    | 0/105                | 2/122              |            | 0.23 (0.01, 4.81)   |
| .iu Y                              | 2016        | China          | 4-27                        | 4                      | 1/82                 | 19/78              |            | 0.04 (0.00, 0.29)   |
| Sheng Q                            | 2018a       | China          | 24-32                       | 4                      | 0/79                 | 2/21               |            | 0.05 (0.00, 1.06)   |
| Sheng Q                            | 2018b       | China          | 24-28                       | 0                      | 0/66                 | 5/46               |            | 0.06 (0.00, 1.05)   |
| Sun W                              | 2017        | China          | 20-28                       | 12                     | 0/123                | 12/65              |            | 0.02 (0.00, 0.30)   |
| an Z                               | 2016        | China          | 14-28                       | NB                     | 0/171                | 15/320             | *          | 0.06 (0.00, 0.97)   |
| Vu Q                               | 2015        | China          | 24-32                       | 0 or 4                 | 0/204                | 14/95 🖛            | *          | 0.01 (0.00, 0.23)   |
| hang H                             | 2014        | China          | 28-30                       | 4                      | 0/257                | 10/352             |            | 0.06 (0.00, 1.09)   |
|                                    | ared = 0.0% | , p = 0.935)   |                             |                        |                      |                    | $\diamond$ | 0.05 (0.02, 0.11)   |
| ubtotal (I-squa                    |             |                |                             |                        |                      |                    | -          |                     |
| ubtotal (I-squa                    |             |                |                             |                        |                      |                    | -          |                     |
| ubtotal (I-squa<br>verall (I-squar | red = 0.0%, | p = 1.000)     |                             |                        |                      |                    | <b>\$</b>  | 0.10 (0.08, 0.13)   |

### Appendix P: Efficacy by risk of bias score for non-RCTs

- TDF 300 mg by risk of bias score for non-RCTs
- High risk (score of 6) (n=5): pooled OR= 0.16 (95% CI: 0.06-0.43), p<0.001,  $I^2=0\%$
- Intermediate risk (score of 7) (n=6): pooled OR=0.22 (95%CI: 0.11-0.46), p<0.001, I<sup>2</sup>=0%
- Low risk (score of 8-9) (n=3): pooled OR=0.08 (95%CI: 0.02-0.29), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.39

| Author          | Year       | Country        | in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control |                   | OR (95% CI)       |
|-----------------|------------|----------------|-----------------------|------------------------|----------------------|--------------------|-------------------|-------------------|
| High risk of bi | as         |                |                       |                        |                      |                    | i                 |                   |
| Gong Q          | 2017       | China          | 1-6                   | NR                     | 1/44                 | 7/44               |                   | 0.12 (0.01, 1.05) |
| Wakano Y        | 2018       | Japan          | 22-28                 | 4-8                    | 0/2                  | 2/3                |                   | 0.12 (0.00, 4.61) |
| Wan JY          | 2017       | China          | 28                    | 0                      | 3/74                 | 7/42               |                   | 0.21 (0.05, 0.87) |
| Xiao XH         | 2017       | China          | 28                    | 0 or 4                 | 0/60                 | 1/61               |                   | 0.33 (0.01, 8.35) |
| Zhang BF        | 2018       | China          | 24-28                 | 0                      | 0/39                 | 15/75              |                   | 0.05 (0.00, 0.85) |
| Subtotal (I-sc  | uared = (  | 0.0%, p = 0.8  | 378)                  |                        |                      |                    | $\Leftrightarrow$ | 0.16 (0.06, 0.43) |
| Intermediate r  | isk of bia | s              |                       |                        |                      |                    |                   |                   |
| Celen MK        | 2013       | Turkey         | 18-27                 | 4                      | 0/21                 | 2/23               |                   | 0.20 (0.01, 4.42) |
| Greenup AJ      | 2014       | Australia      | 32                    | 12                     | 1/69                 | 2/10               |                   | 0.06 (0.00, 0.72) |
| He LL           | 2018       | China          | 28                    | NR                     | 13/50                | 17/35              | ÷                 | 0.37 (0.15, 0.93) |
| Hu MF           | 2018       | China          | 14                    | NR                     | 1/89                 | 3/30               |                   | 0.10 (0.01, 1.02) |
| Huang Q         | 2017       | China          | 24-28                 | 12                     | 0/20                 | 3/20               |                   | 0.12 (0.01, 2.53) |
| Wang HB         | 2018       | China          | 24                    | NR                     | 0/100                | 2/20               |                   | 0.04 (0.00, 0.80) |
| Subtotal (I-sc  | uared = (  | 0.0%, p = 0.5  | 522)                  |                        |                      |                    | $\diamond$        | 0.22 (0.11, 0.46) |
|                 |            |                |                       |                        |                      |                    |                   |                   |
| Low risk of bia | 2015       | Taiwan         | 30-32                 | А                      | 1/65                 | 6/56               |                   | 0 13 (0 02 1 12)  |
|                 | 2013       | China          | 28                    | 0                      | 1/30                 | 16/44              |                   | 0.06 (0.01, 0.49) |
| Zhou V          | 2018       | China          | 24-28                 | 0                      | 0/60                 | 5/36               |                   | 0.05 (0.00, 0.88) |
| Subtotal (Lec   | uared – (  | 00% n = 0.9    | 27-20                 | v                      | 0,00                 | 0,00               |                   | 0.03 (0.00, 0.08) |
|                 | uurou – (  | 5.576, p = 0.6 | ,                     |                        |                      |                    |                   | 0.00 (0.02, 0.28, |
| Overall (I-squ  | ared = 0.  | .0%, p = 0.86  | 60)                   |                        |                      |                    | $\diamond$        | 0.17 (0.10, 0.29  |
|                 |            |                |                       |                        |                      |                    |                   |                   |
|                 |            |                |                       |                        |                      |                    |                   |                   |

### • LAM 100-150 mg by risk of bias for non-RCTs

- High risk (score of 6) (n=12): pooled OR= 0.14 (95%CI: 0.08-0.24), p<0.001,  $I^2=0\%$
- Intermediate risk (score of 8) (n=8): pooled OR=0.13 (95%CI: 0.06-0.29), p<0.001, I<sup>2</sup>=0%
- Low risk (score of 8-9) (n=12): pooled OR=0.22 (95%CI: 0.12-0.40), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.29

| Author<br>High risk of b<br>Chen QR | Year      | Country       | gestation      | weeks nestnartum |           |              |            |                 |
|-------------------------------------|-----------|---------------|----------------|------------------|-----------|--------------|------------|-----------------|
| High risk of b<br>Chen QR           | oias      |               |                | weeks posipartum | Treatment | Control      |            | OR (95% CI)     |
| Chen QR                             |           |               |                |                  |           |              |            |                 |
| Ecoud HM                            | 2018      | China         | 28             | 4                | 1/33      | 5/28         |            | 0.14 (0.02, 1   |
| FUAUU HIVI                          | 2019      | Egypt         | Anytime        | NR               | 0/29      | 1/30         |            | 0.33 (0.01, 8   |
| Jackson V                           | 2015      | reland        | 32             | 0                | 0/21      | 1/6 -        |            | 0.09 (0.00, 2   |
| Ma J                                | 2006      | China         | Pre-pregnancy  | NR               | 0/18      | 9/16         |            | 0.02 (0.00, 0   |
| Pan CQ                              | 2017      | China         | 28-30          | 4                | 0/160     | 5/89         |            | 0.05 (0.00, 0   |
| Shen ML                             | 2016      | China         | 26             | 4                | 0/60      | 11/28 🗲      |            | 0.01 (0.00, 0   |
| Su TB                               | 2009      | China         | 32             | 0                | 5/128     | 13/120       |            | 0.33 (0.12, 0   |
| Wakano Y                            | 2018      | Japan         | 28-32          | 4-8              | 0/3       | 2/3          |            | 0.09 (0.00, 3   |
| Wang TM                             | 2005      | China         | Pre-pregnancy  | 0                | 0/32      | 8/32         |            | 0.04 (0.00, 0   |
| Yuan QF                             | 2012      | China         | 27             | 4                | 1/32      | 3/32         |            | 0.31 (0.03, 3   |
| Zhou DS                             | 2013      | China         | 28             | NR               | 5/113     | 28/95        |            | 0.11 (0.04, 0   |
| Zhu M                               | 2014      | China         | 26             | 0                | 2/24      | 9/24         |            | 0.15 (0.03, 0   |
| Subtotal (I-s                       | quared :  | = 0.0%, p =   | 0.590)         |                  |           |              | $\diamond$ | 0.14 (0.08, 0   |
|                                     |           |               |                |                  |           |              |            |                 |
| Intermediate                        | risk of b | ias           |                |                  |           |              | <u>i</u>   |                 |
| Ge YL                               | 2015      | China         | 28-30          | 12               | 0/16      | 3/22         |            | 0.17 (0.01, 3   |
| Greenup AJ                          | 2014      | Australia     | 32             | 2                | 0/43      | 2/10         |            | · 0.04 (0.00, 0 |
| Han YP                              | 2014      | China         | 28             | 6                | 1/30      | 4/30         |            | 0.22 (0.02, 2   |
| Li JH                               | 2017      | China         | 28             | 4                | 1/33      | 8/27         |            | 0.07 (0.01, 0   |
| Ren YJ                              | 2011      | China         | 28             | 0                | 1/30      | 13/155       |            | 0.38 (0.05, 2   |
| Wang W                              | 2014      | China         | 28             | 4                | 0/35      | 2/28         |            | 0.15 (0.01, 3   |
| Zeng YM                             | 2013      | China         | 28             | Variable (0,4,6) | 0/90      | 3/30         |            | 0.04 (0.00, 0   |
| Zhang YF                            | 2010a     | China         | 28             | 4                | 3/50      | 16/50        |            | 0.14 (0.04, 0   |
| Subtotal (I-s                       | quared :  | = 0.0%, p =   | 0.918)         |                  |           |              | $\sim$     | 0.13 (0.06, 0   |
| Low risk of h                       | ias       |               |                |                  |           |              |            |                 |
| Chena YC                            | 2011      | China         | 32             | 4                | 8/30      | 6/26         |            | 1 21 (0 36 4    |
| Eena HE                             | 2007      | China         | 28             | 4                | 7/48      | 16/42        | -          | 0.28 (0.10.0    |
| Han 7H                              | 2005      | China         | 28             | ф<br>О           | 0/43      | 5/35 =       |            | 0.06 (0.00, 1   |
| Ηο Τ                                | 2003      | China         | 1 st Trimester | NB               | 0/29      | 4/34         |            | 0.00 (0.00, 1   |
| liang HX                            | 2012      | China         | 20-34          | 0                | 0/164     | 8/92         |            | 0.03 (0.00, 0   |
| LIG                                 | 2012      | China         | 20-04          | 0                | 1/35      | 7/32         |            | 0.00 (0.00, 0   |
|                                     | 2000      | China         | 20             | 0                | 1/35      | 7/44         |            | 0.11 (0.01, 0   |
| Bon C I                             | 2000      | China         | 28             | 0                | 2/67      | 10/72        |            | 0.15 (0.02, 1   |
| Tong V                              | 2010      | China         | 20             | 4                | 0/17      | 10/12        |            | 0.13 (0.04, 0   |
| iaily A<br>Mona DM                  | 2009      | China         | 00 00          | 4<br>10          | 1/40      | 4/24<br>E/20 |            | 0.13 (0.01, 2   |
| Wang El                             | 2010      | China         | 20-30          | 12               | 1/42      | 5/20         |            |                 |
| vvang EJ<br>Zhana Ll                | 2012      | China         | 20<br>00 00    | 4                | 1/32      | J2/          |            | T 0.14 (0.02, 1 |
| Znang H                             | 2014      |               | ∠o-30          | 4                | 0/52      | 10/352       |            | 0.31 (0.02, 5   |
| ວບນເບເລເ (I-S                       | squared : | = 11.10%, p = | = 0.331)       |                  |           |              | $\sim$     | 0.22 (0.12, 0   |
| Overall (I-sq                       | quared =  | 0.0%, p = 0   | ).686)         |                  |           |              | \$         | 0.17 (0.12, 0   |
|                                     |           |               |                |                  |           |              |            | <del> </del>    |
|                                     |           |               |                |                  |           | .001         | .01 .1     | 1 10            |

- LdT 600 mg by risk of bias for non-RCTs
  - High risk (score of 6) (n=15): pooled OR= 0.07 (95%CI: 0.04-0.13), p<0.001, I<sup>2</sup>=0%
  - Intermediate risk (score of 8) (n=23): pooled OR=0.09 (95%CI: 0.05-0.15), p<0.001,  $I^2=0\%$
  - Low risk (score of 8-9) (n=24): pooled OR=0.10 (95%CI: 0.06-0.15), p<0.001, I<sup>2</sup>=0%
  - The p-value for heterogeneity between subgroups was 0.75

| High risk of bias<br>Chen QK 2018 China 28 4 0229 528<br>Deng Y 2015 China 13-32 NR 11/41 15/89<br>Deng Y 2015 China 24-36 4 0/82 475<br>Gao P 2016 China 181 Trimester 0 1/51 9/51<br>Jiang S 2017 China 28 NR 11/44 15/44<br>Li CM 2017 China 28 NR 11/44 15/44<br>Li QM 2017 China 28 NR 11/85 9/25<br>Shen ML 2016 China 28 NR 11/85 9/65<br>Shen ML 2016 China 1st Trimester 0 1/53 6/34<br>Shubtlat (I-squared = 0.0%, p = 0.862)<br>Intermediate risk of bias<br>Chen CY 2015 China 18 there 1<br>Chen CY 2015 China 28 28 00 r 4 0/68 16/75<br>Subtlat (I-squared = 0.0%, p = 0.862)<br>Intermediate risk of bias<br>Chen CY 2015 China 28 28 0/46 5/40<br>Hu WH 2016 China 28 28 0/46 5/40<br>Hu MP 2016 China 28 28 0/46 5/40<br>Hu MH 2016 China 28 4 0/20 5/20<br>Sheng Q 2018 China 28 4 0/20 5/20<br>Trim JH 2019 China 28 4 0/21 2/20<br>Sheng Q 2018 China 28 4 0/23 8/37<br>Subtlat (I-squared = 0.0%, p = 1.000)<br>Low risk of bias<br>Chen WU 2017 China 28 0 0 0/41 32/202<br>Sheng J 2018 China 28 4 1/50 15/60<br>Then XU 2017 China 28 0 0 0/41 32/202<br>Sheng J 2018 China 28 4 1/50 15/60<br>Then XU 2017 China 28 0 0 0/41 32/202<br>Sheng J 2018 China 28 4 1/50 15/60<br>Then XU 2017 China 28 0 0 0/41 32/202<br>Sheng J 2018 China 28 4   | 0.07 (0.00, 1.38)  |
|---|--|
| Intermediate risk of bias       NR       1/42       7/40         Chen CY       2015       China       1st Trimester       NR       0/31       6/6/22         Ding XP       2018       China       28       4       0/38       4/38         Fan LY       2013       China       28       24       0/58       6/60         Ge YL       2015       China       28       24       0/58       6/60         Ge YL       2015       China       28       24       0/33       4/30         Hu WH       2016       China       28       28       0/46       5/40         Huang Q       2017       China       28       28       0/46       5/20         Jiang XN       2013       China       28-30       NR       1/65       8/51         Liu J       2017       China       28-36       4       0/20       5/20         Peng BA       2012       China       28-36       4       0/20       5/20         Glu B       2016       China       28-36       4       0/20       5/20         Sun W       2017       China       28       0       0/66       5/46  | 0.10 (0.01, 1.82)<br>0.09 (0.01, 0.77)<br>0.04 (0.01, 0.36)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.04 (0.00, 0.29)<br>0.01 (0.06, 0.69)<br>0.04 (0.00, 0.80)<br>0.02 (0.00, 0.15)<br>0.035 (0.00, 0.92)<br>0.09 (0.01, 0.78)<br>0.07 (0.04, 0.13)  |
| Low risk of bias<br>Chen WJ 2017 China 28 0 4/79 16/44<br>Cui ZL 2015 China 28 4 1/50 13/46<br>Feng XM 2017 China 28 4 1/36 7/36  | $\begin{array}{c} 0.11 & (0.01, 0.98) \\ 0.06 & (0.00, 1.20) \\ 0.10 & (0.01, 1.92) \\ 0.07 & (0.00, 1.30) \\ 0.14 & (0.01, 2.81) \\ 0.10 & (0.00, 1.88) \\ 0.07 & (0.00, 1.30) \\ 0.12 & (0.01, 2.53) \\ 0.08 & (0.01, 0.70) \\ 0.05 & (0.00, 1.17) \\ 0.05 & (0.00, 1.17) \\ 0.05 & (0.00, 1.34) \\ 0.08 & (0.01, 0.63) \\ 0.14 & (0.04, 0.45) \\ 0.06 & (0.00, 1.05) \\ 0.02 & (0.00, 0.33) \\ 0.10 & (0.01, 1.81) \\ 0.10 & (0.01, 1.81) \\ 0.10 & (0.01, 1.81) \\ 0.10 & (0.01, 1.81) \\ 0.10 & (0.01, 2.01) \\ 0.3 & (0.01, 0.36) \\ 0.05 & (0.01, 0.36) \\ 0.09 & (0.01, 0.36) \\ 0.09 & (0.05, 0.15) \\ \end{array}$             |
| Han GR 2015 China 28-32 NR 0/358 8/86<br>He T 2018 China 1st Trimester NR 0/32 4/34<br>Hu Y 2018 China 28-32 3-4 0/105 2/122<br>Li YH 2017 China 28 -36 1/30 5/32<br>Li YH 2017 China 28 NR 4/41 9/41<br>Liu CY 2014 China 28 4 1/34 8/34<br>Lou JJ 2015 China 28 24 4 1/34 8/34<br>Lou JJ 2015 China 28 24 0/81 21/370<br>Ren N 2015 China 28 24 2/46 11/46<br>Sheng Q 2018a China 24-32 4 0/79 2/21<br>Sun WH 2015 China 12 12 0/84 8/46<br>Sheng Q 2018a China 28-30 12 1/36 5/27<br>Wang B 2016 China 28 4 0/10 16/187<br>Wang DM 2016 China 28 4 0/35 8/52<br>Wang DM 2016 China 28 4 0/136 5/27<br>Wang DM 2016 China 28 4 0/136 5/27<br>Wang DM 2016 China 28 4 0/136 5/27<br>Wang DM 2016 China 28 4 0/45 8/27<br>Wang DM 2016 China 28 4 0/45 8/27<br>Wang DM 2015 China 28 4 0/45 8/27<br>Wang DM 2016 China 28 4 0/45 8/27<br>Wang W 2012 China 28 4 0/48 8/45<br>Wu Q 2015 China 28 12 0/48 5/47<br>Yue X 2014 China 28 1 | $\begin{array}{c} 0.09 \; (0.03,\; 0.30) \\ 0.05 \; (0.01,\; 0.42) \\ 0.12 \; (0.01,\; 1.02) \\ 0.01 \; (0.00,\; 0.23) \\ 0.10 \; (0.01,\; 2.02) \\ 0.23 \; (0.01,\; 4.81) \\ 0.19 \; (0.02,\; 1.70) \\ 0.38 \; (0.11,\; 1.37) \\ 0.10 \; (0.01,\; 0.84) \\ 0.06 \; (0.00,\; 1.24) \\ 0.10 \; (0.01,\; 0.84) \\ 0.06 \; (0.00,\; 1.24) \\ 0.10 \; (0.03,\; 0.70) \\ 0.05 \; (0.00,\; 1.06) \\ 0.03 \; (0.00,\; 0.48) \\ 0.06 \; (0.00,\; 0.97) \\ 0.05 \; (0.00,\; 0.07) \\ 0.05 \; (0.00,\; 0.07) \\ 0.05 \; (0.00,\; 0.79) \\ 0.09 \; (0.01,\; 1.54) \\ 0.01 \; (0.00,\; 1.48) \\ (Excluded) \\ 0.10 \; (0.06,\; 0.12) \\ \end{array}$ |

# Appendix Q: Efficacy by study sample size

- TDF 300 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)
  - The p-value for heterogeneity between subgroups was 0.131

| <=30 participar        |         | Country     | gestation          | postpartum | Events,<br>Treatment | Events,<br>Control |   | OR (95% CI)         | %<br>Weight |
|------------------------|---------|-------------|--------------------|------------|----------------------|--------------------|---|---------------------|-------------|
|                        | nts in  | one/both g  | groups             |            |                      |                    |   |                     |             |
| Celen MK 2             | 2013    | Turkey      | 18 <del>-</del> 27 | 4          | 0/21                 | 2/23               | < ₽                                     | - 0.20 (0.01, 4.42) | 2.55        |
| Chen WJ 2              | 2017    | China       | 28                 | 0          | 1/30                 | 16/44              | <                                       | 0.06 (0.01, 0.49)   | 5.61        |
| Greenup AJ 2           | 2014    | Australia   | 32                 | 12         | 1/69                 | 2/10               | < <u> </u>                              | 0.06 (0.00, 0.72)   | 3.87        |
| Hu MF 2                | 2018    | China       | <0-28              | NR         | 1/89                 | 3/30               |   | 0.10 (0.01, 1.02)   | 4.60        |
| Huang Q 2              | 2017    | China       | 24-28              | 12         | 0/20                 | 3/20               | < ■                                     | 0.12 (0.01, 2.53)   | 2.65        |
| Liu MH 2               | 2017    | China       | 28-30              | 0          | 1/20                 | 6/20               |   | 0.12 (0.01, 1.14)   | 4.92        |
| Wakano Y 2             | 2018    | Japan       | 22-28              | 4-8        | 0/2                  | 2/3                | < <u>∗</u>                              | - 0.12 (0.00, 4.61) | 1.83        |
| Wang HB 2              | 2018    | China       | 20-36              | NR         | 0/100                | 2/20               | ★ ★ ★ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ | 0.04 (0.00, 0.80)   | 2.58        |
| Yu CY 2                | 2018    | China       | 24                 | 4          | 0/30                 | 4/30               | ← ■                                     | 0.10 (0.00, 1.88)   | 2.77        |
| Subtotal (I-squ        | uared   | = 0.0%, p   | = 0.998)           |            |                      |                    | $\sim$                                  | 0.09 (0.04, 0.21)   | 31.37       |
| >30 participant        | ts in b | oth groups  | 30-33              | 4          | 1/65                 | 6/56               |   | 0 13 /0 02 1 12)    | 5 28        |
| Shen HL 2              | 2015    | Taiwan      | 30-32              | 4          | 1/65                 | 6/56               |   | 0.13 (0.02, 1.12)   | 5.28        |
|                        | 2017    | Ohina       | 1-0                |            | 1/44                 | 17/44              |   | 0.12 (0.01, 1.05)   | 5.32        |
| Hell 2                 | 2018    | China       | 28                 |            | 13/50                | 17/35              |   | 0.37 (0.15, 0.93)   | 29.08       |
| Jourdain G 2           | 2018    | Thailand    | 26-29              | 8          | 0/149                | 3/14/              |   | 0.14 (0.01, 2.70)   | 2.76        |
| LIN Y 2                | 2018    | Ohina       | 24                 | 4          | 0/58                 | 4/52               |   | 0.09 (0.00, 1.75)   | 2.81        |
| Pan CQ 2               | 2016    | China       | 30-32              | 4          | 0/92                 | 0/88               |   | 0.07 (0.00, 1.24)   | 2.92        |
| wanji 2                | 2017    | China       | 28                 | 0          | 3/74                 | 7/42               |   | 0.21 (0.05, 0.87)   | 12.24       |
|                        | 2017    | Ohina       | 28                 | 0 0r 4     | 0/60                 | 1/01               |   |                     | 2.35        |
| ∠nang BF 2<br>Zhau V 0 | 2010    | China       | 24-28              | 0          | 0/39                 | 15/75              |   | 0.05 (0.00, 0.85)   | 3.01        |
| ZNUUY 2                | 2018    |             | 24-28              | U          | 0/60                 | 5/36               |   | 0.05 (0.00, 0.88)   | 2.85        |
| Subioial (I-Squ        | uared   | = 0.0%, p   | = 0.806)           |            |                      |                    | $\sim$                                  | 0.20 (0.11, 0.37)   | 00.03       |
| Overall (I-squa        | ared =  | = 0.0%, p = | = 0.972)           |            |                      |                    | $\diamond$                              | 0.16 (0.09, 0.25)   | 100.00      |

- LAM 100-150 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)
  - The p-value for heterogeneity between subgroups was 0.838

| Author         Year         Country           <=30 participants in one/both gn         sliXW         2011         China           Chen GR         2018         China         Cheng YC         2013         China           Chen SM         2017         China         Cheng YC         2014         China           Foaud MM         2019         Egypt         Ge YL         2015         China           Greenup JJ         2014         Austral         Jackson V         2015         Ireland           Jackson V         2015         China         Grant Jackson V         2015         China           Mar J         2006         China         Grant Jackson V         2015         China           Mar J         2006         China         Grant Jackson V         2016         China           Mar J         2006         China         Grant Jackson V         2016         China           Mar J         2007         China         Grant Jackson V         2016         China           Mar DM         2012         China         Grant Jackson V         2016         China           Wang DM         2012         China         China         Grant Jachina         China  | start in v               | veeks Tx end in    | Events    | Events.       |  |                   |     |
|--|--------------------------|--------------------|-----------|---------------|--|-------------------|-----|
| Author         Year         Country           <=30 participants in one/both gn         China           Bai XW         2011         China           Chen QR         2018         China           Chen QR         2017         China           Chen QR         2017         China           Chen QR         2017         China           Chen QR         2017         China           Ge YL         2015         Celand           Ge YL         2014         Australl           Gar YL         2015         China           Garcenup AJ         2014         Australl           LI H         2015         China           Jackson V         2016         China           Ma J         2006         China           Ma J         2016         China           Shen ML         2016         China           Wang DW         2012         China           Wang DW         2014         China           Zhu M         2012         China           Zhu M         2014         China           Quang EJ         2012         China           Guo YZ         2008         China  |                          |                    | Eronio,   | ,             |  |                   | %   |
| Sap Darticipants in one/both gr           sai XW         2011         China           Shen QR         2018         China           Shen QR         2018         China           Shen QR         2018         China           Shen QR         2017         China           Shen QR         2017         China           Shen QR         2019         Egypt           Goaud HM         2015         China           Greenup AJ         2014         Austral           dan YP         2014         China           ackson V         2015         Ireland           J JH         2017         China           da J         2006         China           Aug J         2016         China           Ang X         2016         China           Ang X         2012         China           Yang DM         2016         China           Yang DM         2014         China           Yang DM         2014         China           Yang DM         2014         China           Yang HF         2007         China           Yang HF         2008         China           Ya  | Country gestatio         | n weeks postpartum | Treatment | Control       |  | OR (95% CI)       | We  |
| kai XW         2011         China           bhen GR         2013         China           bhen SM         2017         China           band HM         2015         China           areup AJ         2014         Austral           lan YP         2015         China           ackson V         2015         China           ackson V         2017         China           ata Z         2017         China           ata J         2006         China           ata J         2016         China           ata J         2016         China           atar X         2012         China           atarg X         2012         China           atarg X         2013         China           atarg X         2014         China           atarg X         2013         China           atarg X         2013         China           atarg X         2014         China   | ne/both groups           |                    |           |               |  |                   |     |
| Chen QR         2018         China           Chen SM         2017         China           Chen YC         2011         China           Dreng YC         2012         China           Graud HM         2019         Egypt           Gaud HM         2019         Egypt           Gaud HM         2014         Austral           Iar YP         2014         Austral           Jar YP         2014         China           Jar YP         2014         China           Jar YP         2014         China           Jar YP         2015         China           Air J         2006         China           Air JCA         2016         China           Air JCA         2007         China           Air JCA         2010         China           Mang DM         2012         China           Avang DM         2014         China           Mang DM         2014         China           Subtotal         (I-squared = 0.0%, p. =           -S0 participants in both groups         China           Jir Y         2015         China           Jan CQ         2017         China   | China 28                 | 4                  | 3/30      | 8/25          |  | 0.24 (0.05, 1.02) | 3.6 |
| Chen SM         2017         China           Cheng YC         2011         China           Saud HM         2019         Egypt           Gaud HM         2015         China           Gaud HM         2014         Austral           Han YP         2014         China           Jackson V         2018         China           Jackson V         2018         China           Jackson V         2018         China           Jackson V         2017         China           Austral         Jackson V         2016         China           Ada J         2006         China         Sang V         2011         China           Ama J         2009         China         Sang V         2014         China           Mang DM         2012         China         Sang V         2014         China           Subtotal (I-squared = 0.0%, p         =         Sang VI         2014         China           Subtotal (I-squared = 0.0%, p         =         Sang VI         2014         China           Ji YY         2015         China         Sang VI         2015         China           Ji YY         2016         China         Sa  | China 28                 | 4                  | 1/33      | 5/28          | *  | 0.14 (0.02, 1.31) | 1.5 |
| Sheng YC         2011         China           icaud HM         2011         Egypt           icaud HM         2012         China           icaud PM         2014         Austral           areenup AJ         2014         China           lan YP         2014         China           lan YP         2018         China           lata YP         2018         China           lata YP         2015         Ireland           J ZG         2015         China           dat J         2006         China           ata J         2011         China           ata J         2016         China           vang X         2012         China           vang X         2012         China           vang W         2014         China           vang Y         2015         China           vang Y         2015         China           van V         2015         China  | China 28                 | NR                 | 1/30      | 10/30 🗲       |  | 0.07 (0.01, 0.58) | 1.7 |
| coaud HM         2019         Egypt           coaud HM         2019         China           cherup, AJ         2014         Australl           tan YP         2014         China           tan YP         2014         China           tan YP         2014         China           tan YP         2014         China           tan YP         2015         Irelian           tan YD         2017         China           dacson V         2015         China           dat J         2000         China           fan JD         2000         China           ang X         2009         China           Yang DM         2011         China           Yang DM         2012         China           Yang DM         2013         China           Guard M         2014         China           Guard M         2013         China           Subtotal (I-squared = 0.0%, p =         So           Sub YZ         2008         China           YA         2015         China           YA         2016         China           YA         2017         China   | China 32                 | 4                  | 8/30      | 6/26          | · · · · · · · · · · · · · · · · · · ·  | 1.21 (0.36, 4.10) | 5.2 |
| Ba YL         2015         China           Greenup AJ         2014         Austral           Jarnenup AJ         2014         China           Jarnenup AJ         2014         China           Jarn YP         2018         China           Jata YP         2017         China           Jackson V         2015         Ireland           J JG         2017         China           Ad J         2006         China           Yang J         2011         China           Yang X         2016         China           Yang X         2012         China           Yang LJ         2012         China           Yang LJ         2012         China           Yang LJ         2014         China           Yang LJ         2012         China           Yang LJ         2014         China           Yang LJ         2013         China           Yang LJ         2014         China           Yang HF         2007         China           Yang HZ         2018         China           Yang HZ         2014         China           Yan QC         2017         China  | Egypt Anytime            | NR                 | 0/29      | 1/30          |  | 0.33 (0.01, 8.52) | 0.7 |
| ireenup AJ         2014         Austral           ian YP         2014         China           ian YP         2014         China           iet T         2015         China           ackson V         2015         China           ackson V         2015         China           iJH         2017         China           taJ ZG         2016         China           tay ZG         2006         China           any X         2009         China           yang M         2016         China           yang W         2016         China           yang W         2014         China           yang W         2014         China           yang W         2013         China           yang W         2014         China           yang W         2014         China           yang W         2014         China           yang W         2017         China           yang W         2015         China           yang HZ         2020         China           yang HZ         2015         China           yang Chi         2007         China   | China 28-30              | 12                 | 0/16      | 3/22 🗲        |  | 0.17 (0.01, 3.51) | 0.8 |
| tan YP         2014         China           te T         2018         China           ackson V         2017         Ireland           j JH         2017         China           j ZG         2017         China           a J         2006         China           at J         2007         China           at J         2008         China           at J         2009         China           at J         2009         China           ang X         2009         China           ang X         2012         China           Yang DM         2012         China           Yang DM         2014         China           Yang DM         2014         China           China China         China         China           Yang DM         2014         China           Subtotal (I-squared = 0.0%, p =         Soparticipant's in both groups         China           Yang YZ         2008         China         China           Yang X         2012         China         China           Yang X         2012         China         China           Yan Q         2017         China  | Australia 32             | 2                  | 0/43      | 2/10          |  | 0.04 (0.00, 0.89) | 0.7 |
| He T         2018         China           ackson V         2015         Finland           J JH         2015         China           J ZG         2015         China           J ZG         2015         China           J ZG         2016         China           da J         2011         China           da Har J         2011         China           shen ML         2016         China           vang X         2009         China           Vang DM         2016         China           Vang DM         2014         China           Vang DM         2014         China           vang W         2014         China           vang M         2014         China           van QVZ         2008         China           van VZ         2006         China           van VZ         2006         China           van VZ         2006         China   | China 28                 | 6                  | 1/30      | 4/30          | -  | 0.22 (0.02, 2.14) | 1.5 |
| ackson V         2015         Ireland           J JH         2017         China           J ZG         2017         China           Az J         2006         China           Aa J         2006         China           Aa J         2007         China           Aan Y         2011         China           Ang Y         2019         China           Ang X         2009         China           Ang X         2019         China           Yang DM         2012         China           Yang W         2014         China           Yang W         2015         China           Yang TX         2008         China           Yang X         2015         China           Yang X<  | China 1st Trim           | ester NR           | 0/29      | 4/34          |  | 0.11 (0.01, 2.23) | 0.8 |
| J.H.         2017         China           JZG         2015         China           JZG         2015         China           JZG         2016         China           JaJ         2006         China           ten YJ         2011         China           ang X         2009         China           ang X         2012         China           vang DM         2014         China           vang W         2014         China           hu M         2013         China           hu M         2014         China           hu M         2014         China           hu M         2014         China           uag PM         2014         China           ubtotal (I-squared = 0.0%, p =         Soparticipants in both croups           Gang HF         2007         China           iang HX         2012         China           i W         2008         China           i W         2006         China           i W         2006         China           i W         2009         China           i W         2009         China           i Mang TM   | Ireland 32               | 0                  | 0/21      | 1/6           | _  | 0.09 (0.00, 2.39) | 0.7 |
| IZG         2015         China           IzG         2016         China           tan J         2006         China           ten VJ         2016         China           ten VJ         2016         China           ang X         2009         China           yang DM         2016         China           yang DM         2016         China           yang W         2014         China           yubtotal (I-squared = 0.0%, p =         30 participants in both groups           gang HZ         2007         China           yang Z         2008         China           yang Z         2008         China           yang Z         2008         China           yang Z         2008         China           yang Z         2006         China           yang C         2007         China           yang C         2009         China <td>China 28</td> <td>4</td> <td>1/33</td> <td>8/27</td> <td></td> <td>0.07 (0.01, 0.64)</td> <td>1.6</td>   | China 28                 | 4                  | 1/33      | 8/27          |  | 0.07 (0.01, 0.64) | 1.6 |
| AJ         2016         China           Aa         2006         China           Hen YJ         2011         China           Shen ML         2016         China           Shen ML         2016         China           Yang DM         2016         China           Yang DM         2018         Japan           Wang DM         2012         China           Yang DM         2012         China           Grap YM         2014         China           Churd         China         China           Grap YM         2014         China           Subtotal (I-squared = 0.0%, p =         Signarticipants in both groups           Song Articipants in both groups         China           Sub YZ         2008         China           Sub YZ         2008         China           Y         2015         China           YA         2012         China           YA         2016         China           Yang TM         2009         China           Yang TM         2005         China           Yang TM         2005         China           Yang TM         2005         China <td>China 28</td> <td>-<br/>6</td> <td>1/25</td> <td>4/25</td> <td></td> <td>0.22 (0.02, 2.11)</td> <td>1.5</td>   | China 28                 | -<br>6             | 1/25      | 4/25          |  | 0.22 (0.02, 2.11) | 1.5 |
| abit         2001         China           ethr YJ         2011         China           shen ML         2016         China           yang X         2009         China           vang X         2018         Japan           Vang DJ         2016         China           vang W         2012         China           vang W         2014         China           vang W         2014         China           butotal         It-squared = 0.0%, p =           30 participants in both groups         china           iang HZ         2015         China           iang HZ         2016         China           iang HX         2012         China           iang HX         2017         China           iang HX         2012         China           iang HX         2012         China           ian CQ         2017         China           ian XQ         2016         China           ian XQ         2016         China           ian XQ         2015         China           ian XQ         2015         China           ian XQ         2005         China   | China Ere-prer           | anancy NR          | 0/18      | 9/16          |  | 0.02 (0.02, 2.11) | 0.9 |
| John ML         2011         China           ang X         2009         China           yakano Y         2018         Japan           yang DM         2016         China           yang DM         2016         China           yang DM         2012         China           yang W         2013         China           yang W         2013         China           yang W         2014         China           yang W         2013         China           yang W         2014         China           yang W         2014         China           yang W         2017         China           yang W         2016         China           yang TM         2015         China           yang H         2015         China           yang H         2006         China           yang H         2009         China           yang M         2009         China           yang M         2009         China           yang M         2005         China           yang M         2005         China           yang M         2005         China      >yang   | China 29                 | n n                | 1/20      | 12/155        |  | 0.38 (0.05, 3.99) | 1.0 |
| ang X         2016         China ang X           Valkano Y         2018         Japan           Vang DM         2016         China Vang DM         2016         China Vang DM           Vang DM         2014         China Vang DM         2012         China Vang DM         2014         China Vang DM         2017         China Vang VZ         2008         China Vang VZ         2008         China Vang VZ         2005         China Vang VZ         2012         China Vang VZ         2012         China Vang VZ         2016         China Vang VA         2012         China Vang VA         2012         China Vang VA         2012         China Vang VA         2015         China Vang VA         2015         China Vang VA         2015         China Vang VA         2005         China VANg VANg VANg VANg VANg VANg VANg VANg | China 20                 | 4                  | 0/60      | 11/29         |  | 0.01 (0.00, 0.23) | 0.0 |
| ang X         2009         China           Wagn DV         2016         China           Wang DV         2016         China           Wang W         2014         China           Ang W         2014         China           Ang W         2013         China           Zhu M         2013         China           Yu M         2014         China           Subtal         (Hequared = 0.0%, p =           S0 participants in both groups         Fong HF           Ju Y Z         2008         China           Ju Y Z         2005         China           Ju Y Z         2015         China           Ji W Z         2006         China           Ji W F         2006         China           Su TB         2009         China           Su TB         2005         China           Su TB         2005         China           Yang TM  | China 26                 | 4                  | 0/60      | 11/26         | and the second sec | 0.01 (0.00, 0.22) | 0.8 |
| variano y         2018         Japan           wang DM         2016         China           wang DX         2012         China           wang W         2014         China           cheg YM         2013         China           cheg YM         2013         China           shub N         2014         China           shub N         2014         China           shub N         2014         China           source I         a.ovs, p         =           s00 participants in both groups         =           orag HF         2007         China           Suo YZ         2008         China           liang HX         2012         China           i G         2006         China           a Par CQ         2017         China           a UF         2006         China           a UR         2009         China           a UR         2009         China           a Vang TM         2005         China           wang TM         2005         China           wang TM         2005         China           wang TM         2005         China   | China 33                 | 4                  | 0/17      | 4/24          |  | 0.13 (0.01, 2.59) | 0.8 |
| Wang LM         2016         China           Wang EJ         2012         China           Wang W         2014         China           Wang W         2014         China           Zeng YM         2013         China           Dubt 2014         China         China           Subtotal         (I-squared = 0.0%, p =         -           S0 participants in both groups         Gina         -           Jau YZ         2008         China           Jau YZ         2008         China           Jau YZ         2008         China           Jang HX         2012         China           Jang HX         2015         China           J G         2006         China           J WF         2006         China           Vang TM         2011         China           Vang TM         2009         China           Vang TM         2009         China           Vang TM         2009         China           Vang TM         2009         China           Vang TM         2005         China           Vang TM         2009         China           Vang TM         2012  | Japan 28-32              | 4-8                | 0/3       | 2/3           |  | 0.09 (0.00, 3.10) | 0.6 |
| Wang EJ         2012         China           Wang W         2014         China           Yang W         2013         China           Yang W         2014         China           Yang W         2013         China           Yang W         2014         China           Yang W         2014         China           Subtotal (I-squared = 0.0%, p =         -           Subtotal (I-squared = 0.0%, p =         -           Yang Y         2007         China           Yang X         2008         China           Yang X         2015         China           J W         2006         China           J WF         2006         China           Yan C         2017         China           Yan C         2016         China           Yan C         2016         China           Yan C         2016         China           Yan Z         2009         China           Yan Z         2005         China           Yan Z         2005         China           Yan Z         2005         China           Yan Z         2005         China           Yang M  | China 28-30              | 12                 | 1/42      | 5/20          |  | 0.07 (0.01, 0.68) | 1.5 |
| Wang W         2014         China           Cang YM         2013         China           chu M         2014         China           chu M         2014         China           sbubtotal         (I-squarel = 0.0%, p =         500 participants in both groups           seng HF         2007         China           dau YZ         2008         China           dau YZ         2008         China           lau YZ         2015         China           lau YZ         2016         China           lau YZ         2016         China           la G         2007         China           law YZ         2015         China           law R         2012         China           law R         2012         China           law R         2016         China           law R         2009         China           su TB         2009         China           wang TM         2005         China           ku WM         2009         China,           ku WM         2005         China           ku Qun QF         2012         China   | China 28                 | 4                  | 1/32      | 5/27          |  | 0.14 (0.02, 1.30) | 1.5 |
| Zeng YM         2013         China           Auth         2014         China           Subtotal         (H-squared = 0.0%, p =            Subtotal         (H-squared = 0.0%, p =            Subtotal         (H-squared = 0.0%, p =            Sub YZ         2008         China           Jau YZ         2005         China           Ian ZH         2005         China           Ji YY         2015         China           J G         2006         China           J WF         2006         China           Ran CJ         2017         China           Su TB         2009         China           Su TB         2009         China           Su TB         2005         China           Su TB         2009         China           Yang TM         2005         China           Yang TM         2005         China           Yang TM         2009         China,           Yang HW         2014         China   | China 28                 | 4                  | 0/35      | 2/28          |  | 0.15 (0.01, 3.24) | 0.8 |
| thu M         2014         China           subtotal         (I-squared = 0.0%, p =   | China 28                 | Variable (0,4,6)   | 0/90      | 3/30 🗲        |  | 0.04 (0.00, 0.87) | 0.8 |
| Subtotal         (I-squared = 0.0%, p =           -30 participants in both groups         Forg HF         2007         China           3ua VZ         2008         China         AnzH         2005         China           ata ZH         2005         China         AnzH         2005         China           Ii YY         2015         China         AnzH         2006         China           Ji WF         2006         China         AnzH         2016         China           Ji WF         2006         China         Ang CQ         2017         China           V WF         2006         China         Su TB         2009         China           Su TB         2009         China         Nang TM         2005         China           Guang TM         2005         China         China         Yang TM         2009         China,           Grap HW         2014         China         Yang TM         2014         China   | China 26                 | 0                  | 2/24      | 9/24          |  | 0.15 (0.03, 0.80) | 2.7 |
| s30 participants in both groups           eng HF         2007         China           Guo YZ         2008         China           Jan ZH         2005         China           Jan ZH         2015         China           Ji YY         2015         China           Ji YY         2016         China           Ji YY         2017         China           Li WF         2006         China           Ji WF         2006         China           Su TB         2009         China           Su TB         2009         China           Su TB         2009         China           Wang TM         2005         China           Ku WM         2009         China,           Yang TM         2005         China           Yang TM         2014         China   | 0.0%, p = 0.511)         |                    |           |               | $\diamond$   | 0.17 (0.11, 0.28) | 33  |
| Feng HF         2007         China           Guo YZ         2008         China           Han ZH         2005         China           Jul YY         2015         China           Ji YY         2015         China           Li WF         2006         China           Li WF         2006         China           Li WF         2006         China           Su TB         2009         China           Su TB         2009         China           Wang TM         2015         China           Xu WA         2009         China,           Yang TW         2015         China,           Yuan QF         2020         China,  | h aroups                 |                    |           |               |  |                   |     |
| Suo YZ         2008         China           Jan ZH         2005         China           Jiang HX         2012         China           Jiang HX         2012         China           Li G         2006         China           Li MF         2006         China           Li WF         2006         China           Ban CO         2017         China           Su TB         2009         China           Wang TM         2015         China           Xu WM         2009         China           Xu WM         2005         China           Xu WM         2009         China,           Xu WM         2009         China,           Xu WM         2012         China           Xu Qan QF         2012         China  | China 28                 | 4                  | 7/48      | 16/42         |  | 0.28 (0.10, 0.77) | 7.5 |
| Han ZH         2005         China           Ji YY         2015         China           Jiang HX         2012         China           Li G         2006         China           Li WF         2006         China           Li WF         2006         China           Su TB         2009         China           Su TB         2009         China           Wang TM         2005         China           Xu WM         2009         China,           Yang HW         2014         China           Yang HW         2014         China  | China 28                 | 0                  | 3/70      | 13/40         |  | 0.09 (0.02, 0.35) | 4.3 |
| IVY         2015         China           Jiang HX         2012         China           Jiang HX         2012         China           Ji WF         2006         China           Pan CQ         2017         China           Su TB         2009         China           Su TB         2009         China           Ang TM         2005         China           Ku WM         2009         China,           Ku WM         2009         China,           Yang TM         2014         China           Yuan OF         2012         China  | China 28                 | 0                  | 0/43      | 5/35          | - 1  | 0.06 (0.00, 1.20) | 0.9 |
| Long         Long         China           J G         2006         China           J WF         2006         China           Pan CQ         2017         China           Pan CQ         2017         China           Su TB         2009         China           Mang TM         2015         China           Wang TM         2005         China           Ku WM         2009         China           Yuan QF         2015         China  | China 28                 | 4                  | 2/65      | 12/65         |  | 0.14 (0.03, 0.65) | 3.2 |
| Li G         2006         China           Li WF         2006         China           Pan CQ         2017         China           Pan CI         2016         China           Su TB         2009         China           Wang TM         2005         China           Xurg TM         2005         China           Ku WM         2009         China           Yang TM         2014         China           Yuan QF         2012         China   | China 20-34              | 4                  | 0/164     | 8/92          |  | 0.03 (0.00, 0.53) | 0.0 |
| LWF         2006         China           Pan CQ         2017         China           Ren CJ         2016         China           Su TB         2009         China           Mang TM         2005         China           Xu WM         2009         China           Yang TM         2005         China           Yang TM         2005         China           Yang HW         2014         China   | China 28                 | 0                  | 1/25      | 7/22          |  | 0.11 (0.01, 0.01) | 1.0 |
| Swift         2005         China           Ren CJ         2017         China           Ren CJ         2016         China           Su TB         2009         China           Tian XQ         2015         China           Wang TM         2005         China,           Vu WA         2009         China,           Yang HW         2014         China,           Yang HW         2012         China,   | China 20                 | 0                  | 1/00      | 7/44          |  | 0.15 (0.03, 1.03) | 1.0 |
| van Cu         2017         China           Ren CJ         2016         China           Su TB         2009         China           Fian XQ         2015         China           Wang TM         2005         China           Ku WM         2009         China,           yang HW         2014         China           Uan QF         2012         China  | China 24                 | 0                  | 0/160     | 7/44 <b>-</b> |  | 0.15 (0.02, 1.29) | 1.0 |
| Su TB 2009 China<br>Su TB 2009 China<br>Fian XQ 2015 China<br>Wang TM 2005 China,<br>Ku WM 2009 China,<br>Yang HW 2014 China<br>Yuan QF 2012 China   | China 13-30              | 4                  | 0/160     | 5/69          |  | 0.05 (0.00, 0.88) | 0.9 |
| Fian XQ 2015 China<br>Fian XQ 2015 China<br>Wang TM 2005 China<br>Ku WM 2009 China,<br>Yang HW 2014 China<br>Yuan QF 2012 China  | China 28                 | 0                  | 2/67      | 10/72         |  | 0.19 (0.04, 0.91) | 3.1 |
| Iran XQ 2015 China<br>Wang TM 2005 China<br>Ku WM 2009 China,<br>Yang HW 2014 China<br>Yuan QF 2012 China  | China 32                 | 0                  | 5/128     | 13/120        |  | 0.33 (0.12, 0.97) | 5.0 |
| Vang TM 2005 China<br>Ku WM 2009 China,<br>Yang HW 2014 China<br>Yuan QF 2012 China  | China 28                 | 0                  | 11/110    | 49/110        |  | 0.14 (0.07, 0.29) | 14. |
| Ku WM 2009 China,<br>Yang HW 2014 China<br>Yuan QF 2012 China  | China Pre-prec           | gnancy 0           | 0/32      | 8/32 🗬        |  | 0.04 (0.00, 0.81) | 0.9 |
| Yang HW 2014 China<br>Yuan QF 2012 China   | China, Philippines 30-34 | 4                  | 3/49      | 5/41          |  | 0.47 (0.11, 2.10) | 3.4 |
| Yuan QF 2012 China   | China 28                 | 4                  | 1/53      | 4/53          |  | 0.24 (0.03, 2.18) | 1.5 |
|  | China 27                 | 4                  | 1/32      | 3/32          |  | 0.31 (0.03, 3.17) | 1.4 |
| Zhang H 2014 China   | China 28-30              | 4                  | 0/52      | 10/352        |  | 0.31 (0.02, 5.38) | 0.9 |
| Zhang YF 2010a China   | China 28                 | 4                  | 3/50      | 16/50         |  | 0.14 (0.04, 0.50) | 4.5 |
| Zhou DS 2013 China   | China 20-28              | NR                 | 5/113     | 28/95         |  | 0.11 (0.04, 0.30) | 7.7 |
| Subtotal (I-squared = 0.0%, p =  | 0.0%, p = 0.886)         |                    |           |               | $\diamond$   | 0.16 (0.12, 0.23) | 66  |
| Overall (I-squared = 0.0%, p = 0   | .0%, p = 0.830)          |                    |           |               | <b>↔</b>   | 0.17 (0.13, 0.22) | 10  |

- LdT 600 mg by study sample size (<=30 participants in either group versus >30 participants in both groups)
  - The p-value for heterogeneity between subgroups was 0.892

| <ul> <li>Sparticipant</li> <li>Sparticipant</li> <li>Chen GN</li> <li>Chen SM</li> <li>Con SM<!--</th--><th>Its in o)<br/>113<br/>118<br/>117<br/>115<br/>117<br/>115<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>117<br/>116<br/>116</th><th>ne/both 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| ьы ні. 2010<br>Сhen QR 2010<br>Chen QR 2010<br>Chen QR 2010<br>Guo HJ 2010<br>Huang QH 2010<br>Li CM 2010<br>Li CM 2010<br>Li VM 2010<br>Li VM 2010<br>Li VM 2010<br>Li VM 2010<br>Shen QL 2010<br>Wang HB 2010<br>Wang Wang HB 2010<br>Wang Wang HB 2010<br>Wang V 2010<br>Wang V 2010<br>Xing Y 2010<br>Yao LF 2017<br>Yao  | )13<br>)18<br>)17<br>)17<br>)15<br>)11<br>)15<br>)11<br>)15<br>)17<br>)16<br>)17<br>)17<br>)16<br>)17<br>)17<br>)16<br>)16<br>)18<br>)16<br>)18<br>)16<br>)12<br>)18<br>)11<br>)18<br>)18<br>)18<br>)18<br>)18<br>)18<br>)17<br>)18<br>)17<br>)18<br>)17<br>)18<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China                                  | 26-32<br>28<br>28<br>28-30<br>28<br>20-28<br>24-28<br>24-28<br>28<br>30<br>30<br>28-36<br>28-36<br>28-36<br>28-36<br>28-30<br>28<br>20-36<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29- | 4<br>NR<br>12<br>6<br>0<br>12<br>4<br>NR<br>~36<br>NR<br>~36<br>NR<br>NA<br>NA<br>NA<br>0              | 0/27<br>0/29<br>0/30<br>0/20<br>6/28<br>0/30<br>16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/97<br>0/20         | 4/30<br>5/28<br>10/30<br>3/22<br>6/26<br>4/30<br>23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30 |   | 0.11 (0.01, 2.09)<br>0.07 (0.00, 1.38)<br>0.03 (0.00, 0.58)<br>0.14 (0.01, 2.81)<br>0.91 (0.25, 3.28)<br>0.10 (0.00, 1.88)<br>0.07 (0.02, 0.18)<br>0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17) | 0.66<br>0.68<br>0.70<br>0.64<br>3.56<br>0.67<br>5.81<br>0.64<br>1.27<br>1.28<br>1.20 |
| Chain SM         200           Construction         200           Ge YL         200           Han YP         201           Han YP         201           Han YP         201           Huang HY         201           Huang Q         201           Li CM         201           Li Li CM         201           Li Li XB         201           PengML         201           Sheng Q         201           Wang BL         201           Yao LF         201           Yao LF         201           Yao LF         201           Zhang LJ         202           Zhang DB         201   | 017<br>015<br>011<br>014<br>016<br>017<br>016<br>017<br>016<br>017<br>016<br>014<br>016<br>018<br>016<br>012<br>018<br>016<br>012<br>018<br>016<br>012<br>018<br>011<br>012<br>018<br>011<br>012<br>018<br>011<br>011<br>015   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28-30<br>28<br>28<br>28<br>24-28<br>24-28<br>28<br>-0-28<br>28<br>30<br>28<br>30<br>28-36<br>28<br>28<br>26<br>24-32<br>28-30<br>28<br>20-36   | NR<br>12<br>4<br>0<br>12<br>4<br>NR<br>~366<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>0                      | 0/20<br>0/30<br>0/20<br>6/28<br>0/30<br>16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61 | 10/30<br>3/22<br>6/26<br>4/30<br>23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30                 |   | 0.33 (0.00, 1.56)<br>0.14 (0.01, 2.81)<br>0.10 (0.00, 1.88)<br>0.07 (0.02, 0.18)<br>0.07 (0.02, 0.18)<br>0.19 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)  | 0.60<br>0.64<br>3.56<br>0.67<br>5.81<br>0.64<br>1.27<br>1.28<br>1.20                 |
| Car         Car           Gao HJ         200           Han YP         200           Huang HZ         200           Huang HZ         200           Huang HZ         200           Huang HZ         200           Li CM         200           Li YH         200           Li VH         200           Li UX         201           Shen RL         201           Wang DM         201           Wang HB         201           Wang Wang L2         201           Yao LF         201           Yao LF         201           Zhao DB         201           Zhao DB         201  | 015<br>011<br>014<br>016<br>017<br>017<br>017<br>017<br>016<br>017<br>016<br>018<br>016<br>018<br>016<br>012<br>018<br>012<br>018<br>012<br>018<br>012<br>018<br>012<br>018<br>012<br>011<br>012<br>012<br>012<br>012<br>012<br>012<br>012<br>012  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-30<br>28<br>20-28<br>24-28<br>28<br>24-28<br>28<br>28<br>30<br>28-36<br>28-36<br>28-36<br>28-32<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>29-30<br>28-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>29-30<br>200-30<br>200-30<br>200-30<br>200<br>200-30<br>2    | 12<br>4<br>6<br>0<br>12<br>4<br>NR<br>~36<br>NR<br>4<br>NR<br>4<br>NR<br>4<br>0                        | 0/20<br>6/28<br>0/30<br>16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61   | 3/22<br>6/26<br>4/30<br>23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30                          |   | 0.14 (0.01, 2.81)<br>0.91 (0.25, 3.28)<br>0.10 (0.00, 1.88)<br>0.07 (0.02, 0.18)<br>0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)  | 0.64<br>3.56<br>0.67<br>5.81<br>0.64<br>1.27<br>1.28<br>1.20                         |
| juo         juo         juo           Han YP         200           Huang HY         200           Huang Q         200           Li CM         200           Li N         201           Li N         201           Li N         201           Li XB         201           Jui XB         201           Sheng Q         201           Sheng Q         201           Wang BL         200           Wang BL         200           Wang WP         200           Wang WP         201           Yao LF         201           Yao ZC         201           Yao ZC         201           Zhao DB         201           Zheng JC         201   | )11<br>)14<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)16<br>)17<br>)16<br>)17<br>)16<br>)18<br>)16<br>)18<br>)16<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)12<br>)18<br>)12<br>)12<br>)12<br>)12<br>)13<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>20-28<br>24-28<br>28<br>-0-28<br>28<br>-0-28<br>28<br>30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20   | 4<br>6<br>0<br>12<br>4<br>NR<br>~366<br>NR<br>4<br>NR<br>4<br>0<br>0                                   | 6/28<br>0/30<br>16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61   | 6/26<br>4/30<br>23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30                                  |   | 0.91 (0.25, 3.28)<br>0.10 (0.00, 1.88)<br>0.07 (0.02, 0.18)<br>0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.71)   | 3.56<br>0.67<br>5.81<br>0.64<br>1.27<br>1.28<br>1.20                                 |
| Jan YP         20:           Jang HY         20:           Huang Q         20:           I CM         20:           i CM         20:           i N         20:           Ju XB         20:           Ju XB         20:           Ju XB         20:           Shen ML         20:           Shen ML         20:           Wang EJ         20:           Wang EJ         20:           Wang EJ         20:           Wang EJ         20:           Yang LF  | )14<br>)16<br>)17<br>)17<br>)16<br>)17<br>)16<br>)17<br>)16<br>)17<br>)16<br>)14<br>)16<br>)18<br>a<br>)16<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)16<br>)12<br>)18<br>)12<br>)16<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>20-28<br>24-28<br>28<br>30<br>28-36<br>28<br>28<br>26<br>28<br>26<br>24-32<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30<br>28-30  | 6<br>0<br>12<br>4<br>NR<br>~36<br>NR<br>4<br>NR<br>4<br>0  | 0/30<br>16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61   | 4/30<br>23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30  |   | 0.10 (0.00, 1.88)<br>0.07 (0.02, 0.18)<br>0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)  | 0.67<br>5.81<br>0.64<br>1.27<br>1.28<br>1.20   |
| Huang HY         20'           Luang Q         20'           i CM         20'           i N         20'           i N         20'           i J H         20'           Ju J B         20'           Ju J B         20'           PangML         20'           Shen ML         20'           Wang DM         20'           Wang BL         20'           Wang BL         20'           Wang WP         20'           Kao LF         20'           Yao LF         20'           Yao DK         20'           Yang WP         20'           Yao LF         20'           Yao DK         20'           Yao DB         20'           Yae DB         20'   | )16<br>)17<br>)17<br>)17<br>)17<br>)17<br>)17<br>)16<br>)17<br>)16<br>)14<br>)16<br>)14<br>)16<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)12<br>)11<br>)11<br>)11<br>)11<br>)12<br>)12<br>)12<br>)12<br>)12   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 20-28<br>24-28<br>28<br><-0-28<br>28<br>30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28-30<br>28-30<br>28<br>20-36   | 0<br>12<br>4<br>NR<br>~36<br>NR<br>4<br>NR<br>4<br>0   | 16/90<br>0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61   | 23/30<br>3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30  |   | 0.07 (0.02, 0.18)<br>0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)   | 5.81<br>0.64<br>1.27<br>1.28<br>1.20   |
| Huang Q         20:           i CM         20:           i CM         20:           i VH         20:           i J         20:           i J         20:           iu J         20:           iu J         20:           iu XB         20:           sheng ML         20:           Nang DM         20:           Wang MB         20:           Wang HB         20:           Yang DM         20:           Yang DM         20:           Yang LJ         20:           Yao LF         20:           Yao ZC         20:           Yang LJ         20:           Yao ZC         20:           Yang DB         20:           Yao DE         20:           Yao DE         20:           Yao DE         20:   | )17<br>)17<br>)16<br>)17<br>)16<br>)17<br>)16<br>)18<br>)16<br>)18<br>)16<br>)12<br>)18<br>)16<br>)12<br>)18<br>)12<br>)18<br>)14<br>)11<br>)11<br>)11<br>)109   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 24-28<br>28<br><0-28<br>28-36<br>28-36<br>28<br>26<br>24-32<br>24-32<br>28-30<br>28<br>20-36   | 12<br>4<br>~36<br>NR<br>4<br>NR<br>4<br>0  | 0/20<br>1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61  | 3/20<br>8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30   |   | 0.12 (0.01, 2.53)<br>0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)  | 0.64<br>1.27<br>1.28<br>1.20   |
| i CM 201<br>i N 201<br>iu J 201<br>iu J 201<br>iu M 201<br>iu M 201<br>iu M 201<br>in M 201<br>in M 201<br>in M 201<br>Wang DM 201<br>Wang BJ 201<br>Wang BJ 201<br>Wang WP 201<br>Gao LF 201<br>fao ZC 201<br>fhang LJ 200<br>fhang LJ 201<br>fhang LJ 201<br>fh   | )17<br>)16<br>)17<br>)17<br>)16<br>)16<br>)18<br>)16<br>)18<br>)16<br>)12<br>)16<br>)12<br>)11<br>)11<br>)11<br>)11<br>)11<br>)11<br>)109  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br><0-28<br>28<br>30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28-30<br>28<br>20-36   | 4<br>NR<br>~36<br>NR<br>4<br>NR<br>4<br>0  | 1/30<br>1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61  | 8/30<br>9/25<br>5/32<br>2/28<br>5/20<br>8/30   |   | 0.09 (0.01, 0.82)<br>0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)   | 1.27<br>1.28<br>1.20   |
| i N 201<br>i YH 200<br>iu J 200<br>iu XB 200<br>ivengML 201<br>ihen ML 201<br>Vang EJ 200<br>Vang EJ 200<br>Vang EJ 200<br>Vang HZ 201<br>vang WP 201<br>ing Y 201<br>iao LF 200<br>ihang LJ 200<br>ihang LJ 200<br>ihang LJ 201  | )16<br>)17<br>)17<br>)16<br>)16<br>)18<br>)18<br>)16<br>)12<br>)16<br>)12<br>)16<br>)12<br>)18<br>)12<br>)18<br>)12<br>)11<br>)11  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | <0-28<br>28<br>30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28<br>30<br>29<br>20-36  | NR<br>~36<br>NR<br>4<br>NR<br>4<br>0   | 1/65<br>1/30<br>0/97<br>0/20<br>1/30<br>0/61  | 9/25<br>5/32<br>2/28<br>5/20<br>8/30   |   | 0.03 (0.00, 0.24)<br>0.19 (0.02, 1.70)<br>0.05 (0.00, 1.17)  | 1.28   |
| i YH 201<br>iu J 201<br>iu XB 201<br>rengML 201<br>iheng Q 201<br>Vang DM 201<br>Vang BM 201<br>Vang HB 201<br>Vang HB 201<br>Vang HB 201<br>vang HB 201<br>ring Y 201<br>ring Z 201<br>rhang LJ 200<br>rhang LJ 201  | )17<br>)17<br>)16<br>)14<br>)18<br>)18<br>)18<br>)16<br>)12<br>)16<br>)12<br>)18<br>)12<br>)18<br>)12<br>)18<br>)14<br>)11   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28<br>20-36   | ~36<br>NR<br>4<br>NR<br>4<br>0   | 1/30<br>0/97<br>0/20<br>1/30<br>0/61  | 5/32<br>2/28<br>5/20<br>8/30   |   | 0.19 (0.02, 1.70)  | 1.20   |
| u J         201          u XB         201           >engML         201           shen ML         201           Shen Q         201           Vang EJ         201           Vang HB         201           Yang HB         201           Yang HB         201           Yang HB         201           Yang L         201           'ao LF         201           'hang LJ         200           'hang LJ         200           'hang LJ         200  | )17<br>)16<br>)14<br>)16<br>)18a<br>)16<br>)12<br>)16<br>)12<br>)16<br>)12<br>)18<br>)14<br>)11  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 30<br>28-36<br>28<br>26<br>24-32<br>28-30<br>28<br>20-36   | NR<br>4<br>NR<br>4<br>0  | 0/97<br>0/20<br>1/30<br>0/61  | 2/28<br>5/20<br>8/30   |   | 0.05 (0.00 1.17)   | 0.00   |
| JU XB         201           VengML         201           Shen ML         201           Shen ML         201           Vang DM         201           Vang EJ         201           Vang HB         201           Vang HB         201           Gang HB         201           Gang HB         201           Yang VP         201           Yang VP         201           Yao ZC         201           Chang LJ         200           Theng JC         201   | )16<br>)14<br>)16<br>)18a<br>)16<br>)12<br>)16<br>)12<br>)18<br>)14<br>)11   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-36<br>28<br>26<br>24-32<br>28-30<br>28<br>20-36   | 4<br>NR<br>4<br>0  | 0/20<br>1/30<br>0/61  | 5/20<br>8/30   |   | 0.00,0.00, 1.1/)   | 0.02   |
| YengML         201           shen ML         201           sheng Q         201           Vang DM         200           Vang HB         201           Vang WP         201           Vang WP         201           Yang UZ         201           Yang UZ         201           Yang UZ         201           Yang LJ         202           Yhao DB         201  | )14<br>)16<br>)18a<br>)16<br>)12<br>)16<br>)12<br>)18<br>)14<br>)14<br>)11   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>26<br>24-32<br>28-30<br>28<br>20-36  | NH<br>4<br>0   | 1/30<br>0/61  | 8/30   |   | 0.07 (0.00, 1.34)  | 0.66   |
| inen ML         201           wang DM         201           vang EJ         201           vang HB         201           vang WP         201           ing Y         201           iao LF         201           hang ULJ         200           hang DJ         201           iao ZC         201           hang LJ         200           hang JC         201  | )16<br>)18a<br>)16<br>)12<br>)16<br>)12<br>)18<br>)14<br>)14<br>)11  | China<br>China<br>China<br>China<br>China<br>China<br>China   | 26<br>24-32<br>28-30<br>28<br>20-36  | 4  | 0/61  | 11/00  |   | 0.09 (0.01, 0.82)  | 1.27   |
| Wang QC         201           Vang EJ         201           Vang HB         201           Vang HB         201           ing Y         201           ao LF         201           ao ZC         201           hang LJ         200           hao DB         201  | )16a<br>)16<br>)12<br>)16<br>)12<br>)18<br>)14<br>)14<br>)11   | China<br>China<br>China<br>China<br>China<br>China  | 24-32<br>28-30<br>28<br>20-36  | 0  | 0/70  | 11/28  |   | 0.01 (0.00, 0.22)  | 0.71   |
| Jang EJ         201           Jang HB         201           Jang WP         201           ing Y         201           ao LF         201           hang LJ         202           hang LJ         200           hang LJ         200           hang LJ         200   | )12<br>)16<br>)12<br>)12<br>)18<br>)14<br>)11  | China<br>China<br>China<br>China<br>China   | 28-30<br>28<br>20-36   | 1.1.7  | 1/26  | Z/21<br>E/20   |   |  | 1 10   |
| Ang HB 201<br>Jang WP 201<br>ing Y 201<br>ao LF 201<br>ao ZC 201<br>hang LJ 200<br>hao DB 201<br>heng JC 201  | )16<br>)12<br>)18<br>)14<br>)11  | China<br>China<br>China<br>China  | 20-36  | 12   | 0/28  | 5/20   |   |  | 0.67   |
| Ang WP 201<br>ing Y 201<br>ao LF 201<br>ao ZC 201<br>hang LJ 200<br>hao DB 201<br>heng JC 201   | )12<br>)18<br>)14<br>)11   | China<br>China  | 20-00  |  | 0/100   | 2/20   |   | 0.07 (0.00, 1.37)  | 0.07   |
| ing Y 201<br>ao LF 201<br>ao ZC 201<br>hang LJ 200<br>hao DB 201<br>heng JC 201   | )18<br>)14<br>)11<br>)09   | China   | ~27.28   | 0  | 0/47  | 20/198   |   | 0.04(0.00, 0.00)   | 0.02   |
| ao LF 201<br>ao ZC 201<br>hang LJ 200<br>hao DB 201<br>heng JC 201  | )14<br>)11<br>)09  | O mila  | 28   | 4  | 0/30  | 7/30   |   | 0.05 (0.00, 0.95)  | 0.60   |
| ao ZC 201<br>hang LJ 200<br>hao DB 201<br>heng JC 201   | 011<br>009   | China   | 28-32  | 6  | 0/30  | 2/30   |   | 0.19 (0.01, 4.06)  | 0.63   |
| hang LJ 200<br>hao DB 201<br>heng JC 201  | 009  | China   | 28   | 4  | 0/28  | 4/30   | · · · · · · · · · · · · · · · · · · ·   | 0.10 (0.01 2.01)   | 0.64   |
| hao DB 201<br>heng JC 201   |  | China   | 28-32  | 4  | 0/30  | 4/30   |   | 0.10 (0.00. 1.88)  | 0.67   |
| heng JC 201   | 010  | China   | 28   | 4  | 1/30  | 3/30   |   | 0.31 (0.03. 3.17)  | 1.09   |
| -   | )18  | China   | 28   | 4  | 0/23  | 8/37   | + · · · · · · · · · · · · · · · · · · · | 0.07 (0.00, 1.35)  | 0.70   |
| hu LP 201   | 014  | China   | 28   | 4  | 0/30  | 3/30   | ★ + ★ + ★ + ★ + ★ + ★ + ★ + ★ + ★ + ★ + | 0.13 (0.01, 2.61)  | 0.65   |
| ue X 201  | )14  | China   | Anytime  | NR   | 0/31  | 0/30   | L                                       | (Excluded)   | 0.00   |
| ubtotal (I-squa   | ared =   | 0.0%, p =   | 0.848)   |  |   |  | $\Leftrightarrow$                       | 0.10 (0.07, 0.16)  | 29.2   |
| 30 participants   | s in bot   | th groups   |  |  |   |  | <u> </u>                                |  |  |
| hen CY 201  | )15  | China   | 1st Trimester  | NR   | 1/42  | 7/40   |   | 0.11 (0.01, 0.98)  | 1.27   |
| hen F 201   | 016  | China   | Pre-pregnancy  | NR   | 0/31  | 6/32   | ++                                      | 0.06 (0.00, 1.20)  | 0.69   |
| hen WJ 201  | 017  | China   | 28   | 0  | 4/79  | 16/44  |   | 0.09 (0.03, 0.30)  | 4.22   |
| hen ZX 201  | 017  | China   | 13-32  | NR   | 1/41  | 15/89  |   | 0.12 (0.02, 0.97)  | 1.38   |
| ui ZL 201   | 015  | China   | 28   | 4  | 1/50  | 13/46  |   | 0.05 (0.01, 0.42)  | 1.35   |
| eng Y 201   | )15  | China   | 24-36  | 4  | 0/82  | 4/75   | ·                                       | 0.10 (0.01, 1.82)  | 0.68   |
| ing XP 201  | 018  | China   | 28   | 4  | 0/38  | 4/38   | ·                                       | 0.10 (0.01, 1.92)  | 0.67   |
| an LY 201   | 013  | China   | 28   | 24   | 0/58  | 6/60   | •                                       | 0.07 (0.00, 1.30)  | 0.70   |
| eng XM 201  | 017  | China   | 28   | 4  | 1/36  | 7/36   |   | 0.12 (0.01, 1.02)  | 1.26   |
| u PX 201  | 016  | China   | 24-28  | 4  | 1/100   | 3/100  |   | 0.33 (0.03, 3.19)  | 1.10   |
| ao P201   | 016  | China   | 1st Trimester  | 0  | 1/51  | 9/51   |   | 0.09 (0.01, 0.77)  | 1.32   |
| uan ZF 201  | ) /<br>)1E   | China   | 24   |  | 0/123   | 14/122   |   |  | 0.70   |
| an GR 201   | 115  | China   | 20-32  | NR   | 0/358   | 8/80   |   | 0.01 (0.00, 0.23)  | 0.72   |
| 201   | 10   | China   | TSt Trimester  |  | 0/32  | 4/34   |   | 0.10 (0.01, 2.02)  | 0.0  |
| u WH 201  | 10   | China   | 20 22  | 20   | 0/40  | 0/100  |   | 0.07 (0.00, 1.30)  | 0.00   |
| VV 201  | 10   | China   | 20-32  | 4  | 3/65  | 12/65  |   | 0.23 (0.01, 4.81)  | 3.39   |
| ang S 201   | 117  | China   | 28   |  | 1/4/  | 15/44  |   | 0.04 (0.01, 0.36)  | 1 36   |
| ang XN 201  | 113  | China   | 26-30  | NR   | 1/65  | 8/51   |   | 0.08 (0.01, 0.00)  | 1 3  |
| SE 201  | 15   | China   | 28   | 24   | 0/60  | 6/60   |   | 0.07 (0.00, 1.26)  | 0.70   |
| ZY 201  | 118  | China   | 28   | NB   | 4/41  | 9/41   |   | 0.38 (0.11, 1.37)  | 3.6  |
| u CY 201  | 014  | China   | 28   | 4  | 1/34  | 8/34   |   | 0 10 (0 01, 0 84)  | 1.28   |
| u Y 201   | 016  | China   | 4-32   | 4  | 1/82  | 19/78  |   | 0.04 (0.00, 0.29)  | 1.4  |
| ou JJ 201   | 015  | China   | 28   | 4  | 0/125   | 3/58   | •                                       | 0.06 (0.00, 1.24)  | 0.66   |
| JQY 201   | 016  | China   | 28   | 0  | 2/152   | 12/132   |   | 0.13 (0.03, 0.61)  | 2.5  |
| an YC 201   | )17  | China   | 32   | 0  | 0/81  | 21/370   | · · · · · · · · · · · · · · · · · · ·   | 0.10 (0.01, 1.66)  | 0.74   |
| eng BA 201  | )12  | China   | 28   | 0  | 1/40  | 10/40  | •• I                                    | 0.08 (0.01, 0.63)  | 1.32   |
| iu B 201  | 016  | China   | <0 <b>-</b> 24   | 0  | 4/120   | 12/60  | ÷                                       | 0.14 (0.04, 0.45)  | 4.20   |
| en N 201  | 015  | China   | 28   | 24   | 2/46  | 11/46  |   | 0.14 (0.03, 0.70)  | 2.38   |
| heng Q 201  | )18b   | China   | 24-28  | 0  | 0/66  | 5/46   | •                                       | 0.06 (0.00, 1.05)  | 0.69   |
| hi QW 201   | 017  | China   | 24   | 0  | 3/100   | 12/100   |   | 0.23 (0.06, 0.83)  | 3.48   |
| un W 201  | 117  | China   | 12-28  | 12   | 0/123   | 12/65  |   | 0.02 (0.00, 0.30)  | 0.72   |
| un WH 201   | 115  | China   | 12-28  | 12   | 0/84  | 8/46   |   | 0.03 (0.00, 0.48)  | 0.7  |
| an J 201  | 19   | China   | 28   | U  | 0/41  | 6/59   |   | 0.10 (0.01, 1.81)  | 0.69   |
| an Z 201  | 10   | China   | <14-28   |  | 0/171   | 15/320   | - <u></u>                               | 0.06 (0.00, 0.97)  | 0.74   |
| an JH 201   | 10   | China   | Anyume   | NH<br>4  | 0/135   | 17/203   |   | 0.10 (0.01, 1./1)  | 0.7  |
| an nn 201<br>Iona B 201   | 10   | China   | 20   | 7  | 3/310   | 16/107   |   | 0.20 (0.06, 0.69)  | 3.8  |
| ang D 201   | 10   | China   | ∠0<br>12-14  | 4  | 0/110   | 6//0   |   | 0.05 (0.00, 0.79)  | 0.7  |
| ang⊓t 201<br>/ang l 201   | 10   | China   | 12-14<br>24-29   | 24<br>ND   | 1/220   | 0/40   |   | 0.07 (0.00, 1.21)  | 1.00   |
| ang J 201<br>Jang TD 201  | /1/<br>)15   | China   | 24-20  |  | 0/53  | 8/50   |   | 0.02 (0.00, 0.15)  | 0.7  |
| ang 10 201  | 115  | China   | 24-32  |  | 0/204   | 0/02<br>1//0F  |   | 0.03 (0.00, 0.87)  | 0.7  |
| a XH 201  | 117  | China   | 28   | 0 or 4   | 0/62  | 1/61   |   | 0.32 (0.00, 0.23)  | 0.7  |
| a PY 201  | 116  | China   | 28   | 4  | 1/60  | 4/60   |   | 0.02 (0.01, 0.00)  | 1 10   |
| ang HW 201  | 115  | China   | 28   | Ă  | 1/50  | 12/50  |   | 0.06 (0.01 0.52)   | 1.3  |
| hang (?) 201  | )15  | China   | 28   | 12   | 0/48  | 5/47   |   | 0.08 (0.00 1.42)   | 0.60   |
| hang BF 201   | 018  | China   | 24-28  | 0  | 0/36  | 15/75  |   | 0.05 (0.00 0 92)   | 0.73   |
| hang GH 201   | 018  | China   | 28   | 4  | 0/40  | 3/40   |   | 0.13 (0.01, 2.65)  | 0.6  |
| hang H 201  | 014  | China   | 28-30  | 4  | 0/257   | 10/352   |   | 0.06 (0.00. 1.09)  | 0.7  |
| hang Y 201  | 018  | China   | Pre-pregnancy  | NB   | 0/34  | 13/34  |   | 0.02 (0.00, 0.41)  | 0.71   |
| hang YF 201   | 10b  | China   | 28   | 4  | 1/60  | 16/60  | •                                       | 0.05 (0.01, 0.36)  | 1.30   |
| hao J 201   | 013  | China   | 20   | ò  | 0/41  | 23/202   |   | 0.09 (0.01, 1.55)  | 0.74   |
| hao Y 201   | 017  | China   | 12   | 12   | 0/40  | 5/40   |   | 0.08 (0.00 1 49)   | 0.64   |
| hou Y.I 201   | 014  | China   | 1st Trimester  | 0  | 1/53  | 6/34   | <u> </u>                                | 0.09 (0.01 0.78)   | 1.2  |
| hu J 201  | 017  | China   | 28   | ŏ  | 1/60  | 8/54   |   | 0.10 (0.01 0.81)   | 1.31   |
| ubtotal (I-squa   | ared =   | 0.0%. p =   | 0.999)   | -  |   | 0/04   | •                                       | 0.10 (0.08. 0.13)  | 70   |
|   |  | ·····   | ,  |  |   |  | j j                                     | 0.10 (0.00, 0.10)  |  |
| verall (I-square  | red = (  | 0.0%, p = 1   | 1.000)   |  |   |  | <b>Y</b>                                | 0.10 (0.08, 0.13)  | 100  |

#### Appendix R: Efficacy by maternal viral load criteria

- TDF 300 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)
  - The p-value for heterogeneity between subgroups was 0.161

| Author               | Year   | Country    | in weeks<br>gestation | in weeks<br>postpartum | Events,<br>Treatment | Events,<br>Control | OR (95% CI)       |
|----------------------|--------|------------|-----------------------|------------------------|----------------------|--------------------|-------------------|
| HBV DNA th           | reshol | d >=5.3, n | nean HBV I            | DNA reported           |                      | 1                  |                   |
| Celen MK             | 2013   | Turkey     | 18-27                 | 4                      | 0/21                 | 2/23               | 0.20 (0.01, 4.4   |
| Chen HL              | 2015   | Taiwan     | 30-32                 | 4                      | 1/65                 | 6/56               | 0.13 (0.02, 1.1   |
| Chen WJ              | 2017   | China      | 28                    | 0                      | 1/30                 | 16/44              | 0.06 (0.01, 0.4   |
| Greenup AJ           | 2014   | Australia  | 32                    | 12                     | 1/69                 | 2/10               | 0.06 (0.00, 0.7   |
| Hu MF                | 2018   | China      | <0-28                 | NR                     | 1/89                 | 3/30               | 0.10 (0.01, 1.0   |
| Lin Y                | 2018   | China      | 24                    | 4                      | 0/58                 | 4/52               | - 0.09 (0.00, 1.7 |
| Liu MH               | 2017   | China      | 28-30                 | 0                      | 1/20                 | 6/20 +             | 0.12 (0.01, 1.1   |
| Pan CQ               | 2016   | China      | 30-32                 | 4                      | 0/92                 | 6/88               | 0.07 (0.00, 1.2   |
| Wan JY               | 2017   | China      | 28                    | 0                      | 3/74                 | 7/42               | 0.21 (0.05, 0.8   |
| Xiao XH              | 2017   | China      | 28                    | 0 or 4                 | 0/60                 | 1/61               | 0.33 (0.01, 8.3   |
| Zhang BF             | 2018   | China      | 24-28                 | 0                      | 0/39                 | 15/75              | 0.05 (0.00, 0.8   |
| Zhou Y               | 2018   | China      | 24-28                 | 0                      | 0/60                 | 5/36               | 0.05 (0.00, 0.8   |
| Subtotal (I-         | square | d = 0.0%,  | p = 0.993)            |                        |                      | $\diamond$         | 0.11 (0.06, 0.2   |
|                      | rochol | d -5 2 on  | lor throch            | d or moon L            |                      | troported          |                   |
| Gong O               | 2017   | China      |                       |                        |                      |                    | 0 10 (0 01 1 0    |
|                      | 2017   | China      | 1-0                   |                        | 1/44                 | 17/25              | 0.12 (0.01, 1.0   |
|                      | 2010   | China      | 20                    |                        | 0/20                 | 2/20               | 0.37 (0.13, 0.8   |
|                      | 2017   | Theiland   | 24-28                 | 12                     | 0/20                 | 3/20               |                   |
| Jouruain G           | 2010   | Indianu    | 20-29                 | 0                      | 0/149                | 3/14/              | 0.14 (0.01, 2.7   |
|                      | 2010   | Chino      | 22-20                 | 4-0<br>ND              | 0/2                  | 2/3                | 0.12 (0.00, 4.0   |
| wang пр              | 2010   | China      | 20-30                 |                        | 0/100                | 4/20               | - 0.04 (0.00, 0.0 |
| ru Gr<br>Subtotol (L | 2010   |            | 24 n = 0.729)         | 4                      | 0/30                 | 4/30               |                   |
|                      | square | u = 0.0%,  | p = 0.738)            |                        |                      |                    | 0.23 (0.11, 0.4   |
| Overall (I-so        | quared | = 0.0%, p  | = 0.972)              |                        |                      | $\diamond$         | 0.16 (0.09, 0.2   |
|                      |        |            |                       |                        |                      |                    |                   |

• LAM 100-150 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)

| • The p-value for heterogeneity between subgroups was ( | ).781 |
|---|-------|
|---|-------|

| Author      | Year    | Country      | Tx<br>start in weeks<br>gestation | Tx end in<br>weeks postpartu | Events,<br>ımTreatme | Events,<br>nt Control |            |               | OR (95% CI)      |
|-------------|---------|--------------|-----------------------------------|------------------------------|----------------------|-----------------------|------------|---------------|------------------|
| HBV DNA     | thresho | d >=5.3. m   | ean HBV DNA repor                 | ted                          |                      |                       |            |               |                  |
| Cheng YC    | 2011    | China        | 32                                | 4                            | 8/30                 | 6/26                  | _          | <b></b>       | 1.21 (0.36, 4.10 |
| Feng HF     | 2007    | China        | 28                                | 4                            | 7/48                 | 16/42                 |            |               | 0 28 (0 10 0 77  |
| Ge YI       | 2015    | China        | 28-30                             | 12                           | 0/16                 | 3/22                  |            |               | 0 17 (0 01 3 51  |
| Greenun A   | .12014  | Australia    | 32                                | 2                            | 0/43                 | 2/10 -                |            |               |                  |
| Jackson V   | 2015    | Ireland      | 32                                | 0                            | 0/21                 | 1/6                   |            |               |                  |
| li VV       | 2015    | China        | 28                                | 4                            | 2/65                 | 12/65                 |            | _             | 0 14 (0 03 0 65  |
| Jiang HY    | 2013    | China        | 20-24                             | 4                            | 0/164                | 8/02                  |            |               | 0.03 (0.00, 0.05 |
| Ban CO      | 2012    | China        | 13-30                             | 4                            | 0/160                | 5/80                  |            | _             | 0.05 (0.00, 0.33 |
| Ren C L     | 2017    | China        | 28                                | 4                            | 2/67                 | 10/72                 |            |               | 0.10 (0.00, 0.00 |
| Tong V      | 2010    | China        | 20                                | 4                            | 0/17                 | 1/0/12                |            |               | 0 12 (0 01 2 50  |
|             | 2009    | China        | 22                                | 4                            | 11/110               | 4/24                  |            |               | 0.14 (0.07, 2.38 |
| Mang DM     | 2015    | China        | 20                                | 10                           | 1/40                 | 49/110<br>E/00        |            | _             | 0.07 (0.01, 0.28 |
| Wang Divi   | 2010    | China        | 20-30                             | 12                           | 1/42                 | 5/20                  |            | -             | J.07 (0.01, 0.00 |
| Wang EJ     | 2012    | China        | 28                                | 4                            | 1/32                 | 5/27                  |            | <u> </u>      | J.14 (0.02, 1.30 |
| Yang Hw     | 2014    | China        | 28                                | 4                            | 1/53                 | 4/53                  |            |               | J.24 (0.03, 2.18 |
| Zhang H     | 2014    | China        | 28-30                             | 4                            | 0/52                 | 10/352                |            |               | J.31 (0.02, 5.38 |
| Zhang YF    | 20108   | China        | 28                                | 4                            | 3/50                 | 16/50                 |            |               | J.14 (0.04, 0.50 |
| Znou DS     | 2013    | China        | 20-28                             | NR                           | 5/113                | 28/95                 |            |               | J.11 (0.04, 0.30 |
| Subtotal (I | -square | ea = 0.7%, p | ) = 0.445)                        |                              |                      |                       |            |               | J.17 (0.12, 0.25 |
| HBV DNA     | thresho | d <5.3 and   | /or threshold or mea              | n HBV DNA not r              | eported              |                       |            |               |                  |
| Bai XW      | 2011    | China        | 28                                | 4                            | 3/30                 | 8/25                  |            | -             | 0.24 (0.05, 1.02 |
| Chen QR     | 2018    | China        | 28                                | 4                            | 1/33                 | 5/28                  | *          |               | 0.14 (0.02, 1.31 |
| Chen SM     | 2017    | China        | 28                                | NR                           | 1/30                 | 10/30                 | · · · ·    | •             | 0.07 (0.01, 0.58 |
| Foaud HM    | 2019    | Egypt        | Anytime                           | NR                           | 0/29                 | 1/30                  |            |               | 0.33 (0.01, 8.52 |
| Guo YZ      | 2008    | China        | 28                                | 0                            | 3/70                 | 13/40                 |            |               | 0.09 (0.02, 0.35 |
| Han YP      | 2014    | China        | 28                                | 6                            | 1/30                 | 4/30                  |            |               | 0.22 (0.02, 2.14 |
| Han ZH      | 2005    | China        | 28                                | 0                            | 0/43                 | 5/35                  |            |               | 0.06 (0.00, 1.20 |
| He T        | 2018    | China        | 1st Trimester                     | NR                           | 0/29                 | 4/34                  |            |               | 0.11 (0.01, 2.23 |
| Li G        | 2006    | China        | 28                                | 0                            | 1/35                 | 7/32                  |            |               | 0.11 (0.01, 0.91 |
| Li JH       | 2017    | China        | 28                                | 4                            | 1/33                 | 8/27                  |            | -             | 0.07 (0.01, 0.64 |
| Li WF       | 2006    | China        | 24                                | 0                            | 1/36                 | 7/44                  |            |               | 0 15 (0 02, 1 29 |
| Li ZG       | 2015    | China        | 28                                | 6                            | 1/25                 | 4/25                  |            | <b>→</b> }→ , | 0.22 (0.02, 2.11 |
| Ma J        | 2006    | China        | Pre-pregnanc                      | WR                           | 0/18                 | 9/16                  |            |               | 0 02 (0 00, 0 41 |
| Ren YJ      | 2011    | China        | 28                                | 0                            | 1/30                 | 13/155                |            |               | 0 38 (0 05, 2 99 |
| Shen ML     | 2016    | China        | 26                                | 4                            | 0/60                 | 11/28 🗲               |            |               | 0.01 (0.00, 0.22 |
| Su TB       | 2009    | China        | 32                                | 0                            | 5/128                | 13/120                |            | H .           | 0.33 (0.12, 0.97 |
| Wakano Y    | 2018    | Japan        | 28-32                             | 4-8                          | 0/3                  | 2/3                   |            |               | 0.09 (0.00, 3.10 |
| Wang TM     | 2005    | China        | Pre-pregnanc                      | :v0                          | 0/32                 | 8/32                  |            | _             | 0.04 (0.00, 0.81 |
| Wang W      | 2014    | China        | 28                                | 4                            | 0/35                 | 2/28                  |            |               | 0.15 (0.01, 3.24 |
| Xu WM       | 2009    | China, Phi   | ippines0-34                       | 4                            | 3/49                 | 5/41                  |            |               | 0.47 (0.11, 2.10 |
| Yuan QF     | 2012    | China        | 27                                | 4                            | 1/32                 | 3/32                  |            |               | 0.31 (0.03, 3.17 |
| Zena YM     | 2013    | China        | 28                                | Variable (0.4.6)             | 0/90                 | 3/30 -                |            | <b></b>       | 0.04 (0.00, 0.87 |
| Zhu M       | 2014    | China        | 26                                | 0                            | 2/24                 | 9/24                  |            | -             | 0.15 (0.03, 0.80 |
| Subtotal (  | -square | ed = 0.0%, p | o = 0.885)                        | -                            |                      |                       | $\diamond$ |               | 0.16 (0.10, 0.24 |
| Overall (I- | square  | d = 0.0%, p  | = 0.830)                          |                              |                      |                       | <b>•</b>   |               | 0.17 (0.13, 0.22 |
|             |         |              |                                   |                              |                      |                       | i          | - <b> </b>    |                  |
|             |         |              |                                   |                              |                      | .001                  | .01 .1     | 1 10          |                  |
|             |         |              |                                   |                              |                      |                       |            | . 10          |                  |
|             |         |              |                                   |                              |                      |                       |            |               |                  |

- LdT 600 mg by maternal viral load criteria (Pre-specified viral load threshold of ≥5.3 log10 IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low (<5.3 log10 IU/ml) and/or HBV DNA level of participating women not reported)
  - The p-value for heterogeneity between subgroups was 0.546

| Author  | Veer   | Court   | start in weeks   | in weeks  | Events,   | Events,  |          | OB (050) - OF  |
|---|--|---|--|---|---|--|----------|--|
| Author  | Year   | Country   | gestation  | postpartum  | Treatment   | Control  |          | OR (95% CI)  |
| HBV DNA thresho   | old >=5.3, m   | nean HBV DNA  | reported   |   | 0.07  | 100  | 1        |  |
| Bal HL<br>Chen CY   | 2013   | China   | 28-32<br>1st Trimester   | 4<br>NB   | 1/42  | 4/30<br>7/40   |          | 0.11 (0.01, 2.0  |
| Chen F  | 2016   | China   | Pre-pregnancy  | NB  | 0/31  | 6/32   |          | 0.06 (0.00, 1.20   |
| Chen WJ   | 2017   | China   | 28   | 0   | 4/79  | 16/44  |          | 0.09 (0.03, 0.3)   |
| Chen ZX   | 2017   | China   | 13-32  | NB  | 1/41  | 15/89  |          | 0.12 (0.02, 0.9  |
| Cui ZL  | 2015   | China   | 28   | 4   | 1/50  | 13/46  |          | 0.05 (0.01, 0.4  |
| Deng Y  | 2015   | China   | 24-36  | 4   | 0/82  | 4/75   |          | 0.10 (0.01, 1.8  |
| Ding XP   | 2018   | China   | 28   | 4   | 0/38  | 4/38   |          | 0.10 (0.01, 1.9  |
| an LY   | 2013   | China   | 28   | 24  | 0/58  | 6/60   |          | 0.07 (0.00, 1.30   |
| eng XM  | 2017   | China   | 28   | 4   | 1/36  | 7/36   |          | 0.12 (0.01, 1.0  |
| Ge YL   | 2015   | China   | 28-30  | 12  | 0/20  | 3/22   |          | 0.14 (0.01, 2.8  |
| Guan ZF   | 2017   | China   | 24   | 12  | 0/123   | 14/122   |          | 0.03 (0.00, 0.5  |
| auo HJ  | 2011   | China   | 28   | 4   | 6/28  | 6/26   |          | 0.91 (0.25, 3.2)   |
| lan GR  | 2015   | China   | 20-32  | NR  | 0/358   | 8/86   |          | 0.01 (0.00, 0.2  |
| Huang HY  | 2016   | China   | 20-28  | 0   | 16/90   | 23/30  |          | 0.07 (0.02, 0.18   |
| 1 1 1   | 2015   | China   | 28   | 4   | 3/65  | 12/65  |          | 0.21 (0.06, 0.80   |
| .15F  | 2015   | China   | 28   | 24  | 0/60  | 6/60   |          | 0.07 (0.00, 1.20   |
|   | 2017   | China   | 20   | ~30   | 1/30  | 0/41   |          | 0.19 (0.02, 1.70   |
| in CV   | 2010   | China   | 20   | 1   | 4/41  | 9/41   |          | 0.36 (0.11, 1.3)   |
| lu Gr   | 2014   | China   | 20   | 4   | 0/07  | 0/04   |          | 0.10 (0.01, 0.0  |
| iu YB   | 2017   | China   | 30   | 4   | 0/90  | 5/20   |          | 0.03 (0.00, 1.1.   |
| iu V  | 2016   | China   | 4-32   | 4   | 1/82  | 19/78  |          | 0.07 (0.00, 1.0  |
| Pan YC  | 2017   | China   | 32   | -   | 0/81  | 21/370   |          | 0.10 (0.01, 1.23   |
| Peng BA   | 2012   | China   | 28   | ő   | 1/40  | 10/40  |          | 0.08 (0.01, 1.00   |
| Diu B   | 2016   | China   | <0-24  | ő   | 4/120   | 12/60  | I        | 0.14 (0.04 0.44  |
| Ren N   | 2015   | China   | 28   | 24  | 2/46  | 11/46  |          | 0.14 (0.03, 0.7  |
| Shena Q   | 2018b  | China   | 24-28  | 0   | 0/66  | 5/46   |          | 0.06 (0.00. 1 0  |
| Shi QW  | 2017   | China   | 24   | 0   | 3/100   | 12/100   |          | 0.23 (0.06. 0.8  |
| Sun W   | 2017   | China   | 12-28  | - 12  | 0/123   | 12/65  |          | 0.02 (0.00, 0.34   |
| Sun WH  | 2015   | China   | 12-28  | 12  | 0/84  | 8/46   |          | 0.03 (0.00, 0.44   |
| an Z  | 2016   | China   | <14-28   | NB  | 0/171   | 15/320   |          | 0.06 (0.00, 0.9)   |
| ian RH  | 2016   | China   | 28   | 4   | 3/318   | 17/374   |          | 0.20 (0.06, 0.6  |
| Wang B  | 2016   | China   | 28   | 4   | 0/110   | 16/187   |          | 0.05 (0.00. 0 7  |
| Vang DM   | 2016   | China   | 28-30  | 12  | 1/36  | 5/20   |          | 0.09 (0.01, 0.8  |
| Vang EJ   | 2012   | China   | 28   | 4   | 0/28  | 5/27   |          | 0.07 (0.00, 1.3)   |
| Vang HY   | 2018   | China   | 12-14  | 24  | 0/40  | 6/40   |          | 0.07 (0.00, 1.2  |
| Vang J  | 2017   | China   | 24-28  | NB  | 1/329   | 9/65   | -        | 0.02 (0.00, 0.1  |
| Vang TD   | 2015   | China   | 28   | 4   | 0/53  | 8/52   |          | 0.05 (0.00, 0.8  |
| VuQ   | 2015   | China   | 24-32  | 0 or 4  | 0/204   | 14/95  | _        | 0.01 (0.00, 0.2  |
| (iao XH   | 2017   | China   | 28   | 0 or 4  | 0/62  | 1/61   |          | 0.32 (0.01, 8.0  |
| rang HW   | 2015   | China   | 28   | 4   | 1/50  | 12/50  |          | 0.06 (0.01, 0.5  |
| /ao LF  | 2014   | China   | 28-32  | 6   | 0/30  | 2/30   |          | 0.19 (0.01, 4.00   |
| /ao ZC  | 2011   | China   | 28   | 4   | 0/28  | 4/30   |          | 0.10 (0.01, 2.0  |
| thang BF  | 2018   | China   | 24-28  | 0   | 0/36  | 15/75  |          | 0.05 (0.00, 0.9  |
| Ihang H   | 2014   | China   | 28-30  | 4   | 0/257   | 10/352   |          | 0.06 (0.00, 1.09   |
| Zhang LJ  | 2009   | China   | 28-32  | 4   | 0/30  | 4/30   |          | 0.10 (0.00, 1.88   |
| Ihang X   | 2015   | China   | 28   | 12  | 0/48  | 5/47   |          | 0.08 (0.00, 1.4  |
| Thang Y   | 2018   | China   | Pre-pregnancy  | NR  | 0/34  | 13/34  |          | 0.02 (0.00, 0.4  |
| Zhang YF  | 2010b  | China   | 28   | 4   | 1/60  | 16/60  |          | 0.05 (0.01, 0.3  |
| Zhao Y  | 2017   | China   | 12   | 12  | 0/40  | 5/40   |          | 0.08 (0.00, 1.49   |
| fue X<br>Subtotal (Lequar   | 2014   | China<br>n = 0.920)   | Anytime  | NR  | 0/31  | 0/30   | <u> </u> | (Excluded)   |
| subtotal (I-square  | eu = 0.0%,   | p = 0.920)  |  |   |   |  | Y        | 0.11 (0.08, 0.14   |
| HBV DNA thresho   | old <5.3 and   | i/or threshold o  | r mean HBV DNA not re  | eported   |   |  |          |  |
| Chen QH   | 2018   | China   | 28   | 4   | 0/29  | 5/28   |          | 0.07 (0.00, 1.38   |
| Chen SM   | 2017   | China   | 28   | NR  | 0/30  | 10/30  |          | 0.03 (0.00, 0.58   |
| -u PX   | 2016   | China   | 24-28  | 4   | 1/100   | 3/100  |          | 0.33 (0.03, 3.19   |
| aao P   | 2016   | China   | ist inmester   | U   | 1/51  | 9/51   |          | 0.09 (0.01, 0.7  |
| nan YP  | 2014   | China   | 28<br>4 at Trime   | 6   | 0/30  | 4/30   |          | 0.10 (0.00, 1.88   |
| 10 I  | 2018   | China   | ist inmester   | NH<br>00  | 0/32  | 4/34   | - T.     | 0.10 (0.01, 2.0  |
| nu WM   | 2016   | China   | 28<br>00.00  | 28  | 0/46  | 5/40   |          | 0.07 (0.00, 1.30   |
| iu t<br>Juona O   | 2010   | Ching   | 20-32  | 3-4   | 0/105   | 2/122  |          | 0.23 (0.01, 4.8  |
| iana S  | 2017   | Chine   | 24-20  | NB  | 1/44  | 15/44  |          | 0.04 (0.01, 2.5)   |
| manina 63   | 2013   | China   | 26-30  | NB  | 1/65  | 8/51   |          | 0.08 (0.01, 0.3  |
| iang XN   | 2010   | China   | 28   | 4   | 1/30  | 8/30   |          | 0.09 (0.01, 0.01   |
| iang XN<br>i CM   | 2012   | ormia.  | <0-28  | NB  | 1/65  | 9/25   |          | 0.03 (0.00, 0.00   |
| liang XN<br>li CM<br>li N   | 2017   | China   |  | 4   | 0/125   | 3/58   |          | 0.06 (0.00, 1.2  |
| liang XN<br>Li CM<br>Li N<br>Lou JJ   | 2017<br>2016<br>2015   | China<br>China  | 28   |   | 0.120   | 12/132   |          | 0.13 (0.03, 0.6  |
| liang XN<br>Li CM<br>Li N<br>Lou JJ<br>Lu QY  | 2017<br>2016<br>2015<br>2016   | China<br>China<br>China   | 28<br>28   | 0   | 2/152   | Charl Charles  |          | 0.00 (0.01, 0.0  |
| liang XN<br>Li CM<br>Li N<br>Lou JJ<br>Lu QY<br>PengMi  | 2017<br>2016<br>2015<br>2016<br>2014   | China<br>China<br>China<br>China  | 28<br>28<br>28   | 0<br>NB   | 2/152   | 8/30   |          | 11 I M 10 10 10 10 -   |
| iang XN<br>i CM<br>i N<br>ou JJ<br>u QY<br>?engML<br>Shen MI  | 2017<br>2016<br>2015<br>2016<br>2014<br>2016   | China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>26   | 0<br>NR<br>4  | 2/152<br>1/30<br>0/61   | 8/30<br>11/28  |          | 0.09 (0.01, 0.8  |
| iang XN<br>i CM<br>i N<br>ou JJ<br>u QY<br>YengML<br>Shen ML<br>Shen Q  | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a  | China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>26<br>24-32  | 0<br>NR<br>4<br>0   | 2/152<br>1/30<br>0/61<br>0/79   | 8/30<br>11/28  |          | 0.01 (0.00, 0.2  |
| iang XN<br>i CM<br>i N<br>ou JJ<br>u QY<br>PengML<br>Shen ML<br>Sheng Q<br>an J   | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a<br>2018a<br>2019   | China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>26<br>24-32<br>28  | 0<br>NR<br>4<br>0   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41   | 8/30<br>11/28<br>2/21<br>6/59  |          | 0.01 (0.00, 0.22   |
| iang XN<br>i CM<br>i N<br>ou JJ<br>v QY<br>PengML<br>Sheng Q<br>ian J<br>ian JH   | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a<br>2019<br>2018  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anvtime   | NR<br>4<br>0<br>0<br>NR   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135  | 8/30<br>11/28<br>2/21<br>6/59<br>7/203   |          | 0.09 (0.01, 0.8<br>0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7  |
| iang XN<br>i CM<br>i N<br>ou JJ<br>u QY<br>Shen ML<br>Shen ML<br>Sheng Q<br>ian J<br>ian JH<br>Vang HB  | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a<br>2019<br>2018<br>2018<br>2016  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36  | 0<br>NR<br>4<br>0<br>0<br>NR<br>NR  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20   |          | 0.09 (0.01, 0.0<br>0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8   |
| iang XN<br>i CM<br>i N<br>ou JJ<br>u QY<br>PengML<br>Shen ML<br>Sheng Q<br>an J<br>Tan JH<br>Vang HB<br>Vang HB   | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a<br>2019<br>2018<br>2018<br>2016<br>2012  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br><27-28  | 0<br>NR<br>4<br>0<br>0<br>NR<br>NR<br>0   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198   |          | 0.09 (0.01, 0.0<br>0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.09 (0.01, 1.5  |
| aing XN<br>i CM<br>i N<br>ou JJ<br>yengML<br>yengML<br>yeng Q<br>an J<br>ian JH<br>Vang HB<br>Vang WP<br>iie PY   | 2017<br>2016<br>2015<br>2016<br>2014<br>2016<br>2018a<br>2019<br>2018<br>2018<br>2016<br>2012<br>2012<br>2016  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br><27-28<br>28  | NR<br>4<br>0<br>NR<br>NR<br>0<br>4  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60   |          | 0.09 (0.01, 0.02<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.15   |
| liang XN<br>i CM<br>cou JJ<br>.u QY<br>PengML<br>Shen ML<br>Shen Q<br>Tan J<br>Tan JH<br>Wang HB<br>Wang WP<br>Kie PY<br>Kie PY   | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2018<br>2018<br>2018<br>2018<br>2016<br>2012<br>2016<br>2012<br>2016<br>2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br><27-28<br>28<br>28  | ,<br>NR<br>4<br>0<br>NR<br>NR<br>0<br>4   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/30   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30   |          | 0.09 (0.01, 0.02<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.80<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.1)<br>0.05 (0.00, 0.9)  |
| liang XN<br>Li CM<br>Li CM<br>Li N<br>Lu QY<br>YengML<br>Shen ML<br>Shen ML<br>Sheng Q<br>Tan JH<br>Wang HB<br>Wang HB<br>Wang WP<br>King Y<br>Thang GH   | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2019<br>2018<br>2019<br>2018<br>2016<br>2012<br>2016<br>2012<br>2016<br>2012   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br>27-28<br>28<br>28<br>28   | ,<br>NR<br>4<br>0<br>0<br>NR<br>NR<br>0<br>4<br>4<br>4  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/30<br>0/40   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30<br>3/40   |          | 0.01 (0.00, 0.22<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.80<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.19<br>0.05 (0.00, 0.99<br>0.13 (0.01, 2.68  |
| liang XN<br>i CM<br>i CM<br>cou JJ<br>cou J<br>cou J  | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2018<br>2018<br>2018<br>2016<br>2012<br>2016<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>24-32<br>20-36<br><27-28<br>28<br>28<br>28<br>28<br>28   | ,<br>NR<br>4<br>0<br>0<br>NR<br>NR<br>4<br>4<br>4<br>4  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/47<br>1/60<br>0/30<br>0/40<br>1/30                                 | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30<br>3/30   |          | 0.01 (0.00, 0.22<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.86<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.19<br>0.05 (0.00, 0.99<br>0.13 (0.01, 2.66<br>0.31 (0.03, 3.1   |
| liang XN<br>i CM<br>i CM<br>i N<br>Lou JJ<br>Ju QY<br>PengML<br>Sheng Q<br>Tan J<br>Tan JH<br>Wang HB<br>Wang HB<br>Wang WP<br>Kie PY<br>King Y<br>Zhang GH<br>Zhao JB<br>Zhao JB   | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2016<br>2012<br>2016<br>2018<br>2018<br>2018<br>2010<br>2010<br>2010<br>2010   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br>20-36<br><27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28           28<br>28<br>28<br>28<br>28      | 0<br>NR<br>4<br>0<br>NR<br>NR<br>0<br>4<br>4<br>4<br>4  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/30<br>0/40<br>1/30<br>0/41   | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30<br>3/40<br>3/40<br>3/30<br>23/202   |          | 0.05 (0.01, 0.02<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.86<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.15<br>0.05 (0.00, 0.96<br>0.13 (0.01, 2.66<br>0.31 (0.03, 3.13<br>0.09 (0.1, 1.55   |
| iang XN<br>i GM<br>i OM<br>i N<br>ou JJ<br>u QY<br>PengML<br>shen ML<br>shen ML<br>ian J<br>ian JH<br>Vang HB<br>Vang HB<br>Vang WP<br>tie PY<br>ting Y<br>than DB<br>than DB<br>than J<br>then OL  | 2016<br>2015<br>2015<br>2017<br>2018<br>2014<br>2018<br>2019<br>2018<br>2019<br>2018<br>2016<br>2012<br>2018<br>2018<br>2018<br>2018<br>2010<br>2013   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>20-36<br><27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2                                  | 0<br>NR<br>4<br>0<br>0<br>NR<br>NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>0  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/30<br>0/40<br>1/30<br>0/40<br>1/30<br>0/41<br>0/23                 | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30<br>3/30<br>23/202<br>8/37   |          | 0.05 (0.00, 0.22<br>0.05 (0.00, 1.04<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.84<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.1<br>0.05 (0.00, 0.94<br>0.13 (0.01, 2.64<br>0.31 (0.03, 3.1<br>0.09 (0.01, 1.55  |
| liang XN<br>i CM<br>i CM<br>i N<br>i N<br>i N<br>vang HL<br>ian JH<br>Vang HB<br>Vang HB<br>Vang WP<br>Kie PY<br>King Y<br>2hang GH<br>2hao DB<br>2hao J<br>2hao J<br>2h  | 2017<br>2016<br>2015<br>2017<br>2016<br>2014<br>2018<br>2018<br>2018<br>2018<br>2018<br>2016<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>26<br>24-32<br>28<br>4nytime<br>20-36<br><27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>20<br>28                                  | 0<br>NR<br>0<br>0<br>NR<br>NR<br>4<br>4<br>4<br>4<br>4<br>0<br>0<br>4   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/30<br>0/40<br>1/30<br>0/41<br>0/23<br>1/53                         | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>2/30<br>2/20<br>2/30<br>2/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/3/20<br>2/ |          | 0.01 (0.00, 0.22<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.84<br>0.09 (0.01, 1.5<br>0.24 (0.03, 2.1<br>0.05 (0.00, 0.94<br>0.13 (0.01, 2.6<br>0.31 (0.03, 3.1<br>0.09 (0.01, 1.53<br>0.07 (0.00, 1.33<br>0.09 (0.01, 0.7)   |
| liang XN<br>Li CM<br>Li N<br>Li N<br>Vang ML<br>Vang ML<br>Vang ML<br>Vang ML<br>Vang HB<br>Vang HB<br>Vang WP<br>Vang HB<br>Vang WP<br>Vang HB<br>Vang GH<br>Chao DB<br>Chao DB<br>Chao DB<br>Chao DB<br>Chao JC<br>Chou YJ<br>Chu J   | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2019<br>2018<br>2019<br>2018<br>2016<br>2012<br>2016<br>2012<br>2016<br>2018<br>2018<br>2010<br>2013<br>2010<br>2013<br>2018<br>2014   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>24-32<br>28<br>Anytime<br>20-36<br><<27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>20<br>28<br>151 Trimester<br>28          | 0<br>NR<br>0<br>0<br>NR<br>NR<br>4<br>4<br>4<br>4<br>4<br>0<br>4<br>0   | 2/152<br>1/30<br>0/61<br>0/13<br>0/135<br>0/140<br>0/47<br>1/60<br>0/47<br>1/60<br>0/40<br>1/30<br>0/40<br>1/30<br>0/41<br>0/23<br>1/53<br>1/53 | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>2/198<br>4/60<br>7/30<br>3/40<br>3/40<br>3/30<br>23/202<br>8/37<br>6/34<br>8/54  |          | 0.01 (0.00, 0.2<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.9 (0.01, 1.5<br>0.24 (0.03, 2.1)<br>0.05 (0.00, 0.9<br>0.13 (0.01, 2.6<br>0.09 (0.01, 1.5<br>0.09 (0.01, 1.5<br>0.09 (0.01, 1.5<br>0.09 (0.01, 1.5)  |
| liang XN<br>i CM<br>i N<br>i N<br>i N<br>vou JJ<br>vou JJ<br>vou JJ<br>vou JJ<br>vou AJ<br>vou AJ<br>shen ML<br>sheng Q<br>ran J<br>H<br>Wang HB<br>Wang HB<br>Wang HB<br>Wang WP<br>tio PY<br>tio Py   | 2016<br>2016<br>2015<br>2016<br>2014<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26<br>24-32<br>28<br>Anytime<br>20-36<br>-27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2                 | 0<br>NR<br>4<br>0<br>0<br>NR<br>NR<br>NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>0<br>4<br>0<br>0<br>4<br>4<br>4<br>4<br>4<br>4 | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/40<br>0/47<br>1/60<br>0/30<br>0/40<br>1/30<br>0/41<br>0/23<br>1/53<br>1/60<br>0/30          | 8/30<br>11/28 ← 2/21 − 2<br>6/59 − 7/203 − 2/20<br>2/20 − 2/20<br>2/20 − 2/20<br>2/3/30 − 2/3/20<br>2/3/20 − 2/3/20<br>8/37<br>6/34<br>8/54<br>3/30  |          | 0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.09 (0.01, 1.7<br>0.4 (0.00, 0.8<br>0.9 (0.01, 1.5<br>0.4 (0.03, 2.15<br>0.05 (0.00, 0.9<br>0.13 (0.01, 2.6<br>0.07 (0.00, 1.3<br>0.09 (0.01, 0.7<br>0.10 (0.01, 0.7)  |
| lang XN<br>I CM<br>U M<br>Lo U<br>V U<br>VangML<br>Jihen Q<br>VangML<br>Jihen Q<br>Vang WP<br>Vang WP<br>Vang WP<br>Vang WP<br>Vang WP<br>Jihen Q<br>Vang WP<br>Vang WP<br>Jihen Q<br>Vang WP<br>Vang WP<br>Vang W<br>Vang WP<br>Vang W<br>Vang V<br>Vang Vang Vang Vang Vang Vang Vang Vang  | 2017<br>2016<br>2015<br>2016<br>2017<br>2018<br>2018<br>2018<br>2019<br>2018<br>2019<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2018<br>2013<br>2013<br>2014<br>2014<br>2014   | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>24-32<br>28<br>Anytime<br>20-36<br>27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2                  | 0<br>NR<br>4<br>0<br>NR<br>0<br>4<br>4<br>4<br>4<br>4<br>0<br>4<br>0<br>4<br>0<br>4   | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/47<br>1/60<br>0/40<br>1/30<br>0/40<br>1/30<br>0/41<br>0/23<br>1/63<br>1/60<br>0/30          | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>2/30<br>4/60<br>4/60<br>4/60<br>4/60<br>4/60<br>4/60<br>4/60<br>4/6  |          | 0.01 (0.00, 0.2<br>0.05 (0.00, 1.00<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.09 (0.01, 1.5<br>0.05 (0.00, 0.9<br>0.13 (0.01, 2.6<br>0.31 (0.01, 2.6<br>0.31 (0.01, 2.6<br>0.31 (0.01, 0.7<br>0.09 (0.01, 1.5<br>0.09 (0.01, 0.7<br>0.10 (0.01, 0.8<br>0.13 (0.01, 2.6<br>0.9<br>0.13 (0.01, 2.6<br>0.9<br>0.13 (0.01, 2.6<br>0.9<br>0.13 (0.01, 2.6<br>0.9<br>0.00, 0.0<br>0.10 (0.01, 0.7<br>0.10 (0.01, 0.8<br>0.13 (0.01, 2.6<br>0.9<br>0.00, 0.0<br>0.00 (0.01, 0.7<br>0.00, 0.0<br>0.0<br>0.00 (0.01, 0.7<br>0.00, 0.0<br>0.0<br>0.0<br>0.0<br>0.0<br>0.0<br>0.0<br>0.0<br>0.0<br>0.0   |
| iang XN<br>i CM<br>i CM<br>u JJ<br>u JV<br>vang ML<br>ihen ML<br>iheng Q<br>an J<br>ian JH<br>vang MP<br>iang Y<br>vang HB<br>vang WP<br>ig PY<br>vang H<br>hang GH<br>han DB<br>han DB<br>hang CH<br>han DB<br>hang CH<br>han DB<br>hang CH<br>hang  | 2017<br>2016<br>2015<br>2016<br>2014<br>2014<br>2016<br>2018<br>2019<br>2018<br>2016<br>2018<br>2016<br>2018<br>2016<br>2018<br>2010<br>2018<br>2010<br>2013<br>2018<br>2010<br>2013<br>2016<br>2016<br>2016<br>2016<br>2016<br>2016<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2016<br>2016<br>2016<br>2018<br>2019<br>2018<br>2019<br>2018<br>2019<br>2019<br>2019<br>2019<br>2019<br>2019<br>2019<br>2019 | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>20-36<br>20-36<br>20-36<br>20-36<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28 | 0<br>NR<br>0<br>NR<br>0<br>4<br>4<br>4<br>4<br>4<br>0<br>4<br>4<br>0<br>0<br>4  | 2/152<br>1/30<br>0/61<br>0/79<br>0/41<br>0/135<br>0/100<br>0/47<br>1/60<br>0/40<br>1/30<br>0/40<br>1/30<br>0/44<br>0/23<br>1/53<br>1/60<br>0/30 | 8/30<br>11/28<br>2/21<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>2/20<br>3/40<br>3/40<br>3/40<br>3/40<br>22/202<br>8/202<br>6/34<br>8/37<br>6/34<br>3/30   |          | 0.01 (0.00, 0.2<br>0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.04 (0.00, 0.8<br>0.09 (0.01, 1.5<br>0.04 (0.00, 0.8<br>0.01, 1.5<br>0.05 (0.00, 0.9<br>0.13 (0.01, 2.6<br>0.01 (0.01, 0.7<br>0.01 (0.01, 0.8<br>0.13 (0.01, 0.8<br>0.01 (0.01, 0.8<br>0.13 (0.01, 0.8<br>0.13 (0.01, 0.8<br>0.13 (0.01, 0.8) (0.01, |
| lang XN<br>i GM<br>i GM<br>u GM<br>u GV<br>vengML<br>shen ML<br>u GM<br>shen ML<br>sheng Q<br>an J<br>lan JH<br>Wang HB<br>dan J<br>than JH<br>Wang HB<br>dan J<br>than GH<br>than DB<br>than J<br>than DB<br>than J<br>than DB<br>than J<br>than S<br>than J<br>than S<br>than J<br>than S<br>than | 2017<br>2016<br>2015<br>2016<br>2014<br>2018<br>2019<br>2019<br>2019<br>2019<br>2010<br>2010<br>2010<br>2010   | $ \begin{array}{l} {\rm China} \\ {\rm China} $   | 28<br>28<br>28<br>26<br>28<br>44-32<br>29<br>29<br>20-36<br>27-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2           | 0<br>NR<br>0<br>0<br>NR<br>NR<br>0<br>4<br>4<br>4<br>4<br>4<br>0<br>4<br>4<br>0<br>4<br>0<br>0<br>4                                     | 2/152<br>1/30<br>0/F1<br>0/79<br>0/41<br>0/135<br>0/147<br>1/60<br>0/47<br>1/60<br>0/47<br>1/30<br>0/41<br>1/30<br>0/41<br>1/23<br>1/60<br>0/30 | 8/30<br>11/28<br>2/21<br>6/59<br>7/203<br>2/20<br>20/198<br>4/60<br>7/30<br>3/40<br>3/40<br>3/40<br>3/40<br>3/40<br>3/40<br>3/40<br>3  |          | 0.01 (0.00, 0.2<br>0.01 (0.00, 0.2<br>0.05 (0.00, 1.0<br>0.10 (0.01, 1.8<br>0.10 (0.01, 1.7<br>0.4 (0.00, 0.8<br>0.09 (0.01, 1.5<br>0.24 (0.00, 0.8<br>0.03 (0.01, 0.5<br>0.31 (0.03, 3.1<br>0.09 (0.01, 0.5<br>0.07 (0.00, 1.3<br>0.07 (0.00, 1.3<br>0.09 (0.01, 0.7<br>0.10 (0.01, 0.8<br>0.13 (0.01, 26<br>0.09 (0.05, 0.1<br>0.10 (0.08, 0.1)  |

Appendix S: Viral load prior to treatment and prior to delivery in studies comparing second versus third trimester PAP initiation

- Standardized mean difference (SMD) of viral load AT START OF TREATMENT comparing participants starting PAP in the second ("experimental/treatment") versus third trimester ("control")
  - 7/9 studies contributing (appropriate measures not provided by Liu Y, 2016 or Han GR 2015), SMD=0.01 (95%CI: -0.16-0.19) p=0.874

|              |         |                 |             |         |        |           |          |         |                     | Mean   | SD     | Mean   | SD     |
|--------------|---------|-----------------|-------------|---------|--------|-----------|----------|---------|---------------------|--------|--------|--------|--------|
|              |         | Early           | Late        |         |        |           |          |         |                     | HBV    | HBV    | HBV    | HBV    |
| Author       | Year    | start time      | start time  |         |        |           |          |         | SMD (95% CI)        | DNA 2T | DNA 2T | DNA 3T | DNA 3T |
|              |         |                 |             |         |        |           |          |         |                     |        |        |        |        |
| Hu MF        | 2018    | 14 weeks        | 28 weeks    |         | -      |           |          |         | 0.22 (-0.29, 0.73)  | 7.5    | 0.66   | 7.38   | 0.39   |
| Huang HY     | 2016    | 20 weeks        | 28 weeks    |         |        |           | •        |         | 0.05 (-0.45, 0.56)  | 7.29   | 0.54   | 7.26   | 0.57   |
| Pan CQ       | 2017    | 13-26 weeks     | 28-30 weeks | 6       |        |           |          |         | -0.07 (-0.38, 0.25) | 6.52   | 0.61   | 6.56   | 0.55   |
| Wang HB      | 2016    | 20 weeks        | 28 weeks    |         |        | -         |          | -       | -0.16 (-0.78, 0.46) | 6.99   | 1.05   | 7.18   | 1.31   |
| Wang HB      | 2018    | 20 weeks        | 28 weeks    |         |        | *         |          |         | -0.20 (-0.82, 0.42) | 7.01   | 1.01   | 7.23   | 1.15   |
| Wang WP      | 2012    | <27 weeks       | 28 weeks    |         |        | -         |          |         | -0.04 (-0.61, 0.54) | 6.71   | 1.00   | 6.75   | 1.22   |
| Zhou DS      | 2013    | 20 weeks        | 28 weeks    |         |        |           |          | _       | 0.16 (-0.21, 0.53)  | 6.82   | 0.23   | 6.73   | 0.72   |
| Overall (I-s | squared | d = 0.0%, p = 0 | .888)       |         |        | $\langle$ | >        |         | 0.01 (-0.16, 0.19)  |        |        |        |        |
|              |         |                 |             |         |        |           |          |         |                     |        |        |        |        |
|              |         |                 | -           | 1<br>•1 | і<br>5 | 10        | ।<br>⊨.1 | I<br>.5 | 1                   |        |        |        |        |

- Standardized mean difference (SMD) of viral load AT TIME OF DELIVERY comparing participants starting PAP in the second ("experimental/treatment") versus third trimester ("control")
  - 7/9 studies contributing (not Liu Y, 2016 or Zhou DS 2013), SMD= -0.62 (95%CI: -0.77- -0.46) p<0.001

|             |        |              |                      |             |    |         |      |        |                      | Mean   | SD     | Mean   | SD     |
|-------------|--------|--------------|----------------------|-------------|----|---------|------|--------|----------------------|--------|--------|--------|--------|
|             |        | Treatment    | Early                | Late        |    |         |      |        |                      | HBV    | HBV    | HBV    | HBV    |
| Author      | Year   | type         | start time           | start time  |    |         |      |        | SMD (95% CI)         | DNA 2T | DNA 2T | DNA 3T | DNA 3T |
|             |        |              |                      |             |    |         |      |        |                      |        |        |        |        |
| Han GR      | 2015   | LDT 600      | 20-27 weeks          | 28-32 weeks |    |         | -    |        | -0.46 (-0.69, -0.23) | 1.80   | 1.80   | 2.60   | 1.60   |
| Hu MF       | 2018   | TDF 300      | 14 weeks             | 28 weeks    |    |         |      | _      | -0.10 (-0.60, 0.41)  | 5.55   | 1.19   | 5.67   | 1.25   |
| Huang HY    | 2016   | LDT 600      | 20 weeks             | 28 weeks    |    | _       |      |        | -2.84 (-3.57, -2.12) | 2.43   | 0.32   | 3.54   | 0.45   |
| Pan CQ      | 2017   | LAM 100      | 13 <b>-</b> 26 weeks | 28-30 weeks |    |         | -    |        | -0.59 (-0.91, -0.27) | 3.42   | 1.02   | 3.98   | 0.90   |
| Wang HB     | 2018   | TDF 300      | 20 weeks             | 28 weeks    |    | _       |      |        | -0.84 (-1.49, -0.19) | 2.22   | 0.36   | 2.63   | 0.59   |
| Wang HB     | 2016   | LDT 600      | 20 weeks             | 28 weeks    |    |         |      |        | -1.00 (-1.66, -0.34) | 2.63   | 0.70   | 3.41   | 0.85   |
| Wang WP     | 2012   | LDT 600      | <27 weeks            | 28 weeks    |    |         |      |        | -0.45 (-1.03, 0.13)  | 2.54   | 0.83   | 2.92   | 0.83   |
| Overall (I- | square | d = 86.4%, p | = 0.000)             |             |    |         |      |        | -0.62 (-0.77, -0.46) |        |        |        |        |
|             |        |              |                      |             |    |         |      |        |                      |        |        |        |        |
|             |        |              |                      |             |    |         |      |        |                      |        |        |        |        |
|             |        |              |                      | 1<br>-4     | -3 | ו<br>-2 | -1 0 | 1<br>1 |                      |        |        |        |        |

# **Appendix T: Maternal safety 1. Fetal deaths**

#### • TDF 300 mg risk difference for fetal death

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0%
  I<sup>2</sup> statistic RCTs = 0%
  I<sup>2</sup> statistic non-RCTs = 0%

| Author         | Year      | Country           | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |         |               |              | RD (95% CI)         | Events,<br>Treatment | Events,<br>Control |
|----------------|-----------|-------------------|-----------------------------------|----------------------------------|---------|---------------|--------------|---------------------|----------------------|--------------------|
| Randomised     | controlle | d tria <b>l</b> s |                                   |                                  |         |               |              |                     |                      |                    |
| Jourdain G     | 2018      | Thailand          | 26-29                             | 8                                |         | -             |              | 0.01 (-0.01, 0.02)  | 1/162                | 0/160              |
| Lin Y          | 2018      | China             | 24                                | 4                                |         |               |              | 0.02 (-0.03, 0.06)  | 1/60                 | 0/52               |
| Liu MH         | 2017      | China             | 28-30                             | 0                                |         | <u> </u>      |              | 0.00 (-0.09, 0.09)  | 0/20                 | 0/20               |
| Pan CQ         | 2016      | China             | 30-32                             | 4                                |         |               |              | 0.01 (-0.02, 0.04)  | 1/97                 | 0/100              |
| Yu CY          | 2018      | China             | 24                                | 4                                |         |               |              | 0.00 (-0.06, 0.06)  | 0/30                 | 0/30               |
| Subtotal (I-so | uared =   | 0.0%, p = 0       | .990)                             |                                  |         | •             |              | 0.01 (-0.01, 0.02)  | 3/369                | 0/362              |
| Non-randomis   | sed cont  | rolled trials     |                                   |                                  |         |               |              |                     |                      |                    |
| Celen MK       | 2013      | Turkey            | 18-27                             | 4                                |         |               |              | -0.04 (-0.15, 0.07) | 0/21                 | 1/24               |
| Chen HL        | 2015      | Taiwan            | 30-32                             | 4                                |         | <del>~~</del> |              | 0.00 (-0.03, 0.03)  | 0/62                 | 0/56               |
| Chen WJ        | 2017      | China             | 28                                | 0                                |         |               |              | 0.00 (-0.05, 0.05)  | 0/30                 | 0/44               |
| Gong Q         | 2017      | China             | 1-6                               | NR                               |         |               |              | 0.00 (-0.04, 0.04)  | 0/44                 | 0/44               |
| Greenup AJ     | 2014      | Australia         | 32                                | 12                               |         | - <del></del> | ,            | 0.00 (-0.07, 0.07)  | 0/58                 | 0/20               |
| He LL          | 2018      | China             | 28                                | NR                               |         | _             |              | 0.00 (-0.05, 0.05)  | 0/50                 | 0/35               |
| Hu MF          | 2018      | China             | <0-28                             | NR                               |         | <b>_</b>      |              | 0.00 (-0.05, 0.05)  | 0/90                 | 0/30               |
| Huang Q        | 2017      | China             | 24-28                             | 12                               |         |               | -            | 0.00 (-0.08, 0.08)  | 0/20                 | 0/30               |
| Wakano Y       | 2018      | Japan             | 22-28                             | 4-8                              | ←       |               |              | 0.00 (-0.53, 0.53)  | 0/2                  | 0/3                |
| Wan JY         | 2017      | China             | 28                                | 0                                |         |               |              | 0.00 (-0.04, 0.04)  | 0/74                 | 0/42               |
| Wang HB        | 2018      | China             | 20-36                             | NR                               |         | -             |              | 0.00 (-0.07, 0.07)  | 0/100                | 0/20               |
| Xiao XH        | 2017      | China             | 28                                | 0 or 4                           |         |               |              | 0.00 (-0.03, 0.03)  | 0/60                 | 0/60               |
| Zhang BF       | 2018      | China             | 24-28                             | 0                                |         |               |              | 0.00 (-0.04, 0.04)  | 0/39                 | 0/75               |
| Zhou Y         | 2018      | China             | 24-28                             | 0                                |         |               |              | 0.00 (-0.04, 0.04)  | 0/60                 | 0/36               |
| Subtotal (I-so | uared =   | 0.0%, p = 1       | .000)                             |                                  |         | •             |              | -0.00 (-0.01, 0.01) | 0/710                | 1/519              |
| Overall (I-squ | uared = ( | 0.0%, p = 1.0     | 000)                              |                                  |         |               |              | 0.00 (-0.01, 0.01)  | 3/1079               | 1/881              |
|                |           |                   |                                   |                                  | .3 .2 . | I Î<br>1 0    | I I<br>.1 .2 | 3                   |                      |                    |

# • LAM 100-150 mg risk difference for fetal death

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

|                  | Year             | Country            | gestation     | weeks postpartum | RD (95% CI)          | Events,<br>Treatment | Events<br>Contro |
|------------------|------------------|--------------------|---------------|------------------|----------------------|----------------------|------------------|
| landomised       | controlle        | ed trials          |               |                  | 1                    |                      |                  |
| ai XW            | 2011             | China              | 28            | 4 –              | 0.00 (-0.07, 0.07)   | 0/30                 | 0/25             |
| hen SM           | 2017             | China              | 28            | NR -             | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30             |
| iuo YZ           | 2008             | China              | 28            | 0                | 0.00 (-0.04, 0.04)   | 0/70                 | 0/40             |
| I YY             | 2015             | China              | 28            | 4                | ➡ 0.00 (-0.03, 0.03) | 0/65                 | 0/65             |
| i ZG             | 2015             | China              | 28            | 6 –              | 0.00 (-0.07, 0.07)   | 0/25                 | 0/25             |
| ian XQ           | 2015             | China              | 28            | 0                | ➡ 0.00 (-0.02, 0.02) | 0/110                | 0/110            |
| u WM             | 2009             | China, Philippines | 30-34         | 4                | 0.01 (-0.02, 0.05)   | 1/89                 | 0/61             |
| ang HW           | 2014             | China              | 28            | 4                | 0.00 (-0.04, 0.04)   | 0/53                 | 0/53             |
| ubtotal (I-so    | quared =         | = 0.0%, p = 1.000) |               |                  | 0.00 (-0.01, 0.01)   | 1/472                | 0/409            |
| lon-randomi:     | sed con          | trolled trials     |               |                  |                      |                      |                  |
| hen QR           | 2018             | China              | 28            | 4 –              | 0.00 (-0.06, 0.06)   | 0/33                 | 0/28             |
| heng YC          | 2011             | China              | 32            | 4                | 0.00 (-0.07, 0.07)   | 0/30                 | 0/26             |
| eng HF           | 2007             | China              | 28            | 4                | 0.00 (-0.04, 0.04)   | 0/48                 | 0/42             |
| ie YL            | 2015             | China              | 28-30         | 12               | 0.00 (-0.10, 0.10)   | 0/16                 | 0/22             |
| ireenup AJ       | 2014             | Australia          | 32            | 2 –              | 0.00 (-0.07, 0.07)   | 0/52                 | 0/20             |
| lan YP           | 2014             | China              | 28            | 6 -              | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30             |
| lan ZH           | 2005             | China              | 28            | 0                | 0.00 (-0.05, 0.05)   | 0/43                 | 0/35             |
| le T             | 2018             | China              | 1st Trimester | NR               | -0.06 (-0.15, 0.04)  | 0/27                 | 2/35             |
| iang HX          | 2012             | China              | 20-34         | 0                | ➡ 0.00 (-0.02, 0.02) | 0/164                | 0/92             |
| i G              | 2006             | China              | 28            | 0                | 0.00 (-0.06, 0.06)   | 0/35                 | 0/32             |
| i JH             | 2017             | China              | 28            | 4 –              | 0.00 (-0.06, 0.06)   | 0/33                 | 0/27             |
| i WF             | 2006             | China              | 24            | 0                | 0.00 (-0.05, 0.05)   | 0/36                 | 0/44             |
| 1a J             | 2006             | China              | Pre-pregnancy | NR               | -0.27 (-0.47, -0.08) | 0/18                 | 6/22             |
| an CQ            | 2017             | China              | 13-30         | 4                | + 0.00 (-0.02, 0.02) | 0/160                | 0/89             |
| ten CJ           | 2016             | China              | 28            | 0                | ➡ 0.00 (-0.03, 0.03) | 0/67                 | 0/72             |
| ten YJ           | 2011             | China              | 28            | 0                | 0.00 (-0.05, 0.05)   | 0/30                 | 0/155            |
| hen ML           | 2016             | China              | 26            | 4                | → 0.00 (-0.03, 0.03) | 0/60                 | 0/60             |
| u TB             | 2009             | China              | 32            | 0                | ➡ 0.00 (-0.02, 0.02) | 0/128                | 0/120            |
| ang X            | 2009             | China              | 33            | 4                | 0.00 (-0.09, 0.09)   | 0/17                 | 0/24             |
| Vakano Y         | 2018             | Japan              | 28-32         | 4-8              | 0.00 (-0.46, 0.46)   | 0/3                  | 0/3              |
| /ang DM          | 2016             | China              | 28-30         | 12 -             |                      | 0/42                 | 0/20             |
| Vang E.I         | 2012             | China              | 28            | 4 -              |                      | 0/32                 | 0/27             |
| lang TM          | 2005             | China              | Pre-pregnancy | -                |                      | 0/32                 | 0/32             |
| lang W           | 2014             | China              | 28            | 4 -              |                      | 0/35                 | 0/28             |
| uan OF           | 2012             | China              | 27            | 4                |                      | 0/30                 | 0/30             |
| aan an<br>ana VM | 2012             | China              | 28            | Variable (0.4.6) | 0.00 (-0.05, 0.05)   | 0/90                 | 0/30             |
| hang H           | 2014             | China              | 28-30         | 4                |                      | 0/53                 | 0/363            |
| hang VE          | 2014             | China              | 20.00         | -                |                      | 0/50                 | 0/50             |
| hou DC           | 20108            | China              | 20.29         | T NR             |                      | 0/112                | 0/05             |
| hu M             | 2013             | China              | 20-20         |                  |                      | 0/113                | 1/95             |
| ubtotal (Esc     | 2014<br>auared = | = 0.0%, p = 0.998) | 20            |                  | -0.04 (-0.15, 0.07)  | 0/24                 | 9/167            |
| )verall (I-sq    | uared =          | 0.0%, p = 1.000)   |               |                  | -0.00 (-0.01, 0.01)  | 1/2003               | 9/208            |

# LdT 600 mg risk difference for fetal death Weighted pooled risk difference: 0.00 (95% CI: 0.00 – 0.00). I<sup>2</sup> statistic overall = 0.0% I<sup>2</sup> statistic RCTs = 0.0% I<sup>2</sup> statistic non-RCTs = 0.0%

| Author  | Year  | Country  | Tx<br>start in weeks<br>gestation   | Tx end<br>in weeks<br>postpartun   | 1 | RD (95% CI)  | Events,<br>Treatment   | Events,<br>Control  |
|---|---|--|---|--|---|--|--|---|
| Randomisee<br>Bai HL<br>Chen SM<br>Fu PX<br>Guan ZF<br>Guo HJ<br>Huang HY<br>Ji YY<br>Li SF<br>Lu QY<br>PengML<br>Wang HY<br>Zhang LJ<br>Zhang Y<br>Zhao DB<br>Zhao Y<br>Zhu J<br>Zhu LP<br>Subtotal (I-  | d controlle<br>2013<br>2017<br>2016<br>2017<br>2016<br>2015<br>2016<br>2015<br>2016<br>2015<br>2016<br>2014<br>2018<br>2016<br>2018<br>2018<br>2018<br>2018<br>2019<br>2018<br>2019<br>2017<br>2017<br>2017<br>2017                               | ed trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>Ch | 28-32<br>28<br>24-28<br>24<br>20-28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2  | 4<br>NR<br>4<br>12<br>4<br>0<br>4<br>24<br>0<br>NR<br>4<br>4<br>4<br>4<br>4<br>4<br>12<br>0<br>4   |   | $\begin{array}{c} 0.00 \ (-0.06 \ 0.06) \\ 0.00 \ (-0.06 \ 0.06) \\ 0.00 \ (-0.02 \ 0.02) \\ 0.00 \ (-0.02 \ 0.02) \\ 0.00 \ (-0.02 \ 0.02) \\ 0.00 \ (-0.05 \ 0.05) \\ 0.00 \ (-0.05 \ 0.05) \\ 0.00 \ (-0.05 \ 0.05) \\ 0.00 \ (-0.06 \ 0.06) \$ | 0/30<br>0/30<br>0/100<br>0/120<br>0/25<br>0/90<br>0/65<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/31<br>0/34<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/30<br>0/40<br>0/4  | 0/30<br>0/30<br>0/120<br>0/120<br>0/25<br>0/30<br>0/65<br>0/60<br>0/32<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/3   |
| . Non-random<br>Chen CY<br>Chen F<br>Chen QR<br>Chen F<br>Chen WJ<br>Chen ZX<br>Deng Y<br>Ding XP<br>Fan LY<br>Feng XM<br>Gao P<br>Ge YL<br>Han YP<br>He T<br>Hu WH<br>Hu Y<br>Huang S<br>Jiang XN<br>Li CM<br>Li YH<br>Li SY<br>Li CM<br>Li XB<br>Li YH<br>Lou JJ<br>CM<br>Shen ML<br>Sheng Q<br>Shorn W<br>Sun W<br>Tan Z<br>Tian JH<br>Tian SH<br>Wang DM<br>Wang LB<br>Wang JD<br>Wang HB<br>Wang CM<br>Xiao XH<br>Yao ZC<br>Yue X<br>Zhang BF<br>Zhang XF<br>Zhang YF<br>Zhang YF<br>Zhang JC<br>Zhou YJ<br>Zhong JC | nised con<br>2015<br>2016<br>2018<br>2017<br>2017<br>2017<br>2015<br>2018<br>2017<br>2015<br>2018<br>2017<br>2015<br>2018<br>2017<br>2016<br>2018<br>2017<br>2016<br>2014<br>2018<br>2017<br>2017<br>2017<br>2017<br>2017<br>2017<br>2017<br>2017 | trolled trials<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 1st Trimester           Pre-pregnancy           28           28           28           28           28           28           28           28           28           28           28           28           28           28           28           28           28           28           28-30           28           24-28           28           26-30           28           26-30           28           26-30           28           28           28           28           28           28           28           28           28           28           24-28           28           24-28           28           28           29           21-228           28           20-36           24-28           28           28 | NRR 4<br>0 NR 4<br>4 4<br>4 4<br>4 4<br>4 0<br>1 6<br>6 NR8 4<br>1 2 NRR 4<br>NR 4<br>NA 4<br>4 4<br>0 0<br>0 2<br>4 4<br>0 0<br>1 1 2<br>0 NR 4<br>4 2<br>4 0<br>0 0 0<br>6 4<br>NR 4<br>4 4<br>0 0<br>0 0<br>6 4<br>NR 4<br>4 4<br>0 0<br>0 0<br>6 4<br>NR 4<br>4 4<br>0 0<br>0 0<br>6 1 2<br>8<br>4 1 2<br>4 0<br>0 0<br>6 1 2<br>8<br>4 1 2<br>4 0<br>0 0<br>0 0<br>6 1 2<br>8<br>4 1 2<br>4 0<br>0 0<br>6 1 2<br>8<br>4 1 2<br>4 0<br>0 0<br>0 0<br>6 1 2<br>8<br>4 1 2<br>4 0<br>0 0<br>0 0<br>1 2<br>0 0<br>1 2<br>0 0<br>0 0<br>0 0<br>1 2<br>0 0<br>1 2<br>0 0<br>0 0<br>0 0<br>0 0<br>0 0<br>0 0<br>0 0<br>0 0<br>0 0<br>0 |   | $\begin{array}{c} 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.04, \ 0.04) \\ 0.05 \ (-0.02, \ 0.12) \\ -0.08 \ (-0.16, \ 0.00) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.04, \ 0.04) \\ 0.00 \ (-0.04, \ 0.04) \\ 0.00 \ (-0.04, \ 0.04) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 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0/42<br>0/31<br>0/29<br>0/79<br>2/43<br>0/50<br>0/82<br>0/38<br>0/58<br>0/36<br>0/36<br>0/36<br>0/30<br>0/32<br>0/46<br>0/149<br>0/20<br>0/44<br>0/65<br>0/30<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/32<br>0/32<br>0/36<br>0/32<br>0/32<br>0/36<br>0/32<br>0/36<br>0/34<br>0/102<br>0/32<br>0/36<br>0/34<br>0/127<br>0/81<br>0/40<br>0/127<br>0/81<br>0/40<br>0/120<br>0/32<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/36<br>0/37<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/53<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0/57<br>0 | 0/40<br>0/32<br>0/28<br>0/24<br>4/50<br>0/38<br>0/60<br>0/38<br>0/36<br>0/36<br>0/38<br>0/36<br>0/37<br>0/30<br>0/30<br>0/20<br>0/40<br>0/70<br>0/20<br>0/40<br>0/20<br>0/20<br>0/20<br>0/20<br>0/20<br>0/2 |
| Subtotal (I-<br>Overall (I-s  | squared =<br>quared =   | = 0.0%, p = 1<br>0.0%, p = 1   | 000)<br>000)  |  | Į | -0.00 (-0.00, 0.00)<br>-0.00 (-0.00, 0.00)   | 3/4538<br>3/5645   | 14/4797<br>20/5823  |
|   |   |  |   |  |   | 2  |  |   |

# **Appendix U: Maternal safety 2. Postpartum hemorrhage**

- TDF 300 mg risk difference for postpartum hemorrhage

   Weighted pooled risk difference: 0.00 (95%CI: -0.02 0.02).
   I<sup>2</sup> statistic overall = 0.0%
   I<sup>2</sup> statistic RCTs = 0.0%
   I<sup>2</sup> statistic non-RCTs = 0.0%

|              |          |              | in weeks     | in weeks   |                 | Events,    | Events |
|--------------|----------|--------------|--------------|------------|-----------------|------------|--------|
| Author       | Year     | Country      | gestation    | postpartum | RD (95% CI)     | Treatment  | Contro |
| Randomise    | ed contr | olled trials | 6            |            |                 |            |        |
| Lin Y        | 2018     | China        | 24           | 4          | 0.00 (-0.03, 0  | .03) 0/60  | 0/52   |
| Liu MH       | 2017     | China        | 28-30        | 0          | 0.00 (-0.09, 0  | .09) 0/20  | 0/20   |
| Pan CQ       | 2016     | China        | 30-32        | 4          | 0.00 (-0.05, 0  | .06) 4/97  | 4/100  |
| Subtotal (I  | square   | d = 0.0%,    | , p = 0.999) | 1          | 0.00 (-0.03, 0  | .03) 4/177 | 4/172  |
|              |          |              |              |            |                 |            |        |
| Non-randor   | nised c  | ontrolled    | trials       |            |                 |            |        |
| Chen WJ      | 2017     | China        | 28           | 0          | 0.00 (-0.05, 0  | .05) 0/30  | 0/44   |
| Greenup A    | J 2014   | Australia    | 32           | 12         | -0.06 (-0.24,   | ).11)5/58  | 3/20   |
| Wang HB      | 2018     | China        | 20-36        | NR         | 0.00 (-0.07, 0  | .07) 0/100 | 0/20   |
| Subtotal (I  | square   | d = 0.0%,    | p = 0.587)   | 1          | -0.00 (-0.04, - | ).04)5/188 | 3/84   |
| •            |          |              |              |            |                 |            |        |
| Overall (I-s | squared  | l = 0.0%,    | p = 0.980)   |            | -0.00 (-0.02, 0 | ).02)9/365 | 7/256  |
|              |          |              |              |            |                 |            |        |
|              |          |              |              | <u> </u>   | <del></del>     |            |        |

#### • LAM 100-150 mg risk difference for postpartum hemorrhage

- Weighted pooled risk difference: 0.01 (95% CI: -0.01 0.03).
- I<sup>2</sup> statistic overall = 0.0%
   I<sup>2</sup> statistic RCTs = not enough studies
   I<sup>2</sup> statistic non-RCTs = 0.0%

| Author        | Year     | Country            | start in weeks<br>gestation | in weeks<br>postpartum |          | RD (95% CI)         | Events,<br>Treatment | Events<br>Contro |
|---------------|----------|--------------------|-----------------------------|------------------------|----------|---------------------|----------------------|------------------|
| Randomised    | controll | ed tria <b>l</b> s |                             |                        |          |                     |                      |                  |
| Yang HW       | 2014     | China              | 28                          | 4                      | -        | 0.00 (-0.04, 0.04)  | 0/53                 | 0/53             |
| Subtotal (I-s | quared   | = .%, p = .)       |                             |                        |          | 0.00 (-0.04, 0.04)  | 0/53                 | 0/53             |
| Non-randomi   | sed cor  | trolled trials     | 6                           |                        |          |                     |                      |                  |
| Greenup AJ    | 2014     | Australia          | 32                          | 2 —                    |          | -0.05 (-0.23, 0.12) | 5/52                 | 3/20             |
| Не Т          | 2018     | China              | 1st Trimester               | NR                     |          | 0.08 (-0.05, 0.21)  | 3/27                 | 1/35             |
| Jiang HX      | 2012     | China              | 20-34                       | 0                      |          | 0.04 (-0.08, 0.16)  | 69/164               | 35/92            |
| Pan CQ        | 2017     | China              | 13-30                       | 4                      |          | 0.02 (-0.02, 0.07)  | 7/160                | 2/89             |
| Ren CJ        | 2016     | China              | 28                          | 0                      |          | -0.01 (-0.15, 0.12) | 13/67                | 15/72            |
| Wang W        | 2014     | China              | 28                          | 4                      | <u> </u> | 0.00 (-0.06, 0.06)  | 0/35                 | 0/28             |
| Zhang H       | 2014     | China              | 28-30                       | 4                      |          | 0.01 (-0.03, 0.04)  | 1/53                 | 5/363            |
| Subtotal (I-s | quared   | = 0.0%, p =        | 0.862)                      |                        |          | 0.01 (-0.01, 0.04)  | 98/558               | 61/69            |
| Overall (I-sq | uared =  | 0.0%, p = 0        | 0.877)                      |                        | ¢        | 0.01 (-0.01, 0.03)  | 98/611               | 61/75            |

### • LdT 600 mg risk difference for postpartum hemorrhage

- Weighted pooled risk difference: -0.001 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = not enough studies
  I<sup>2</sup> statistic non-RCTs = 0.0%

| Author      | Year     | Country       | Tx<br>start in weeks<br>gestation | Tx end<br>in weeks<br>postpartum | Events,<br>RD (95% CI) Treatmen | Events,<br>t Control |
|-------------|----------|---------------|-----------------------------------|----------------------------------|---------------------------------|----------------------|
| Randomise   | ed cont  | rolled trial: | s                                 |                                  |                                 |                      |
| Guan ZF     | 2017     | China         | 24                                | 12                               | 0.03 (-0.09, 0.14) 38/120       | 35/120               |
| Zhu J       | 2017     | China         | 28                                | 0                                | -0.03 (-0.10, 0.03) 1/60        | 3/60                 |
| Subtotal (I | l-square | ed = 34.5%    | %, p = 0.216)                     |                                  | -0.01 (-0.09, 0.06) 39/180      | 38/180               |
| Non-rando   | mised o  | controlled    | trials                            |                                  |                                 |                      |
| Chen WJ     | 2017     | China         | 28                                | 0                                | 0.00 (-0.04, 0.04) 0/79         | 0/44                 |
| Cui ZL      | 2015     | China         | 28                                | 4                                | -0.02 (-0.09, 0.05) 1/50        | 2/50                 |
| He T        | 2018     | China         | 1st Trimester                     | NR                               | 0.03 (-0.07, 0.13) 2/32         | 1/35                 |
| Hu Y        | 2018     | China         | 28-32                             | 3-4                              | -0.00 (-0.04, 0.03) 4/149       | 5/179                |
| Jiang XN    | 2013     | China         | 26-30                             | NR                               | -0.08 (-0.16, 0.00) 0/65        | 4/51                 |
| Liu Y       | 2016     | China         | 4-32                              | 4                                | → 0.00 (-0.02, 0.02) 0/82       | 0/78                 |
| Lou JJ      | 2015     | China         | 28                                | 4                                | 0.00 (-0.05, 0.06) 5/127        | 2/58                 |
| Pan YC      | 2017     | China         | 32                                | 0                                | → 0.00 (-0.02, 0.02) 0/81       | 0/366                |
| Peng BA     | 2012     | China         | 28                                | 0                                | 0.00 (-0.05, 0.05) 0/40         | 0/40                 |
| Sun W       | 2017     | China         | 12-28                             | 12                               | -0.02 (-0.14, 0.09) 20/123      | 12/65                |
| Sun WH      | 2015     | China         | 12-28                             | 12                               | -0.03 (-0.20, 0.14) 25/83       | 15/45                |
| Tan J       | 2019     | China         | 28                                | 0                                | -0.00 (-0.09, 0.08) 2/41        | 3/59                 |
| Tan Z       | 2016     | China         | <14-28                            | NR                               | 0.00 (-0.03, 0.03) 5/169        | 9/316                |
| Wang HB     | 2016     | China         | 20-36                             | NR                               | 0.00 (-0.07, 0.07) 0/100        | 0/20                 |
| Yue X       | 2014     | China         | Anytime                           | NR —                             | -0.10 (-0.30, 0.10) 5/31        | 8/31                 |
| Zhang GH    | 2018     | China         | 28                                | 4                                | 0.03 (-0.18, 0.23) 13/40        | 12/40                |
| Zhang H     | 2014     | China         | 28-30                             | 4                                | → 0.00 (-0.02, 0.02) 4/257      | 5/363                |
| Subtotal (I | -square  | ed = 0.0%     | , p = 0.973)                      |                                  | -0.00 (-0.01, 0.01) 86/1549     | 78/1840              |
| Overall (I- | square   | d = 0.0%,     | p = 0.985)                        |                                  | -0.00 (-0.01, 0.01) 125/1729    | 116/2020             |

# Appendix V: Maternal safety 3. Postpartum hepatitis flare

• Table: Summary of postpartum hepatitis flare after discontinuation of PAP in treated group, and during the comparable period for control group

| Study                               | Definition of flare  | Timing of<br>PAP<br>discontinu<br>-ation in<br>treated<br>group | Results  | Include<br>d in<br>meta-<br>analysis   | Any very<br>severe case<br>(decompen-<br>sation,<br>death)? | Clinical course of<br>flare cases                               |
|-------------------------------------|--|---|--|--|---|---|
|                                     |  |   | TDF  |  |   |   |
| Celen<br>MK,<br>2013                | None given<br>(until 4 weeks<br>postpartum)                                  | 4 weeks   | No hepatic flare was<br>observed in treated group<br>until 4 weeks postpartum.<br>No data reported for control<br>group. | No (no<br>control)                     | Unknown<br>(not<br>mentioned)                               | Unknown (not<br>mentioned)                                      |
| Chen HL,<br>2015                    | ALT >5 x ULN<br>(evaluated at 1, 2,<br>4, and 6 months<br>postpartum)        | 4 weeks   | At 2 months postpartum (1<br>month after discontinuation)<br>1/62 in treated group and<br>8/56 in control group.         | Yes                                    | No case of<br>hepatic<br>decompens<br>ation                 | Unknown (not<br>mentioned)                                      |
| Chen WJ,<br>2017                    | Hepatic<br>insufficiency<br>(no time-point<br>specified)                     | At delivery   | 0/30 in treated, 0/44 in<br>control  | No (no<br>time-<br>point<br>specified) | No hepatic<br>insufficienc<br>y                             | N/A   |
| Greenup<br>AJ, 2014<br>(&<br>Nguyen | Moderate: ALT ≥5 x<br>ULN (i.e. ≥95 U/L)<br>(within 24 weeks<br>postpartum). | 12 weeks  | In Greenup, vague saying no<br>correlation with flare.<br>In Nguyen (subset n=43) it<br>states 17/43 in treated group    | Yes                                    | No case of<br>hepatic<br>decompen-<br>sation                | 8/15 in treated and<br>3/4 in control<br>group<br>spontaneously |

| V,<br>2014)*        | Severe: ALT ≥20 x<br>ULN (i.e. ≥380 U/L)<br>(within 24 weeks<br>postpartum)   |           | and 4/14 in control group<br>had post-partum flare. Severe<br>flare was observed 2/17 in<br>treated group and 2/4 in<br>control group.  |  |  | resolved. 6/15 in<br>treated and 1/4 in<br>control group<br>resolved with<br>antiviral therapy.  |
|---------------------|---|-----------|---|--|--|--|
| Jourdain<br>G, 2018 | ALT >300 IU/L<br>(after the<br>discontinuation of<br>PAP)   | 8 weeks   | 9/154 in treated, 5/157 in<br>control   | Yes                                    | No<br>symptomat<br>ic case                   | No women started<br>or restarted TDF<br>after flares that<br>occurred within 6<br>months<br>postpartum.  |
| Lin Y,<br>2018      | ALT >5 x ULN<br>(no time-point<br>specified)  | 4 weeks   | 2/60 in treated, 0/52 in control  | No (no<br>time-<br>point<br>specified) | Unknown<br>(not<br>mentioned)                | Unknown (not<br>mentioned)   |
| Pan CQ,<br>2016     | Severe: ALT 5-10 x<br>ULN<br>(no time-point<br>specified).<br>Serious: ALT >10 x<br>ULN<br>(after child<br>delivery until 28<br>weeks<br>postpartum). | 4 weeks   | 5 severe and 1 serious = 6<br>total (6/97 in treated group);<br>6 severe and 3 serious = 9<br>total (9/100 in the control<br>group).<br>It is unclear whether "severe"<br>flare included only those<br>occurred postpartum or<br>throughout the study period.<br>We therefore used "serious<br>flare" in the meta-analysis. | Yes                                    | No case of<br>hepatic<br>decompen-<br>sation | All cases of serious<br>flare (1 in treated<br>and 3 in control<br>group) normalized<br>their ALT levels<br>after<br>restarting/starting<br>antiviral therapy. |
| Wakano<br>Y, 2018   | Elevation of ALT<br>(no time-point<br>specified)  | 4-8 weeks | No ALT elevation was<br>observed in treated group.<br>No data reported for control<br>group.  | No (no<br>control)                     | Unknown<br>(not<br>mentioned)                | Unknown (not<br>mentioned)   |

| Zhou Y,<br>2018                                      | Impairment of liver<br>function<br>(during treatment)   | At delivery   | 0/60 in treated group.<br>No data reported for control<br>group  | No (no<br>control)                     | No                            | N/A   |
|--|---|---|--|--|-------------------------------|---|
|  | · · ·   |   | LAM  |  | ·                             |   |
| Cheng<br>YC, 2011                                    | Cheng<br>YC, 2011 None given<br>(after<br>discontinuation of<br>treatment)<br>Abnormality for   |   | 7/30 in treated group, 5/26<br>in control group<br>Note: in these cases there<br>was elevation of ALT levels<br>during treatment, but still<br><10×ULN   | Yes                                    | Unknown<br>(not<br>mentioned) | Resolved after<br>restarting/ starting<br>antiviral therapy.  |
| Ge YL,<br>2015                                       | Abnormality for<br>liver function<br>(during treatment)   | 3 months  | 0/16 in treated group.<br>No data reported for control<br>group.   | No (no<br>control)                     | No                            | N/A   |
| Greenup<br>AJ, 2014<br>(&<br>Nguyen<br>V,<br>2014)** | Moderate: ALT ≥5 x<br>ULN (i.e. ≥95 U/L)<br>(within 24 weeks<br>postpartum).<br>Severe: ALT ≥20 x<br>ULN (i.e. ≥380 U/L)<br>(within 24 weeks<br>postpartum) | 2 weeks   | In the paper from Greenup et<br>al., which had the full cohort,<br>it was stated that there were<br>'no differences' in flare<br>between the treated and non-<br>treated group. In a subset<br>presented in Nguyen et al.,<br>22/44 in treated group and<br>4/14 in control group had<br>postpartum flare. | Yes                                    | Unknown<br>(not<br>mentioned) | 15/20 in treated<br>and 3/4 in control<br>group<br>spontaneously<br>resolved. 5/20 in<br>treated and 1/4 in<br>control group<br>resolved with<br>antiviral therapy. |
| He T,<br>2018  | ALT >2 x baseline<br>(after child<br>delivery)  | All women<br>continued<br>treatment<br>after child<br>delivery,<br>stop time<br>not | 0/27 in treated, 6/35 in<br>control.<br>However, all women in<br>treated group continued<br>antiviral therapy after child<br>delivery, so this is not used<br>for the meta-analysis of flare.  | No<br>(treatmen<br>t<br>continued<br>) | Unknown<br>(not<br>mentioned) | All flare cases<br>spontaneously<br>resolved without<br>antiviral therapy.  |

|                     |  | mentioned.  |  |  |                               |   |
|---------------------|--|-------------|--|--|-------------------------------|---|
| Jackson<br>V, 2015  | ALT >3 x ULN<br>(postpartum<br>following<br>discontinuation of<br>PAP) | At delivery | 5/26 in treated.<br>No data reported for control<br>group.   | No (no<br>control)   | Unknown<br>(not<br>mentioned) | Unknown (not<br>mentioned)  |
| Pan CQ,<br>2017     | ALT >10 x ULN or<br>>5 x baseline<br>(after child<br>delivery)         | 4 weeks     | <ul> <li>1/147 in treated, 5/89 in control.</li> <li>13 mothers in treated group who continued treatment beyond postpartum week 4 were excluded from this analysis.</li> </ul> | <ul> <li>/147 in treated, 5/89 in control.</li> <li>mothers in treated group the continued treatment yond postpartum week 4 were excluded from this analysis.</li> <li>0 /20 in treated group</li> </ul> |                               | One flare case in<br>treated group<br>improved ALT level<br>without antiviral<br>therapy. Five flare<br>cases in control all<br>started antiviral<br>therapy. |
| Ren YJ,<br>2011     | Impairment of liver<br>function<br>(before and after<br>delivery)      | At delivery | 0/30 in treated group.<br>No data reported for control<br>group.   | No (no<br>control)   | No                            | N/A   |
| Wakano<br>Y, 2018   | Elevation of ALT<br>(no time-point<br>specified)                       | 4-8 weeks   | No ALT elevation was<br>observed in treated group.<br>No data reported for control<br>group.   | No (no<br>control)   | Unknown<br>(not<br>mentioned) | Unknown (not<br>mentioned)  |
| Wang<br>DM,<br>2016 | None given   | 12 weeks    | 1/42 in treated group.<br>No data reported for control<br>group.<br>Note: in this one case there<br>was elevation of ALT levels<br>during treatment, but still<br><5×ULN       | No (no<br>control)   | Unknown<br>(not<br>mentioned) | Transient, resolved<br>spontaneously  |
| Wang                | Abnormality for  | At delivery | 0/30 in treated, 0/30 in   | No (no   | No                            | N/A   |

| TM,<br>2005         | liver function<br>(no time-point<br>specified)   |   | control.   | time-<br>point<br>specified)           |   |                            |
|---------------------|--|---|--|--|---|----------------------------|
| Wang W,<br>2014     | Impairment of liver<br>function<br>(no time-point<br>specified)                                  | 4 weeks                                   | 0/35 in treated, 0/28 in control.  | No (no<br>time-<br>point<br>specified) | No  | N/A                        |
| Xu WM,<br>2009      | ALT >3 x ULN<br>(from postpartum<br>week 4 to week 12)   | 4 weeks                                   | 16/83 in treated, 15/46 in<br>control  | Yes                                    | No case of<br>ALT<br>elevations<br>in<br>association<br>with signs<br>of hepatic<br>insufficienc<br>y | Unknown (not<br>mentioned) |
| Yang<br>HW,<br>2014 | Impairment of liver<br>function<br>(no time-point<br>specified)                                  | 4 weeks                                   | 0/53 in treated, 0/53 in control.  | No (no<br>time-<br>point<br>specified) | No  | N/A                        |
| Zeng<br>YM,<br>2013 | Elevated ALT and<br>AST outside of the<br>normal range (>50<br>U/L)<br>(after child<br>delivery) | At delivery,<br>4 weeks<br>and 6<br>weeks | In treated group:<br>I. discontinuation at delivery:<br>4/30 (1, 2 and 1 case at 1, 3<br>and 6 months after<br>discontinuation,<br>respectively);<br>II. discontinuation at 4<br>weeks: 4/30 (1 and 3 cases at<br>1 and 3 months after<br>discontinuation, | Yes                                    | No case of<br>ALT<br>elevation<br>with<br>jaundice;<br>No case of<br>severe<br>hepatitis              | Unknown (not<br>mentioned) |

|                  |   |   | respectively);<br>III. discontinuation at 6<br>weeks: 5/30, (2 and 3 cases<br>at 1 and 3 months after<br>discontinuation,<br>respectively)<br>In control group: 5/30: (2<br>cases at 3 months after<br>dolivery 2 cases at 6 months |   |  |  |
|------------------|---|---|---|---|--|--|
|                  |   |   | after delivery)   |   |  |  |
| Zhang H,<br>2014 | ALT >10 x ULN or<br>>5 x baseline<br>(from postpartum<br>week 4 to week 52) | 4 weeks   | 0/53 in treated, 0/363 in<br>control  | Yes                                     | No case of<br>hepatic<br>decompen-<br>sation | N/A  |
| Zhu M,<br>2014   | Aggravation of<br>liver function<br>impairment<br>(during pregnancy)        | At delivery   | 0/24 in treated, 1/25 in control  | No (not<br>post-<br>partum)             | Unknown<br>(not<br>mentioned)                | Unknown (not<br>mentioned)   |
|                  |   |   | LdT   |   |  |  |
| Chen CY,<br>2015 | None given<br>(no time-point<br>specified)                                  | Treatment<br>continued<br>after<br>delivery,<br>unless<br>discontin-<br>uation<br>criteria met.<br>Disaggregate<br>d numbers<br>not | 1/41 in control group<br>(severe hepatitis at 28<br>weeks of gestation).<br>No data reported for<br>treated group.  | No (no<br>data for<br>treated<br>group) | Unknown<br>(not<br>mentioned)                | Unknown (not<br>mentioned)<br>(receiving<br>treatment<br>thereafter and<br>dropping out) |

|                     |   | available.  |   |  |                               |                                   |
|---------------------|---|---|---|--|-------------------------------|-----------------------------------|
| Chen WJ,<br>2017    | Hepatic<br>insufficiency<br>(no time-point<br>specified)                            | At delivery   | 0/79 in treated, 0/44 in<br>control   | No (no<br>time-<br>point<br>specified) | No hepatic<br>insufficiency   | N/A                               |
| Chen<br>QR,<br>2018 | ALT elevation<br>(during pregnancy)   | 4 weeks   | 1/29 in treated, 1/28 in control  | No (not<br>post-<br>partum)            | Unknown<br>(not<br>mentioned) | Both cases resolved spontaneously |
| Deng Y,<br>2015     | Obvious<br>abnormality for<br>liver biochemical<br>indicators<br>(during treatment) | 1 month   | 0/82 in treated group.<br>No data reported for<br>control group.  | No (no<br>control)                     | No                            | N/A                               |
| Ding XP,<br>2018    | Impairment of liver<br>function<br>(during<br>intervention)                         | 1 month   | 0/38 in treated, 0/38 in<br>control   | No (no<br>time-<br>point<br>specified) | No                            | N/A                               |
| Ge YL,<br>2015      | Obvious<br>abnormality for<br>liver function<br>(during treatment)                  | 3 months  | 0/20 in treated group.<br>No data reported for<br>control group.  | No (no<br>control)                     | No                            | N/A                               |
| Fan LY,<br>2013     | Severe impairment<br>of liver function<br>(after PAP<br>discontinuation)            | At least 6<br>months (9 in<br>60 pregnant<br>women<br>discontinued<br>treatment 1<br>month after<br>delivery) | 0/9 pregnant women who<br>discontinued antiviral<br>treatment at 1 month after<br>delivery.<br>No data reported for<br>control group. | No (no<br>control<br>data)             | No                            | N/A                               |
| Han GR,             | Flare: ALT >5 x   | Variable  | In treated group: 3/236   | No (no                                 | No                            | 6 of 46 with any                  |

| 2015              | ULN<br>(after<br>discontinuation of<br>PAP).<br>Severe: ALT >10 x<br>ULN<br>(after<br>discontinuation of<br>PAP). | (236<br>stopped at 4<br>weeks and<br>126<br>continued<br>after 4<br>weeks) | had >5 x ULN, 0/236 with<br>>10 x ULN.<br>126 mothers in treated<br>group who continued<br>treatment beyond<br>postpartum week 4 were<br>excluded from above.<br>No data reported for<br>control group. | control)                               |   | ALT elevation had<br>clinical therapies to<br>reduce ALT levels<br>and by 7-12 months<br>post-partum, ALT of<br>all mothers had<br>returned to normal. |
|-------------------|---|--|---|--|---|--|
| He T,<br>2018     | ALT > 2 x baseline<br>(after child<br>delivery)   | All women<br>continued<br>treatment<br>after child<br>delivery.            | 0/32 in treated, 6/35 in<br>control.<br>However, all women in<br>treated group continued<br>antiviral therapy after<br>child delivery, so this is<br>not used for the meta-<br>analysis of flare.       | No<br>(treatmen<br>t<br>continued<br>) | Unknown<br>(not<br>mentioned)                                     | All flare cases<br>spontaneously<br>resolved without<br>antiviral therapy.   |
| Hu Y,<br>2018     | ALT > 40 U/L<br>(by the 7-14<br>months<br>postpartum)   | 3-4 weeks  | 22/103 in treated, 25/124<br>in control   | Yes                                    | No case of<br>elevated<br>bilirubin or<br>fulminant<br>hepatitis. | ALT normalized within 2-4 weeks.   |
| Jiang S,<br>2017  | Abnormal liver<br>function<br>(no time-point<br>specified)  | None given   | 0/44 in treated group.<br>No data reported for<br>control group.  | No (no<br>control)                     | No  | N/A  |
| Jiang XN,<br>2013 | Abnormal ALT<br>(7 months after<br>delivery)  | All women<br>continued<br>treatment  | 0/65 in treated, 4/51 in control.   | No<br>(treatmen<br>t                   | 3/51 in<br>control<br>group                                       | Unknown (not<br>mentioned)   |

|               |  | after child                    |  | continued          | progressed                    |  |
|---------------|--|--------------------------------|--|--------------------|-------------------------------|--|
|               |  | delivery                       |  | )                  | to severe                     |  |
|               |  |                                |  |                    | hepatitis                     |  |
|               |  |                                |  |                    | before                        |  |
|               |  |                                |  |                    | delivery;                     |  |
|               |  |                                |  |                    | 2/51 in                       |  |
|               |  |                                |  |                    | control                       |  |
|               |  |                                |  |                    | group                         |  |
|               |  |                                |  |                    | developed                     |  |
|               |  |                                |  |                    | ascites and                   |  |
|               |  |                                |  |                    | liver                         |  |
|               |  |                                |  |                    | cirrhosis at 7                |  |
|               |  |                                |  |                    | months after                  |  |
|               |  |                                |  |                    | delivery                      |  |
| Li N,<br>2016 | None given<br>(no time-point<br>specified) | Not<br>specified/<br>clarified | 1/35 in treated group a<br>(re-bounce of ALT,<br>breakthrough during<br>treatment, due to antiviral<br>resistance)<br>2/30 in treated group b<br>(in one case, ALT elevated<br>to 416 U/L during<br>treatment and then<br>declined gradually to 102<br>U/L at delivery; in the<br>other case, ALT elevated to<br>336 U/L during treatment<br>and then declined to 86<br>U/L at delivery)<br>No data reported for | No (no<br>control) | Unknown<br>(not<br>mentioned) | Transient for both<br>cases in treated<br>group b (treatment<br>starting from 28<br>weeks of gestation);<br>Unknown (not<br>mentioned) for the<br>case in treated<br>group a (treatment<br>starting before<br>pregnancy) |

|                 |  |  | control group.   |   |                                |   |
|-----------------|--|--|--|---|--------------------------------|---|
| Li YH,<br>2017  | ALT elevation<br>(no time-point<br>specified)                            | Approximate<br>ly 36 weeks<br>postpartum<br>(treatment<br>started at 28<br>weeks<br>gestation<br>and went for<br>48 weeks)                       | 1/30 in treated group.<br>No data reported for<br>control group.<br>Mild elevation of ALT<br>levels at 34 weeks of<br>gestation, ALT<5×ULN | No (no<br>control)                      | Unknown<br>(not<br>mentioned)  | Transient, resolved<br>spontaneously<br>without liver<br>protecting drugs   |
| Liu J,<br>2017  | Elevation in ALT<br>levels<br>(1 month and 6<br>months<br>postpartum)    | Treatment<br>continued<br>after<br>delivery,<br>unless<br>discontinuat<br>ion criteria<br>met<br>(disaggregat<br>ed numbers<br>not<br>available) | 2/102 in treated, 1/28 in<br>control at 1 month after<br>delivery.<br>4/102 in treated, 1/28 in<br>control at 6 months after<br>delivery.  | No (some<br>continued<br>treatment<br>) | Unknown<br>(not<br>mentioned)  | Unknown (not<br>mentioned)  |
| Liu XB,<br>2016 | Abnormality for<br>liver biochemical<br>indicators<br>(during treatment) | 1 month  | 0/20 in treated group.<br>No data reported for<br>control group.   | No (no<br>control)                      | No                             | N/A   |
| Liu Y,<br>2016  | ALT ≥2 x ULN<br>(from<br>discontinuation of<br>PAP to postpartum         | 4 weeks  | 5/71 in treated, 1/78 in<br>control.<br>11 mothers in treated<br>group who continued   | Yes                                     | No case of<br>ALT >8 x<br>ULN. | Four flare cases in<br>treated group<br>restarted antiviral<br>(entecavir). |

|                   | week 51)  |             | treatment beyond<br>postpartum week 4 were<br>excluded from this<br>analysis.   |                    |                               |  |
|-------------------|---|-------------|---|--------------------|-------------------------------|--|
| Lou JJ,<br>2015   | ALT between<br>2×ULN and 5×ULN<br>(no time-point<br>specified)                                  | 30 days     | 2/127 in treated group.<br>No data reported for<br>control group.   | No (no<br>control) | Unknown<br>(not<br>mentioned) | Active hepatitis,<br>without obvious<br>symptoms, stable<br>after antiviral<br>treatment with NA |
| Lu QY,<br>2016    | Impairment of liver<br>function<br>(during and after<br>treatment)                              | At delivery | 0/152 in treated group.<br>No data reported for<br>control group.   | No (no<br>control) | No                            | N/A  |
| Pan YC,<br>2017   | High ALT levels<br>(after child<br>delivery)  | At delivery | 3/22 in treated group at 7<br>months after delivery.<br>No data reported for<br>control group.  | No (no<br>control) | Unknown<br>(not<br>mentioned) | All cases resolved<br>spontaneously at 1<br>year after delivery                                  |
| Peng BA,<br>2012  | Abnormal liver<br>function<br>(no time-point<br>specified)                                      | At delivery | 0/40 in treated group.<br>No data reported for<br>control group.  | No (no<br>control) | No                            | N/A  |
| Qiu B,<br>2016    | Abnormality for<br>liver function<br>indicators<br>(until 48 weeks<br>after<br>discontinuation) | At delivery | 0/120 in treated group<br>(60 starting treatment<br>before pregnancy and 60<br>starting treatment at 24<br>weeks of gestation).<br>No data reported for<br>control group. | No (no<br>control) | No                            | N/A  |
| Sheng Q,<br>2018a | ALT ≥2 x ULN<br>(after  | At delivery | 3/87 in treated.<br>4 mothers in treated  | No (no<br>control) | No case of<br>hepatic         | All flare cases in treated group   |

|                     | discontinuation of<br>PAP)   |                     | group who continued<br>treatment after child<br>delivery were excluded<br>from the analysis.<br>No data reported for<br>control group. |  | decompen-<br>sation                          | restarted antiviral<br>and resolved.   |
|---------------------|--|---------------------|--|--|--|--|
| Shi QW,<br>2017     | Elevation in ALT<br>levels<br>(during treatment)                                   | At delivery         | 3/100 in treated group.<br>No data reported for<br>control group.  | No (no<br>control)                     | Unknown<br>(not<br>mentioned)                | Resolved<br>spontaneously 1-<br>2 weeks after<br>discontinuation                                   |
| Tian JH,<br>2018    | Unstable liver<br>function<br>(during treatment)                                   | At least 1<br>month | 0/135 in treated group.<br>No data reported for<br>control group.  | No (no<br>control)                     | No   | N/A  |
| Wang EJ,<br>2012    | ALT elevation<br>(no time-point<br>specified)                                      | 4 weeks             | 1/28 in treated, 1/27 in<br>control.<br>Mild elevation of ALT<br>levels (ALT<5×ULN)  | No (no<br>time-<br>point<br>specified) | Unknown<br>(not<br>mentioned)                | Transient, resolved<br>spontaneously<br>without use of liver<br>protecting drugs                   |
| Wang<br>WP,<br>2012 | ALT elevation<br>(no time-point<br>specified)                                      | At delivery         | 5/47 in treated group.<br>No data reported for<br>control group.   | No (no<br>control)                     | Unknown<br>(not<br>mentioned)                | Resolved after liver<br>protecting<br>treatment  |
| Yao LF,<br>2014     | ALT elevation<br>(during pregnancy)  | 6 weeks             | 7/30 in treated group.<br>No data reported for<br>control group.   | No (no<br>control<br>group)            | Unknown<br>(not<br>mentioned)                | Resolved<br>spontaneously<br>without<br>interventions, back<br>to normal levels<br>before delivery |
| Zhang H,<br>2014    | Severe: ALT >10 x<br>ULN or 5 x baseline<br>(from postpartum<br>week 4 to week 52) | 4 weeks             | 0/257 in treated, 0/363 in control   | Yes                                    | No case of<br>hepatic<br>decompen-<br>sation | N/A  |

| Zhou YJ,<br>2014 | Abnormal live<br>biochemical<br>indicators<br>(17 weeks of<br>gestation) | Trea<br>cont<br>deli<br>deli<br>disco<br>ion c<br>ion c<br>n<br>(disaş<br>ed nu<br>r<br>avai | tment<br>inued<br>iter<br>very,<br>less<br>ntinuat<br>riteria<br>net<br>ggregat<br>umbers<br>iot<br>lable) | 5/39 in cor<br>No data re<br>treated | itrol grouj<br>ported foi<br>group. | p.<br>r | No (no<br>data for<br>treated<br>group) | 1 case<br>death<br>wom<br>receiv<br>treatm<br>from<br>weeks<br>delive<br>she die<br>larg<br>hemorr<br>(unspee<br>type)<br>delive | e of<br>(this<br>an<br>ved<br>nent<br>17<br>s to<br>ery,<br>ed of<br>ge<br>thage<br>cified<br>at<br>ery) | 4 cases stoppe<br>pregnancy; 1 cas<br>death (continu<br>pregnancy an<br>receiving treatm<br>from 17 weeks<br>delivery, die<br>massive<br>hemorrhage a<br>delivery) | ed<br>se of<br>ing<br>d<br>nent<br>to<br>of<br>at |
|------------------|--|--|--|--------------------------------------|-------------------------------------|---------|---|--|--|--|---|
| * In Nguye       | en V, 2014, 12% (S   | 5/43) in the   | e interven   | ition group red                      | ceived LA                           | M.      |   |  |  |  |   |
| in In            | nguyen v   | , ZU14   | 18%  | ້0 (8/44)                            | 111                                 | uie     | interven                                | uon  | group  | received   | IDF.  |

• Figure: Forest plot for TDF 300 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation

| Author        | Year     | Country       | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |   |                 |    |                   | RD (95% CI)          | Events,<br>Treatment | Events,<br>Control |
|---------------|----------|---------------|-----------------------------------|----------------------------------|---|-----------------|----|-------------------|----------------------|----------------------|--------------------|
| Randomised    | contro   | lled trials   |                                   |                                  |   |                 |    |                   |                      |                      |                    |
| Jourdain G    | 2018     | Thailand      | 26-29                             | 8                                |   | H               | •— |                   | 0.03 (-0.02, 0.07)   | 9/154                | 5/157              |
| Pan CQ        | 2016     | China         | 30-32                             | 4                                |   |                 |    |                   | -0.02 (-0.06, 0.02)  | 1/97                 | 3/100              |
| Subtotal (I-s | quared   | = 61.7%,      | p = 0 <b>.</b> 106)               |                                  |   | $\triangleleft$ | >  |                   | 0.00 (-0.05, 0.05)   | 10/251               | 8/257              |
| •             |          |               |                                   |                                  |   |                 |    |                   |                      |                      |                    |
| Non-random    | ised co  | ntrolled tria | als                               |                                  |   |                 |    |                   |                      |                      |                    |
| Chen HL       | 2015     | Taiwan        | 30-32                             | 4                                |   |                 |    |                   | -0.13 (-0.22, -0.03) | 1/62                 | 8/56               |
| Greenup AJ    | 2014     | Australia     | 32                                | 12                               |   | i               |    | $\longrightarrow$ | 0.11 (-0.17, 0.39)   | 17/43                | 4/14               |
| Subtotal (I-s | quared   | = 67.7%,      | p = 0 <b>.</b> 078)               | ~                                | < |                 | >  | >                 | -0.04 (-0.29, 0.21)  | 18/105               | 12/70              |
| Overall (I-sq | juared : | = 66.5%, p    | = 0.030)                          |                                  |   |                 | >  |                   | -0.02 (-0.08, 0.04)  | 28/356               | 20/327             |
|               |          |               |                                   | 3                                | 2 | 1 0             | .1 | .2 .              | 3                    |                      |                    |
- Tx start in weeks Tx end in Events. Events RD (95% CI) Author Country gestation weeks postpartum Treatment Control Year Randomised controlled trials Xu WM 2009 China, Philippines 30-34 4 -0.13 (-0.29, 0.03) 16/83 15/46 Subtotal (I-squared = .%, p = .) -0.13 (-0.29, 0.03) 16/83 15/46 Non-randomised controlled trials Cheng YC 32 4 0.04 (-0.17, 0.26) 7/30 5/26 2011 China 2014 Australia 32 2 → 0.21 (-0.06, 0.49) 4/14 Greenup AJ 22/44 Pan CQ 2017 China 13-30 4 -0.05 (-0.10, 0.00) 1/147 5/89 Zeng YM 2013 China 28 Variable (0,4,6) -0.02 (-0.17, 0.13) 13/90 5/30 Zhang H 2014 China 4 0.00 (-0.03, 0.03) 0/363 28-30 0/53 Subtotal (I-squared = 33.2%, p = 0.200) -0.01 (-0.05, 0.03) 19/522 43/364 Overall (I-squared = 46.5%, p = 0.096) -0.02 (-0.07, 0.03) 59/447 34/568 -.3 | .2 1 .3 - 2 1 0 1
- Figure: Forest plot for LAM 100-150 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation

# • Figure: Forest plot for LdT 600 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation

|            |          |                       | Tx start   | Tx end     |   |   |           |    |         |                    |           |         |
|------------|----------|-----------------------|------------|------------|---|---|-----------|----|---------|--------------------|-----------|---------|
|            |          |                       | in weeks   | in weeks   |   |   |           |    |         |                    | Events,   | Events, |
| Author     | Year     | Country               | gestation  | postpartum |   |   |           |    |         | RD (95% CI)        | Treatment | Control |
| Non vonde  |          | o natura II o al turi |            |            |   |   |           |    |         |                    |           |         |
| Non-rando  | misea c  | controlled tri        | ais        |            |   |   |           |    |         |                    |           |         |
| Hu Y       | 2018     | China                 | 28-32      | 3-4        |   |   | -         |    |         | 0.01 (-0.09, 0.12) | 22/103    | 25/124  |
| Liu Y      | 2016     | China                 | 4-32       | 4          |   |   | -         | -  |         | 0.06 (-0.01, 0.12) | 5/71      | 1/78    |
| Zhang H    | 2014     | China                 | 28-30      | 4          |   |   | +         |    |         | 0.00 (-0.01, 0.01) | 0/257     | 0/363   |
| Subtotal ( | I-square | ed = 85.5%,           | p = 0.001) |            |   | < | $\langle$ | >  |         | 0.02 (-0.06, 0.11) | 27/431    | 26/565  |
|            |          |                       |            |            |   |   |           |    |         |                    |           |         |
|            |          |                       |            |            |   |   |           |    |         |                    |           |         |
|            |          |                       |            |            |   |   |           |    |         |                    |           |         |
|            |          |                       |            | 3          | 2 | 1 | 0         | .1 | І<br>.2 | .3                 |           |         |

## Appendix W: Maternal and Infant Safety Subgroup Analysis

• TDF 300 mg risk difference of neonatal death by timing of treatment initiation

| Author        | Year     | Country                | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum | RD (95% CI)          | Events,<br>Treatment | Events<br>Contro |
|---------------|----------|------------------------|-----------------------------------|----------------------------------|----------------------|----------------------|------------------|
| Median >28    | weeks o  | f gestation            |                                   |                                  |                      |                      |                  |
| Liu MH        | 2017     | China                  | 28-30                             | 0                                | • 0.00 (-0.09, 0.09) | 0/20                 | 0/20             |
| Pan CQ        | 2016     | China                  | 30-32                             | 4                                | 0.01 (-0.02, 0.04)   | 1/95                 | 0/88             |
| Chen HL       | 2015     | Taiwan                 | 30-32                             | 4                                |                      | 0/65                 | 0/56             |
| Greenup AJ    | 2014     | Australia              | 32                                | 12                               | 0.00 (-0.07, 0.07)   | 0/58                 | 0/20             |
| Subtotal (I-s | quared : | = 0.0%, p =            | 0.967)                            |                                  | 0.00 (-0.02, 0.03)   | 1/238                | 0/184            |
| Median 28 w   | eeks of  | gestation              |                                   |                                  |                      |                      |                  |
| Jourdain G    | 2018     | Thailand               | 26-29                             | 8                                | -0.01 (-0.02, 0.01)  | 0/163                | 1/160            |
| Chen WJ       | 2017     | China                  | 28                                | 0                                | 0.00 (-0.05, 0.05)   | 0/30                 | 0/44             |
| He LL         | 2018     | China                  | 28                                | NR                               | 0.00 (-0.05, 0.05)   | 0/50                 | 0/35             |
| Wan JY        | 2017     | China                  | 28                                | 0                                | 0.00 (-0.04, 0.04)   | 0/74                 | 0/42             |
| Xiao XH       | 2017     | China                  | 28                                | 0 or 4                           | 0.00 (-0.03, 0.03)   | 0/60                 | 0/60             |
| Subtotal (I-s | quared   | = 0.0%, p =            | 0.994)                            |                                  | -0.00 (-0.02, 0.01)  | 0/377                | 1/341            |
| Median <28 v  | weeks o  | f gestation            |                                   |                                  |                      |                      |                  |
| Lin Y         | 2018     | China                  | 24                                | 4                                | 0.02 (-0.03, 0.06)   | 1/59                 | 0/52             |
| Yu CY         | 2018     | China                  | 24                                | 4                                | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30             |
| Celen MK      | 2013     | Turkey                 | 18-27                             | 4                                | 0.00 (-0.08, 0.08)   | 0/21                 | 0/23             |
| Gong Q        | 2017     | China                  | 1-6                               | NR                               | 0.00 (-0.04, 0.04)   | 0/44                 | 0/44             |
| Huang Q       | 2017     | China                  | 24-28                             | 12                               | 0.00 (-0.09, 0.09)   | 0/20                 | 0/20             |
| Wakano Y      | 2018     | Japan                  | 22-28                             | 4-8 🔶                            | → 0.00 (-0.53, 0.53) | 0/2                  | 0/3              |
| Wang HB       | 2018     | China                  | 20-36                             | NR                               | 0.00 (-0.07, 0.07)   | 0/100                | 0/20             |
| Zhang BF      | 2018     | China                  | 24-28                             | 0                                | 0.00 (-0.04, 0.04)   | 0/39                 | 0/75             |
| Zhou Y        | 2018     | China                  | 24-28                             | 0                                | 0.00 (-0.04, 0.04)   | 0/60                 | 0/36             |
| Subtotal (I-s | quared   | = 0.0%, p =            | 1.000)                            |                                  | 0.00 (-0.02, 0.02)   | 1/375                | 0/303            |
| Heterogeneit  | y betwe  | en groups:             | p = 0.738                         |                                  |                      |                      |                  |
| Overall (l-se | uared =  | 0.0%, p = <sup>-</sup> | 1.000)                            |                                  | -0.00 (-0.01, 0.01)  | 2/990                | 1/828            |

### • TDF 300 mg risk difference of preterm birth by timing of treatment initiation

|               |          |              | Tx start  | Tx end     |        |               |           |        |
|---------------|----------|--------------|-----------|------------|--------|---------------|-----------|--------|
|               |          |              | in weeks  | in weeks   |        |               | Events,   | Events |
| Author        | Year     | Country      | gestation | postpartum | RD (S  | ∂5% CI)       | Treatment | Contro |
| Median >28    | weeks c  | of gestation |           |            |        |               |           |        |
| Liu MH        | 2017     | China        | 28-30     | 0          | 0.00   | (-0.09, 0.09) | 0/20      | 0/20   |
| Pan CQ        | 2016     | China        | 30-32     | 4          | 0.01   | (-0.03, 0.05) | 2/95      | 1/88   |
| Chen HL       | 2015     | Taiwan       | 30-32     | 4          | 0.04   | (-0.04, 0.12) | 5/65      | 2/56   |
| Greenup AJ    | 2014     | Australia    | 32        | 12         | 0.02   | (-0.06, 0.09) | 1/58      | 0/20   |
| Subtotal (I-s | quared   | = 0.0%, p =  | = 0.900)  |            | 0.01 ( | (-0.02, 0.04) | 8/238     | 3/184  |
|               |          |              |           |            |        |               |           |        |
| Median <28    | weeks o  | of gestation |           |            |        |               |           |        |
| Lin Y         | 2018     | China        | 24        | 4          | -0.02  | (-0.08, 0.04) | 1/59      | 2/52   |
| Wakano Y      | 2018     | Japan        | 22-28     | 4-8        | → 0.00 | (-0.53, 0.53) | 0/2       | 0/3    |
| Wang HB       | 2018     | China        | 20-36     | NR         | 0.00   | (-0.07, 0.07) | 0/100     | 0/20   |
| Subtotal (I-s | quared   | = 0.0%, p =  | = 0.897)  |            | -0.01  | (-0.06, 0.03) | 1/161     | 2/75   |
|               |          |              |           |            |        |               |           |        |
| Heterogeneit  | ty betwe | en groups    | p = 0.355 |            |        |               |           |        |
| Overall (I-sq | uared =  | = 0.0%, p =  | 0.948)    |            | 0.01 ( | (-0.02, 0.03) | 9/399     | 5/259  |
|               |          |              |           |            |        |               |           |        |
|               |          |              |           |            |        |               |           |        |

## • TDF 300 mg risk difference of congenital abnormalities by timing of treatment initiation

| Author      | Year     | Country    | in weeks<br>gestation | in weeks<br>postpartum | Events,<br>RD (95% Cl) Treatment | Events<br>Contro |
|-------------|----------|------------|-----------------------|------------------------|----------------------------------|------------------|
| Median >2   | 8 week   | s of gesta | ation                 |                        |                                  |                  |
| Liu MH      | 2017     | China      | 28-30                 | 0                      | 0.00 (-0.09, 0.09) 0/20          | 0/20             |
| Pan CQ      | 2016     | China      | 30-32                 | 4                      | 0.01 (-0.03, 0.05) 2/95          | 1/88             |
| Chen HL     | 2015     | Taiwan     | 30-32                 | 4                      | 0.02 (-0.03, 0.06) 1/65          | 0/56             |
| Greenup A   | J 2014   | Australia  | a 32                  | 12                     | 0.02 (-0.06, 0.09) 1/58          | 0/20             |
| Subtotal (I | -square  | ed = 0.0%  | b, p = 0.989          | 9)                     | 0.01 (-0.01, 0.04) 4/238         | 1/184            |
| Median 28   | weeks    | of gestat  | ion                   |                        |                                  |                  |
| Jourdain G  | i 2018   | Thailanc   | 26-29                 | 8                      | → -0.01 (-0.02, 0.01)0/163       | 1/160            |
| Chen WJ     | 2017     | China      | 28                    | 0                      | 0.00 (-0.05, 0.05) 0/30          | 0/44             |
| Xiao XH     | 2017     | China      | 28                    | 0 or 4                 | -0.03 (-0.09, 0.02)0/60          | 2/60             |
| Subtotal (I | -square  | ed = 0.0%  | b, p = 0.622          | 2)                     | -0.01 (-0.02, 0.01)0/253         | 3/264            |
| Median <2   | 8 week   | s of gesta | ation                 |                        |                                  |                  |
| Lin Y       | 2018     | China      | 24                    | 4                      | 0.00 (-0.03, 0.03) 0/59          | 0/52             |
| Yu CY       | 2018     | China      | 24                    | 4                      | -0.03 (-0.12, 0.05)0/30          | 1/30             |
| Celen MK    | 2013     | Turkey     | 18-27                 | 4                      | 0.00 (-0.08, 0.08) 0/21          | 0/23             |
| Wakano Y    | 2018     | Japan      | 22-28                 | 4-8                    | → 0.00 (-0.53, 0.53) 0/2         | 0/3              |
| Wang HB     | 2018     | China      | 20-36                 | NR                     |                                  | 0/20             |
| Zhang BF    | 2018     | China      | 24-28                 | 0                      | 0.00 (-0.04, 0.04) 0/39          | 0/75             |
| Zhou Y      | 2018     | China      | 24-28                 | 0                      | 0.00 (-0.04, 0.04) 0/60          | 0/36             |
| Subtotal (I | -square  | ed = 0.0%  | b, p = 0.997          | 7)                     | -0.00 (-0.02, 0.02)0/311         | 1/239            |
| Heterogen   | eity bet | ween gro   | ups: p = 0.           | 429                    |                                  |                  |
| Overall (L  | square   | d = 0.0%,  | p = 0.997)            | 1                      | -0.00 (-0.01, 0.01)4/802         | 5/687            |

### • TDF 300 mg risk difference of foetal death by timing of treatment initiation

|               |          |             | Tx start  | Tx end     |                      |           |        |
|---------------|----------|-------------|-----------|------------|----------------------|-----------|--------|
|               |          |             | in weeks  | in weeks   |                      | Events,   | Events |
| Author        | Year     | Country     | gestation | postpartum | RD (95% CI)          | Treatment | Contro |
| Median >28 v  | weeks o  | f gestation |           |            |                      |           |        |
| Liu MH        | 2017     | China       | 28-30     | 0          | - 0.00 (-0.09, 0.09) | 0/20      | 0/20   |
| Pan CQ        | 2016     | China       | 30-32     | 4          | 0.01 (-0.02, 0.04)   | 1/97      | 0/100  |
| Chen HL       | 2015     | Taiwan      | 30-32     | 4          | 0.00 (-0.03, 0.03)   | 0/62      | 0/56   |
| Greenup AJ    | 2014     | Australia   | 32        | 12         | 0.00 (-0.07, 0.07)   | 0/58      | 0/20   |
| Subtotal (I-s | quared   | = 0.0%, p = | 0.967)    |            | 0.01 (-0.01, 0.03)   | 1/237     | 0/196  |
| Median 28 w   | eeks of  | gestation   |           |            |                      |           |        |
| Jourdain G    | 2018     | Thailand    | 26-29     | 8          | 0.01 (-0.01, 0.02)   | 1/162     | 0/160  |
| Chen WJ       | 2017     | China       | 28        | 0          | 0.00 (-0.05, 0.05)   | 0/30      | 0/44   |
| He LL         | 2018     | China       | 28        | NR         | 0.00 (-0.05, 0.05)   | 0/50      | 0/35   |
| Van JY        | 2017     | China       | 28        | 0          | 0.00 (-0.04, 0.04)   | 0/74      | 0/42   |
| (iao XH       | 2017     | China       | 28        | 0 or 4     | 0.00 (-0.03, 0.03)   | 0/60      | 0/60   |
| Subtotal (I-s | quared : | = 0.0%, p = | 0.995)    |            | 0.00 (-0.01, 0.02)   | 1/376     | 0/341  |
| Median <28 v  | weeks o  | f gestation |           |            |                      |           |        |
| _in Y         | 2018     | China       | 24        | 4          | 0.02 (-0.03, 0.06)   | 1/60      | 0/52   |
| /u CY         | 2018     | China       | 24        | 4          | 0.00 (-0.06, 0.06)   | 0/30      | 0/30   |
| Celen MK      | 2013     | Turkey      | 18-27     | 4          | -0.04 (-0.15, 0.07)  | 0/21      | 1/24   |
| aong Q        | 2017     | China       | 1-6       | NR         | 0.00 (-0.04, 0.04)   | 0/44      | 0/44   |
| luang Q       | 2017     | China       | 24-28     | 12         | 0.00 (-0.08, 0.08)   | 0/20      | 0/30   |
| Vakano Y      | 2018     | Japan       | 22-28     | 4-8        | → 0.00 (-0.53, 0.53) | 0/2       | 0/3    |
| Vang HB       | 2018     | China       | 20-36     | NR         | 0.00 (-0.07, 0.07)   | 0/100     | 0/20   |
| Thang BF      | 2018     | China       | 24-28     | 0          | 0.00 (-0.04, 0.04)   | 0/39      | 0/75   |
| Zhou Y        | 2018     | China       | 24-28     | 0          | 0.00 (-0.04, 0.04)   | 0/60      | 0/36   |
| Subtotal (I-s | quared   | = 0.0%, p = | 0.998)    |            | 0.00 (-0.02, 0.02)   | 1/376     | 1/314  |
| -leterogeneit | y betwe  | en groups:  | p = 0.964 |            |                      |           |        |
| Overall (I-sq | uared =  | 0.0%, p = 1 | .000)     |            | 0.00 (-0.01, 0.01)   | 3/989     | 1/851  |

- TDF 300 mg risk difference of postpartum hemorrhage by timing of treatment initiation
  - Too few studies for subgroup analysis
- TDF 300 mg risk difference of postpartum hepatitis flare by timing of treatment initiation
  - Too few studies for subgroup analysis

## • LAM 100-150 mg risk difference of neonatal death by timing of treatment initiation

| of gestation<br>China, Philippines<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | 30-34<br>32<br>28-30<br>32<br>13-30<br>32<br>28-30<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 4<br>4<br>12<br>2<br>4<br>0<br>4<br>4-8<br>12<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | يلاطعها المحاصر   |   | 0.00 (-0.05,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.07,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00  | 0.05) 1/56<br>0.07) 0/30<br>0.10) 0/16<br>0.07) 0/53<br>0.02) 0/160<br>0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.03) 0/54<br>0.03) 0/59<br>0.07) 0/30<br>0.06) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53  | 1/59<br>0/26<br>0/22<br>0/20<br>0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/370<br>0/40<br>0/65<br>0/25<br>0/25  |
|--|---|---|---|---|---|---|--|
| China, Philippines<br>China<br>China<br>Australia<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 30-34<br>32<br>28-30<br>32<br>33<br>28-30<br>28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 4<br>4<br>12<br>2<br>4<br>0<br>4<br>4-8<br>12<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | يلاطعها المناصل   |   | 0.00 (-0.05,<br>0.00 (-0.07,<br>0.00 (-0.10,<br>0.00 (-0.10,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.09,<br>0.00 (-0.09,<br>0.00 (-0.046,<br>0.00 (-0.07,<br>0.00 (-0.01,<br>0.00 (-0.06,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0  | 0.05) 1/56<br>0.07) 0/30<br>0.10) 0/16<br>0.07) 0/53<br>0.02) 0/160<br>0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.03) 0/54<br>0.03) 0/54<br>0.03) 0/59<br>0.06) 0/30<br>0.06) 0/30<br>0.06) 0/30<br>0.065<br>0.07) 0/25<br>0.02) 0/110<br>0.024 0/73   | 1/59<br>0/26<br>0/22<br>0/20<br>0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/25   |
| China<br>China<br>Australia<br>China<br>China<br>China<br>Japan<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 32<br>28-30<br>32<br>13-30<br>32<br>28-32<br>28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 4<br>12<br>2<br>4<br>0<br>4<br>4-8<br>↓<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | للصالب للملمة   |   | 0.00 (-0.07,<br>0.00 (-0.10,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.04,<br>0.00 (-0.07,<br>0.00 (-0.01,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.  | 0.07) 0/30<br>0.07) 0/53<br>0.07) 0/53<br>0.02) 0/160<br>0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.07) 0/42<br>0.07) 0/42<br>0.07) 0/55<br>0.07) 0/30<br>0.08) 0/30<br>0.08) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04] 0/53  | 0/26<br>0/22<br>0/20<br>0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>Australia<br>China<br>China<br>Japan<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28-30<br>32<br>13-30<br>32<br>28-32<br>28-30<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 12<br>2<br>4<br>0<br>4<br>4-8<br>↓<br>12<br>4   | المطالب للمشمل  |   | 0.00 (-0.10,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.08,<br>0.00 (-0.08,<br>0.00 (-0.046,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.04,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.04,<br>0.00 | 0.10) 0/16<br>0.07) 0/53<br>0.02) 0/160<br>0.02) 0/170<br>0.02) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.07) 0/59<br>0.07) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.04) 0/10   | 0/22<br>0/20<br>0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| Australia<br>China<br>China<br>China<br>Japan<br>China<br>= 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 32<br>13-30<br>32<br>33<br>28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 2<br>4<br>0<br>4<br>4-8<br>12<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | halles that   |   | 0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.01,<br>0.00 (-0.01,<br>0.00 (-0.01,<br>0.00 (-0.06,<br>0.00 (-0.06,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,  | 0.07) 0/53<br>0.02) 0/160<br>0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.03) 0/54<br>0.03) 0/54<br>0.03) 0/59<br>0.06) 0/30<br>0.06) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53  | 0/20<br>0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>Japan<br>China<br>China<br>= 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 13-30<br>32<br>33<br>28-32<br>28-30<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 4<br>0<br>4<br>4-8<br>12<br>4<br>4<br>8<br>4<br>8<br>6<br>0<br>4<br>4<br>4  | كالد للملحظ   |   | 0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.04,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.01,<br>0.00 (-0.01,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,  | 0.02) 0/160<br>0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.041 0/53   | 0/89<br>0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>Japan<br>China<br>China<br>e 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 32<br>33<br>28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 0<br>4<br>4-8<br>12<br>4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4   | والمراجع المراجع  |   | 0.00 (-0.02,<br>0.00 (-0.09,<br>0.00 (-0.08,<br>0.00 (-0.046,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.00 (-0.04,   | 0.02) 0/128<br>0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.07) 0/59<br>0.06) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/73   | 0/120<br>0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>Japan<br>China<br>= 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 33<br>28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 4<br>4-8<br>12<br>4<br>4<br>4<br>4<br>4<br>6<br>0<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4  | hine the  |   | 0.00 (-0.09,<br>0.00 (-0.46,<br>0.00 (-0.47,<br>0.00 (-0.07,<br>0.00 (-0.01,<br>0.00 (-0.06,<br>0.00 (-0.06,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.04,<br>0.00 (-0.04,<br>0.  | 0.09) 0/17<br>0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/24<br>0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110   |
| Japan<br>China<br>China<br>= 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-32<br>28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 4-8 ← 12<br>4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  | de traint   |   | 0.00 (-0.46;<br>0.00 (-0.07;<br>0.00 (-0.07;<br>0.00 (-0.01;<br>0.00 (-0.01;<br>0.00 (-0.06;<br>0.00 (-0.06;<br>0.00 (-0.04;<br>0.00 (-0.03;<br>0.00 (-0.04;<br>0.00 (-0.04;<br>0.00 (-0.04;  | 0.46) 0/3<br>0.07) 0/42<br>0.03) 0/54<br>0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.021 0/110<br>0.04) 0/53   | 0/3<br>0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110   |
| China<br>China<br>e 1.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-30<br>28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 12<br>4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  |   |   | 0.00 (-0.07,<br>0.00 (-0.03,<br>0.00 (-0.01,<br>0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.04,<br>0.00 (-0.04,  | 0.07) 0/42<br>0.03) 0/54<br>0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53  | 0/20<br>0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>= 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  |   |   | 0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.06,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.03,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.03) 0/54<br>0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.02) 0/13  | 0/370<br>1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| = 0.0%, p = 1.000)<br>gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2   | 4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  |   |   | 0.00 (-0.01,<br>0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,<br>0.00 (-0.04,  | 0.01) 1/559<br>0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53  | 1/753<br>0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110   |
| gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2   | 4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  |   |   | 0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.02,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>2   | 4<br>NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4  |   |   | 0.00 (-0.07,<br>0.00 (-0.06,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.07) 0/30<br>0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/25<br>0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | NR<br>0<br>4<br>6<br>0<br>4<br>4<br>4   | 1   |   | 0.00 (-0.06,<br>0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.06) 0/30<br>0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/30<br>0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 0<br>4<br>6<br>0<br>4<br>4<br>4   | 1   | -   | 0.00 (-0.04,<br>0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.04) 0/70<br>0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/40<br>0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 4<br>6<br>0<br>4<br>4<br>4  | 1   | -   | 0.00 (-0.03,<br>0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.03) 0/65<br>0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/65<br>0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28  | 6<br>0<br>4<br>4<br>4   | 1   | ÷   | 0.00 (-0.07,<br>0.00 (-0.02,<br>0.00 (-0.04,  | 0.07) 0/25<br>0.02) 0/110<br>0.04) 0/53   | 0/25<br>0/110  |
| China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>28<br>28  | 0<br>4<br>4<br>4  | - 4   | ÷   | 0.00 (-0.02, 0.00 (-0.04, 0.00 (-0.04, 0.00 (-0.04, 0.00 (-0.04))))   | 0.02) 0/110<br>0.04) 0/53   | 0/110  |
| China<br>China<br>China<br>China   | 28<br>28<br>28<br>28  | 4<br>4<br>4   |   | ÷   | 0.00 (-0.04,  | 0.04) 0/53  |  |
| China<br>China<br>China  | 28<br>28<br>28  | 4<br>4  |   |   | 0.00 ( 0.00   |   | 0/53   |
| China<br>China   | 28<br>28  | 4   |   | ÷   | 0.00 (-0.06,  | 0.06) 0/33  | 0/28   |
| China  | 28  |   | _   | •   | 0.00 (-0.04,  | 0.04) 0/48  | 0/42   |
|  | 20  | 6   |   | •   | 0.00 (-0.06,  | 0.06) 0/30  | 0/30   |
| China  | 28  | 0   |   | •   | 0.00 (-0.05,  | 0.05) 0/43  | 0/35   |
| China  | 28  | 0   |   | •   | 0.00 (-0.06,  | 0.06) 0/35  | 0/32   |
| China  | 28  | 4   |   | ÷   | 0.00 (-0.06,  | 0.06) 0/33  | 0/27   |
| China  | 28  | 0   | _   | <b></b>   | 0.00 (-0.03,  | 0.03) 0/67  | 0/72   |
| China  | 28  | 0   |   | ÷   | 0.00 (-0.05,  | 0.05) 0/30  | 0/155  |
| China  | 28  | 4   |   | ÷   | 0.00 (-0.06,  | 0.06) 0/32  | 0/27   |
| China  | 28  | 4   |   | ÷   | 0.00 (-0.06,  | 0.06) 0/35  | 0/28   |
| China  | 28  | Variable (0,4,6)  |   | ÷   | 0.00 (-0.05,  | 0.05) 0/90  | 0/30   |
| China  | 28  | 4   |   | ÷   | 0.00 (-0.04,  | 0.04) 0/50  | 0/50   |
| China  | 20-28   | NR  | -   | ÷   | 0.00 (-0.02,  | 0.02) 0/113   | 0/95   |
| = 0.0%, p = 1.000)   |   |   |   | <b>◇</b>  | 0.00 (-0.01,  | 0.01) 0/1022  | 0/999  |
| of gestation   |   |   | _   | 1   |   |   |  |
| China  | 1st Trimester   | NR  |   | ·   | 0.00 (-0.06,  | 0.06) 0/29  | 0/34   |
| China  | 24  | 0   |   | ÷   | 0.00 (-0.05,  | 0.05) 0/36  | 0/44   |
| China  | 26  | 4   |   | •   | 0.00 (-0.05,  | 0.05) 0/60  | 0/28   |
| China  | 27  | 4   |   | <del></del>   | 0.00 (-0.06,  | 0.06) 0/32  | 0/32   |
| China  | 26  | 0   |   | ÷   | 0.00 (-0.08,  | 0.08) 0/24  | 0/24   |
| = 0.0%, p = 1.000)   |   |   | <   | $\mathbf{P}$  | 0.00 (-0.03,  | 0.03) 0/181   | 0/162  |
| een groups: p = 1.000<br>= 0.0%, p = 1.000)  |   |   |   |   | 0.00 (-0.01.  | 0.01) 1/1762  | 1/191  |
| =  | China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | China 28<br>China 28<br>China 28<br>China 28<br>China 28<br>China 28<br>China 28<br>China 28<br>China 28<br>China 20-28<br>≡ 0.0%, p = 1.000<br>Sestation 1st Trimester<br>China 24<br>China 26<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26<br>China 26<br>China 26<br>China 27<br>China 26<br>China 26 | China 28 4<br>China 28 0<br>China 28 0<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 Variable (0,4,6)<br>China 28 4<br>China 20-28 NR<br>= 0.0%, p = 1.000<br>Gestation<br>China 1st Trimester NR<br>China 24 0<br>China 26 4<br>China 26 4<br>China 26 0<br>= 0.0%, p = 1.000<br>0,0%, p = 1.000 | China 28 4<br>China 28 0<br>China 28 0<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 Variable (0,4,6)<br>China 28 4<br>China 28 4<br>China 28 NR<br>= 0.0%, p = 1.000<br>rgestation<br>China 24 0<br>China 26 4<br>China 26 4<br>China 26 0<br>= 0.0%, p = 1.000<br>an groups: p = 1.000<br>0.0%, p = 1.000 | China 28 4<br>China 28 0<br>China 28 0<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 Variable (0,4,6)<br>China 28 4<br>China 28 4<br>China 28 4<br>China 20-28 NR<br>= 0.0%, p = 1.000<br>rgestation<br>China 26 4<br>China 26 4<br>China 26 0<br>= 0.0%, p = 1.000<br>an groups: p = 1.000<br>0.0%, p = 1.000  | China       28       4       0.00 (0.00,<br>0.000 (0.00,<br>China       0.00 (0.00,<br>China | China       28       4       0.00 (4.06, 0.06) 0/33         China       28       0       0.00 (4.03, 0.03) 0/67         China       28       0       0.00 (4.06, 0.06) 0/32         China       28       4       0.00 (4.06, 0.06) 0/32         China       20.28       NR       0.00 (4.06, 0.06) 0/29         china       1st Trimester       NR       0.00 (4.06, 0.06) 0/29         China       24       0       0.00 (4.06, 0.06) 0/32         China       26       4       0.00 (4.06, 0.06) 0/32         China       26       0       0.00 (4.06, 0.06) 0/32         China       26       0       0.00 (4.03, 0.03) 0/181         angroups: p = 1.000       0.00 (4.00, 0.00) 0/24       0.00 |

# • LAM 100-150 mg risk difference of preterm birth by timing of treatment initiation

|               |          |             | in weeks  | in weeks   |                |                     | Events,   | Events |
|---------------|----------|-------------|-----------|------------|----------------|---------------------|-----------|--------|
| Author        | Year     | Country     | gestation | postpartum |                | RD (95% CI)         | Treatment | Contro |
| Median >28 v  | weeks o  | f gestation |           |            |                |                     |           |        |
| Greenup AJ    | 2014     | Australia   | 32        | 2          | +              | 0.06 (-0.04, 0.15)  | 3/53      | 0/20   |
| Pan CQ        | 2017     | China       | 13-30     | 4          | +              | -0.00 (-0.03, 0.02) | 1/160     | 1/89   |
| Wakano Y      | 2018     | Japan       | 28-32     | 4-8        | <u> </u>       | 0.00 (-0.46, 0.46)  | 0/3       | 0/3    |
| Subtotal (I-s | quared = | = 0.0%, p = | 0.453)    |            | $\diamond$     | -0.00 (-0.02, 0.02) | 4/216     | 1/112  |
| Median 28 w   | ooks of  | aestation   |           |            |                |                     |           |        |
| Guo YZ        | 2008     | China       | 28        | 0          | -              | 0.00 (-0.04, 0.04)  | 0/70      | 0/40   |
| Yang HW       | 2014     | China       | 28        | 4          |                | 0.00 (-0.04, 0.04)  | 0/53      | 0/53   |
| Wang W        | 2014     | China       | 28        | 4          | - <del>-</del> | 0.00 (-0.06, 0.06)  | 0/35      | 0/28   |
| Subtotal (I-s | quared = | = 0.0%, p = | 1.000)    |            | ¢              | 0.00 (-0.02, 0.02)  | 0/158     | 0/121  |
| Heterogeneit  | y betwe  | en groups:  | p = 0.965 |            |                |                     |           |        |
| Overall (I-sq | uared =  | 0.0%, p = 0 | 0.903)    |            | \$             | -0.00 (-0.02, 0.02) | 4/374     | 1/233  |
|               |          |             |           |            |                |                     |           |        |

# • LAM 100-150 mg risk difference of congenital abnormalities by timing of treatment initiation

| Author        | Year    | Country              | start in weeks gestation | Tx end in weeks postpartum | RD (95% CI)          | Events,<br>Treatment | Events<br>Contro |
|---------------|---------|----------------------|--------------------------|----------------------------|----------------------|----------------------|------------------|
| Median >28    | weeks   | of gestation         |                          |                            |                      |                      |                  |
| Xu WM         | 2009    | China, Philippines   | 30-34                    | 4                          | - 0.02 (-0.03, 0.07) | 1/56                 | 0/59             |
| Ge YL         | 2015    | China                | 28-30                    | 12                         | 0.00 (-0.10, 0.10)   | 0/16                 | 0/22             |
| Greenup AJ    | 2014    | Australia            | 32                       | 2                          | 0.04 (-0.05, 0.12)   | 2/53                 | 0/20             |
| Pan CQ        | 2017    | China                | 13-30                    | 4                          | 0.03 (-0.00, 0.06)   | 5/160                | 0/89             |
| Wakano Y      | 2018    | Japan                | 28-32                    | 4-8                        | → 0.00 (-0.46, 0.46) | 0/3                  | 0/3              |
| Wang DM       | 2016    | China                | 28-30                    | 12                         | 0.00 (-0.07, 0.07)   | 0/42                 | 0/20             |
| Zhang H       | 2014    | China                | 28-30                    | 4                          | -0.01 (-0.03, 0.02)  | 0/54                 | 2/370            |
| Subtotal (I-s | quared  | = 0.0%, p = 0.730)   |                          | ρ                          | 0.01 (-0.01, 0.03)   | 8/384                | 2/583            |
| Median 28 w   | eeks of | gestation            |                          |                            |                      |                      |                  |
| Tian XQ       | 2015    | China                | 28                       | 0 🔶                        | 0.00 (-0.02, 0.02)   | 0/110                | 0/110            |
| Yang HW       | 2014    | China                | 28                       | 4                          | 0.00 (-0.04, 0.04)   | 0/53                 | 0/53             |
| Wang W        | 2014    | China                | 28                       | 4                          | - 0.00 (-0.06, 0.06) | 0/35                 | 0/28             |
| Zeng YM       | 2013    | China                | 28                       | Variable (0,4,6)           | 0.00 (-0.05, 0.05)   | 0/90                 | 0/30             |
| Subtotal (I-s | quared  | = 0.0%, p = 1.000)   |                          | \$                         | 0.00 (-0.01, 0.01)   | 0/288                | 0/221            |
| Median <28    | weeks   | of gestation         |                          |                            |                      |                      |                  |
| Не Т          | 2018    | China                | 1st Trimester            | NR                         | -0.09 (-0.20, 0.02)  | 0/29                 | 3/34             |
| Shen ML       | 2016    | China                | 26                       | 4                          | - 0.00 (-0.05, 0.05) | 0/60                 | 0/28             |
| Yuan QF       | 2012    | China                | 27                       | 4                          | - 0.00 (-0.06, 0.06) | 0/32                 | 0/32             |
| Subtotal (I-s | quared  | = 9.6%, p = 0.331)   |                          | $\diamond$                 | -0.01 (-0.05, 0.03)  | 0/121                | 3/94             |
| Heterogeneit  | y betw  | een groups: p = 0.48 | 9                        |                            |                      |                      |                  |
| Overall (I-sq | uared = | = 0.0%, p = 0.889)   |                          | <b>•</b>                   | 0.00 (-0.01, 0.01)   | 8/793                | 5/898            |
|               |         |                      |                          | · · · · · ·                |                      |                      |                  |

## • LAM 100-150 mg risk difference of foetal death by timing of treatment initiation

| Author        | Year      | Country              | start in weeks<br>gestation | weeks postpartum                      | RD (95% CI)          | Events,<br>Treatment | Events<br>Contro |
|---------------|-----------|----------------------|-----------------------------|---------------------------------------|----------------------|----------------------|------------------|
| Median >28    | weeks o   | f gestation          |                             |                                       |                      |                      |                  |
| Xu WM         | 2009      | China, Philippines   | 30-34                       | 4 –                                   | ► 0.01 (-0.02, 0.05) | 1/89                 | 0/61             |
| Cheng YC      | 2011      | China                | 32                          | 4                                     | 0.00 (-0.07, 0.07)   | 0/30                 | 0/26             |
| Ge YL         | 2015      | China                | 28-30                       | 12                                    | 0.00 (-0.10, 0.10)   | 0/16                 | 0/22             |
| Greenup AJ    | 2014      | Australia            | 32                          | 2                                     | 0.00 (-0.07, 0.07)   | 0/52                 | 0/20             |
| Pan CQ        | 2017      | China                | 13-30                       | 4 🗕                                   | 0.00 (-0.02, 0.02)   | 0/160                | 0/89             |
| Su TB         | 2009      | China                | 32                          | 0                                     | 0.00 (-0.02, 0.02)   | 0/128                | 0/120            |
| Tang X        | 2009      | China                | 33                          | 4                                     | 0.00 (-0.09, 0.09)   | 0/17                 | 0/24             |
| Wakano Y      | 2018      | Japan                | 28-32                       | 4-8                                   | 0.00 (-0.46, 0.46)   | 0/3                  | 0/3              |
| Wang DM       | 2016      | China                | 28-30                       | 12                                    | 0.00 (-0.07, 0.07)   | 0/42                 | 0/20             |
| Zhang H       | 2014      | China                | 28-30                       | 4                                     | - 0.00 (-0.03, 0.03) | 0/53                 | 0/363            |
| Subtotal (I-  | quared    | = 0.0%, p = 1.000)   |                             | · · · · · · · · · · · · · · · · · · · | 0.00 (-0.01, 0.01)   | 1/590                | 0/748            |
| Median 28 v   | eeks of   | gestation            |                             |                                       |                      |                      |                  |
| Bai XW        | 2011      | China                | 28                          | 4                                     | 0.00 (-0.07, 0.07)   | 0/30                 | 0/25             |
| Chen SM       | 2017      | China                | 28                          | NR 🛁                                  | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30             |
| Guo YZ        | 2008      | China                | 28                          | 0                                     | - 0.00 (-0.04, 0.04) | 0/70                 | 0/40             |
| Ji YY         | 2015      | China                | 28                          | 4 _ →                                 | - 0.00 (-0.03, 0.03) | 0/65                 | 0/65             |
| Li ZG         | 2015      | China                | 28                          | 6                                     | 0.00 (-0.07, 0.07)   | 0/25                 | 0/25             |
| Tian XQ       | 2015      | China                | 28                          | •                                     | 0.00 (-0.02, 0.02)   | 0/110                | 0/110            |
| Yang HW       | 2014      | China                | 28                          | 4                                     | - 0.00 (-0.04, 0.04) | 0/53                 | 0/53             |
| Chen OB       | 2018      | China                | 28                          | 4                                     | - 0.00 (-0.06, 0.06) | 0/33                 | 0/28             |
| Fena HF       | 2007      | China                | 28                          | 4                                     | 0.00(-0.04,0.04)     | 0/48                 | 0/42             |
| Han YP        | 2014      | China                | 28                          | 6                                     | 0.00 (-0.06 0.06)    | 0/30                 | 0/30             |
| Han 7H        | 2005      | China                | 28                          | <u> </u>                              |                      | 0/43                 | 0/35             |
| liG           | 2006      | China                | 28                          | 0                                     |                      | 0/35                 | 0/32             |
| LiJH          | 2017      | China                | 28                          | 4                                     |                      | 0/33                 | 0/27             |
| Ben C.I       | 2016      | China                | 28                          | 0                                     |                      | 0/67                 | 0/72             |
| Ren V.I       | 2011      | China                | 28                          |                                       | 0.00 (-0.05, 0.05)   | 0/30                 | 0/155            |
| Wang E I      | 2012      | China                | 28                          | 4                                     | 0.00 (-0.06, 0.06)   | 0/32                 | 0/27             |
| Wang W        | 2012      | China                | 20                          |                                       | 0.00 (-0.06, 0.06)   | 0/35                 | 0/28             |
| Zong VM       | 2014      | China                | 20                          | Variable (0.4.6)                      | 0.00 (-0.05, 0.05)   | 0/90                 | 0/20             |
| Zeng Tw       | 2010      | China                | 20                          | variable (0,4,0)                      |                      | 0/50                 | 0/50             |
| Zhang TF      | 2010a     | China                | 20                          |                                       | - 0.00 (-0.04, 0.04) | 0/50                 | 0/05             |
| Subtotal (I-: | squared : | = 0.0%, p = 1.000)   | 20-20                       |                                       | 0.00 (-0.02, 0.02)   | 0/1022               | 0/95             |
| Median <28    | weeks o   | frestation           |                             |                                       |                      |                      |                  |
| He T          | 2018      | China                | 1st Trimester               | NB T                                  | -0.06 (-0 15, 0.04)  | 0/27                 | 2/35             |
| Li WF         | 2006      | China                | 24                          | 0                                     | 0.00 (-0.05, 0.05)   | 0/36                 | 0/44             |
| Shen ML       | 2016      | China                | 26                          | 4                                     | - 0.00 (-0.03, 0.03) | 0/60                 | 0/60             |
| Yuan QE       | 2012      | China                | 27                          | 4                                     |                      | 0/30                 | 0/30             |
| Zhu M         | 2014      | China                | 26                          | ·                                     | -0.04 (-0.15, 0.07)  | 0/24                 | 1/25             |
| Subtotal (I-  | squared : | = 0.0%, p = 0.789)   | 20                          | Ŭ o                                   | -0.01 (-0.03, 0.02)  | 0/177                | 3/194            |
| Heterogene    | ty betwe  | en groups: p = 0.892 |                             |                                       |                      | 1/1700               | 0/10.1           |
| Jverall (I-s  | uared =   | 0.0%, p = 1.000)     |                             | Ī                                     | -0.00 (-0.01, 0.01)  | 1/1/89               | 3/194            |
|               |           |                      |                             |                                       |                      |                      |                  |

# • LAM 100-150 mg risk difference of postpartum hemorrhage by timing of treatment initiation

| Author                        | Year               | Country                   | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |    |            |    | RD (95% CI)         | Events,<br>Treatment | Events,<br>Control |
|-------------------------------|--------------------|---------------------------|-----------------------------------|----------------------------------|----|------------|----|---------------------|----------------------|--------------------|
| Median >28 v                  | weeks o            | f gestation               |                                   |                                  |    |            |    |                     |                      |                    |
| Greenup AJ                    | 2014               | Australia                 | 32                                | 2                                |    | -          |    | -0.05 (-0.23, 0.12) | 5/52                 | 3/20               |
| Pan CQ                        | 2017               | China                     | 13-30                             | 4                                |    |            |    | 0.02 (-0.02, 0.07)  | 7/160                | 2/89               |
| Zhang H                       | 2014               | China                     | 28-30                             | 4                                |    |            |    | 0.01 (-0.03, 0.04)  | 1/53                 | 5/363              |
| Subtotal (I-s                 | quared             | = 0.0%, p =               | 0.664)                            |                                  |    | $\diamond$ |    | 0.01 (-0.02, 0.04)  | 13/265               | 10/472             |
| Median 28 w                   | eeks of            | gestation                 |                                   |                                  |    |            |    |                     |                      |                    |
| Yang HW                       | 2014               | China                     | 28                                | 4                                |    |            |    | 0.00 (-0.04, 0.04)  | 0/53                 | 0/53               |
| Ren CJ                        | 2016               | China                     | 28                                | 0                                |    | -          |    | -0.01 (-0.15, 0.12) | 13/67                | 15/72              |
| Wang W                        | 2014               | China                     | 28                                | 4                                |    |            |    | 0.00 (-0.06, 0.06)  | 0/35                 | 0/28               |
| Subtotal (I-s                 | quared             | = 0.0%, p =               | 0.979)                            |                                  |    | $\Phi$     |    | -0.00 (-0.03, 0.03) | 13/155               | 15/153             |
| Heterogeneit<br>Overall (I-sq | y betwe<br>uared = | en groups:<br>0.0%, p = 0 | p = 0.603<br>0.951)               |                                  |    | ♦          |    | 0.01 (-0.02, 0.03)  | 26/420               | 25/625             |
|                               |                    |                           |                                   | 3                                | 21 | 0.1        | .2 | 3                   |                      |                    |

- LAM 100-150 mg risk difference of postpartum flare by timing of treatment initiation
  - Too few studies for subgroup analysis

### • LdT 600 mg risk difference of neonatal death by timing of treatment initiation

| Median 28 weeks of gestation   | Author Year Country   | Tx<br>start in weeks<br>gestation  | Tx end<br>in weeks<br>postpartum   | RD (95% CI)   | Events,<br>Treatment   | Events,<br>Control  |
|--|---|--|--|---|--|---|
| Median 28 weeks of pestilion         Cons (M)         C | Median >28 weeks of gestation           Bai HL         2013         China           Zhang LJ         2009         China           Ge YL         2015         China           Hu Y         2013         China           Liu J         2017         China           Liu XB         2016         China           Liu Y         2017         China           Yang LM         2016         China           Yang LM         2016         China           Yang LM         2016         China           Yang LM         2016         China           Zhang H         2014         China           Subtotal (I-squared = 0.0%, p =         0.0%, p = | 28-32<br>28-32<br>28-30<br>28-36<br>4-32<br>32<br>28-36<br>4-32<br>28-30<br>28-30<br>28-30<br>28-30<br>1.000)  | 4<br>4<br>12<br>3-4<br>NR<br>4<br>4<br>0<br>12<br>6<br>4<br>0<br>0                         | $\begin{array}{c} 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.06) \\ 0.00 \ (-0.09, \ 0.09) \\ 0.00 \ (-0.01, \ 0.01) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.01, \ 0.01) \\ 0.00 \ (-0.01, \ 0.01) \\ 0.00 \ (-0.01, \ 0.01) \end{array}$   | 0/30<br>0/31<br>0/20<br>0/149<br>0/104<br>0/20<br>0/82<br>0/81<br>0/36<br>0/30<br>0/30<br>0/262<br>0/845   | 0/30<br>0/30<br>0/22<br>0/179<br>0/28<br>0/20<br>0/78<br>0/370<br>0/20<br>0/30<br>0/370<br>0/370<br>0/370<br>0/370  |
| Median <28 weeks of gestation  | $\begin{array}{llllllllllllllllllllllllllllllllllll$  | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4                        | $\begin{array}{c} 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.07, \ 0.07) \\ 0.00 \ (-0.07,$ | 0/30<br>0/28<br>0/65<br>0/60<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30   | 0/30<br>0/26<br>0/60<br>0/60<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/3   |
|  | $\begin{array}{llllllllllllllllllllllllllllllllllll$  | 24-28<br>24<br>20-28<br>24<br>12-14<br>15 Trimester<br>1st Trimester<br>1st Trimester<br>24-28<br>26<br>24-28<br>12-28<br>12-28<br>12-28<br>12-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-3 | 4<br>12<br>0<br>24<br>12<br>NR<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12 | $\begin{array}{c} 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.05, \ 0.02) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.06, \ 0.06) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.03, \ 0.03) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.02) \\ 0.00 \ (-0.02, \ 0.05) \\ 0.00 \ (-0.05, \ 0.05) \\ 0.00 \ (-0.01, \ 0.01) \\ 0.00 \ (-0.01, \ 0.01) \\ 0.00 \ (-0.00, \ 0.00) \end{array}$   | 0/100<br>0/123<br>0/90<br>0/100<br>0/40<br>0/41<br>0/51<br>0/51<br>0/51<br>0/61<br>0/61<br>0/66<br>0/103<br>0/84<br>0/171<br>0/100<br>0/57<br>0/57<br>0/36<br>0/41<br>0/53<br>0/1739<br>0/4906 | 0/100<br>0/122<br>0/300<br>0/40<br>0/40<br>0/40<br>0/40<br>0/51<br>0/28<br>0/46<br>0/28<br>0/46<br>0/28<br>0/46<br>0/420<br>0/52<br>0/45<br>0/46<br>0/202<br>0/320<br>0/20<br>0/20<br>0/22<br>0/34<br>0/107<br>0/202<br>0/34<br>0/107<br>0/2146 |

### • LdT 600 mg risk difference of preterm birth by timing of treatment initiation

| of gestatic<br>China<br>China<br>China<br>d = 0.0%, p<br>f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China | 28-32<br>32<br>28-32<br>0 = 0.982)<br>28<br>28<br>28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 3-4<br>0<br>6<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4  |  |  |   | -0.01 (-0.06, 0.04)<br>-0.00 (-0.05, 0.04)<br>0.00 (-0.06, 0.06)<br>-0.00 (-0.03, 0.03)<br>0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04) | 8/149<br>3/81<br>0/30<br>11/260<br>1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60 | 11/179<br>15/370<br>0/30<br>26/579<br>0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
|---|---|--|--|--|---|---|---|---|
| China<br>China<br>China<br>d = 0.0%, p<br>f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China                | 28-32<br>32<br>28-32<br>0 = 0.982)<br>28<br>28<br>28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 3-4<br>0<br>6<br>24<br>NR<br>NR<br>4<br>0<br>0 or 4<br>12<br>4   |  |  |   | -0.01 (-0.06, 0.04)<br>-0.00 (-0.05, 0.04)<br>0.00 (-0.06, 0.06)<br>-0.00 (-0.03, 0.03)<br>0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04) | 8/149<br>3/81<br>0/30<br>11/260<br>1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60 | 11/179<br>15/370<br>0/30<br>26/579<br>0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| China<br>China<br>d = 0.0%, p<br>f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China                                  | 32<br>28-32<br>28-32<br>28<br>28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 0<br>6<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4   |  |  |   | -0.00 (-0.05, 0.04)<br>0.00 (-0.06, 0.06)<br>-0.00 (-0.03, 0.03)<br>0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)                        | 3/81<br>0/30<br>11/260<br>1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60          | 15/370<br>0/30<br>26/579<br>0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| China<br>d = 0.0%, p<br>f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28-32<br>28-32<br>28<br>28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 6<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4  |  |  |   | 0.00 (-0.06, 0.06)<br>-0.00 (-0.03, 0.03)<br>0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)   | 0/30<br>11/260<br>1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60                  | 0/30<br>26/579<br>0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| d = 0.0%, p<br>f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | <ul> <li>a = 0.982)</li> <li>28</li> <li>28</li> <li>26-30</li> <li>28</li> </ul> | 0<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4  |  | <b>╺</b> ╺╺╸ <b>╸</b> ╸<br><b>╸</b> ╸╸<br><b>╸</b> ╸<br><b>╸</b> ╸<br><b>╸</b> ・<br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b><br><b>・</b> |   | -0.00 (-0.03, 0.03)<br>0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)   | 11/260<br>1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60                          | 26/579<br>0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| f gestation<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 0<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4  |  |  |   | 0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60                                    | 0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 0<br>24<br>NR<br>NR<br>4<br>0<br>0<br>0<br>0 or 4<br>12<br>4   |  |  |   | 0.01 (-0.01, 0.03)<br>0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 1/152<br>2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60                                    | 0/132<br>2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60   |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | 24<br>NR<br>NR<br>4<br>0<br>0<br>0<br>0 or 4<br>12<br>4  |  |  |   | 0.00 (-0.06, 0.07)<br>0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 2/58<br>6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60   | 2/60<br>4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | NR   |  |  |   | 0.05 (-0.09, 0.18)<br>-0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 6/44<br>2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60   | 4/44<br>9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>China<br>China<br>China<br>China  | 26-30<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | NR -<br>NR<br>4<br>0<br>0<br>0 or 4<br>12<br>4   |  |  |   | -0.15 (-0.26, -0.03)<br>-0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 2/65<br>1/41<br>7/127<br>5/40<br>5/41<br>2/60   | 9/51<br>5/41<br>3/58<br>3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | NR<br>4<br>0<br>0 or 4<br>12<br>4  |  |  | _   | -0.10 (-0.21, 0.01)<br>0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)  | 1/41<br>7/127<br>5/40<br>5/41<br>2/60   | 5/41<br>3/58<br>3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>China<br>China  | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28  | 4<br>0<br>0 or 4<br>12<br>4  | Ξ  | ŧ  | _   | 0.00 (-0.07, 0.07)<br>0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)   | 7/127<br>5/40<br>5/41<br>2/60   | 3/58<br>3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>China   | 28<br>28<br>28<br>28<br>28<br>28  | 0<br>0<br>0 or 4<br>12<br>4  | _  |  |   | 0.05 (-0.08, 0.18)<br>0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)   | 5/40<br>5/41<br>2/60  | 3/40<br>7/59<br>4/60  |
| China<br>China<br>China<br>China<br>- 13 8%   | 28<br>28<br>28<br>28  | 0<br>0 or 4<br>12<br>4   | _  | +  | _   | 0.00 (-0.13, 0.13)<br>-0.03 (-0.11, 0.04)   | 5/41<br>2/60  | 7/59<br>4/60  |
| China<br>China<br>China   | 28<br>28<br>28  | 0 or 4<br>12<br>4  | -  |  |   | -0.03 (-0.11, 0.04)   | 2/60  | 4/60  |
| China<br>China  | 28<br>28  | 12<br>4  |  | <b></b>  |   | ( , ,   |   |   |
| China   | 28  | 4  |  |  |   | 0.00 (-0.04, 0.04)  | 0/48  | 0/47  |
| 1 - 13 89/  |   |  |  |  |   | 0.00 (-0.07, 0.07)  | 0/23  | 0/37  |
| ı — 13.0%,  | p = 0.313)  |  |  | $\overline{\mathbf{\Phi}}$   |   | 0.00 (-0.01, 0.01)  | 31/699  | 37/629  |
| of gestatic   | n   |  |  |  |   |   |   |   |
| China   | 24  | 0  |  |  |   | 0.00 (-0.02, 0.02)  | 0/100   | 0/100   |
| China   | 20-32   | NR   |  | <u> </u>   |   | 0.02 (-0.03, 0.07)  | 22/365  | 4/92  |
| China   | 1st Trimester   | NR   |  | i  |   | 0.00 (-0.08, 0.08)  | 1/32  | 1/34  |
| China   | 24-28   | 0  |  | <u> </u>   |   | 0.00 (-0.04, 0.04)  | 0/66  | 0/46  |
| China   | <14-28  | NR   |  |  |   | -0.01 (-0.06, 0.05)   | 14/171  | 28/320  |
| China   | 24-28   | NR   |  | <u> </u>   |   | 0.02 (-0.02, 0.05)  | 10/329  | 1/65  |
| China   | 1st Trimester   | 0  |  |  |   | 0.00 (-0.05, 0.05)  | 0/53  | 0/34  |
| d = 0.0%, p   | o = 0.985)  |  |  | Ŷ  |   | 0.00 (-0.01, 0.02)  | 47/1116   | 34/691  |
| een group   | s: p = 0.894  |  |  |  |   |   |   |   |
| = 0.0%, p   | = 0.883)  |  |  | Ŷ  |   | 0.00 (-0.01, 0.01)  | 89/2075   | 97/1899   |
| 1<br>   | China<br>China<br>China<br>China<br>= 0.0%, p<br>een group<br>: 0.0%, p   | China 24-28<br>China <14-28<br>China 24-28<br>China 1st Trimester<br>= 0.0%, p = 0.985)<br>een groups: p = 0.894<br>: 0.0%, p = 0.883) | China 24-28 0<br>China <14-28 NR<br>China 24-28 NR<br>China 1st Trimester 0<br>= 0.0%, p = 0.985)<br>ten groups: p = 0.894<br>: 0.0%, p = 0.883) | China 24-28 0<br>China <14-28 NR<br>China 24-28 NR<br>China 1st Trimester 0<br>= 0.0%, p = 0.985)<br>ten groups: p = 0.894<br>:0.0%, p = 0.883)  | China 24-28 0<br>China <14-28 NR<br>China 24-28 NR<br>China 1st Trimester 0<br>= 0.0%, p = 0.985)<br>ten groups: p = 0.894<br>:0.0%, p = 0.883) | China 24-28 0<br>China <14-28 NR<br>China 24-28 NR<br>China 1st Trimester 0<br>= 0.0%, p = 0.895)<br>ten groups: p = 0.894<br>:0.0%, p = 0.883)   | China       24-28       0       0.00 (-0.04, 0.04)         China       <14-28                             | China $24-28$ 0 $0.00(-0.04, 0.04)$ $0/66$ China $-14-28$ NR $-0.01(-0.06, 0.05)$ $14/171$ China $24-28$ NR $0.02(-0.02, 0.05)$ $10/329$ China       1st Trimester       0 $0.00(-0.01, 0.02)$ $0/53$ $= 0.0\%, p = 0.985$ ) $0.00(-0.01, 0.02)$ $47/1116$ ren groups: $p = 0.894$ $0.00(-0.01, 0.01)$ $89/2075$ $= 0.0\%, p = 0.883$ ) $0.00(-0.01, 0.01)$ $89/2075$ |

# • LdT 600 mg risk difference of congenital abnormalities by timing of treatment initiation

| Median >28 weeks of gestation       0.00 (-0.09, 0.09)       0/20         Ge YL       2016 China       28-32       3-4       0.00 (-0.09, 0.09)       0/20         Liu XB       2016 China       28-36       4       0.00 (-0.09, 0.09)       0/20         Liu XB       2016 China       28-30       12       0.00 (-0.09, 0.09)       0/20         Wang DM       2016 China       28-30       12       0.00 (-0.08, 0.08)       0/36         Zharg H       2014 China       28-30       4       0.00 (-0.06, 0.06)       0/30         Zharg H       2014 China       28-30       4       -0.00 (-0.01, 0.01)       1/52         Subtotal (I-squared = 0.0%, p = 0.877)       0.00 (-0.01, 0.01)       1/52       0.00 (-0.01, 0.01)       1/52         Median 28 weeks of gestation       10.07       2016 China       28       0       0.00 (-0.03, 0.03)       0/58         Jiang XN       2013 China       28       4       0.00 (-0.05, 0.05)       0/38       Fan LY       0.00 (-0.05, 0.05)       0/31         Li YH       2013 China       28       NR       0.00 (-0.05, 0.05)       0/41       0.00 (-0.05, 0.05)       0/41         Lou JJ       2015 China       28       NR       0.00 (-0.05, 0.05)   | Events,<br>Control | Events,<br>Treatment | RD (95% CI)         |  | Tx end<br>in weeks<br>postpartum | Tx<br>start in weeks<br>gestation | Country                | Year                | Author                   |
|--|--------------------|----------------------|---------------------|--|----------------------------------|-----------------------------------|------------------------|---------------------|--------------------------|
| Ge YL       2015       China       28-30       12       0.00 (-0.09, 0.09)       0/20         Hu Y       2018       China       28-32       3-4       0.00 (-0.09, 0.09)       0/20         Liu XB       2016       China       28-32       3-4       0.00 (-0.09, 0.09)       0/20         Liu Y       2016       China       28-32       4       0.00 (-0.09, 0.09)       0/20         Yao LF       2014       China       28-32       6       0.00 (-0.09, 0.09)       0/20         Zharg H       2014       China       28-30       4       0.00 (-0.01, 0.01)       1/259         Median 28 weeks of gestation       Lu QY       2016       China       28       0       0.00 (-0.01, 0.01)       0/152         Chen WJ 2017       China       28       0       0.00 (-0.01, 0.01)       0/152         Chen WJ 2017       China       28       4       0.00 (-0.03, 0.03)       0/68         Jiang XN 2013       China       28       NR       0.00 (-0.05, 0.05)       0/30         Li YH       2017       China       28       NR       0.00 (-0.05, 0.05)       0/40         Li YH       2016       China       28       NR       0.00 (-0.0   |                    |                      |                     |  |                                  | tion                              | s of gesta             | 3 week              | Median >2                |
| Hu Y       2018 China       28-32       3-4       0.02 (0.01, 0.05)       3/149         Liu XB       2016 China       28-36       4       0.00 (0.09, 0.09)       0/20         Wang DM       2016 China       28-30       12       0.00 (0.08, 0.08)       0/30         Zhang H       2014 China       28-30       4       0.00 (0.00, 0.00, 0.00)       0/30         Subtotal (I-squared = 0.0%, p = 0.877)       0.00 (0.01, 0.01)       1/259       0.00 (0.01, 0.01)       1/259         Median 28 weeks of gestation       1       1       0.00 (0.00, 0.00, 0.00)       0.00 (0.01, 0.01)       1/259         Ding XP       2013 China       28       2       0.00 (0.01, 0.01)       0/152         Ding XP       2013 China       28       24       0.00 (0.03, 0.03)       0/65         Jiang XN       2013 China       28       24       0.00 (0.04, 0.04)       0/12         Lou JJ       2015 China       28       24       0.00 (0.04, 0.04)       0/30         Li XY       2015 China       28       4       0.00 (0.04, 0.04)       0/30         Li XY       2015 China       28       4       0.00 (0.04, 0.04)       0/30         Li XY       2015 China       28       4  | 0/22               | 0/20                 | 0.00 (-0.09, 0.09)  | <u>+</u>                                     | 12                               | 28-30                             | China                  | 2015                | Ge YL                    |
| Liu XB 2016 China 28-36 4<br>Liu Y 2016 China 28-36 4<br>Wang DM 2016 China 28-32 4<br>Wang DM 2016 China 28-32 6<br>Zhang H 2014 China 28-32 6<br>Zhang H 2014 China 28-32 6<br>Lu Y 2016 China 28-32 6<br>Chen WJ 2017 China 28 0<br>Chen WJ 2017 China 28 0<br>Li YY 2018 China 28 4<br>Chen WJ 2013 China 28 4<br>Li YY 2018 China 28 4<br>Li YY 2018 China 28 4<br>Li YY 2018 China 28 4<br>China 20-30 NR<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 4<br>China 28 4<br>China 20-30 NR<br>China 20-30 N | 0/179              | 3/149                | 0.02 (-0.01, 0.05)  | <b>+</b>                                     | 3-4                              | 28-32                             | China                  | 2018                | Hu Y                     |
| Liu Y 2016 China 4-32 4<br>Wang DM 2016 China 28-30 12<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 weeks of gestation<br>Lu QY 2016 China 28 0<br>Lu QY 2017 China 28 24<br>Cool (-0.01, 0.01) 1/152<br>Chen WJ 2017 China 28 0<br>Li YH 2017 China 28 0<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 weeks of gestation<br>Shi QW 2017 China 28 0<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Week of Orgentation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 4<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 28 12<br>Shen ML 2016 China 28 12<br>Shen ML 2016 China 28 12<br>Shen ML 2016 China 28 NR<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 24-28 NR<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Shi QW 2017 China 24-28 NR<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Subtotal (I-squared = 0.0%, p = 1.000)<br>Median -28 Weeks of gestation<br>Subtotal (I-   | 0/20               | 0/20                 | 0.00 (-0.09, 0.09)  | <u>+</u>                                     | 4                                | 28-36                             | China                  | 2016                | Liu XB                   |
| Wang DM       2016       China       28-30       12       0.00       (-0.08, 0.08)       0.36         Yao LF       2014       China       28-30       4       0.00       (-0.01, 0.01)       1/262         Subtotal       (I-squared = 0.0%, p = 0.877)       0.00       (-0.01, 0.01)       1/262       0.00       (-0.01, 0.01)       1/262         Median 28 weeks of gestation       1       0.00       (-0.01, 0.01)       1/262       0.00       (-0.01, 0.01)       1/262         Obig XP       2016       China       28       0       0.00       (-0.04, 0.04)       0/79         Jiang XN       2013       China       28       24       0.00       (-0.08, 0.03)       0/65         Li YH       2017       China       28       -36       0.00       (-0.04, 0.04)       0.07         Li YH       2017       China       28       4       -0.00       (-0.04, 0.04)       0.06       0.030         Li YH       2015       China       28       4       -0.00       (-0.04, 0.04)       0.06       0.030       0.06       0.030       0.06       0.030       0.06       0.030       0.06       0.030       0.06       0.030       0.06       0.0   | 0/78               | 0/82                 | 0.00 (-0.02, 0.02)  |  | 4                                | 4-32                              | China                  | 2016                | Liu Y                    |
| Yao F       2014       China       28-32       6       0.00 (-0.06, 0.06)       0.30         Zhang H       2014       China       28-30       4       -0.00 (-0.01, 0.01)       1/282         Subtotal (I-squared = 0.0%, p = 0.877)   | 0/20               | 0/36                 | 0.00 (-0.08, 0.08)  | +  | 12                               | 28-30                             | China                  | 2016                | Wang DM                  |
| Zhang H       2014       China       28-30       4       -0.00(-0.01, 0.01)       1/282         Subtotal (I-squared = 0.0%, p = 0.877)       Median 28 weeks of gestation       0.00(-0.01, 0.01)       4/599         Median 28 weeks of gestation       0.00(-0.01, 0.01)       0/152         Lu QY       2016       China       28       0       0.00(-0.01, 0.01)       4/599         Median 28 weeks of gestation       0.00(-0.04, 0.04)       0/79       0.00(-0.03, 0.03)       0/68         Jang XN       2013       China       28       24       0.00(-0.03, 0.03)       0/65         Li YH       2017       China       28       -36       0.00(-0.05, 0.05)       0/41         Lou JJ       2015       China       28       NR       0.00(-0.04, 0.04)       0/79         Li YH       2017       China       28       NR       0.00(-0.05, 0.05)       0/40         Lou JJ       2015       China       28       24       -0.00(-0.04, 0.04)       0/53         Zhang GH       2018       China       28       4       -0.00(-0.04, 0.04)       0/63         Subtotal (I-squared = 0.0%, p = 1.000)       Median <28   | 0/30               | 0/30                 | 0.00 (-0.06, 0.06)  | ÷  | 6                                | 28-32                             | China                  | 2014                | Yao LF                   |
| Subtotal (I-squared = 0.0%, p = 0.877)       0.00 (-0.01, 0.01) 4/599         Median 28 weeks of gestation       0.00 (-0.01, 0.01) 0/152         Lu QY       2016 China       28       0         Ding XP       2018 China       28       0         Jang XN       2013 China       28       4       0.00 (-0.04, 0.04) 0/79         Jiang XN       2013 China       28       24       0.00 (-0.05, 0.05) 0/38         Li YH       2017 China       28       -36       0.00 (-0.03, 0.03) 0/65         Li YH       2015 China       28       -36       0.00 (-0.04, 0.04) 2/127         Peng BA       2015 China       28       4       -0.00 (-0.04, 0.04) 2/127         Peng BA       2015 China       28       4       -0.00 (-0.05, 0.05) 0/40         Ren N       2015 China       28       4       -0.00 (-0.04, 0.04) 0/63         Xiao XH       2017 China       28       4       -0.00 (-0.05, 0.05) 0/40         Subtotal (I-squared = 0.0%, p = 1.000)       -0.00 (-0.05, 0.05) 0/40       -0.00 (-0.05, 0.05) 0/40         Median <28 weeks of gestation   | 2/370              | 1/262                | -0.00 (-0.01, 0.01) | -  | 4                                | 28-30                             | China                  | 2014                | Zhang H                  |
| Median 28 weeks of gestation       0.00 (-0.01, 0.01) 0/152         Lu QY       2016 China       28       0         Ding XP       2018 China       28       4         Fan LY       2013 China       28       24       0.00 (-0.05, 0.05) 0/38         Jiang XN       2013 China       28       24       0.00 (-0.03, 0.03) 0/58         Jiang XN       2013 China       28   | 2/719              | 4/599                | 0.00 (-0.01, 0.01)  | <b>◇</b>                                     |                                  | , p = 0.877)                      | ed = 0.0%              | -square             | Subtotal (I              |
| Lu QY       2016       China       28       0       ••       0.00 (-0.01, 0.01) 0/152         Chen WJ       2017       China       28       0       ••       0.00 (-0.04, 0.04) 0/79         Ding XP       2018       China       28       4       0.00 (-0.05, 0.05) 0/38         Fan LY       2013       China       28       24       0.00 (-0.03, 0.03) 0/58         Jiang XN       2013       China       28       -36       0.00 (-0.05, 0.05) 0/41         Li YH       2015       China       28       NR       0.00 (-0.05, 0.05) 0/41         Lou JJ       2015       China       28       0       -0.00 (-0.04, 0.04) 0/45         Wang TD       2015       China       28       0       -0.00 (-0.04, 0.04) 0/46         Wang TD       2015       China       28       0 or 4       -0.00 (-0.05, 0.05) 0/40         Shang GH       2018       China       12.14       24       0.00 (-0.05, 0.05) 0/40         Shi QW       2017       China       12.14       24       0.00 (-0.05, 0.05) 0/40         Shi QW       2017       China       12.14       24       0.00 (-0.05, 0.05) 0/40         Shen ML       2016       China       15.1 Trimest   |                    |                      |                     | <u></u>                                      |                                  | on                                | of gestatio            | weeks               | Median 28                |
| Chen WJ 2017 China 28       0         Ding XP 2013 China 28       4         Fan LY 2013 China 28       24         Jiang XN 2013 China 26-30 NR       0.00 (-0.03, 0.03) 0/55         Li YH 2017 China 28       -36         Li YH 2017 China 28       -36         Li YH 2013 China 28       -36         Li YH 2013 China 28       -36         Li ZY 2018 China 28       -0.00 (-0.06, 0.06) 0/30         Li ZY 2018 China 28       4         Peng BA 2012 China 28       4         Quit S China 28       4         Quit C China 12-14       24         Quit C China 12-14       24         Quit C China 12-28       12         Quit C China 12-28       12         Quit C Ch  | 0/132              | 0/152                | 0.00 (-0.01, 0.01)  |  | 0                                | 28                                | China                  | 2016                | Lu QY                    |
| Ding XP       2018       China       28       4         Jiang XN       2013       China       28       24         Jiang XN       2013       China       28       24         Jiang XN       2013       China       28       24         Jiang XN       2013       China       28       0.00       (-0.03, 0.03)       0/58         Li YH       2017       China       28       -36       0.00       (-0.04, 0.04)       2/12         Peng BA       2012       China       28       0       0.00       (-0.05, 0.05)       0/30         Ren N       2015       China       28       0       0.00       (-0.04, 0.04)       2/127         Peng BA       2017       China       28       0       0.00       (-0.05, 0.05)       0/40         Stao XH       2017       China       28       0 or 4       -0.02       (-0.07, 0.04)       1/60         Sthe ML       2016       China       12 14       24       0.00       (-0.05, 0.05)       0/40         Wang HP       2018       China       15 Trimester       NR       -0.02       (-0.01, 0.01)       3/829         Median <28  | 0/44               | 0/79                 | 0.00 (-0.04, 0.04)  |  | 0                                | 28                                | China                  | 2017                | Chen W.I                 |
| Fan LY       2013       China       28       24         Jiang XN       2013       China       26-30       NR         Li YH       2017       China       28       -36         Li YH       2017       China       28       -36         Li YH       2017       China       28       NR         Lou JJ       2015       China       28       4         Peng BA       2012       China       28       0         Ren N       2015       China       28       24         Wang TD       2015       China       28       4         Ondo (-0.04, 0.04)       0/40       0.00 (-0.05, 0.05)       0/40         Wang TD       2015       China       28       4       -0.00 (-0.04, 0.04)       0/53         Xiao XH       2017       China       28       4       -0.00 (-0.05, 0.05)       0/40         Subtotal (I-squared = 0.0%, p = 1.000)       Vang GH       2015       China       12-14       24         Median <28  | 0/38               | 0/38                 | 0.00 (-0.05, 0.05)  | -  | 4                                | 28                                | China                  | 2018                | Ding XP                  |
| Jiang XN       2013       China       26-30       NR         Li YH       2017       China       28       ~36       0.00 (-0.03, 0.03)       0/65         Li YY       2018       China       28       NR       0.00 (-0.06, 0.06)       0/30         Li ZY       2018       China       28       NR       0.00 (-0.04, 0.04)       2/127         Peng BA       2012       China       28       0       0.00 (-0.04, 0.04)       2/127         Peng BA       2015       China       28       4       0.00 (-0.04, 0.04)       2/127         Wang TD       2015       China       28       4       0.00 (-0.04, 0.04)       0/46         Wang TD       2015       China       28       4       -0.02 (-0.07, 0.04)       1/60         Subtotal (I-squared = 0.0%, p = 1.000)       Wang TD       2017       China       28       4       -0.00 (-0.05, 0.05)       0/40         Median <28  | 0/60               | 0/58                 | 0.00 (-0.03, 0.03)  | <u> </u>                                     | 24                               | 28                                | China                  | 2013                | Fan LY                   |
| Li YH 2017 China 28 ~36<br>Li YH 2017 China 28 NR<br>Lou JJ 2015 China 28 NR<br>Peng BA 2012 China 28 0<br>Xiao XH 2015 China 28 24<br>Xiao XH 2017 China 28 4<br>Xiao XH 2017 China 28 4<br>Xiao XH 2017 China 28 4<br>NR   | 0/51               | 0/65                 | 0.00 (-0.03, 0.03)  | • • •  | NB                               | 26-30                             | China                  | 2013                | Jiang XN                 |
| Li TY 2018 China 28 NR<br>Lou JJ 2015 China 28 4<br>Peng BA 2015 China 28 24<br>Wang TD 2015 China 28 24<br>Wang TD 2015 China 28 4<br>Subotal (I-squared = 0.0%, p = 1.000)<br>Median <28 weeks of gestation<br>Shi QW 2017 China 24 0<br>Median <28 weeks of gestation<br>Shi QW 2017 China 12-14 24<br>China 12-14 24<br>Han GR 2015 China 1st Trimester NR<br>He T 2018 China 12-14 24<br>China 1st Trimester NR<br>Ha CR 2015 China 26 4<br>Sub 2017 China 24 0<br>Sub 2017 China 26 4<br>Sub 2017 China 24 0<br>Sub 2017 China 26 4<br>Sub 2017 China 26 4<br>Sub 2017 China 24-28 NR<br>Sub 2018 China 24-28 NR   | 0/32               | 0/30                 | 0.00 (-0.06, 0.06)  | <u>.                                    </u> | ~36                              | 28                                | China                  | 2017                |                          |
| Lou J       2015       China       28       4       -0.00 (0.04, 0.04) 2/127         Peng BA       2012       China       28       0       0.00 (0.05, 0.05) 0/40         Ren N       2015       China       28       24       0.00 (0.04, 0.04) 0/45         Wang TD       2015       China       28       4       0.00 (0.04, 0.04) 0/45         Xiao XH       2017       China       28       0 or 4       -0.02 (-0.07, 0.04) 1/60         Zhang GH       2018       China       28       4       0.00 (-0.05, 0.05) 0/40         Subtotal (I-squared = 0.0%, p = 1.000)       -0.00 (-0.01, 0.01) 3/829       -0.00 (-0.02, 0.02) 0/100         Median <28  | 0/41               | 0/41                 | 0.00 (-0.05, 0.05)  | <u>.                                    </u> | NB                               | 28                                | China                  | 2018                | LiZY                     |
| Deng BA       2012       China       28       0         Ren N       2015       China       28       24       0.00 (-0.05, 0.05)       0/40         Wang TD       2015       China       28       24       0.00 (-0.04, 0.04)       0/53         Xiao XH       2017       China       28       0 or 4       -0.02 (-0.07, 0.04)       1/60         Zhang GH       2018       China       28       4       0.00 (-0.05, 0.05)       0/40         Subtotal (I-squared = 0.0%, p = 1.000)       Median <28   | 1/58               | 2/127                | -0.00 (-0.04 0.04)  | <u> </u>                                     | 4                                | 28                                | China                  | 2015                | Loudd                    |
| Ren N       2015       China       28       24       0.00 (-0.04, 0.04)       0/46         Wang TD       2015       China       28       4       0.00 (-0.04, 0.04)       0/53         Xiao XH       2017       China       28       4       0.00 (-0.04, 0.04)       0/53         Zhang GH       218       China       28       4       0.00 (-0.05, 0.05)       0/40         Subtotal (I-squared = 0.0%, p = 1.000)       Median <28   | 0/40               | 0/40                 | 0.00 (-0.05, 0.05)  | <u> </u>                                     | 0                                | 28                                | China                  | 2012                | Peng BA                  |
| Wang TD 2015 China 28       4         Xiao XH 2017 China 28       0 or 4         Zhang GH 2018 China 28       4         Subtotal (I-squared = 0.0%, p = 1.000)       -0.02 (-0.07, 0.04) 1/60         Median <28 weeks of gestation  | 0/46               | 0/46                 | 0.00(-0.04, 0.04)   | <u> </u>                                     | 24                               | 28                                | China                  | 2015                | Ren N                    |
| Xiao XH       2017       China       28       0 or 4       -0.02 (-0.07, 0.04) 1/60         Zhang GH       2018       China       28       4       -0.02 (-0.07, 0.04) 1/60         Subtotal (I-squared = 0.0%, p = 1.000)       Median <28  | 0/52               | 0/53                 | 0.00(-0.04, 0.04)   | <u> </u>                                     | 4                                | 28                                | China                  | 2015                | Wang TD                  |
| Zhang GH 2018 China 28       4       000 (-0.05, 0.05) 0/40         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.05, 0.05) 0/40         Median <28 weeks of gestation   | 2/60               | 1/60                 | -0.02 (-0.07 0.04)  | <del></del>                                  | 0 or 4                           | 28                                | China                  | 2017                | Xiao XH                  |
| Subtotal (I-squared = 0.0%, p = 1.000)       -0.00 (-0.01, 0.01) 3/829         Median <28 weeks of gestation   | 0/40               | 0/40                 |                     | <u> </u>                                     | 4                                | 28                                | China                  | 2018                | Zhang GH                 |
| Median <28 weeks of gestation  | 3/694              | 3/829                | -0.00 (-0.01, 0.01) | $\overline{\mathbf{\Phi}}$                   |                                  | , p = 1.000)                      | ed = 0.0%              | -square             | Subtotal (I              |
| Shi QW 2017       China       24       0       0.00 (-0.02, 0.02) 0/100         Wang HY 2018       China       12-14       24       0.00 (-0.05, 0.05) 0/40         Chen CY 2015       China       1st Trimester       NR       0.00 (-0.02, 0.02) 0/100         Han GR 2015       China       1st Trimester       NR       0.00 (-0.05, 0.05) 0/42         He T       2018       China       1st Trimester       NR         Har GR 2015       China       1st Trimester       NR         Multiple       2016       China       26       4         Shen ML       2016       China       26       4       0.00 (-0.02, 0.02) 0/103         Star Z       2016       China       26       4       0.00 (-0.02, 0.02) 0/103         Tan Z       2016       China       20-36       NR       0.00 (-0.07, 0.07) 0/100         Wang JB       2017       China       24-28       NR       0.00 (-0.02, 0.03) 1/329         Zhau GF       2018       China       24-28       NR       0.00 (-0.04, 0.04) 0/36         Zhou YJ       2014       China       24-28       0       0.00 (-0.05, 0.05) 0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.00, 0.00) 10/2859       0.00  |                    |                      |                     |  |                                  | tion                              | e of goeta             | 2 wook              | Modian -2                |
| Sin GW       2017       China       12-14       24       0.00       (-0.05, 0.05)       0/40         Chen CY       2015       China       1st Trimester       NR       0.00       (-0.05, 0.05)       0/40         Han GR       2015       China       1st Trimester       NR       0.00       (-0.05, 0.05)       0/40         Han GR       2015       China       1st Trimester       NR       0.00       (-0.05, 0.05)       0/40         Shen ML       2016       China       26       4       0.00       (-0.05, 0.05)       0/61         Sun W       2017       China       12-28       12       -0.03       (-0.05, 0.05)       0/61         Wang HZ       2016       China       22-28       NR       -0.00       (-0.02, 0.02)       0/365         Tan Z       2016       China       24-28       NR       0.00       (-0.07, 0.07)       0/100         Wang HZ       2017       China       24-28       NR       0.00       (-0.02, 0.03)       1/329         Zhang BF       2018       China       24-28       NR       0.00       (-0.04, 0.04)       0/36         Zhou YJ       2014       China       1st Trimester  | 0/100              | 0/100                | 0.00 (-0.02, 0.02)  |  | 0                                | 24                                | China                  | 2017                |                          |
| Waing HT       2015       China       12-14       24       0.00 (-0.05, 0.05)       0/42         Chen CY       2015       China       12 Trimester       NR       0.00 (-0.05, 0.05)       0/42         Han GR       2015       China       1st Trimester       NR       -0.03 (-0.15, 0.10)       2/32         Shen ML       2016       China       1st Trimester       NR       -0.03 (-0.15, 0.10)       2/32         Shen ML       2016       China       26       4       0.00 (-0.02, 0.02)       0/365         Sun W       2017       China       12-28       12       -0.00 (-0.02, 0.02)       0/103         Tan Z       2016       China       24-28       NR       0.00 (-0.02, 0.02)       0/103         Wang J       2017       China       24-28       NR       0.00 (-0.02, 0.03)       1/329         Zhau RJ       2018       China       24-28       NR       0.00 (-0.02, 0.05)       0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00       0.00 (-0.01, 0.01)       3/1431   | 0/100              | 0/100                | 0.00(-0.02, 0.02)   |  | 0                                | 10 14                             | China                  | 2017                | Wong UV                  |
| Han GR 2015       China       131       Timester       NR       0.00 (-0.02, 0.02)       0/365         He T       2018       China       1st Trimester       NR       -0.03 (-0.15, 0.10)       2/32         Shen ML       2016       China       26       4       -0.00 (-0.02, 0.02)       0/365         Sun W       2017       China       12-28       12       -0.00 (-0.02, 0.02)       0/103         Tan Z       2016       China       214-28       NR       -0.00 (-0.02, 0.02)       0/103         Wang J       2017       China       24-28       NR       0.00 (-0.02, 0.02)       0/100         Wang J       2017       China       24-28       NR       0.00 (-0.02, 0.03)       1/329         Zhang BF       2018       China       24-28       NR       0.00 (-0.02, 0.05)       0/51         Zhou YJ       2018       China       24-28       NR       0.00 (-0.02, 0.05)       0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00       -0.01       0.01       3/1431         Heterogeneity between groups: p = 0.959       0.00       0.00       -0.00       0.00       10/2859  | 0/40               | 0/40                 | 0.00 (-0.05, 0.05)  | 1  |                                  | 1ct Trimostor                     | China                  | 2010                | Chop CV                  |
| He T       2018       China       125 China       126 China       126 China       127  | 0/40               | 0/365                | 0.00(-0.03, 0.03)   | <u> </u>                                     |                                  | 20-32                             | China                  | 2015                | Han GR                   |
| Shen ML       2016       China       26       4         Sun W       2017       China       12-28       12         Tan Z       2016       China       24-28       NR         Wang HB       2016       China       24-28       NR         Wang HB       2016       China       24-28       NR         Zhang BF       2018       China       24-28       NR         Zhang BF       2018       China       24-28       NR         Zhou YJ       2014       China       24-28       NR         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01)       3/1431   | 3/3/               | 2/22                 | -0.03(-0.15, 0.02)  |  |                                  | 1et Trimostor                     | China                  | 2013                | Hat                      |
| Sin W       2017       China       12-28       12         Tan Z       2016       China       21-28       12         Wang HB       2016       China       20-36       NR         Wang J       2017       China       24-28       NR         Zhang JF       2018       China       24-28       NR         Zhang BF       2018       China       24-28       NR         Zhou YJ       2014       China       13 Trimester       0         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01)       3/1431  | 0/28               | 0/61                 |                     | _  | 4                                | 26                                | China                  | 2010                | Shen MI                  |
| Jan Z       2016       China       14-28       NR       0.00 (-0.01, 0.01)       0/170         Wang HB       2016       China       24-28       NR       0.00 (-0.02, 0.02)       0/100         Wang J       2017       China       24-28       NR       0.00 (-0.02, 0.02)       0/100         Zhang JF       2018       China       24-28       NR       0.00 (-0.02, 0.03)       1/329         Zhang BF       2018       China       24-28       0       0.00 (-0.02, 0.05)       0/56         Zhou YJ       2014       China       17 imseter       0       0.00 (-0.05, 0.05)       0/56         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01)       3/1431         Heterogeneity between groups: p = 0.959       0.00 (-0.00, 0.00)       10/2859         Overall (I-squared = 0.0%, p = 1.000)       0.00 (-0.00, 0.00)       10/2859   | 0/65               | 0/103                | 0.00(-0.03, 0.03)   |  | 4                                | 12-28                             | China                  | 2010                |                          |
| Wang HB 2016       China       20-36       NR       0.00 (-0.07, 0.07)       0/100         Wang JB 2017       China       24-28       NR       0.00 (-0.07, 0.07)       0/100         Zhang BF 2018       China       24-28       0       0.00 (-0.04, 0.04)       0/36         Zhou YJ       2014       China       1st Trimester       0       0.00 (-0.05, 0.05)       0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00       0.00 (-0.00, 0.00)       10/2859  | 0/320              | 0/170                | 0.00(-0.02, 0.02)   | -  |                                  | ~1/-28                            | China                  | 2017                | Tan Z                    |
| Wang J 2017 China 24-28 NR       0.00 (-0.02, 0.03) 1/329         Zhang BF 2018 China 24-28 0       0.00 (-0.04, 0.04) 0/36         Zhou YJ 2014 China 1st Trimester 0       0.00 (-0.05, 0.05) 0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01) 3/1431         Heterogeneity between groups: p = 0.959       0.00 (-0.00, 0.00) 10/2859   | 0/20               | 0/100                |                     |  | NB                               | 20-36                             | China                  | 2016                | Wang HR                  |
| Zhang BF 2018       China       24-28       0       0.00 (-0.04, 0.04)       0/36         Zhou YJ       2014       China       1st Trimester       0       0.00 (-0.05, 0.05)       0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01)       3/1431         Heterogeneity between groups: p = 0.959       0.00 (-0.00, 0.00)       10/2859   | 0/65               | 1/329                |                     |  | NB                               | 24-28                             | China                  | 2017                | Wang I                   |
| Zhou YJ 2014       China       1st Trimester       0       0.00 (-0.05, 0.05)       0/53         Subtotal (I-squared = 0.0%, p = 1.000)       0.00 (-0.01, 0.01)       3/1431         Heterogeneity between groups: p = 0.959       0.00 (-0.00, 0.00)       10/2859   | 0/75               | 0/36                 | 0.00(-0.02, 0.03)   |  | 0                                | 24-28                             | China                  | 2018                | Zhang BE                 |
| Subtotal (I-squared = 0.0%, p = 1.000)         0.00 (-0.01, 0.01) 3/1431           Heterogeneity between groups: p = 0.959         0.00 (-0.00, 0.00) 10/2859  | 0/34               | 0/53                 |                     | <u> </u>                                     | 0                                | 1st Trimpstor                     | China                  | 2014                | Zhou V.I                 |
| Heterogeneity between groups: p = 0.959           Overall (I-squared = 0.0%, p = 1.000)  | 3/913              | 3/1431               |                     | <u>a</u>                                     | U U                              | n = 1.000                         | ad = 0.0%              | -501154             | Subtotal /I              |
| Heterogeneity between groups: p = 0.959<br>Overall (I-squared = 0.0%, p = 1.000) 0.00 (-0.00, 0.00) 10/2859  | 5/815              | 0/1401               | 0.00 (-0.01, 0.01)  | T  |                                  | , p = 1.000)                      | 5u = 0.0%              | -square             | Subiolal (I              |
|  | 8/2326             | 10/2859              | 0.00 (-0.00, 0.00)  | •  |                                  | ups: p = 0.959<br>p = 1.000)      | ween grou<br>d = 0.0%, | eity bet<br>squared | Heterogen<br>Overall (I- |

### • LdT 600 mg risk difference of foetal death by timing of treatment initiation

| Author Year Country  | Tx<br>start in weeks<br>gestation  | Tx end<br>in weeks<br>postpartum  | RD (95% CI)   | Events,<br>Treatment   | Events,<br>Control  |
|--|--|---|---|--|---|
| Median >28 weeks of gestation<br>Bai HL 2013 China<br>Chang LJ 2019 China<br>Ge YL 2015 China<br>Hu Y 2018 China<br>Liu J 2017 China<br>Liu XB 2016 China<br>Liu YB 2016 China<br>Hu Y 2016 China<br>Wang DM 2016 China<br>Yao LF 2014 China<br>Zhang H 2014 China<br>Subtotal (I-squared = 0.0%, p =  | 28-32<br>28-32<br>28-30<br>28-32<br>30<br>28-36<br>4-32<br>28-30<br>28-32<br>28-30<br>28-32<br>28-30<br>1.000)   | 4<br>4<br>12<br>3-4<br>NR<br>4<br>0<br>12<br>6<br>4<br>•<br>•<br>•<br>•   | 0.00 (-0.06, 0.06)<br>0.00 (-0.09, 0.09)<br>0.00 (-0.01, 0.01)<br>0.00 (-0.01, 0.01)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.08, 0.08)<br>0.00 (-0.06, 0.06)<br>0.00 (-0.01, 0.01)  | 0/30<br>0/31<br>0/20<br>0/149<br>0/102<br>0/20<br>0/82<br>0/81<br>0/36<br>0/30<br>0/257<br>0/838   | 0/30<br>0/32<br>0/22<br>0/179<br>0/28<br>0/20<br>0/78<br>0/366<br>0/20<br>0/30<br>0/363<br>0/363<br>0/1166                    |
| Median 28 weeks of gestation<br>Chen SM 2017 China<br>Guo HJ 2011 China<br>Li SF 2015 China<br>Li SF 2015 China<br>Li SF 2016 China<br>PengML 2014 China<br>Xing Y 2018 China<br>Yang HW 2015 China<br>Zhao DB 2010 China<br>Zhao DB 2010 China<br>Zhu J 2017 China<br>Zhu J 2017 China<br>Chen QR 2018 China<br>Chen QR 2018 China<br>Chen QR 2018 China<br>China China<br>China<br>China China<br>China China<br>Li 2017 China<br>Jiang XN 2017 China<br>Jiang XN 2013 China<br>Jiang XN 2013 China<br>Li CM 2017 China<br>Li CM 2017 China<br>Li XY 2018 China<br>Li XY 2018 China<br>Li XY 2018 China<br>Li XY 2016 China<br>Xiao XH 2017 China | 28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28<br>28   | NR<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4<br>4   | $\begin{array}{c} 0.00 & (-0.06, \ 0.06) \\ 0.00 & (-0.07, \ 0.07) \\ 0.00 & (-0.03, \ 0.03) \\ 0.00 & (-0.03, \ 0.03) \\ 0.00 & (-0.03, \ 0.03) \\ 0.00 & (-0.06, \ 0.06) \\ 0.00 & (-0.04, \ 0.04) \\ 0.00 & (-0.04,$ | 0/30<br>0/25<br>0/65<br>0/65<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/3  | 0/30<br>0/25<br>0/65<br>0/60<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30<br>0/30  |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$   | 24-28<br>24<br>20-28<br>12-14<br>12<br>1st Trimester<br>1st Trimester<br>1st Trimester<br>24-28<br>26<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-39<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>24-28<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20-36<br>20- | 4<br>12<br>0<br>24<br>12<br>NR<br>0<br>NR<br>12<br>4<br>0<br>12<br>12<br>NR<br>NR<br>12<br>4<br>0<br>12<br>12<br>NR<br>0<br>12<br>12<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 | 0.00 (-0.02, 0.02)<br>0.00 (-0.05, 0.05)<br>0.00 (-0.05, 0.05)<br>0.00 (-0.05, 0.05)<br>0.00 (-0.05, 0.05)<br>0.00 (-0.05, 0.05)<br>0.00 (-0.04, 0.04)<br>-0.06 (-0.15, 0.04)<br>0.00 (-0.09, 0.09)<br>0.00 (-0.09, 0.09)<br>0.00 (-0.03, 0.03)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.02, 0.02)<br>0.00 (-0.03, 0.03)<br>-0.00 (-0.04, 0.04)<br>0.00 (-0.01, 0.01)<br>-0.00 (-0.00, 0.00)   | 0/100<br>0/120<br>0/40<br>0/40<br>0/42<br>0/51<br>0/32<br>0/60<br>0/66<br>0/103<br>0/84<br>0/169<br>0/100<br>0/329<br>0/57<br>0/36<br>0/41<br>1/70<br>1/1650 | 0/100<br>0/120<br>0/40<br>0/40<br>0/41<br>0/40<br>0/45<br>0/20<br>0/45<br>0/45<br>0/45<br>0/45<br>0/45<br>0/45<br>0/45<br>0/4 |
|  |  | I I I I<br>21 0 .1  | .2  |  |   |

## • LdT 600 mg risk difference of postpartum hemorrhage by timing of treatment initiation

| Author                  | Year                | Country                | Tx<br>start in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |     |                 |                       | RD (95% CI)    | Events,<br>Treatment | Events,<br>Control |
|-------------------------|---------------------|------------------------|-----------------------------------|----------------------------------|-----|-----------------|-----------------------|----------------|----------------------|--------------------|
| Median >2               | 28 wee              | ks of gest             | ation                             |                                  |     |                 |                       |                |                      |                    |
| Hu Y                    | 2018                | China                  | 28-32                             | 3-4                              |     | - <b>- -</b> -  |                       | -0.00 (-0.04,  | 0.03)4/149           | 5/179              |
| Liu Y                   | 2016                | China                  | 4-32                              | 4                                |     | <b></b>         |                       | 0.00 (-0.02, 0 | 0.02) 0/82           | 0/78               |
| Pan YC                  | 2017                | China                  | 32                                | 0                                |     |                 |                       | 0.00 (-0.02, 0 | 0.02) 0/81           | 0/366              |
| Wang HB                 | 2016                | China                  | 20-36                             | NR                               |     |                 |                       | 0.00 (-0.07, 0 | 0.07) 0/100          | 0/20               |
| Zhang H                 | 2014                | China                  | 28-30                             | 4                                |     |                 |                       | 0.00 (-0.02, 0 | 0.02) 4/257          | 5/363              |
| Subtotal (              | l-squa              | red = 0.0°             | %, p = 1.000)                     |                                  |     | Ŷ               |                       | 0.00 (-0.01, 0 | 0.01) 8/669          | 10/1006            |
| Median 28               | 3 week              | s of gesta             | tion                              |                                  |     |                 |                       |                |                      |                    |
| Zhu J                   | 2017                | China                  | 28                                | 0                                |     | <u></u>         |                       | -0.03 (-0.10,  | 0.03)1/60            | 3/60               |
| Chen WJ                 | 2017                | China                  | 28                                | 0                                |     | <b></b>         |                       | 0.00 (-0.04, 0 | 0.04) 0/79           | 0/44               |
| Cui ZL                  | 2015                | China                  | 28                                | 4                                |     | <u> </u>        |                       | -0.02 (-0.09,  | 0.05)1/50            | 2/50               |
| Jiang XN                | 2013                | China                  | 26-30                             | NR                               |     |                 |                       | -0.08 (-0.16,  | 0.00)0/65            | 4/51               |
| Lou JJ                  | 2015                | China                  | 28                                | 4                                |     | _               |                       | 0.00 (-0.05, 0 | 0.06) 5/127          | 2/58               |
| Peng BA                 | 2012                | China                  | 28                                | 0                                |     |                 |                       | 0.00 (-0.05, 0 | 0.05) 0/40           | 0/40               |
| Tan J                   | 2019                | China                  | 28                                | 0                                |     |                 |                       | -0.00 (-0.09,  | 0.08)2/41            | 3/59               |
| Zhang GH                | 2018                | China                  | 28                                | 4                                |     |                 |                       | 0.03 (-0.18, 0 | 0.23) 13/40          | 12/40              |
| Subtotal (              | I-squa              | red = 0.0°             | %, p = 0.739)                     |                                  |     | •               |                       | -0.01 (-0.03,  | 0.01)22/502          | 26/402             |
| Median <2               | 28 wee              | ks of gest             | ation                             |                                  |     |                 |                       |                |                      |                    |
| Guan ZF                 | 2017                | China                  | 24                                | 12                               |     |                 | _                     | 0.03 (-0.09, 0 | 0.14) 38/120         | 35/120             |
| He T                    | 2018                | China                  | 1st Trimester                     | NR                               |     |                 | _                     | 0.03 (-0.07, 0 | 0.13) 2/32           | 1/35               |
| Sun W                   | 2017                | China                  | 12-28                             | 12                               |     |                 |                       | -0.02 (-0.14,  | 0.09)20/123          | 12/65              |
| Sun WH                  | 2015                | China                  | 12-28                             | 12                               |     |                 | _                     | -0.03 (-0.20,  | 0.14)25/83           | 15/45              |
| Tan Z                   | 2016                | China                  | <14-28                            | NR                               |     |                 |                       | 0.00 (-0.03, 0 | 0.03) 5/169          | 9/316              |
| Subtotal (              | I-squa              | red = 0.09             | %, p = 0.930)                     |                                  |     | $\mathbf{\Phi}$ |                       | 0.00 (-0.03, 0 | 0.03) 90/527         | 72/581             |
| Heteroger<br>Overall (I | neity be<br>-square | etween gr<br>ed = 0.0% | oups: p = 0.650<br>, p = 0.992)   | •                                |     | ¢               |                       | -0.00 (-0.01,  | 0.01)120/1698        | 108/1989           |
|                         |                     |                        |                                   | І<br>3                           | - 2 | 1 0 <sup></sup> | <b>I I</b><br>1 .2 .3 |                |                      |                    |

- LdT 600 mg risk difference of postpartum flare by timing of treatment initiation
  - Not enough studies for subgroup analysis

### **Appendix X: Infant safety 1. Neonatal deaths**

## • TDF 300 mg risk difference for neonatal death

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

| Author         | Year      | Country           | Tx start<br>in weeks<br>gestation | Tx end<br>in weeks<br>postpartum |    |                 |             | RD (95% CI)         | Events,<br>Treatment | Events,<br>Control |
|----------------|-----------|-------------------|-----------------------------------|----------------------------------|----|-----------------|-------------|---------------------|----------------------|--------------------|
| Randomised     | controlle | d tria <b>l</b> s |                                   |                                  |    |                 |             |                     |                      |                    |
| Jourdain G     | 2018      | Thailand          | 26-29                             | 8                                |    |                 |             | -0.01 (-0.02, 0.01) | 0/163                | 1/160              |
| Lin Y          | 2018      | China             | 24                                | 4                                |    |                 |             | 0.02 (-0.03, 0.06)  | 1/59                 | 0/52               |
| Liu MH         | 2017      | China             | 28-30                             | 0                                |    | *               | _           | 0.00 (-0.09, 0.09)  | 0/20                 | 0/20               |
| Pan CQ         | 2016      | China             | 30-32                             | 4                                |    | <b></b>         |             | 0.01 (-0.02, 0.04)  | 1/95                 | 0/88               |
| Yu CY          | 2018      | China             | 24                                | 4                                | -  | <u> </u>        |             | 0.00 (-0.06, 0.06)  | 0/30                 | 0/30               |
| Subtotal (I-so | uared =   | 0.0%, p = 0       | .797)                             |                                  |    | $\Phi$          |             | -0.00 (-0.01, 0.01) | 2/367                | 1/350              |
| Non-randomis   | sed cont  | rolled trials     |                                   |                                  |    |                 |             |                     |                      |                    |
| Celen MK       | 2013      | Turkey            | 18-27                             | 4                                |    | <u> </u>        |             | 0.00 (-0.08, 0.08)  | 0/21                 | 0/23               |
| Chen HL        | 2015      | Taiwan            | 30-32                             | 4                                |    |                 |             | 0.00 (-0.03, 0.03)  | 0/65                 | 0/56               |
| Chen WJ        | 2017      | China             | 28                                | 0                                |    | <u> </u>        |             | 0.00 (-0.05, 0.05)  | 0/30                 | 0/44               |
| Gong Q         | 2017      | China             | 1-6                               | NR                               |    |                 |             | 0.00 (-0.04, 0.04)  | 0/44                 | 0/44               |
| Greenup AJ     | 2014      | Australia         | 32                                | 12                               | -  |                 |             | 0.00 (-0.07, 0.07)  | 0/58                 | 0/20               |
| He LL          | 2018      | China             | 28                                | NR                               |    |                 |             | 0.00 (-0.05, 0.05)  | 0/50                 | 0/35               |
| Hu MF          | 2018      | China             | <0-28                             | NR                               |    |                 |             | 0.00 (-0.05, 0.05)  | 0/89                 | 0/30               |
| Huang Q        | 2017      | China             | 24-28                             | 12                               |    | -               | _           | 0.00 (-0.09, 0.09)  | 0/20                 | 0/20               |
| Wakano Y       | 2018      | Japan             | 22-28                             | 4-8                              | ←  |                 | <b>&gt;</b> | 0.00 (-0.53, 0.53)  | 0/2                  | 0/3                |
| Wan JY         | 2017      | China             | 28                                | 0                                |    |                 |             | 0.00 (-0.04, 0.04)  | 0/74                 | 0/42               |
| Wang HB        | 2018      | China             | 20-36                             | NR                               | -  | -               |             | 0.00 (-0.07, 0.07)  | 0/100                | 0/20               |
| Xiao XH        | 2017      | China             | 28                                | 0 or 4                           |    |                 |             | 0.00 (-0.03, 0.03)  | 0/60                 | 0/60               |
| Zhang BF       | 2018      | China             | 24-28                             | 0                                |    |                 |             | 0.00 (-0.04, 0.04)  | 0/39                 | 0/75               |
| Zhou Y         | 2018      | China             | 24-28                             | 0                                |    |                 |             | 0.00 (-0.04, 0.04)  | 0/60                 | 0/36               |
| Subtotal (I-so | uared =   | 0.0%, p = 1       | .000)                             |                                  |    | $\mathbf{\Phi}$ |             | 0.00 (-0.01, 0.01)  | 0/712                | 0/508              |
| Overall (I-squ | uared = ( | 0.0%, p = 1.0     | 000)                              |                                  |    | \$              |             | -0.00 (-0.01, 0.01) | 2/1079               | 1/858              |
|                |           |                   |                                   | :                                | 21 | 0               | .1 .1       | 2                   |                      |                    |

### • LAM 100-150 mg risk difference for neonatal death

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

| Author        | Year      | Country            | start in weeks gestation | Tx end in<br>weeks postpartum | RD (95% CI)          | Events,<br>Treatment | Event<br>Contr |
|---------------|-----------|--------------------|--------------------------|-------------------------------|----------------------|----------------------|----------------|
| Randomised    | controlle | ed trials          |                          |                               |                      |                      |                |
| Bai XW        | 2011      | China              | 28                       | 4                             | 0.00 (-0.07, 0.07)   | 0/30                 | 0/25           |
| Chen SM       | 2017      | China              | 28                       | NR                            | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30           |
| Guo YZ        | 2008      | China              | 28                       | 0                             | - 0.00 (-0.04, 0.04) | 0/70                 | 0/40           |
| Ji YY         | 2015      | China              | 28                       | 4                             | 0.00 (-0.03, 0.03)   | 0/65                 | 0/65           |
| Li ZG         | 2015      | China              | 28                       | 6                             | 0.00 (-0.07, 0.07)   | 0/25                 | 0/25           |
| Tian XQ       | 2015      | China              | 28                       | 0                             | 0.00 (-0.02, 0.02)   | 0/110                | 0/110          |
| Xu WM         | 2009      | China, Philippines | 30-34                    | 4                             | 0.00 (-0.05, 0.05)   | 1/56                 | 1/59           |
| Yang HW       | 2014      | China              | 28                       | 4                             | - 0.00 (-0.04, 0.04) | 0/53                 | 0/53           |
| Subtotal (I-s | quared =  | = 0.0%, p = 1.000) |                          | ·<br>•                        | 0.00 (-0.01, 0.01)   | 1/439                | 1/40           |
| Non-random    | ised cont | trolled trials     |                          |                               |                      |                      |                |
| Chen QR       | 2018      | China              | 28                       | 4                             | 0.00 (-0.06.0.06)    | 0/33                 | 0/28           |
| Cheng YC      | 2011      | China              | 32                       | 4                             |                      | 0/30                 | 0/26           |
| Eena HE       | 2007      | China              | 28                       | 4                             |                      | 0/48                 | 0/42           |
| Foaud HM      | 2019      | Egypt              | Anvtime                  | NB                            | 0.00 (-0.04, 0.04)   | 0/34                 | 0/30           |
| Go VI         | 2015      | China              | 28-30                    | 12                            |                      | 0/16                 | 0/00           |
| Gen           | 2013      | Australia          | 20-30                    | 2                             | 0.00 (-0.10, 0.10)   | 0/10                 | 0/22           |
|               | 2014      | China              | 32                       |                               | 0.00 (-0.07, 0.07)   | 0/33                 | 0/20           |
|               | 2014      | China              | 20                       | 0                             | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30           |
| nan zn        | 2005      | China              | ∠o<br>1 at Tsimo atau    |                               | 0.00 (-0.05, 0.05)   | 0/43                 | 0/35           |
|               | 2018      | China              | TSt Trimester            |                               | 0.00 (-0.08, 0.08)   | 0/29                 | 0/34           |
| Jiang HX      | 2012      | China              | 20-34                    |                               | 0.00 (-0.02, 0.02)   | 0/164                | 0/92           |
| LIG           | 2006      | China              | 28                       |                               | 0.00 (-0.06, 0.06)   | 0/35                 | 0/32           |
|               | 2017      | China              | 28                       | 4                             | 0.00 (-0.06, 0.06)   | 0/33                 | 0/27           |
|               | 2006      | China              | 24                       | 0                             | 0.00 (-0.05, 0.05)   | 0/36                 | 0/44           |
| Maj           | 2006      | China              | Pre-pregnancy            | NR                            | 0.00 (-0.11, 0.11)   | 0/18                 | 0/16           |
| Pan CQ        | 2017      | China              | 13-30                    | 4                             | 0.00 (-0.02, 0.02)   | 0/160                | 0/89           |
| Ren CJ        | 2016      | China              | 28                       | 0                             | 0.00 (-0.03, 0.03)   | 0/67                 | 0/72           |
| Ren YJ        | 2011      | China              | 28                       | 0                             | 0.00 (-0.05, 0.05)   | 0/30                 | 0/15           |
| Shen ML       | 2016      | China              | 26                       | 4                             | 0.00 (-0.05, 0.05)   | 0/60                 | 0/28           |
| Su TB         | 2009      | China              | 32                       | 0                             | 0.00 (-0.02, 0.02)   | 0/128                | 0/12           |
| Tang X        | 2009      | China              | 33                       | 4                             | 0.00 (-0.09, 0.09)   | 0/17                 | 0/24           |
| Wakano Y      | 2018      | Japan              | 28 <b>-</b> 32           | 4-8                           | • 0.00 (-0.46, 0.46) | 0/3                  | 0/3            |
| Wang DM       | 2016      | China              | 28-30                    | 12                            | 0.00 (-0.07, 0.07)   | 0/42                 | 0/20           |
| Wang EJ       | 2012      | China              | 28                       | 4                             | 0.00 (-0.06, 0.06)   | 0/32                 | 0/27           |
| Wang TM       | 2005      | China              | Pre-pregnancy            | 0                             | 0.00 (-0.06, 0.06)   | 0/32                 | 0/32           |
| Wang W        | 2014      | China              | 28                       | 4                             | 0.00 (-0.06, 0.06)   | 0/35                 | 0/28           |
| Yuan QF       | 2012      | China              | 27                       | 4                             | 0.00 (-0.06, 0.06)   | 0/32                 | 0/32           |
| Zeng YM       | 2013      | China              | 28                       | Variable (0,4,6)              | 0.00 (-0.05, 0.05)   | 0/90                 | 0/30           |
| Zhang H       | 2014      | China              | 28-30                    | 4                             | 0.00 (-0.03, 0.03)   | 0/54                 | 0/37           |
| Zhang YF      | 2010a     | China              | 28                       | 4                             | 0.00 (-0.04, 0.04)   | 0/50                 | 0/50           |
| Zhou DS       | 2013      | China              | 20-28                    | NR 🗕                          | 0.00 (-0.02, 0.02)   | 0/113                | 0/95           |
| Zhu M         | 2014      | China              | 26                       | 0                             | 0.00 (-0.08, 0.08)   | 0/24                 | 0/24           |
| Subtotal (I-s | quared =  | = 0.0%, p = 1.000) |                          | •                             | 0.00 (-0.01, 0.01)   | 0/1571               | 0/16           |
| Overall (I-so | uared =   | 0.0%, p = 1.000)   |                          | •                             | 0.00 (-0.01, 0.01)   | 1/2010               | 1/20           |
|               |           |                    |                          | <del> </del>                  |                      |                      |                |

### • LdT 600 mg risk difference for neonatal death

- Weighted pooled risk difference: 0.00 (95%CI: -0.00 0.00).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

| Author             | Year             | Country           | start in weeks<br>gestation | in weeks<br>postpartum |                | RD (95% CI)                              | Events,<br>Treatment | Events,<br>Control |
|--------------------|------------------|-------------------|-----------------------------|------------------------|----------------|--|----------------------|--------------------|
| Randomised         | controlle        | d tria <b>l</b> s |                             |                        |                |  |                      |                    |
| Bai HL<br>Chon SM  | 2013             | China             | 28-32                       | 4<br>NR                |                | 0.00 (-0.06, 0.06)                       | 0/30                 | 0/30               |
| Fu PX              | 2016             | China             | 24-28                       | 4                      |                | 0.00 (-0.02, 0.02)                       | 0/100                | 0/100              |
| Guan ZF            | 2017             | China             | 24                          | 12                     |                | 0.00 (-0.02, 0.02)                       | 0/123                | 0/122              |
| Guo HJ<br>Huang HV | 2011             | China             | 28                          | 4                      | 1              | 0.00 (-0.07, 0.07)                       | 0/28                 | 0/26               |
| Ji YY              | 2015             | China             | 28                          | 4                      | - <b>i</b> -   | 0.00 (-0.03, 0.03)                       | 0/65                 | 0/65               |
| Li SF              | 2015             | China             | 28                          | 24                     |                | 0.00 (-0.03, 0.03)                       | 0/60                 | 0/60               |
| Lu QY<br>PengMI    | 2016             | China             | 28                          | 0<br>NB                |                | 0.00 (-0.01, 0.01)                       | 0/152                | 0/132              |
| Shi QW             | 2017             | China             | 24                          | 0                      | ÷              | 0.00 (-0.02, 0.02)                       | 0/100                | 0/100              |
| Wang HY            | 2018             | China             | 12-14                       | 24                     | <del></del>    | 0.00 (-0.05, 0.05)                       | 0/40                 | 0/40               |
| Xie PY<br>Xing X   | 2016             | China             | 28                          | 4                      |                | 0.00 (-0.03, 0.03)                       | 0/60                 | 0/60               |
| Yang HW            | 2015             | China             | 28                          | 4                      | _ <u>+</u>     | 0.00 (-0.04, 0.04)                       | 0/50                 | 0/50               |
| Zhang LJ           | 2009             | China             | 28-32                       | 4                      |                | 0.00 (-0.06, 0.06)                       | 0/31                 | 0/30               |
| Zhang Y<br>Zhao DB | 2018             | China             | Pre-pregnancy               | NR<br>4                |                | 0.00 (-0.06, 0.06)                       | 0/34                 | 0/34               |
| Zhao Y             | 2017             | China             | 12                          | 12                     | <u> </u>       | 0.00 (-0.05, 0.05)                       | 0/40                 | 0/40               |
| Zhu J              | 2017             | China             | 28                          | 0                      |                | 0.00 (-0.03, 0.03)                       | 0/60                 | 0/54               |
| Zhu LP             | 2014<br>guarad - | China             | 28                          | 4                      |                | 0.00 (-0.06, 0.06)                       | 0/30                 | 0/30               |
| Subiolal (I-s      | qualeu =         | 0.0 %, p = 1      | .000)                       |                        | Ť              | 0.00 (-0.01, 0.01)                       | 0/1213               | 0/1123             |
| Non-random         | ised contr       | olled trials      | d at Trime a stars          | ND                     |                | 0.00 ( 0.05, 0.05)                       | 0/40                 | 0/40               |
| Chen F             | 2015             | China             | Pre-pregnancy               | NR                     |                | 0.00 (-0.05, 0.05)                       | 0/42                 | 0/40               |
| Chen QR            | 2018             | China             | 28                          | 4                      | <u> </u>       | 0.00 (-0.07, 0.07)                       | 0/29                 | 0/28               |
| Chen WJ            | 2017             | China             | 28                          | 0<br>NB                | <u></u>        | 0.00 (-0.04, 0.04)                       | 0/79                 | 0/44               |
| Cnen ∠x<br>Cui ZI  | 2017             | China             | 13-32<br>28                 | 1NP1<br>4              |                | 0.00 (-0.04, 0.04)<br>0.00 (-0.04, 0.04) | 0/41                 | 0/89               |
| Deng Y             | 2015             | China             | 24-36                       | 4                      |                | 0.00 (-0.02, 0.02)                       | 0/82                 | 0/75               |
| Ding XP            | 2018             | China             | 28                          | 4                      | <u></u>        | 0.00 (-0.05, 0.05)                       | 0/38                 | 0/38               |
| Fan LY<br>Feng XM  | 2013             | China             | 28                          | 24                     |                | 0.00 (-0.03, 0.03)                       | 0/58<br>0/36         | 0/60               |
| Gao P              | 2016             | China             | 1st Trimester               | ò                      | <del></del>    | 0.00 (-0.04, 0.04)                       | 0/51                 | 0/51               |
| Ge YL              | 2015             | China             | 28-30                       | 12                     |                | 0.00 (-0.09, 0.09)                       | 0/20                 | 0/22               |
| Han YP<br>He T     | 2014             | China             | 28<br>1st Trimester         | 6<br>NB                |                | 0.00 (-0.06, 0.06)                       | 0/30                 | 0/30               |
| Hu WH              | 2016             | China             | 28                          | 28                     |                | 0.00 (-0.04, 0.04)                       | 0/46                 | 0/40               |
| Hu Y               | 2018             | China             | 28-32                       | 3-4                    | ÷              | 0.00 (-0.01, 0.01)                       | 0/149                | 0/179              |
| Huang Q            | 2017             | China             | 24-28                       | 12<br>NB               |                | 0.00 (-0.09, 0.09)                       | 0/20<br>0/44         | 0/20               |
| Jiang XN           | 2013             | China             | 26-30                       | NR                     | <u> </u>       | 0.00 (-0.03, 0.03)                       | 0/65                 | 0/51               |
| LICM               | 2017             | China             | 28                          | 4                      | <u> </u>       | 0.00 (-0.06, 0.06)                       | 0/30                 | 0/30               |
|                    | 2016             | China             | <0-28<br>28                 | NR<br>~36              |                | 0.00 (-0.06, 0.06)                       | 0/65                 | 0/25               |
| Li ZY              | 2018             | China             | 28                          | NR                     | <u> </u>       | 0.00 (-0.05, 0.05)                       | 0/41                 | 0/41               |
| Liu CY             | 2014             | China             | 28                          | 4                      | — <u>i</u> —   | 0.00 (-0.06, 0.06)                       | 0/34                 | 0/34               |
| Liu J<br>Liu XB    | 2017             | China             | 30<br>28-36                 | NR<br>4                |                | 0.00 (-0.05, 0.05)                       | 0/104                | 0/28               |
| Liu Y              | 2016             | China             | 4-32                        | 4                      |                | 0.00 (-0.02, 0.02)                       | 0/82                 | 0/78               |
| Lou JJ             | 2015             | China             | 28                          | 4                      |                | 0.00 (-0.03, 0.03)                       | 0/127                | 0/58               |
| Pan YC<br>Peng BA  | 2017             | China             | 32                          | 0                      |                | 0.00 (-0.02, 0.02)                       | 0/81                 | 0/370              |
| Qiu B              | 2016             | China             | <0-24                       | 0                      |                | 0.00 (-0.03, 0.03)                       | 0/120                | 0/60               |
| Ren N              | 2015             | China             | 28                          | 24                     | - <del></del>  | 0.00 (-0.04, 0.04)                       | 0/46                 | 0/46               |
| Shen ML<br>Sheng O | 2016<br>2018a    | China             | 26<br>24-32                 | 4                      |                | 0.00 (-0.05, 0.05)                       | 0/61                 | 0/28               |
| Sheng Q            | 2018b            | China             | 24-28                       | Ő                      | <u> </u>       | 0.00 (-0.04, 0.04)                       | 0/66                 | 0/46               |
| Sun Ŵ              | 2017             | China             | 12-28                       | 12                     |                | 0.00 (-0.02, 0.02)                       | 0/103                | 0/65               |
| Sun WH<br>Tan J    | 2015             | China             | 12-28<br>28                 | 12                     |                | 0.00 (-0.03, 0.03)                       | 0/84<br>0/41         | 0/46<br>0/59       |
| Tan Z              | 2016             | China             | <14-28                      | ŇR                     | +              | 0.00 (-0.01, 0.01)                       | 0/171                | 0/320              |
| Tian JH            | 2018             | China             | Anytime                     | NR                     | ÷              | 0.00 (-0.01, 0.01)                       | 0/135                | 0/203              |
| Han RH<br>Wang B   | 2016<br>2016     | China             | 28                          | 4<br>4                 | -              | 0.00 (-0.01, 0.01)                       | 0/318                | 0/3/4              |
| Wang DM            | 2016             | China             | 28-30                       | 12                     |                | 0.00 (-0.08, 0.08)                       | 0/36                 | 0/20               |
| Wang EJ            | 2012             | China             | 28                          | 4                      |                | 0.00 (-0.07, 0.07)                       | 0/28                 | 0/27               |
| Wang HB            | 2016             | China             | 20-36                       | NR                     |                | 0.00 (-0.07, 0.07)                       | 0/100                | 0/20               |
| Wang TD            | 2015             | China             | 28                          | 4                      |                | 0.00 (-0.04, 0.04)                       | 0/53                 | 0/52               |
| Wang WP            | 2012             | China             | <27-28                      | 0                      |                | 0.00 (-0.02, 0.02)                       | 0/57                 | 0/198              |
| Wu Q<br>Xiao X⊔    | 2015             | China             | 24-32<br>28                 | 0 or 4                 |                | 0.01 (-0.01, 0.02)                       | 2/280                | 0/173              |
| Yao LF             | 2014             | China             | 28-32                       | 6                      | <del></del>    | 0.00 (-0.06, 0.06)                       | 0/30                 | 0/30               |
| Yao ZC             | 2011             | China             | 28                          | 4                      |                | 0.00 (-0.06, 0.06)                       | 0/28                 | 0/30               |
| Yue X              | 2014             | China             | Anytime                     | NR                     |                | 0.00 (-0.06, 0.06)                       | 0/31                 | 0/30               |
| Zhang GH           | 2018             | China             | 28                          | 4                      |                | 0.00 (-0.05, 0.04)                       | 0/40                 | 0/40               |
| Zhang H            | 2014             | China             | 28-30                       | 4                      | +              | 0.00 (-0.01, 0.01)                       | 0/262                | 0/370              |
| Zhang X            | 2015             | China             | 28                          | 12                     |                | 0.00 (-0.04, 0.04)                       | 0/48                 | 0/47               |
| Zhang TF<br>Zhao J | 20100            | China             | 20                          | 4<br>0                 |                | 0.00 (-0.03, 0.03)                       | 0/41                 | 0/202              |
| Zheng JC           | 2018             | China             | 28                          | 4                      | <del></del>    | 0.00 (-0.07, 0.07)                       | 0/23                 | 0/37               |
| Zhou YJ            | 2014             | China             | 1st Trimester               | 0                      | <del></del>    | 0.00 (-0.05, 0.05)                       | 0/53                 | 0/34               |
| Subiotal (I-s      | quarea =         | 0.0%, p = 1       | .000)                       |                        | T              | 0.00 (-0.00, 0.00)                       | 2/4039               | 0/4/40             |
| Overall (Fsc       | uared = 0        | 0.0%, p = 1.0     | 000)                        |                        | <b>†</b>       | 0.00 (-0.00, 0.00)                       | 2/5752               | 0/5863             |
|                    |                  |                   |                             |                        |                | 1  |                      |                    |
|                    |                  |                   |                             | <br>- 2                | I I I<br>1 0 1 | .2                                       |                      |                    |

### Appendix Y: Infant safety 2. Preterm birth

- TDF 300 mg risk difference for preterm birth

   Weighted pooled risk difference: 0.00 (95%CI: -0.02 0.02).
   I<sup>2</sup> statistic overall = 0.0%
   I<sup>2</sup> statistic RCTs = 0.0%
   I<sup>2</sup> statistic non-RCTs = 0.0%

|               |          |               | Tx start  | Tx end       |      |            |                   |                     | <b>F</b>  | <b>F</b> |
|---------------|----------|---------------|-----------|--------------|------|------------|-------------------|---------------------|-----------|----------|
|               |          | o .           | in weeks  | in weeks     |      |            |                   |                     | Events,   | Events,  |
| Autnor        | Year     | Country       | gestation | postpartun   | 1    |            |                   | RD (95% CI)         | Treatment | Control  |
| Randomised    | l contro | lled trials   |           |              |      |            |                   |                     |           |          |
| Jourdain G    | 2018     | Thailand      | 26-29     | 8            |      |            |                   | -0.03 (-0.09, 0.02) | 8/163     | 13/160   |
| Lin Y         | 2018     | China         | 24        | 4            |      | <u> </u>   |                   | -0.02 (-0.08, 0.04) | 1/59      | 2/52     |
| Liu MH        | 2017     | China         | 28-30     | 0            |      | -          |                   | 0.00 (-0.09, 0.09)  | 0/20      | 0/20     |
| Pan CQ        | 2016     | China         | 30-32     | 4            |      | <u> </u>   |                   | 0.01 (-0.03, 0.05)  | 2/95      | 1/88     |
| Subtotal (I-s | squarec  | = 0.0%, p     | = 0.476)  |              |      | $\diamond$ |                   | -0.01 (-0.03, 0.02) | 11/337    | 16/320   |
|               |          |               |           |              |      |            |                   |                     |           |          |
| Non-random    | ised co  | ntrolled tria | als       |              |      |            |                   |                     |           |          |
| Chen HL       | 2015     | Taiwan        | 30-32     | 4            |      |            |                   | 0.04 (-0.04, 0.12)  | 5/65      | 2/56     |
| Greenup AJ    | 2014     | Australia     | 32        | 12           |      |            | _                 | 0.02 (-0.06, 0.09)  | 1/58      | 0/20     |
| Wakano Y      | 2018     | Japan         | 22-28     | 4 <b>-</b> 8 | ←    |            | $\longrightarrow$ | 0.00 (-0.53, 0.53)  | 0/2       | 0/3      |
| Wang HB       | 2018     | China         | 20-36     | NR           |      |            |                   | 0.00 (-0.07, 0.07)  | 0/100     | 0/20     |
| Xiao XH       | 2017     | China         | 28        | 0 or 4       | -    | · · ·      |                   | -0.03 (-0.11, 0.04) | 2/60      | 4/60     |
| Subtotal (I-s | squarec  | = 0.0%, p     | = 0.769)  |              |      | $\diamond$ |                   | 0.01 (-0.03, 0.04)  | 8/285     | 6/159    |
|               |          |               |           |              |      |            |                   |                     |           |          |
| Overall (I-so | quared   | = 0.0%, p =   | = 0.832)  |              |      | $\diamond$ |                   | -0.00 (-0.02, 0.02) | 19/622    | 22/479   |
|               |          |               |           |              |      |            |                   |                     |           |          |
|               |          |               |           |              | 1 1  |            | <u> </u>          |                     |           |          |
|               |          |               |           |              | 32 - | .1 0       | .1 .2 .3          | •                   |           |          |

### • LAM 100-150 mg risk difference for preterm birth

- Weighted pooled risk difference: 0.00 (95%CI: -0.03 0.02).
  I<sup>2</sup> statistic overall = 43.0%
  I<sup>2</sup> statistic RCTs = not enough studies
  I<sup>2</sup> statistic non-RCTs = 55.6%

|               |          |                | Тх             | Tx end     |                |     |      |          |                      |           |         |
|---------------|----------|----------------|----------------|------------|----------------|-----|------|----------|----------------------|-----------|---------|
|               |          |                | start in weeks | in weeks   |                |     |      |          |                      | Events,   | Events, |
| Author        | Year     | Country        | gestation      | postpartum | n              |     |      |          | RD (95% CI)          | Treatment | Control |
|               |          |                |                |            |                |     |      |          |                      |           |         |
| Randomised    | a contro | lied trials    |                |            |                |     |      |          |                      |           |         |
| Guo YZ        | 2008     | China          | 28             | 0          |                | -   | -    |          | 0.00 (-0.04, 0.04)   | 0/70      | 0/40    |
| Yang HW       | 2014     | China          | 28             | 4          |                | -   | -    |          | 0.00 (-0.04, 0.04)   | 0/53      | 0/53    |
| Subtotal (I-  | squarec  | l = 0.0%, p    | = 1.000)       |            |                |     | >    |          | 0.00 (-0.03, 0.03)   | 0/123     | 0/93    |
|               |          |                |                |            |                |     |      |          |                      |           |         |
| Non-random    | nised co | ontrolled tria | als            |            |                |     |      |          |                      |           |         |
| Greenup AJ    | 2014     | Australia      | 32             | 2          |                | -   | •    |          | 0.06 (-0.04, 0.15)   | 3/53      | 0/20    |
| He T          | 2018     | China          | 1st Trimester  | NR         |                |     |      |          | 0.21 (0.05, 0.38)    | 7/29      | 1/34    |
| Jiang HX      | 2012     | China          | 20-34          | 0          |                |     |      |          | -0.03 (-0.07, 0.02)  | 3/164     | 4/92    |
| Ma J          | 2006     | China          | Pre-pregnancy  | NR         | <del>← =</del> |     |      |          | -0.31 (-0.55, -0.08) | 0/18      | 5/16    |
| Pan CQ        | 2017     | China          | 13-30          | 4          |                |     | -    |          | -0.00 (-0.03, 0.02)  | 1/160     | 1/89    |
| Wakano Y      | 2018     | Japan          | 28-32          | 4-8        |                |     |      |          | 0.00 (-0.46, 0.46)   | 0/3       | 0/3     |
| Wang W        | 2014     | China          | 28             | 4          |                |     | -    |          | 0.00 (-0.06, 0.06)   | 0/35      | 0/28    |
| Zhu M         | 2014     | China          | 26             | 0          |                |     | ÷    |          | 0.00 (-0.08, 0.08)   | 0/24      | 0/24    |
| Subtotal (I-  | squared  | l = 55.6%,     | p = 0.027)     |            |                | <   | >    |          | 0.00 (-0.04, 0.04)   | 14/486    | 11/306  |
|               |          |                |                |            |                |     |      |          |                      |           |         |
| Overall (I-se | quared   | = 43.0%, p     | = 0.071)       |            |                | <   | >    |          | -0.00 (-0.03, 0.02)  | 14/609    | 11/399  |
|               |          |                |                |            |                |     |      |          |                      |           |         |
|               |          |                |                |            | <del></del>    |     |      | <u> </u> |                      |           |         |
|               |          |                |                |            | 53             | 1 C | ) .1 | .3 .5    |                      |           |         |

- LdT 600 mg risk difference for preterm birth

   Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
   I<sup>2</sup> statistic overall = 0.0%
   I<sup>2</sup> statistic RCTs = not enough studies
   I<sup>2</sup> statistic non-RCTs = 0.0%

| Author       | Year      | Country       | start in weeks<br>gestation | in weeks<br>postpartum | RD (95% CI)          | Events,<br>Treatment | Events,<br>Control |
|--------------|-----------|---------------|-----------------------------|------------------------|----------------------|----------------------|--------------------|
| Randomise    | ed contro | lled trials   |                             |                        |                      |                      |                    |
| Lu QY        | 2016      | China         | 28                          | 0                      | 0.01 (-0.01, 0.03)   | 1/152                | 0/132              |
| Shi QW       | 2017      | China         | 24                          | 0 🔶                    | 0.00 (-0.02, 0.02)   | 0/100                | 0/100              |
| Subtotal (I  | -squared  | l = 0.0%, p   | = 0.629)                    |                        | 0.00 (-0.01, 0.02)   | 1/252                | 0/232              |
| Non-randoi   | mised co  | ntrolled tria | als                         |                        |                      |                      |                    |
| Chen ZX      | 2017      | China         | 13-32                       | NR                     | -0.01 (-0.09, 0.07)  | 2/41                 | 5/89               |
| Fan LY       | 2013      | China         | 28                          | 24                     | 0.00 (-0.06, 0.07)   | 2/58                 | 2/60               |
| Han GR       | 2015      | China         | 20-32                       | NR                     | 0.02 (-0.03, 0.07)   | 22/365               | 4/92               |
| He T         | 2018      | China         | 1st Trimester               | NR                     | 0.00 (-0.08, 0.08)   | 1/32                 | 1/34               |
| Hu Y         | 2018      | China         | 28-32                       | 3-4                    | -0.01 (-0.06, 0.04)  | 8/149                | 11/179             |
| Jiang S      | 2017      | China         | 28                          | NR                     | 0.05 (-0.09, 0.18)   | 6/44                 | 4/44               |
| Jiang XN     | 2013      | China         | 26-30                       | NR                     | -0.15 (-0.26, -0.03) | 2/65                 | 9/51               |
| Li ZY        | 2018      | China         | 28                          | NR 📃                   | -0.10 (-0.21, 0.01)  | 1/41                 | 5/41               |
| Lou JJ       | 2015      | China         | 28                          | 4                      | 0.00 (-0.07, 0.07)   | 7/127                | 3/58               |
| Pan YC       | 2017      | China         | 32                          | 0                      | -0.00 (-0.05, 0.04)  | 3/81                 | 15/370             |
| Peng BA      | 2012      | China         | 28                          | •                      | 0.05 (-0.08, 0.18)   | 5/40                 | 3/40               |
| Sheng Q      | 2018b     | China         | 24-28                       | 0                      | 0.00 (-0.04, 0.04)   | 0/66                 | 0/46               |
| Tan J        | 2019      | China         | 28                          | 0                      | 0.00 (-0.13, 0.13)   | 5/41                 | 7/59               |
| Tan Z        | 2016      | China         | <14-28                      | NR -                   | -0.01 (-0.06, 0.05)  | 14/171               | 28/320             |
| Wang J       | 2017      | China         | 24-28                       | NR 🛶                   | 0.02 (-0.02, 0.05)   | 10/329               | 1/65               |
| Wu Q         | 2015      | China         | 24-32                       | 0 or 4                 | -0.04 (-0.09, 0.01)  | 12/280               | 14/173             |
| Xiao XH      | 2017      | China         | 28                          | 0 or 4                 | -0.03 (-0.11, 0.04)  | 2/60                 | 4/60               |
| Yao LF       | 2014      | China         | 28-32                       | 6                      | 0.00 (-0.06, 0.06)   | 0/30                 | 0/30               |
| Yue X        | 2014      | China         | Anytime                     | NR -                   | -0.07 (-0.22, 0.08)  | 2/31                 | 4/30               |
| Zhang X      | 2015      | China         | 28                          | 12                     | 0.00 (-0.04, 0.04)   | 0/48                 | 0/47               |
| Zheng JC     | 2018      | China         | 28                          | 4                      | 0.00 (-0.07, 0.07)   | 0/23                 | 0/37               |
| Zhou YJ      | 2014      | China         | 1st Trimester               | 0                      | - 0.00 (-0.05, 0.05) | 0/53                 | 0/34               |
| Subtotal (I  | -squared  | l = 0.0%, p   | = 0.734)                    | 4                      | -0.00 (-0.02, 0.01)  | 104/2175             | 120/195            |
| Overall (I-s | squared   | = 0.0%, p =   | = 0.660)                    | •                      | -0.00 (-0.01, 0.01)  | 105/2427             | 120/219            |

### **Appendix Z: Infant safety 3. Congenital abnormalities**

# TDF 300 mg risk difference for congenital abnormalities Weighted pooled risk difference: -0.00 (95%CI: -0.01 – 0.01). I<sup>2</sup> statistic overall = 0.0% I<sup>2</sup> statistic RCTs = 0.0% I<sup>2</sup> statistic non-RCTs = 0.0%

| Author        | Year     | Country       | in weeks<br>gestation | in weeks<br>postpartu | m |   |               |   | F             | RD (95% CI)        | Events,<br>Treatment | Events<br>Contro |
|---------------|----------|---------------|-----------------------|-----------------------|---|---|---------------|---|---------------|--------------------|----------------------|------------------|
| Randomised    | contro   | lled trials   |                       |                       |   |   | 1             |   |               |                    |                      |                  |
| Jourdain G    | 2018     | Thailand      | 26-29                 | 8                     |   |   |               |   | -             | 0.01 (-0.02, 0.01) | 0/163                | 1/160            |
| Lin Y         | 2018     | China         | 24                    | 4                     |   |   | _             |   | (             | 0.00 (-0.03, 0.03) | 0/59                 | 0/52             |
| Liu MH        | 2017     | China         | 28-30                 | 0                     |   | - |               | _ | (             | 0.00 (-0.09, 0.09) | 0/20                 | 0/20             |
| Pan CQ        | 2016     | China         | 30-32                 | 4                     |   |   | _             |   | (             | 0.01 (-0.03, 0.05) | 2/95                 | 1/88             |
| Yu CY         | 2018     | China         | 24                    | 4                     |   | _ | -             |   | -             | 0.03 (-0.12, 0.05) | 0/30                 | 1/30             |
| Subtotal (I-s | quared   | = 0.0%, p     | = 0.895)              |                       |   |   | •             |   | -             | 0.00 (-0.02, 0.01) | 2/367                | 3/350            |
| Non-random    | ised co  | ntrolled tria | als                   |                       |   |   |               |   |               |                    |                      |                  |
| Celen MK      | 2013     | Turkey        | 18-27                 | 4                     |   |   |               | _ | (             | 0.00 (-0.08, 0.08) | 0/21                 | 0/23             |
| Chen HL       | 2015     | Taiwan        | 30-32                 | 4                     |   |   |               |   | C             | 0.02 (-0.03, 0.06) | 1/65                 | 0/56             |
| Chen WJ       | 2017     | China         | 28                    | 0                     |   |   | - <del></del> |   | C             | 0.00 (-0.05, 0.05) | 0/30                 | 0/44             |
| Greenup AJ    | 2014     | Australia     | 32                    | 12                    |   |   | -             | _ | C             | 0.02 (-0.06, 0.09) | 1/58                 | 0/20             |
| Wakano Y      | 2018     | Japan         | 22-28                 | 4-8                   | ← |   |               |   | $\rightarrow$ | 0.00 (-0.53, 0.53) | 0/2                  | 0/3              |
| Wang HB       | 2018     | China         | 20-36                 | NR                    |   |   |               | - | C             | 0.00 (-0.07, 0.07) | 0/100                | 0/20             |
| Xiao XH       | 2017     | China         | 28                    | 0 or 4                |   | - | •             |   | -             | 0.03 (-0.09, 0.02) | 0/60                 | 2/60             |
| Zhang BF      | 2018     | China         | 24-28                 | 0                     |   |   |               |   | (             | 0.00 (-0.04, 0.04) | 0/39                 | 0/75             |
| Zhou Y        | 2018     | China         | 24-28                 | 0                     |   |   |               |   | (             | 0.00 (-0.04, 0.04) | 0/60                 | 0/36             |
| Subtotal (I-s | quared   | = 0.0%, p     | = 0.976)              |                       |   |   | •             |   | -             | 0.00 (-0.02, 0.02) | 2/435                | 2/337            |
| Overall (I-sq | juared : | = 0.0%, p =   | = 0.997)              |                       |   |   | ¢             |   | -             | 0.00 (-0.01, 0.01) | 4/802                | 5/687            |

### • LAM 100-150 mg risk difference for congenital abnormalities

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 0.01).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

|                       |           |                             | Тх             |                  |       |   |          |    |                     |           |         |
|-----------------------|-----------|-----------------------------|----------------|------------------|-------|---|----------|----|---------------------|-----------|---------|
|                       |           |                             | start in weeks | Tx end in        |       |   |          |    |                     | Events,   | Events, |
| Author                | Year      | Country                     | gestation      | weeks postpartur | n     |   |          |    | RD (95% CI)         | Treatment | Control |
|                       |           |                             |                |                  |       |   |          |    |                     |           |         |
| Randomised            | l control | led trials                  |                |                  |       |   |          |    |                     |           |         |
| Tian XQ               | 2015      | China                       | 28             | 0                |       | _ | -        |    | 0.00 (-0.02, 0.02)  | 0/110     | 0/110   |
| Xu WM                 | 2009      | China, Phi <b>l</b> ippines | 30-34          | 4                |       |   |          |    | 0.02 (-0.03, 0.07)  | 1/56      | 0/59    |
| Yang HW               | 2014      | China                       | 28             | 4                |       | - | <u> </u> |    | 0.00 (-0.04, 0.04)  | 0/53      | 0/53    |
| Subtotal (I-s         | squared   | = 0.0%, p = 0.730)          |                |                  |       |   | Ŷ        |    | 0.00 (-0.01, 0.02)  | 1/219     | 0/222   |
| •                     |           |                             |                |                  |       |   |          |    |                     |           |         |
| Non-random            | ised cor  | ntrolled trials             |                |                  |       |   |          |    |                     |           |         |
| Foaud HM              | 2019      | Egypt                       | Anytime        | NR               |       | - | <u> </u> |    | 0.00 (-0.05, 0.05)  | 0/34      | 0/39    |
| Ge YL                 | 2015      | China                       | 28-30          | 12               |       |   | *        |    | 0.00 (-0.10, 0.10)  | 0/16      | 0/22    |
| Greenup AJ            | 2014      | Australia                   | 32             | 2                |       | - | -        |    | 0.04 (-0.05, 0.12)  | 2/53      | 0/20    |
| He T                  | 2018      | China                       | 1st Trimester  | NR               |       |   | +        |    | -0.09 (-0.20, 0.02) | 0/29      | 3/34    |
| Ma J                  | 2006      | China                       | Pre-pregnancy  | NR               |       |   | <u>+</u> |    | 0.00 (-0.11, 0.11)  | 0/18      | 0/16    |
| Pan CQ                | 2017      | China                       | 13-30          | 4                |       |   |          |    | 0.03 (-0.00, 0.06)  | 5/160     | 0/89    |
| Shen ML               | 2016      | China                       | 26             | 4                |       | - |          |    | 0.00 (-0.05, 0.05)  | 0/60      | 0/28    |
| Wakano Y              | 2018      | Japan                       | 28-32          | 4-8              | ←     |   | -        |    | 0.00 (-0.46, 0.46)  | 0/3       | 0/3     |
| Wang DM               | 2016      | China                       | 28-30          | 12               |       |   | ÷        |    | 0.00 (-0.07, 0.07)  | 0/42      | 0/20    |
| Wang W                | 2014      | China                       | 28             | 4                |       | _ | <u>+</u> |    | 0.00 (-0.06, 0.06)  | 0/35      | 0/28    |
| Yuan QF               | 2012      | China                       | 27             | 4                |       |   | <u>.</u> |    | 0.00 (-0.06, 0.06)  | 0/32      | 0/32    |
| Zeng YM               | 2013      | China                       | 28             | Variable (0,4,6) |       | - | <u>.</u> |    | 0.00 (-0.05, 0.05)  | 0/90      | 0/30    |
| Zhang H               | 2014      | China                       | 28-30          | 4                |       |   | <b></b>  |    | -0.01 (-0.03, 0.02) | 0/54      | 2/370   |
| Subtotal (I-s         | squared   | = 0.0%, p = 0.872)          |                |                  |       |   | 0        |    | 0.00 (-0.01, 0.02)  | 7/626     | 5/731   |
|                       |           |                             |                |                  |       |   |          |    |                     |           |         |
| Overall ( <b>⊢</b> so | quared =  | = 0.0%, p = 0.950)          |                |                  |       |   | 6        |    | 0.00 (-0.01, 0.01)  | 8/845     | 5/953   |
|                       |           |                             |                |                  |       |   |          |    |                     |           |         |
|                       |           |                             |                |                  |       |   |          |    |                     |           |         |
|                       |           |                             |                |                  | .3 .2 | 1 | 0.1      | .2 | 3                   |           |         |
|                       |           |                             |                |                  |       |   |          |    |                     |           |         |

### • LdT 600 mg risk difference of congenital abnormalities

- Weighted pooled risk difference: 0.00 (95%CI: -0.00 0.00).
  I<sup>2</sup> statistic overall = 0.0%
  I<sup>2</sup> statistic RCTs = 0.0%
  I<sup>2</sup> statistic non-RCTs = 0.0%

| Author      | Year      | Country            | start in weeks<br>gestation | in weeks<br>postpartum | Events,<br>RD (95% CI) Treatment | : C      |
|-------------|-----------|--------------------|-----------------------------|------------------------|----------------------------------|----------|
| Randomise   | ed contro | ed trials          |                             |                        |                                  |          |
| Lu QY       | 2016      | China              | 28                          | 0 🔶                    | 0.00 (-0.01, 0.01) 0/152         | 0/       |
| Shi QW      | 2017      | China              | 24                          | 0                      | 0.00 (-0.02, 0.02) 0/100         | 0/       |
| Wang HY     | 2018      | China              | 12-14                       | 24                     | 0.00 (-0.05, 0.05) 0/40          | 0/       |
| Zhang Y     | 2018      | China              | Pre-pregnancy               | NR -                   | 0.00 (-0.06, 0.06) 0/34          | 0/       |
| Subtotal (I | -squared  | d = 0.0%,          | p = 1.000)                  | \$                     | 0.00 (-0.01, 0.01) 0/326         | 0/       |
| Non-rando   | mised co  | ontrolled tr       | ials                        |                        |                                  |          |
| Chen CY     | 2015      | China              | 1st Trimester               | NR —                   | 0.00 (-0.05, 0.05) 0/42          | 0/       |
| Chen F      | 2016      | China              | Pre-pregnancy               | NR -                   | 0.00 (-0.06, 0.06) 0/31          | 0/       |
| Chen WJ     | 2017      | China              | 28                          | 0                      | - 0.00 (-0.04, 0.04) 0/79        | 0/       |
| Chen ZX     | 2017      | China              | 13-32                       | NR                     | - 0.00 (-0.04, 0.04) 0/41        | 0/       |
| Deng Y      | 2015      | China              | 24-36                       | 4                      | 0.00 (-0.02, 0.02) 0/82          | 0/       |
| Ding XP     | 2018      | China              | 28                          | 4                      | 0.00 (-0.05, 0.05) 0/38          | 0/       |
| Fan LY      | 2013      | China              | 28                          | 24                     | - 0.00 (-0.03, 0.03) 0/58        | 0/       |
| Ge YL       | 2015      | China              | 28-30                       | 12                     | 0.00 (-0.09, 0.09) 0/20          | 0/       |
| Han GR      | 2015      | China              | 20-32                       | NR 🔶                   | 0.00 (-0.02, 0.02) 0/365         | 0/       |
| Не Т        | 2018      | China              | 1st Trimester               | NB                     | -0.03 (-0.15, 0.10) 2/32         | 3/       |
| Hu Y        | 2018      | China              | 28-32                       | 3-4                    | 0.02 (-0.01, 0.05) 3/149         | 0/       |
| Jiang XN    | 2013      | China              | 26-30                       | NB                     | - 0.00 (-0.03, 0.03) 0/65        | 0/       |
| LiYH        | 2017      | China              | 28                          | ~36                    |                                  | 0/       |
| LiZY        | 2018      | China              | 28                          | NR                     |                                  | 0/       |
| LiuXB       | 2016      | China              | 28-36                       | 4                      |                                  | 0/       |
| LiuY        | 2016      | China              | 4-32                        | 4                      | 0.00(-0.02,0.02) 0/82            | 0/       |
| Loudd       | 2015      | China              | 28                          | 4                      | -0.00(-0.04, 0.04) 2/127         | 1/       |
| Pena BA     | 2012      | China              | 28                          |                        | 0.00 (-0.05, 0.05) 0/40          | 0/       |
| Ren N       | 2015      | China              | 28                          | 24                     |                                  | 0/       |
| Shen MI     | 2016      | China              | 26                          | 4                      |                                  | 0/       |
| Sheng O     | 2018a     | China              | 24-32                       |                        |                                  | 0/       |
| Sun W       | 2017      | China              | 12-28                       | 12                     | 0.00 (-0.02, 0.02) 0/103         | 0/       |
| Tan 7       | 2016      | China              | ~14-28                      | NB                     |                                  | 0,       |
| Tian IH     | 2018      | China              | Anytime                     | NB                     |                                  | 0,       |
| Wang DM     | 2016      | China              | 28-30                       | 12                     |                                  | 0,       |
| Wang HB     | 2010      | China              | 20-36                       |                        |                                  | 0/       |
| Wang I      | 2010      | China              | 24-28                       |                        |                                  | 0,       |
| Wang TD     | 2017      | China              | 28                          |                        |                                  | 0        |
|             | 2015      | China              | 24-32                       |                        |                                  | 1        |
|             | 2015      | China              | 24-32                       | 0 01 4                 |                                  | 2        |
|             | 2017      | China              | 20                          | 6                      |                                  | 2/       |
|             | 2014      | China              | Anutimo                     |                        |                                  | 0/       |
|             | 2014      | China              | Anyume                      |                        |                                  | 0/       |
|             | 2010      | China              | 24-20                       |                        |                                  | 0/       |
| Zhang GH    | 2018      | China              | 28                          | 4                      | 0.00 (-0.05, 0.05) 0/40          | 0/       |
| Zhang H     | 2014      | China              | ∠o-30<br>1 at Trime at      | 4                      |                                  | 2/       |
| Subtotal (  | -squared  | onina<br>d = 0.0%, | p = 1.000                   | · •                    | 0.00 (-0.05, 0.05) 0/53          | 0/<br>9/ |
| Overall (I  | squared   | = 0.0%, p          | = 1.000)                    | •                      | 0.00 (-0.00, 0.00) 11/3585       | 9/       |
|             |           |                    |                             |                        | 1 1                              |          |

### Appendix AA: Publication Bias Assessment (Funnel Plots) Efficacy (HBsAg)

TDF 300 mg

### MTCT indicated by HBsAg positivity at 6-12 months, non-RCTs

• Possible publication bias/small study effects, Egger's test p-value=0.002



## LAM 100-150 mg

MTCT indicated by HBsAg positivity at 6-12 months, non-RCTs
 Possible publication bias/small study effects, Egger's test p-value=0.002



### LdT 600 mg

### MTCT indicated by HBsAg positivity at 6-12 months, RCTs

• No evidence of publication bias, Egger's test p-value=0.119



MTCT indicated by HBsAg positivity at 6-12 months, non-RCTs

• Possible publication bias/small study effects, Egger's test p-value<0.001



### Safety outcomes

### TDF 300 mg

### Neonatal deaths, non-RCTs

• No evidence of publication bias



### Fetal deaths, non-RCTs



## LAM 100-150 mg



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• No evidence of publication bias



## LdT 600 mg

Neonatal deaths, RCTsoNo evidence of publication bias



### Neonatal deaths, non-RCTs



## Prematurity, non-RCTs

• Unclear/no evidence of publication bias







### Fetal deaths, RCTs

• No evidence of publication bias



### Fetal deaths, non-RCTs

• No evidence of publication bias



### Postpartum hemorrhage, non-RCTs

• No evidence of publication bias


#### **Appendix AB: GRADE Evidence Profiles**

#### GRADE review process methods

For each examined treatment comparison, the quality of the evidence studied was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology (GRADE). We used this tool to evaluate the risk of bias, inconsistency (high heterogeneity), imprecision (confidence intervals), indirectness (use of surrogate outcomes), reporting and publication bias, and other factors, within each intervention group (i.e. antiviral treatment used as the intervention) from which the evidence was summarized within the review. This eventually gave a score of high (further research is very unlikely to change the effect estimate), moderate, low or very low (all estimates are very uncertain). Decisions for the complex judgments within the GRADE table were made through study group consensus. The study group reviewers were supported in the process of completing this GRADE template through discussion and advice from a WHO-designated methodological expert, (RC). For this specific metaanalysis, the following rules were used to determine whether or not a group of studies had no serious, serious, or very serious issues with regards to GRADE criteria:

*Limitations* – this was rated as 'no serious' only in the following circumstances: for RCTs, if multiple studies ( $\geq 2$ ) were of high quality with low risk of bias for the majority of criteria; for non-RCTs, if  $\geq 50\%$  of studies had a 'low risk of bias' assessment as per the Newcastle-Ottawa risk of bias assessment tool

*Inconsistency*–  $I^2$ <30%='no serious',  $I^2$ >=30&<60%='serious',  $I^2$ >60%='very serious'

*Indirectness* – all studies were considered to have 'no serious' issues as this was guaranteed by the PICO question specifications

*Imprecision* – for odds ratios, an absolute range in the 95% confidence intervals of 0.5 was considered as 'no serious', a range  $\geq=0.5$  and <1.0 was considered as 'serious', and a range of  $\geq=1$  was considered as 'very serious'. For risk difference estimates, an absolute range in the 95% confidence intervals of <0.01 (i.e. <10/1000) was allowed for a set of studies to be considered as having 'no serious' limitations in this area.

If the absolute range of the risk difference was >=0.01 and <0.1 then it was considered as having 'serious' limitations, and if it was >=0.1 (i.e. 100 per 1000) then it was considered as having 'very serious' limitations. Note: wherever odds ratios were available, the range of this estimate was used to define imprecision; if no odds ratio was available then risk difference range was used.

*Publication bias* – An Eggers test with p-value of <0.05 led to assumption of 'possible evidence of publication bias or small study effects' if odds ratios had been estimated. Where risk difference estimates, only, were estimated, an obviously asymmetrical funnel plot led to the same assumption.

*Other* – a non-RCT study set could be upgraded for 'magnitude of effect' if the protective odds ratio was <0.5 and was not considered as imprecise.

### TDF 300 mg

|                          |  |               |               | Quality a     | ssessment     |   |                                | Number of patient |                  | patients Effect                |   |                           |
|--------------------------|--|---------------|---------------|---------------|---------------|---|--------------------------------|-------------------|------------------|--------------------------------|---|---------------------------|
| Numbe<br>r of<br>studies | Design                                     | Limitations   | Inconsistency | Indirectness  | Imprecision   | Publication<br>Bias   | Other                          | AVT<br>(%)        | No<br>AVT<br>(%) | OR<br>(95%CI<br>)              | Absolut<br>e<br>(95%CI<br>)                                 | Quality                   |
|                          | ·  |               |               | HB            | SAg positiv   | rity at 6-12  | months                         |                   |                  |                                |   |                           |
| 5                        | Randomize<br>d<br>controlled<br>trials     | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Not able to<br>examine<br>publication<br>bias.                        | N/A                            | 1/349<br>(0.3)    | 23/337<br>(6.8)  | <b>0.10</b><br>(0.03-<br>0.35) | <b>80 fewer</b><br>per 1000<br>(10-140<br>fewer)            | High <sup>a</sup>         |
| 14                       | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Evidence of<br>possible<br>publication<br>bias/small<br>study effects | Magnitude<br>of the<br>effect. | 21/723<br>(2.9)   | 88/499<br>(17.6) | <b>0.17</b><br>(0.10-<br>0.29) | <b>140</b><br><b>fewer</b><br>per 1000<br>(80-200<br>fewer) | Low <sup>b</sup>          |
|                          | ·  |               |               | HBV           | DNA posit     | ivity at 6-1  | 2 months                       |                   |                  |                                |   |                           |
| 4                        | Randomize<br>d<br>controlled<br>trials     | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Not able to<br>examine<br>publication<br>bias.                        | N/A                            | 1/319<br>(0.3)    | 20/307<br>(6.5)  | <b>0.11</b><br>(0.03-<br>0.43) | <b>70 fewer</b><br>per 1000<br>(0-150<br>fewer)             | High <sup>c</sup>         |
| 7                        | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Not able to<br>examine<br>publication<br>bias.                        | Magnitude<br>of the<br>effect. | 0/451<br>(0.0)    | 38/308<br>(12.3) | <b>0.06</b><br>(0.02-<br>0.19) | <b>110</b><br><b>fewer</b><br>per 1000<br>(50-170<br>fewer) | Moderat<br>e <sup>d</sup> |
|                          | -  |               | -             | In            | fant safety   | : neonatal d  | leaths                         |                   |                  |                                |   |                           |
| 5                        | Randomize<br>d                             | No<br>serious | No<br>serious | No<br>serious | Serious       | Not able to<br>examine<br>publication                                 | N/A                            | 2/367<br>(0.5)    | 1/350<br>(0.3)   | -                              | <b>0</b><br>(10   | Moderat<br>e <sup>e</sup> |

|   | controlled                                 |               |               |                       |                         | bias.   |                |                 |                 |   | fewer -  |                           |  |
|---|--|---------------|---------------|-----------------------|-------------------------|---|----------------|-----------------|-----------------|---|--|---------------------------|--|
|   | trials                                     |               |               |                       |                         |   |                |                 |                 |   | 10  more)  |                           |  |
| 14                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious         | Serious                 | No evidence<br>of publication<br>bias                         | None           | 0/712<br>(0.0)  | 0/508<br>(0.0)  | - | 0<br>(10<br>fewer -<br>10 more)  | Very<br>low <sup>f</sup>  |  |
|   |  |               |               |                       | Infant safe             | ty: prematu   | rity           |                 |                 |   |  |                           |  |
| 4                                       | Randomize<br>d<br>controlled<br>trials     | No<br>serious | No<br>serious | No<br>serious         | Serious                 | Not able to<br>examine<br>publication<br>bias.                | N/A            | 11/337<br>(3.3) | 16/320<br>(5.0) | - | <b>10 fewer</b><br>(30<br>fewer –<br>20 more)                                  | Moderat<br>e <sup>g</sup> |  |
| 4                                       | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious         | Serious                 | Not able to<br>examine<br>publication<br>bias.                | None           | 8/285<br>(2.8)  | 6/159<br>(3.8)  | - | <b>10 more</b><br>(30<br>fewer to<br>40 more)                                  | Very<br>low <sup>h</sup>  |  |
| Infant safety: congenital abnormalities |  |               |               |                       |                         |   |                |                 |                 |   |  |                           |  |
| 5                                       | Randomize<br>d<br>controlled<br>trials     | No<br>serious | No<br>serious | No<br>serious         | Serious                 | Not able to<br>examine<br>publication<br>bias.                | N/A            | 2/367<br>(0.5)  | 3/350<br>(0.9)  | - | <b>0</b><br>(20<br>fewer -<br>10 more)   | Moderat<br>e <sup>i</sup> |  |
| 9                                       | Non-<br>randomized<br>controlled           | No<br>serious | No<br>serious | No<br>serious         | Serious                 | Not able to<br>examine<br>publication<br>bias.                | None           | 2/435<br>(0.5)  | 2/337<br>(0.6)  | - | <b>0</b><br>(20<br>fewer -<br>20 more)   | Very<br>low <sup>j</sup>  |  |
| Infant safety: bone mineral density     |  |               |               |                       |                         |   |                |                 |                 |   |  |                           |  |
|   | trials                                     |               |               | Infa                  | nt safety: b            | one mineral   | density        |                 | I               |   | · · · · · · · · · · · · · · · · · · ·  |                           |  |
| 1                                       | Randomize<br>d<br>controlled<br>trials     | No<br>serious | N/A           | Infa<br>No<br>serious | nt safety: b<br>Serious | one mineral<br>Not able to<br>examine<br>publication<br>bias. | density<br>N/A | N/A             | N/A             | - | <b>-0.006</b><br>g/cm2<br>(-0.019 to<br>0.007 g/cm <sup>2</sup> );<br>P =0.38) | Low <sup>k</sup>          |  |

| 5                                      | Randomize<br>d<br>controlled<br>trials     | No<br>serious | No<br>serious                            | No<br>serious | Serious         | Not able to<br>examine<br>publication<br>bias. | N/A       | 3/372<br>(0.8)   | 0/362<br>(0.0)  | - | <b>10 more</b><br>(10)<br>fewer -<br>20 more)      | Moderat<br>e <sup>1</sup> |  |
|--|--|---------------|--|---------------|-----------------|--|-----------|------------------|-----------------|---|--|---------------------------|--|
| 14                                     | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious                            | No<br>serious | Serious         | No evidence<br>of publication<br>bias          | None      | 0/570<br>(0.0)   | 1/520<br>(0.2)  | - | 0<br>(10<br>fewer -<br>10 more)                    | Very<br>low <sup>m</sup>  |  |
| Maternal safety: postpartum hemorrhage |  |               |  |               |                 |  |           |                  |                 |   |  |                           |  |
| 3                                      | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious                            | No<br>serious | Serious         | Not able to<br>examine<br>publication<br>bias. | N/A       | 4/177<br>(2.3)   | 5/172<br>(2.9)  | - | <b>0</b><br>(30<br>fewer -<br>30 more)             | Low <sup>n</sup>          |  |
| 3                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious                            | No<br>serious | Serious         | Not able to<br>examine<br>publication<br>bias. | None      | 5/188<br>(2.7)   | 3/84<br>(3.6)   | - | <b>0</b><br>(40<br>fewer -<br>40 more)             | Very<br>low <sup>o</sup>  |  |
|  |  | Ma            | ternal safe                              | ety: postpar  | tum hepati      | tis flare aft                                  | er treatm | ent discon       | tinuatio        | n |  |                           |  |
| 2                                      | Randomize<br>d<br>controlled<br>trials     | No<br>serious | Serious<br>I <sup>2</sup> =43.7%         | No<br>serious | Serious         | Not able to<br>examine<br>publication<br>bias. | N/A       | 10/251<br>(4.0)  | 8/257<br>(3.1)  | - | <b>2 more</b><br>(47<br>fewer -<br>51 more)        | Low <sup>p</sup>          |  |
| 2                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | Very<br>serious<br>I <sup>2</sup> =80.6% | No<br>serious | Very<br>serious | Not able to<br>examine<br>publication<br>bias. | None      | 18/105<br>(17.1) | 12/70<br>(17.1) | - | <b>38 fewer</b><br>(289<br>fewer -<br>212<br>more) | Very<br>low <sup>q</sup>  |  |

<sup>a</sup>No downgrading <sup>b</sup>Downgrading due to possible publication bias/small study effects, upgrading due to magnitude of effect. <sup>c</sup>No downgrading <sup>d</sup>Upgrading due to magnitude of effect. <sup>e</sup>No downgrading

<sup>f</sup>No upgrading or downgrading <sup>g</sup>Downgrading due to imprecision of risk difference estimate <sup>h</sup> Downgrading due to imprecision of risk difference estimate <sup>i</sup>No downgrading <sup>j</sup>No upgrading or downgrading <sup>k</sup>Downgrading due to inability to examine certain elements (e.g. inconsistency), and for imprecision due to the fact that there was only one RCT included. <sup>1</sup>No downgrading <sup>m</sup>No upgrading or downgrading <sup>n</sup>Downgrading due to 'serious' study design limitations (the majority of RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to imprecision. <sup>o</sup>Downgrading due to imprecision (OR absolute range >1.0) <sup>p</sup>Downgrading due to inconsistency, downgrading due to imprecision

<sup>q</sup>Downgrading due to inconsistency, downgrading due to imprecision

## LAM 100-150 mg

| Number        |  |               |                                  | Quality a     | ssessment    |   |                             | Number of        | patients               | patients Effect                |   |                          |
|---------------|--|---------------|----------------------------------|---------------|--------------|---|-----------------------------|------------------|------------------------|--------------------------------|---|--------------------------|
| of<br>studies | Design                                     | Limitations   | Inconsistency                    | Indirectness  | Imprecision  | Publication<br>Bias   | Other                       | AVT<br>(%)       | No<br>AVT<br>(%)       | OR<br>(95%C<br>I)              | Absolute<br>(95%CI)   | Quality                  |
|               |  |               |                                  | HBs           | Ag positivi  | ty at 6-12 n  | nonths                      |                  |                        |                                |   |                          |
| 8             | Randomized<br>controlled<br>trials         | Serious       | No serious                       | No<br>serious | No serious   | Not possible<br>to examine<br>publication<br>bias.                    | N/A                         | 25/432<br>(5.8)  | 105/38<br>9 (27.0)     | <b>0.16</b><br>(0.10-<br>0.26) | <b>190</b><br><b>fewer</b><br>per 1000<br>(90-280<br>fewer)           | Moderate<br><sup>a</sup> |
| 32            | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No serious                       | No<br>serious | No serious   | Evidence of<br>possible<br>publication<br>bias/small<br>study effects | Magnitude of the effect.    | 41/1575<br>(2.6) | 233/16<br>55<br>(14.1) | <b>0.17</b><br>(0.12-<br>0.24) | <b>140</b><br><b>fewer</b><br>per 1000<br>(110-180<br>fewer)          | Low <sup>b</sup>         |
|               |  |               |                                  | HBV           | DNA positi   | vity at 6-12  | months                      |                  |                        |                                |   |                          |
| 5             | Randomized<br>controlled<br>trials         | Serious       | Serious<br>I <sup>2</sup> =39.8% | No<br>serious | No serious   | Not possible<br>to examine<br>publication<br>bias.                    | N/A                         | 21/312<br>(6.7)  | 73/269<br>(27.1)       | <b>0.22</b> (0.10-0.47)        | <b>160</b><br><b>fewer</b><br>per 1000<br>(320<br>fewer to<br>4 more) | Low <sup>c</sup>         |
| 18            | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No serious                       | No<br>serious | No serious   | No evidence<br>of publication<br>bias.                                | Magnitude<br>of the effect. | 22/1014<br>(2.2) | 137/10<br>57<br>(13.0) | <b>0.14</b> (0.09-0.23)        | <b>140</b><br><b>fewer</b><br>per 1000<br>(90 - 190<br>fewer)         | Moderate                 |
|               |  |               |                                  | Inf           | tant safety: | neonatal d  | eaths                       |                  |                        |                                |   |                          |

| 8                          | Randomized<br>controlled<br>trials         | Serious       | No<br>serious               | No serious | Serious      | Not possible<br>to examine<br>publication<br>bias. | N/A         | 1/439<br>(0.2)  | 1/407<br>(0.2)  | - | <b>0</b><br>(10 fewer<br>- 10<br>more) | Low <sup>e</sup>         |  |  |
|----------------------------|--|---------------|-----------------------------|------------|--------------|--|-------------|-----------------|-----------------|---|--|--------------------------|--|--|
| 31                         | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious               | No serious | Serious      | No evidence<br>of publication<br>bias.             | None        | 0/1571<br>(0.0) | 0/1686<br>(0.0) | - | <b>0</b><br>(10 fewer<br>- 10<br>more) | Very<br>low <sup>f</sup> |  |  |
| Infant safety: prematurity |  |               |                             |            |              |  |             |                 |                 |   |  |                          |  |  |
| 2                          | Randomized<br>controlled<br>trials         | Serious       | No<br>serious               | No serious | Serious      | Not possible<br>to examine<br>publication<br>bias. | N/A         | 0/123<br>(0.0)  | 0/93<br>(0.0)   | - | <b>0</b><br>(30 fewer<br>- 30<br>more) | Low <sup>g</sup>         |  |  |
| 8                          | Non-<br>randomized<br>controlled<br>trials | Serious       | Serious<br>$I^2 =$<br>55.6% | No serious | Serious      | Not possible<br>to examine<br>publication<br>bias. | None        | 14/486<br>(2.9) | 11/306<br>(3.6) | - | 0<br>(40 fewer<br>- 40<br>more)        | Very<br>low <sup>h</sup> |  |  |
|                            | •  |               |                             | Infant s   | safety: cong | genital abno                                       | ormalities  |                 |                 |   |  |                          |  |  |
| 3                          | Randomized<br>controlled<br>trials         | Serious       | No<br>serious               | No serious | Serious      | Not possible<br>to examine<br>publication<br>bias. | N/A         | 1/219<br>(0.5)  | 0/222<br>(0.0)  | - | 0<br>(10 fewer<br>- 20<br>more)        | Low <sup>i</sup>         |  |  |
| 13                         | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious               | No serious | Serious      | No evidence<br>of publication<br>bias.             | None        | 7/626<br>(1.1)  | 5/953<br>(0.5)  | - | 0<br>(10 fewer<br>- 20<br>more)        | Very<br>low <sup>j</sup> |  |  |
|                            |  |               |                             | Maternal   | safety: mis  | scarriage an                                       | nd stillbir | th              |                 |   |  |                          |  |  |
| 8                          | Randomized<br>controlled<br>trials         | Serious       | No<br>serious               | No serious | Serious      | Not possible<br>to examine<br>publication<br>bias  | N/A         | 1/472<br>(0.2)  | 0/409<br>(0.0)  | - | <b>0 more</b><br>(10 fewer<br>- 10     | Low <sup>k</sup>         |  |  |

|  |  |               |                             |              |                 |  |           |                  |                 |   | more)  |                          |  |
|--|--|---------------|-----------------------------|--------------|-----------------|--|-----------|------------------|-----------------|---|--|--------------------------|--|
| 31                                     | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious               | No serious   | Serious         | No evidence<br>of publication<br>bias.             | None      | 0/1531<br>(0.0)  | 9/1678<br>(0.5) | - | 0<br>(10 fewer<br>- 10<br>more)                | Very<br>low <sup>1</sup> |  |
| Maternal safety: postpartum hemorrhage |  |               |                             |              |                 |  |           |                  |                 |   |  |                          |  |
| 1                                      | Randomized<br>controlled<br>trials         | Serious       | Not<br>applicable           | No serious   | Serious         | Not possible<br>to examine<br>publication<br>bias. | N/A       | 0/53<br>(0.0)    | 0/53<br>(0.0)   | - | <b>0</b><br>(40 fewer<br>- 40<br>more)         | Very<br>low <sup>m</sup> |  |
| 7                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious               | No serious   | Serious         | Not possible<br>to examine<br>publication<br>bias. | None      | 98/558<br>(17.6) | 61/699<br>(8.7) | - | <b>10 more</b><br>(10 less -<br>40 more)       | Very<br>low <sup>n</sup> |  |
|  |  | Mat           | ternal safet                | ty: postpart | um hepatit      | is flare afte                                      | r treatme | nt discont       | inuation        | l |  |                          |  |
| 1                                      | Randomized<br>controlled<br>trials         | Serious       | Not<br>applicable           | No serious   | Very<br>serious | Not possible<br>to examine<br>publication<br>bias. | N/A       | 16/83<br>(19.3)  | 15/46<br>(32.6) | - | <b>130 less</b><br>(290<br>fewer -<br>30 more) | Very<br>low <sup>o</sup> |  |
| 5                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | Serious<br>$I^2 =$<br>33.2% | No serious   | Serious         | Not possible<br>to examine<br>publication<br>bias. | None      | 43/364<br>(11.8) | 19/522<br>(3.6) | - | <b>10 fewer</b><br>(50 fewer<br>-30<br>more)   | Very<br>low <sup>p</sup> |  |

<sup>a</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>b</sup>Downgrading due to evidence of possible publication bias, however, upgrading due to magnitude of effect.

<sup>c</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inconsistency >30%.

<sup>d</sup>Upgrading due to magnitude of effect.

<sup>e</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>f</sup>No upgrading or downgrading

<sup>g</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to imprecision <sup>h</sup>Downgrading due to 'serious' study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle-Ottawa scale), downgrading due to inconsistency >30%, downgrading due to imprecision

<sup>i</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>j</sup>No upgrading or downgrading

<sup>k</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>1</sup>No upgrading or downgrading

<sup>m</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included, downgrading due to imprecision.

<sup>n</sup>Downgrading due to imprecision.

<sup>o</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included, downgrading due to serious imprecision.

<sup>p</sup>Downgrading due to some inconsistency >30%, downgrading due to imprecision

# LdT 600 mg

| Numbe                             |  |               |               | Quality a     | ssessment     |   |                                | Number           | of patients            | E                              | ffect  |                           |  |
|-----------------------------------|--|---------------|---------------|---------------|---------------|---|--------------------------------|------------------|------------------------|--------------------------------|--|---------------------------|--|
| r of<br>studies                   | Design                                     | Limitations   | Inconsistency | Indirectness  | Imprecision   | Publication<br>Bias   | Other                          | AVT<br>(%)       | No AVT<br>(%)          | OR<br>(95%C<br>I)              | Absolute<br>(95%CI)                                    | Quality                   |  |
|                                   |  |               |               | H             | BsAg positi   | vity at 6-12  | months                         |                  |                        |                                |  |                           |  |
| 21                                | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | No<br>serious | No evidence<br>of publication<br>bias                                 | N/A                            | 36/1209<br>(3.0) | 175/112<br>3 (15.6)    | <b>0.14</b> (0.09-0.21)        | <b>150 fewer</b><br>per 1000<br>(100-200<br>fewer)     | Moderat<br>e <sup>a</sup> |  |
| 62                                | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Evidence of<br>possible<br>publication<br>bias/small<br>study effects | Magnitude<br>of the<br>effect. | 34/4762<br>(0.7) | 521/467<br>4<br>(11.1) | <b>0.09</b><br>(0.06-<br>0.12) | <b>130 fewer</b><br>per 1000<br>(110-150<br>fewer)     | Low <sup>b</sup>          |  |
| HBV DNA positivity at 6-12 months |  |               |               |               |               |   |                                |                  |                        |                                |  |                           |  |
| 8                                 | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | No<br>serious | Not possible<br>to examine<br>publication<br>bias.                    | N/A                            | 6/382<br>(1.6)   | 58/374<br>(15.5)       | <b>0.12</b> (0.05-0.26)        | <b>160 fewer</b><br>per 1000<br>(60 to 250<br>fewer)   | Moderat<br>e <sup>c</sup> |  |
| 45                                | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | No<br>serious | Evidence of<br>possible<br>publication<br>bias/small<br>study effects | Magnitude<br>of the<br>effect. | 18/3648<br>(0.5) | 377/336<br>7<br>(11.2) | <b>0.07</b><br>(0.05-<br>0.10) | <b>130 fewer</b><br>per 1000<br>(100 - 150<br>fewer)   | Low <sup>d</sup>          |  |
|                                   |  | _             |               | Ι             | nfant safet   | y: neonatal   | deaths                         | _                |                        | -                              | -  |                           |  |
| 21                                | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | Serious       | No evidence<br>of publication<br>bias                                 | N/A                            | 0/1213<br>(0.0)  | 0/1123<br>(0.0)        | -                              | <b>0 per</b><br><b>1000</b><br>(10 fewer<br>- 10 more) | Low <sup>e</sup>          |  |
| 61                                | Non-                                       | No            | No            | No            | No            | No evidence of publication  | None                           | 2/4539           | 0/4740                 | -                              | 0 per  | Low <sup>f</sup>          |  |

|    | randomized                                 | serious       | serious       | serious       | serious       | bias   |            | (0.0)              | (0.0)              |   | <b>1000</b>  |                          |  |  |
|----|--|---------------|---------------|---------------|---------------|--|------------|--------------------|--------------------|---|--|--------------------------|--|--|
|    | trials                                     |               |               |               |               |  |            |                    |                    |   | (2  newer - 3  more)                                       |                          |  |  |
|    |  |               |               |               | Infant saf    | ety: premat  | urity      |                    |                    |   | /  |                          |  |  |
| 2  | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | Serious       | Not possible<br>to examine<br>publication<br>bias. | N/A        | 1/252<br>(0.4)     | 0/232<br>(0.0)     | - | <b>0 per</b><br><b>1000</b><br>(10 fewer<br>- 20<br>more)  | Low <sup>g</sup>         |  |  |
| 22 | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | Serious       | No evidence<br>of publication<br>bias              | None       | 104/217<br>5 (4.8) | 120/195<br>9 (6.1) | - | <b>0 per</b><br><b>1000</b><br>(20 fewer<br>- 10 more)     | Very<br>low <sup>h</sup> |  |  |
|    | Infant safety: congenital abnormalities    |               |               |               |               |  |            |                    |                    |   |  |                          |  |  |
| 4  | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | Serious       | Not possible<br>to examine<br>publication<br>bias. | N/A        | 0/326<br>(0.0)     | 0/306<br>(0.0)     | - | <b>0 per</b><br><b>1000</b><br>(10 fewer<br>- 10 more)     | Low <sup>i</sup>         |  |  |
| 36 | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious | No<br>serious | No<br>serious | No evidence<br>of publication<br>bias              | None       | 11/3529<br>(0.3)   | 9/2677<br>(0.3)    | - | <b>0 per</b><br><b>1000</b><br>(4 fewer –<br>4 more)       | Low <sup>j</sup>         |  |  |
|    |  |               |               | Matern        | al safety: r  | niscarriage  | and stillb | irth               |                    |   |  |                          |  |  |
| 20 | Randomize<br>d<br>controlled<br>trials     | Serious       | No<br>serious | No<br>serious | Serious       | No evidence<br>of publication<br>bias              | N/A        | 0/1107<br>(0.0)    | 6/1026<br>(0.6)    | - | <b>1 fewer</b><br><b>per 1000</b><br>(8 fewer -<br>6 more) | Low <sup>k</sup>         |  |  |
| 61 | Non-<br>randomized<br>controlled           | No<br>serious | No<br>serious | No<br>serious | No<br>serious | No evidence<br>of publication<br>bias              | None       | 3/4538<br>(0.1)    | 14/4797<br>(0.3)   | - | <b>0 per</b><br><b>1000</b><br>(3 fewer -                  | Low <sup>1</sup>         |  |  |

|  | trials                                     |               |  |               |                 |  |            |                  |                  |   | 2 more)                                      |                          |  |
|--|--|---------------|--|---------------|-----------------|--|------------|------------------|------------------|---|--|--------------------------|--|
| Maternal safety: postpartum hemorrhage |  |               |  |               |                 |  |            |                  |                  |   |  |                          |  |
| 2                                      | Randomize<br>d<br>controlled<br>trials     | Serious       | Serious<br>I <sup>2</sup> =34.5%         | No<br>serious | Serious         | Not possible<br>to examine<br>publication<br>bias. | N/A        | 39/180<br>(21.7) | 38/180<br>(21.1) | - | <b>10 fewer</b><br>(90 fewer<br>- 60 more)   | Very<br>low <sup>m</sup> |  |
| 17                                     | Non-<br>randomized<br>controlled<br>trials | No<br>serious | No<br>serious                            | No<br>serious | Serious         | No evidence<br>of publication<br>bias              | None       | 86/1549<br>(5.6) | 78/1840<br>(4.2) | - | <b>1 fewer</b><br>(10 less -<br>8 more)      | Very<br>low <sup>n</sup> |  |
|  |  | Μ             | laternal saf                             | ety: postpa   | rtum hepa       | titis flare af                                     | ter treatn | nent disco       | ntinuatior       | 1 |  |                          |  |
| 3                                      | Non-<br>randomized<br>controlled<br>trials | No<br>serious | Very<br>serious<br>I <sup>2</sup> =85.5% | No<br>serious | Very<br>serious | Not possible<br>to examine<br>publication<br>bias. | N/A        | 27/431<br>(6.3)  | 26/565<br>(4.6)  | - | <b>20 less</b><br>(60 fewer<br>-110<br>more) | Very<br>low <sup>o</sup> |  |

<sup>a</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>b</sup>Downgrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.

<sup>c</sup>Downgrading due to <sup>s</sup>erious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high.

<sup>d</sup> Downgrading due to possible evidence of publication bias/small study effects, upgrading due to magnitude of effect.

<sup>e</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). <sup>f</sup>No upgrading or downgrading

<sup>g</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high). <sup>h</sup>No upgrading or downgrading

<sup>i</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>j</sup>No upgrading or downgrading

<sup>k</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).

<sup>1</sup>No upgrading or downgrading

<sup>m</sup>Downgrading due to 'serious' study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to 'serious' inconsistency ( $I^2$ >30%), downgrading due to imprecision.

<sup>n</sup>Downgrading due to 'very serious' inconsistency ( $l^2$ >60%), downgrading due to imprecision, downgrading due to evidence of possible publication bias/small study effects. <sup>o</sup>Downgrading due to 'very serious' inconsistency ( $l^2$ >60%), downgrading due to imprecision