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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

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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 Chinese-language (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

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 cost-effectiveness 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 systematically 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-language 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 English-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  $N \leq 30$  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  $\geq 5.3 \log_{10}$  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 log<sub>10</sub> 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 log<sub>10</sub> 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 English- versus 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 ( $\geq 5.3 \log_{10}$  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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**Table 1. Efficacy of peripartum antiviral prophylaxis (PAP) in the prevention of MTCT\*, by subgroups**

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

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

† 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 peripartum antiviral prophylaxis**

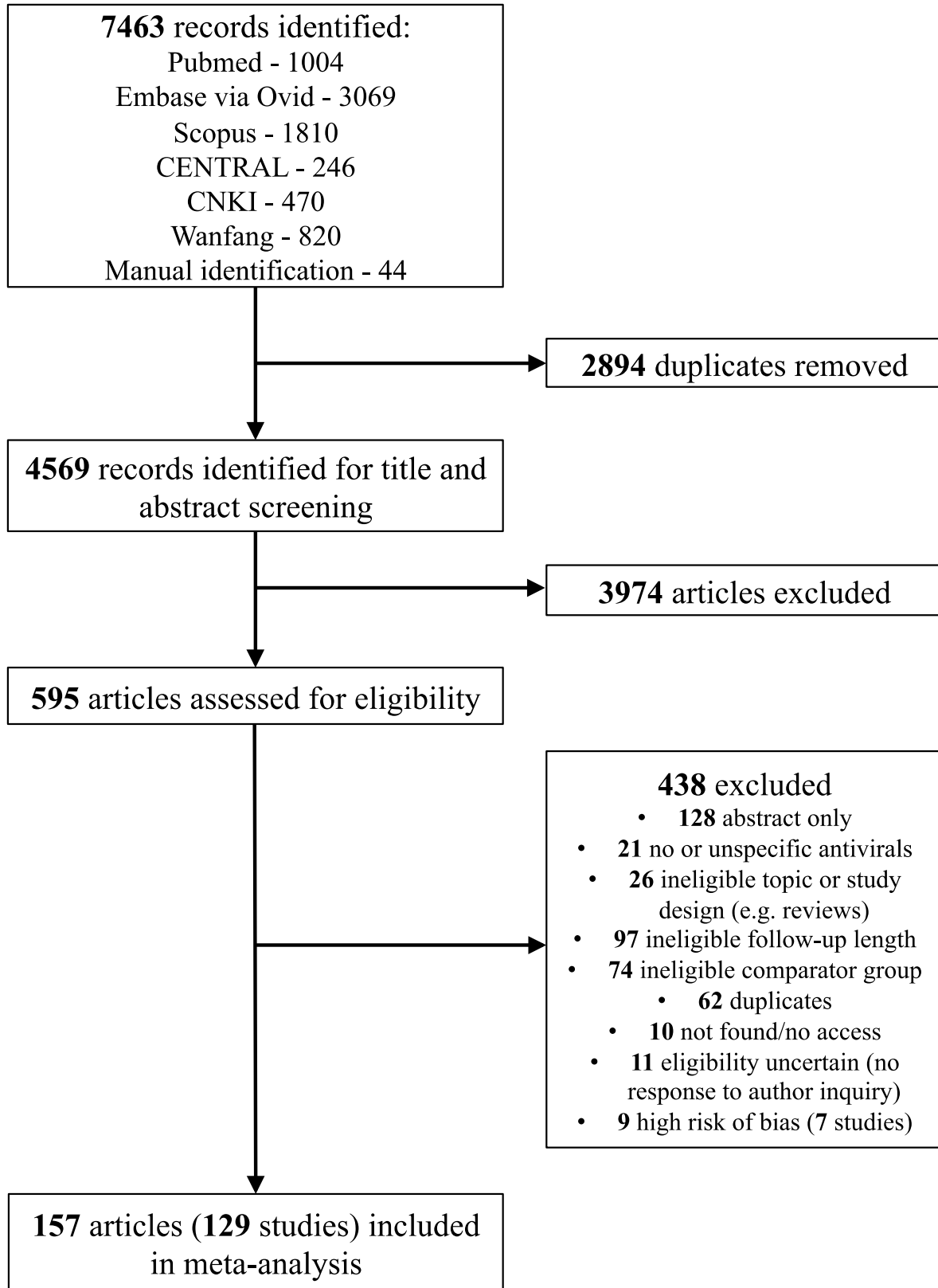
Safety measure	TDF 300 mg (N=19)				LAM 100-150 mg (N=40)				LdT 600 mg (N=83)			
	No. of studies	Events/Participants		RD (95% CI)	No. of studies	Events/Participants		RD (95% CI)	No. of studies	Events/Participants		RD (95% CI)
		Treated	Control			Treated	Control			Treated	Control	
<b>Maternal safety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

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 ( $I^2 \geq 30\%$  &  $< 75\%$ )

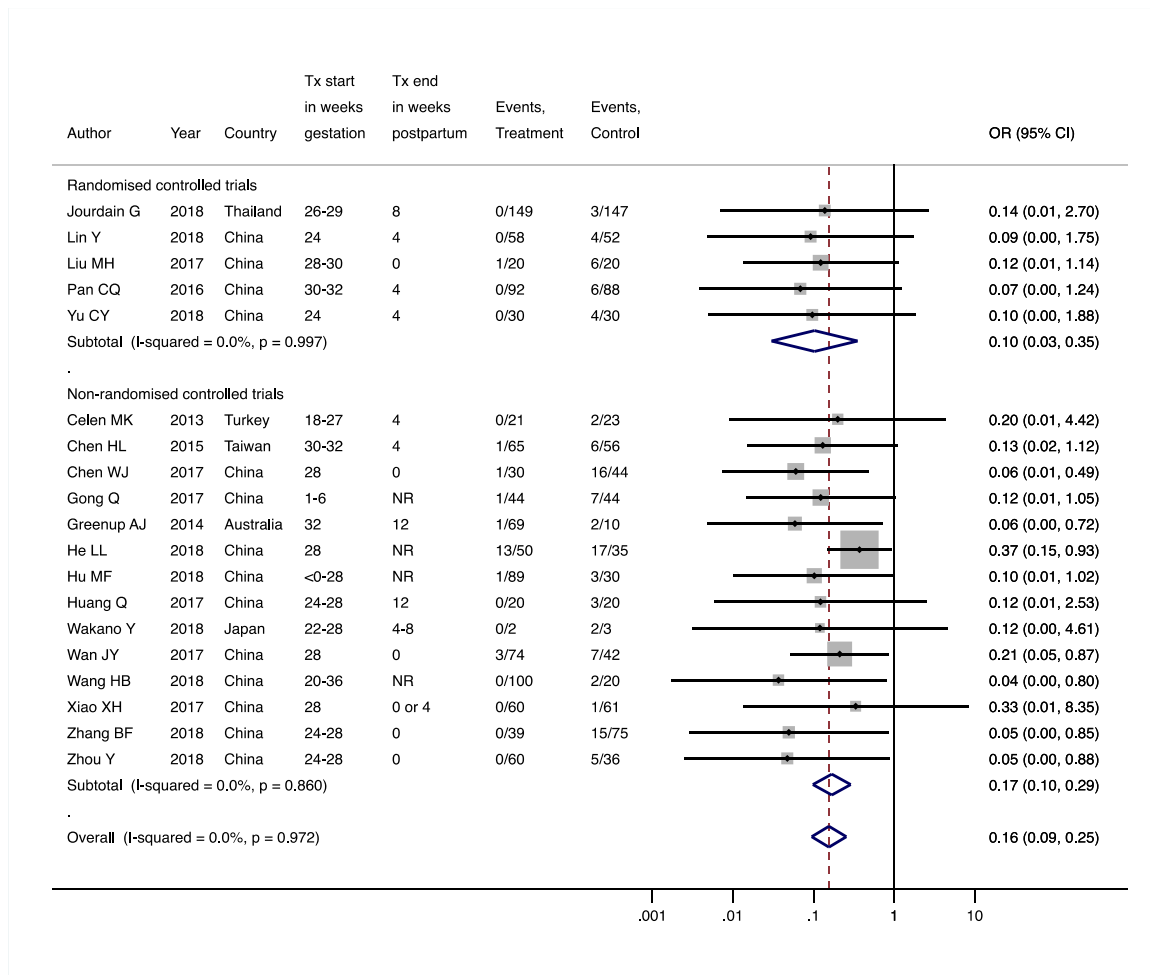
† Considerable heterogeneity ( $I^2 \geq 75\%$ )

**Figure 1: Flowchart of study selection**



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

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

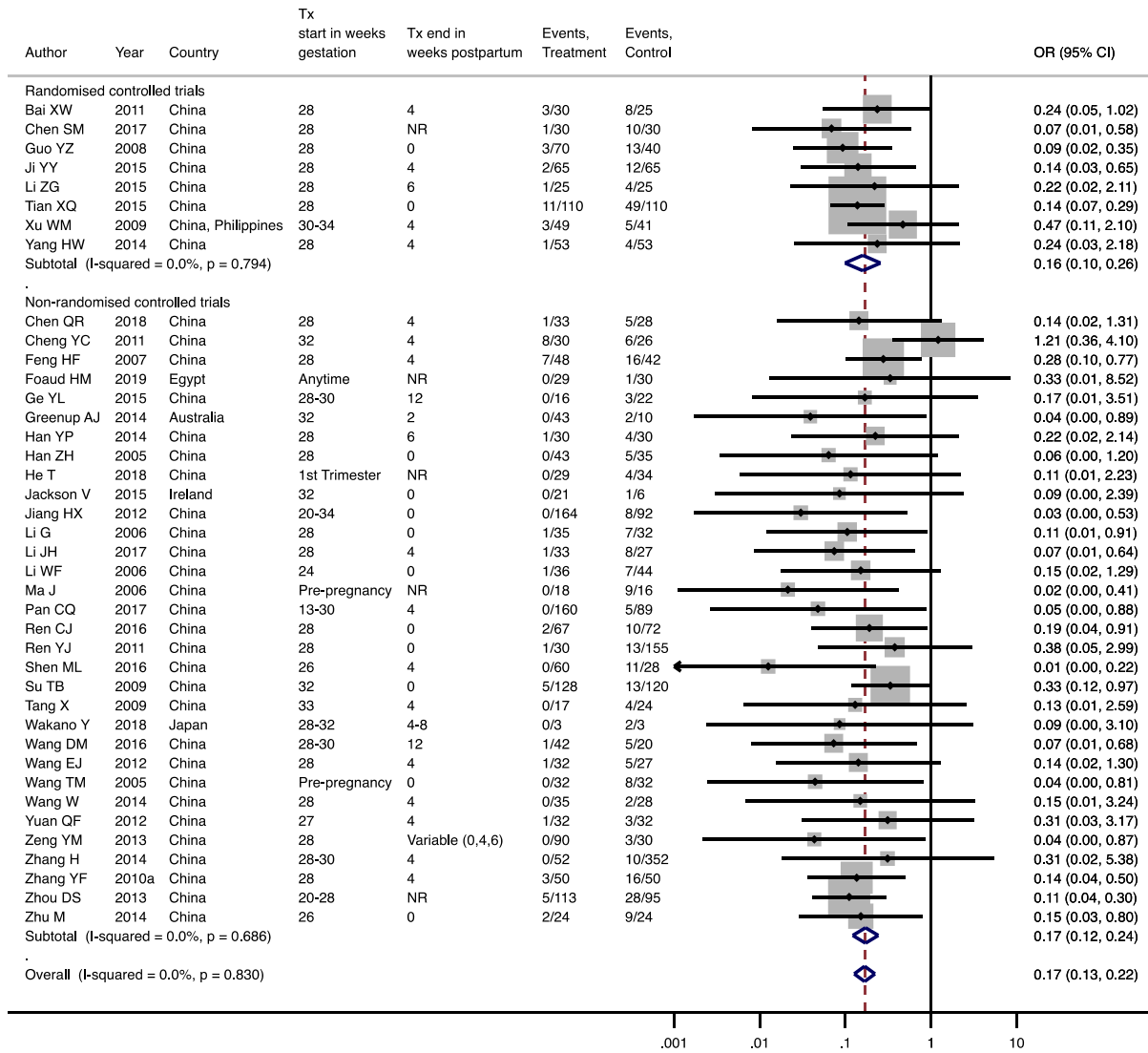
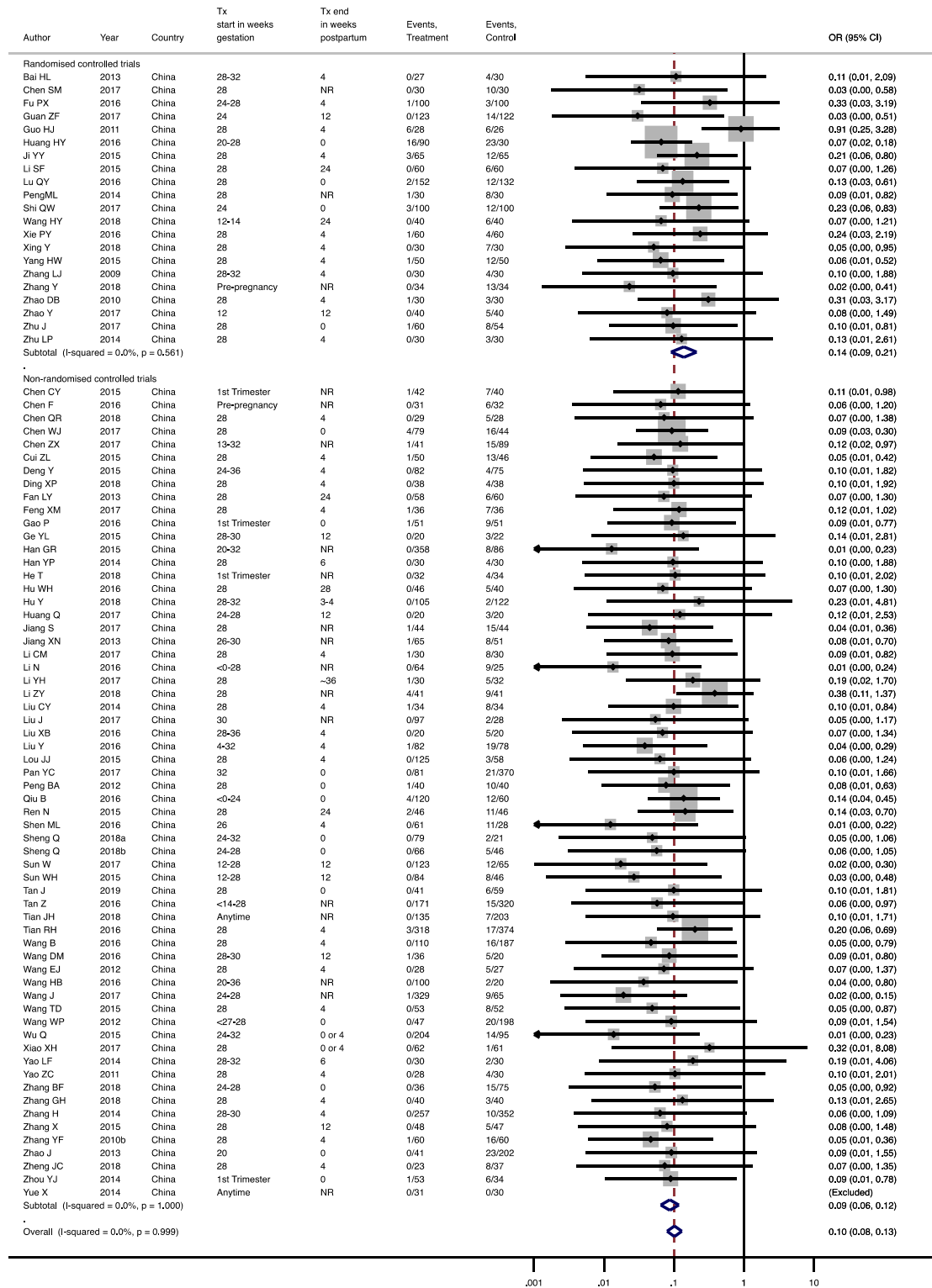
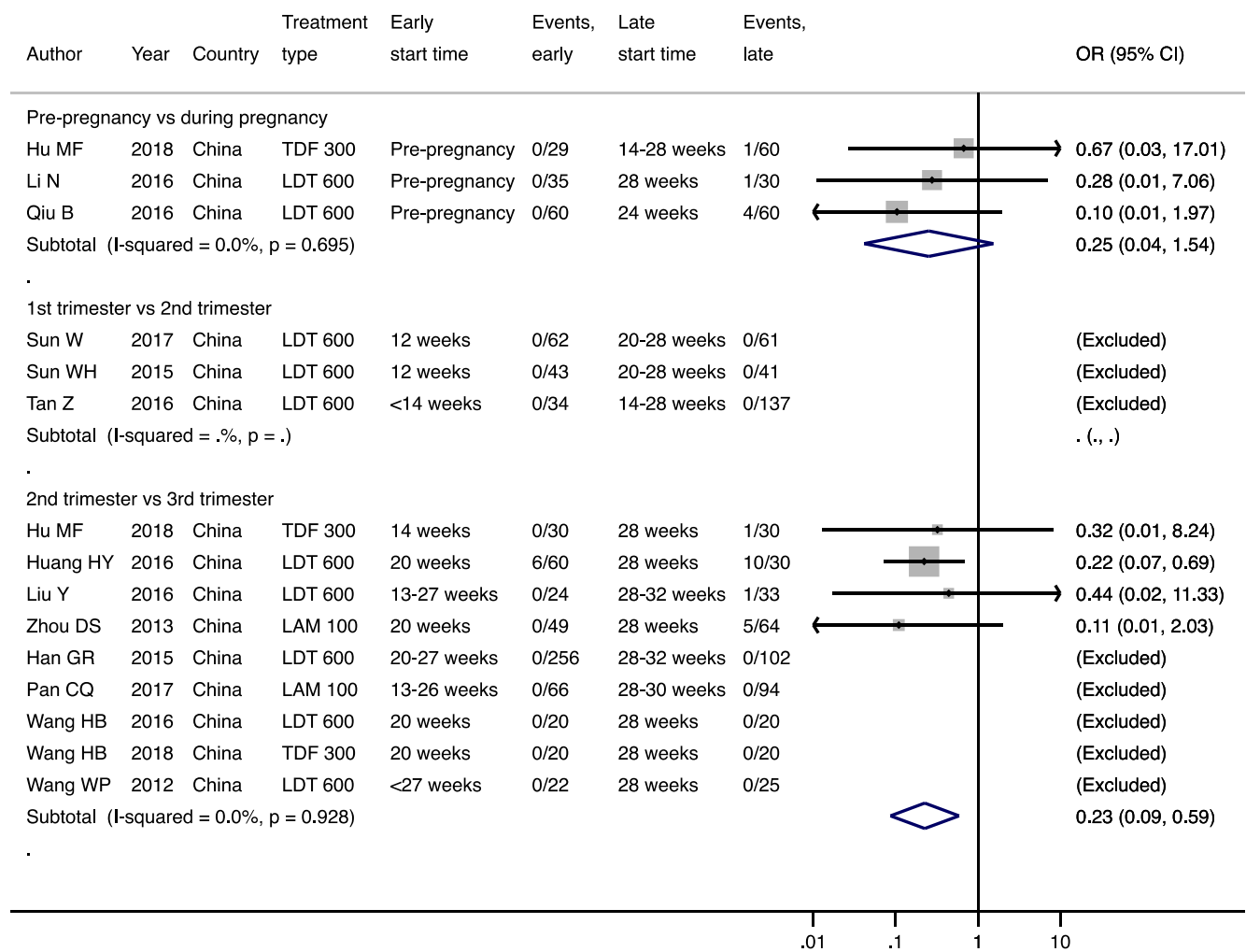


Figure 2C. Efficacy of telbivudine (LdT) 600 mg, by study design





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



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

## 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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## Appendix A: Search strategies

Database: PubMed

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

Search Strategy:

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

	antenatal*[Text] OR ante-natal*[Text] OR prenatal*[Text] OR pre-natal*[Text] OR perinatal*[Text] OR perinatal*[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

Search Strategy:

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 OR vhb OR hep b OR hbsag OR hbs ag OR hbs antigen*).mp.	158 928
3	1 OR 2	158 928
4	exp antiviral therapy/ OR exp antiviral agent/ OR exp nucleoside/ OR exp nucleotide/ OR exp adefovir/ OR exp 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/	1 657 284
5	(antiviral* OR nucleoside* OR nucleotide* OR (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).mp.	1 421 448
6	4 OR 5	2 708 549
7	exp pregnancy/ OR exp pregnant women/ OR exp mother fetus relationship/ OR exp vertical transmission/ OR exp pregnancy complication/ OR exp prenatal diagnosis/	807 598
8	(pregnan* OR trimest* OR gestation* OR 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 MTCT OR TME).mp.	2 268 793
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

Search Strategy:

Item	Search words	# Records
1	TITLE-ABS-KEY (“hepatitis b” OR “type b hepatitis” OR “hepatitis type b” OR “hbv” OR “vhb” OR “hep b” OR “hbsag” OR “hbs ag” OR “hbs antigen*”)	138 899
2	TITLE-ABS-KEY (“antiviral*” OR “nucleoside*” OR “nucleotide*” OR (“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”)	1 781 759
3	TITLE-ABS-KEY (“pregnan*” OR “trimest*” OR “gestation*” OR “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 “MTCT” OR “TME”)	2 892 112
4	#1 AND #2 AND #3	1 810

Database: CENTRAL Database (The Cochrane Library)

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

Search Strategy:

Item	Search words	# Trials and Reviews
1	hepatitis b [MeSH, exp] OR hepatitis b virus [MeSH, exp]	2 462
2	"hepatitis b" OR "type b hepatitis" OR "hepatitis type b" OR hbv OR vhb OR "hep b" OR hbsag OR "hbs ag" OR "hbs antigen" OR "hbs antigens"	7 692
3	1 OR 2	7 692
4	antiviral agents [MeSH, exp] OR nucleosides [MeSH, exp] OR nucleotides [MeSH, exp] OR emtricitabine [MeSH, exp] OR lamivudine [MeSH, exp] OR telbivudine [MeSH, exp] OR tenofovir [MeSH, exp]	17 552
5	antiviral* OR nucleoside* OR nucleotide* OR (nucleos* AND analog*) OR (nucleot* AND analog*) OR NA OR adefovir OR hepsera OR preveon OR "bis-POM PME A" 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 vmlidy OR TAF	34 424
6	4 OR 5	44 913
7	pregnancy [MeSH, exp] OR pregnant women [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]	8 802
8	pregnan* OR trimest* OR gestation* OR 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	74 080



	foetal* OR fetus OR foetus OR offspring* OR 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'+ 'hepsara'+ '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'

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"+"hepsara"+"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

(Table taken directly Higgins JPT et al., 2011)

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



**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.
  - o 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.

*(Adapted to the systematic review questions)*

*Note: 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](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) Representativeness of the exposed cohort (0 or 1 star)**

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) Selection of the non-exposed cohort (0 or 1 star)**

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) Ascertainment of exposure (exposure = treatment) (0 or 1 star)**

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) Demonstration that outcome of interest was not present at start of study (0 or 1 star)**

- a) Yes\*
  - 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) Was follow-up long enough for outcomes to occur (0 or 1 star)**

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

Treatment	# Studies	Study countries (% studies)	Study design (% studies)	Time period	# Pregnant women included (treated/not treated)	HBeAg # studies/total studies	Range of mean viral load at baseline (# studies reporting)	Range of treatment start times	Range of treatment discontinuation times	# Infants assessed (of mothers treated/untreated)	Infants prophylaxis # studies/total studies
<b>TDF 300 mg</b>	19	Australia (5.3) China (73.7) Japan (5.3) Taiwan (5.3) Thailand (5.3) Turkey (5.3)	<b>RCT</b> = 5 (26.3) <b>non-RCT</b> = 14 (73.7)	2010-2018	1974 (1092/882)	All positive: 11/19 All negative: 0/19 Mixed: 1/19 NR: 7/19	3.6 - 8.3 log <sub>10</sub> IU/mL (n=16)	Pre-pregnancy to 36 weeks gestation	0 to 12 weeks post partum	1908 (1072/836)	HBIG, Hep-B-BD, infant vaccines: 16/19
<b>LAM 100-150 mg</b>	40	Australia (2.5) China <sup>b</sup> (88.8) Egypt (2.5) Ireland (2.5) Japan	<b>RCT</b> = 8 (20.0) <b>non-RCT</b> = 32	2001-2016	4200 (2080/2120)	All positive: 30/40 All negative: 0/40 Mixed: 4/40 NR: 6/40	6.0 - 8.7 log <sub>10</sub> IU/mL (n=26)	Pre-pregnancy to 34 weeks gestation <sup>c</sup>	0 to 12 weeks post partum <sup>c</sup>	4051 (2007/2044)	HBIG, Hep-B-BD, infant vaccines: 34/40

		(2.5) Phillipines <sup>b</sup> (1.3)	(80.0)								
<b>LdT 600 mg</b>	83	China (100.0)	<b>RCT=</b> 21 (25.3) <b>non- RCT=</b> 62 (74.7)	2001- 2016	12104 (6036/6068)	All positive: 52/83 All negative: 1/83 Mixed: 6/83 NR: 24/83	2.0- 8.3 log10 IU/mL (n=73)	Pre- pregnanc y to 36 weeks gestation <sub>d</sub>	0 to 36 weeks post partum	11768 (5971/5797)	HBIG, Hep-B- BD, infant vaccines: 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

General study details and design				Treated pregnant women (tx)							Untreated pregnant women (control)					Infant immunoprophylaxis (all infants)		
Author, year	Country	Recruitment period	Criteria for maternal HBV DNA (log IU/mL)	#	Treatment start (gestation weeks) / Treatment discontinuation (postpartum weeks)	Mean/median age (years)	HBeAg (%)	Mean/median HBV DNA at baseline (log IU/mL)	# Infants assessed for MTCT	#	Mean/median age (years)	HBeAg (%)	Mean/median HBV DNA at baseline (log IU/mL)	# Infants assessed for MTCT	HBIG at birth, timing	HepB-BD, timing	Infant vaccine, dose 1/dose 2... in months	
<b>TDF 300 mg</b>																		
<i>Randomized controlled trials (RCT)</i>																		
Jourdain G, 2018 <sup>14, 15, 23</sup>	Thailand	2013-2015	None	168	26-29	8	25.5 [18.3-42.2]	100	7.6	149	163	26.7 [18.4-40.9]	100	7.3	147	Yes, <3hr	Yes, <3hr	Yes, 1/2/4/6
Lin Y, 2018 <sup>24, 25</sup>	China	2013-2016	≥6.3	60	24	4	28.3 ±3.6	100	7.4	58	60	28.1 ±3.4	100	7.7	52	Yes, <24hr	Yes, 12hr	Yes, 1/6
Liu MH, 2017 <sup>26</sup>	China	2014-2016	≥5.3	20	28-30	0	30 [22-38]	100	6.5	20	20	29 [21-38]	100	6.5	20	Yes, <24hr	Yes, <24hr	Yes, 1/6
Pan CQ, 2016 <sup>13</sup>	China	2012-2013	≥5.3	100	30-32	4	27.4 ±3.0	100	8.2	92	100	26.8 ±3.0	100	8.0	88	Yes, <12hr	Yes, <12hr	Yes, 1/6
Yu CY, 2018 <sup>27</sup>	China	2017	≥6.0	30	24	4	26.8 ±4.2	NR	NR	30	30	27.6 ±3.6	NR	NR	30	Yes, <24hr	Yes, <24hr	NR
<i>Non-randomized controlled trials (Non-RCT)</i>																		
Celen MK, 2013 <sup>28</sup>	Turkey	2010-2012	≥6.3	21	18-27	4	28.2 ±4.1	100	8.3	21	24	26.9 ±2.9	100	8.3	23	Yes, <24hr	No	Yes, 1/2/6
Chen HL, 2015 <sup>29</sup>	China (Taiwan)	2011-2013	≥7.5	62	30-32	4	32.4 ±3.1	100	8.3	65	56	32.5 ±3.2	100	8.2	56	Yes, <24hr	Yes, NR	Yes, 1/6
Chen WJ, 2017 <sup>30</sup>	China	2014-2015	≥6.0	30	28	0	28.7 ±5.7	100	7.5	30	44	29.9 ±5.1	100	7.5	44	Yes, At birth	Yes, At birth	Yes, 1/6
Gong Q, 2017 <sup>31</sup>	China	2015-2016	NR	44	1-6	NR	29.1 ±1.0	NR	NR	44	44	29.1 ±1.2	NR	NR	44	Yes, <24hr	Yes, <24hr	Yes, 1/6
Greenup AJ, 2014 <sup>32-35</sup>	Australia	2007-2013	≥7.0±0.5	62	32	12	30 ±8.5	94.8	7.9	69	20	28±5	100	8.0	10	Yes, NR	Yes, At birth	Yes, 2/4/6

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

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

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

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

<b>Zhou DS, 2013</b> <sup>87</sup>	China	2009-2012	≥5.3	49	20	NR	27.4 ±6.7	NR	6.8	49	95	29.2 ±6.1	NR	6.9	95	Yes, <12hr	Yes, At birth	Yes, 1/6
				64	28	NR	28.1 ±5.3	NR	6.7	64								
<b>Zhu M, 2014</b> <sup>88</sup>	China	2012-2013	NR	24	26	0	NR	100	NR	24	25	NR	100	NR	24	Yes, <8hr	Yes, <8hr	Yes, 1/6
<b>LDT 600 mg</b>																		
<i>Randomized controlled trials (RCT)</i>																		
<b>Bai HL, 2013</b> <sup>89</sup>	China	2009-2011	≥6.3	30	28-32	4	NR	NR	6.5	27	30	NR	NR	6.6	30	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Chen SM, 2017</b> <sup>46</sup>	China	2013-2014	≥4.3	30	28	NR	27.4 ±3.5	100	7.8	30	30	27.5 ±3.9	100	8.0	30	Yes, NR	Yes, NR	Yes, NR
<b>Fu PX, 2016</b> <sup>90</sup>	China	2014-2015	NR	100	24-28	4	31.5 ±1.5	NR	NR	100	100	31.7 ±1.6	NR	NR	100	Yes, At birth	Yes, At birth	Yes, NR
<b>Guan ZF, 2017</b> <sup>91,92</sup>	China	2005-2015	≥6.3	12	24	12	26.5 ±9.5	100	7.1	123	120	27.2 ±9.4	100	7.1	122	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Guo HJ, 2011</b> <sup>93</sup>	China	2008-2010	≥6.3	25	28	4	28 ±3	100	7.0	28	25	27±4	100	7.2	26	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Huang HY, 2016</b> <sup>94</sup>	China	2012-2013	≥5.3	30	20	0	28.2 ±3.5	100	7.3	30	30	28.9 ±3.5	100	7.2	30	NR	NR	NR
				30	24	0	28.6 ±3.4	100	7.3	30								
				30	28	0	28.4±3.2	100	7.3	30								
<b>Ji YY, 2015</b> <sup>50</sup>	China	2010-2013	≥5.3	65	28	4	27.2 ±3.6	100	7.7	65	65	27.5 ±4.1	100	7.7	65	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Li SF, 2015</b> <sup>95</sup>	China	2012-2014	≥6.3	60	28	24	NR	NR	6.9	60	60	NR	NR	6.7	60	Yes, At birth	No	Yes, 1/6

<b>Lu QY, 2016</b> <sup>96</sup>	China	2013-2014	NR	152	28	0	[29-36]	47	NR	152	132	[29-36]	41	NR	132	Yes, <12hr	Yes, <12hr	Yes, 1/6
<b>Peng ML, 2014</b> <sup>97</sup>	China	2011-2012	NR	30	28	NR	25.9 ±4.2	100	6.1	30	30	26.4 ±4.4	100	6.1	30	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Shi QW, 2017</b> <sup>98</sup>	China	NR	≥5.3	100	24	0	[23-40]	NR	7.1	100	100	[23-40]	NR	6.9	100	Yes, <2hr	Yes, At birth	Yes, 1/6
<b>Wang HY, 2018</b> <sup>99</sup>	China	2015-2017	≥5.3	40	12-14	24	NR	100	6.8	40	40	NR	100	6.9	40	Yes, <6hr	Yes, <6hr	Yes, 1/6
<b>Xie PY, 2016</b> <sup>100</sup>	China	2015-2015	NR	60	28	4	26.6 ±12.5	NR	NR	60	60	26.1 ±11.6	NR	NR	60	Yes, NR	Yes, NR	Yes, NR
<b>Xing Y, 2018</b> <sup>101</sup>	China	2013-2015	NR	30	28	4	29.0 ±6.0	NR	6.5	30	30	29.5 ±5.3	NR	6.5	30	Yes, <6hr	Yes, <6hr	Yes, 1
<b>Yang HW, 2015</b> <sup>102</sup>	China	2012-2014	≥5.3	50	28	4	NR	100	6.1	50	50	NR	100	6.1	50	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Zhang LJ, 2009</b> <sup>103</sup>	China	2007-2008	≥6.3	31	28-32	4	NR	NR	6.6	30	30	NR	NR	6.7	30	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Zhang Y, 2018</b> <sup>104</sup>	China	2015-2017	≥6.3	34	Pre-pregnancy	NR	28.4 ±3.1	NR	6.6	34	34	28.0 ±3.1	NR	6.9	34	Yes, NR	Yes, NR	Yes, NR
<b>Zhao DB, 2010</b> <sup>105</sup>	China	2006-2008	NR	30	28	4	NR	100	NR	30	30	NR	100	NR	30	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Zhao Y, 2017</b> <sup>106</sup>	China	2013-2016	≥6.3	40	12	12	28.1 ±4.1	100	7.3	40	40	27.9 ±3.9	100	7.2	40	Yes, At birth	Yes, At birth	Yes, 1/6
<b>Zhu J, 2017</b> <sup>107</sup>	China	2012-2015	NR	60	28	0	NR	NR	7.4	60	60	NR	NR	6.9	54	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Zhu LP, 2014</b> <sup>108</sup>	China	2011-2012	NR	30	28	4	NR	NR	6.7	30	30	NR	NR	6.6	30	Yes, <6hr	Yes, At birth	Yes, 1/6
<b><i>Non-randomized controlled trials (Non-RCT)</i></b>																		
<b>Chen CY, 2015</b> <sup>109</sup>	China	2008-2011	≥6.3	43	1 <sup>st</sup> trimester	NR	29.7 ±8.9	100	7.1	42	41	27.5 ±6.6	100	7.0	40	Yes, NR	Yes, NR	Yes, NR

<b>Chen F, 2016</b> <sup>110</sup>	China	2008-2014	$\geq 6.3$	31	Pre-pregnancy	NR	26.5 $\pm 4.0$	100	6.9	31	33	26.0 $\pm 4.4$	100	6.7	32	Yes, NR	Yes, NR	Yes, NR
<b>Chen QR, 2018</b> <sup>56</sup>	China	2014-2016	NR	29	28	4	26.9 $\pm 4.3$	100	7.8	29	28	24.1 $\pm 4.7$	100	7.7	28	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Chen WJ, 2017</b> <sup>30</sup>	China	2014-2015	$\geq 6.0$	79	28	0	31.1 $\pm 6.3$	100	8.3	79	44	29.9 $\pm 5.1$	100	7.5	44	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Chen ZX, 2017</b> <sup>111-113</sup>	China	2001-2015	$\geq 5.3$	43	13-32	NR	28.1 $\pm 6.7$	70	6.5	41	89	26.2 $\pm 4.5$	83	6.5	89	Yes, <6hr	Yes, <6hr	Yes, 1/6
<b>Cui ZL, 2015</b> <sup>114</sup>	China	2013-2014	$\geq 5.3$	50	28	4	28.0 $\pm 1.8$	100	7.1	50	50	27.6 $\pm 2.1$	100	6.9	46	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Deng Y, 2015</b> <sup>115</sup>	China	2011-2014	$\geq 6.0$	82	24-36	4	25.4 $\pm 3.7$	NR	7.0	82	75	25.7 $\pm 3.6$	NR	7.0	75	Yes, At birth	Yes, At birth	Yes, 1/6
<b>Ding XP, 2018</b> <sup>116</sup>	China	2013-2017	$\geq 6.3$	38	28	4	NR	100	7.3	38	38	NR	100	7.2	38	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Fan LY, 2013</b> <sup>117</sup>	China	2010-2011	$\geq 5.3$	58	28	24	27.8 $\pm 3.0$	100	6.9	58	60	29.0 $\pm 2.9$	100	6.7	60	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Feng XM, 2017</b> <sup>118</sup>	China	2014-2016	$\geq 6.3$	36	28	4	29.6 $\pm 6.3$	100	6.9	36	36	28.4 $\pm 5.1$	100	6.7	36	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Gao P, 2016</b> <sup>119</sup>	China	2012-2014	NR	51	1 <sup>st</sup> trimester	0	28.4 $\pm 3.8$	NR	7.1	51	51	27.2 $\pm 3.6$	NR	7.0	51	Yes, NR	Yes, NR	Yes, NR
<b>Ge YL, 2015</b> <sup>60</sup>	China	NR	$\geq 5.3$	20	28-30	12	28.6 $\pm 3.5$	100	7.1	20	22	26.5 $\pm 4.2$	100	6.9	22	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Han GR, 2015</b> <sup>120-125</sup>	China	2008-2010	$\geq 5.3$	257	20-27	Variable	27 [20-35]	100	7.9	256	92	26 [20-35]	100	7.9	86	Yes, <3hr	Yes, <12hr	Yes, 1/6
				105	28-32	Variable	28 [20-38]	100	7.8	102								
<b>Han YP, 2014</b> <sup>62</sup>	China	2010-2012	$\geq 4.3$	30	28	6	26 $\pm 4$	100	7.7	30	30	26 $\pm 4$	100	7.7	30	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>He T, 2018</b> <sup>64,126</sup>	China	2008-2016	NR	32	1 <sup>st</sup> trimester	Continued	29.2 $\pm 2.9$	84	6.6	32	35	29.0 $\pm 3.6$	80	6.2	34	Yes, <6hr	Yes, <12hr	Yes, 1/6



<b>Hu WH, 2016</b> <sup>127</sup>	China	2013-2015	NR	46	28	28	28.9 ±3.3	NR	6.7	46	40	29.2 ±3.4	NR	6.6	40	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Hu Y, 2018</b> <sup>128,129</sup>	China	2012-2014	NR	149	28-32	3-4	25.9 ±3.7	100	7.4	105	179	26.4 ±3.4	100	7.3	122	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Huang Q, 2017</b> <sup>38</sup>	China	2015-2015	≥6.0	20	24-28	12	26.8 ±2.5	100	NR	20	20	27.0 ±2.3	100	NR	20	Yes, <6hr	Yes, <6hr	Yes, 1/6
<b>Jiang S, 2017</b> <sup>130</sup>	China	2015-2016	NR	44	28	NR	28.3 ±3.4	NR	6.1	44	44	NR	NR	6.1	44	Yes, At birth	Yes, At birth	Yes, 1/6
<b>Jiang XN, 2013</b> <sup>131</sup>	China	2010-2011	≥4.3	65	26-30	NR	NR	100	6.0	65	51	NR	100	5.9	51	Yes, NR	Yes, At birth	Yes, 1/6
<b>Li CM, 2017</b> <sup>132</sup>	China	2013-2015	≥2.3	30	28	4	43.2 ±1.3	NR	6.1	30	30	43.2 ±1.3	NR	6.1	30	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Li N, 2016</b> <sup>133</sup>	China	2012-2015	≥4.3	35	Pre-pregnancy	NR	NR	NR	5.1	35	25	NR	NR	5.0	25	Yes, <6hr	Yes, <6hr	Yes, 1/6
				30	28	NR	NR	NR	5.1	30								
<b>Li YH, 2017</b> <sup>134</sup>	China	2015-2017	≥6.3	30	28	~36	29.5 ±2.7	100	3.2	30	31	28.8 ±3.5	100	3.2	32	Yes, <24hr	Yes, NR	Yes, NR
<b>Li ZY, 2018</b> <sup>135</sup>	China	2015-2016	≥5.3	41	28	NR	26.2 ±4.4	100	6.1	41	41	26.3 ±4.2	100	6.1	41	Yes, <24hr	No	Yes, 1/6
<b>Liu CY, 2014</b> <sup>136</sup>	China	2011-2011	≥5.3	34	28	4	27.2 ±3.6	100	7.1	34	34	26.9 ±4.1	100	7.4	34	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Liu J, 2017</b> <sup>137</sup>	China	2013-2015	≥6.0	102	30	NR	27.8 ±4.1	100	8.1	97	28	26.7 ±3.9	100	8.1	28	NR	Yes, <12hr	Yes, 1/6
<b>Liu XB, 2016</b> <sup>138</sup>	China	2014-2015	≥6.0	20	28-36	4	25.4 ±3.7	100	7.0	20	20	25.4 ±3.6	100	7.0	20	Yes, At birth	Yes, At birth	Yes, 1/6
<b>Liu Y, 2016</b> <sup>139</sup>	China	2010-2012	≥6.0	50	4-27	4	27.9 ±3.7	94	7.7	50	78	27.5 ±3.5	97	7.5	78	Yes, NR	Yes, At birth	Yes, 1/6
				32	28-32	4	28.3 ±3.8	97	7.5	32								

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

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

<b>Wu QX, 2015</b> <sup>160,161</sup>	China	2008-2014	≥6.0	279	24-32	0 or 4	27 [17-38]	100	7.2	204	171	28 [18-40]	100	7.4	95	Yes, At birth	Yes, At birth	Yes, 1/6
<b>Xiao XH, 2017</b> <sup>42</sup>	China	2014-2015	≥6.0	60	28	0 or 4	28.6 ±3.2	NR	7.5	62	60	28.5 ±3.6	NR	7.5	61	Yes, NR	Yes NR	Yes, NR
<b>Yao LF, 2014</b> <sup>162</sup>	China	2012-2013	≥6.0	30	28-32	6	NR	100	7.3	30	30	NR	100	8.2	30	Yes, NR	Yes, NR	Yes, NR
<b>Yao ZC, 2011</b> <sup>163,164</sup>	China	2008-2010	≥5.3	28	28	4	NR	NR	6.8	28	30	NR	NR	6.8	30	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Yue X, 2014</b> <sup>165</sup>	China	2007-2012	≥5.3	31	Any-time	NR	29.7 ±5.1	0	5.5	31	31	27.6 ±2.9	0	5.6	30	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Zhang BF, 2018</b> <sup>43</sup>	China	2016-2017	≥6.0	36	24-28	0	NR	100	5.0	36	75	NR	100	NR	75	Yes, <6hr	Yes, At birth	Yes, 1/6
<b>Zhang GH, 2018</b> <sup>166,167</sup>	China	2012-2014	≥6.3	40	28	4	NR	100	NR	40	40	NR	100	NR	40	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Zhang H, 2014</b> <sup>85</sup>	China	2009-2011	≥5.3	263	28-30	4	29.8 ±6.3	100	6.9	257	374	29.0 ±4.6	100	6.8	352	Yes, <6hr	Yes, <6hr	Yes, 1/6
<b>Zhang X, 2015</b> <sup>168</sup>	China	2012-2013	≥6.3	48	28	12	NR	100	7.0	48	47	NR	100	6.8	47	Yes, <24hr	Yes, At birth	Yes, 1/6
<b>Zhang YF, 2010b</b> <sup>169</sup>	China	2008-2009	≥5.3	60	28	4	NR	100	6.1	60	60	NR	100	6.1	60	Yes, <24hr	Yes, <24hr	Yes, 1/6
<b>Zhao J, 2013</b> <sup>170</sup>	China	2010-2011	≥6.3	41	20	0	NR	100	NR	41	202	NR	100	NR	202	Yes, <6hr	Yes, <6hr	Yes, 1/6
<b>Zheng JC, 2018</b> <sup>171</sup>	China	2012-2015	≥5.3	23	28	4	NR	100	NR	23	37	NR	100	NR	37	Yes, <6hr	Yes, <24hr	Yes, 1/6
<b>Zhou YJ, 2014</b> <sup>172,173</sup>	China	2007-2013	≥6.3	70	1 <sup>st</sup> trimester	0	NR	NR	NR	53	39	NR	NR	NR	34	Yes, NR	Yes, At birth	Yes, 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 (year), journal, No.	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			Selective reporting
					MTCT	Infant Safety	Mother safety	
<b>Pan CQ, (2016), N Engl J Med, 13</b>	<b>Low risk</b> <i>Quotes:</i> “Enrollment at each center was performed with the use of blocks and randomized for sample balance. Using a randomization table, we randomly assigned 200 mothers, in a 1:1 ratio”	<b>High risk</b> <i>Comment:</i> no concealment described	<b>High risk</b> <i>Quotes:</i> “open-label”	<b>High risk</b> <i>Quotes:</i> “open-label”	<b>Low risk</b> <i>Comment:</i> Loss to follow-up detailed carefully in Figure 1. Minimal loss to follow-up (95% in treated group, 88% in control group), and <10% points different between control and treated groups.	<b>Low risk</b> <i>Comment:</i> Reports on all infant adverse events of interest for 88% and 97.8% of control and treated group, respectively. This excludes bone density measurements.	<b>Low risk</b> <i>Comment:</i> Reports on all maternal adverse events of interest for >95% of both treated and control groups, including antiviral resistance testing.	<b>Low risk</b> <i>Comment:</i> the protocol is available in a separate publication as well as online at NEJM.org. The current outcomes of interest that this meta-analysis is recording were pre-specified.
<b>Jourdain G, (2018), N Engl J Med, 14</b>	<b>Low risk</b> <i>Quotes:</i> “participants were randomly assigned in a 1:1 ratio” “Randomization	<b>Low/Unclear Risk</b> <i>Quotes:</i> “The participants, the trial staff on site and at the coordination	<b>Low Risk</b> <i>Quotes:</i> “The participants, the trial staff on site and at the coordination center, the investigators, and	<b>Low Risk</b> <i>Quotes:</i> “The participants, the trial staff on site and at the coordination center, the investigators, and the laboratory	<b>Low Risk</b> <i>Comment:</i> 88 and 90% with full follow-up in treated and control group respectively.	<b>Low risk</b> <i>Comment:</i> 95 and 98% of infants included in this analysis from treated and control,	<b>High risk</b> <i>Comment:</i> although >90% women considered until discontinuatio	<b>Low risk</b> <i>Comment:</i> the protocol is available in a separate publication as well as online

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

## B. Chinese language studies

Study (year), journal, No.	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			Selective reporting
					MTCT	Infant Safety	Mother safety	
Yu CY, (2018), J of Pub Health and Prev med, 27	<b>Low risk/Unclear</b> <i>Quotes:</i> “60 cases of pregnant women with asymptomatic hepatitis B virus were selected and randomly divided into liver protection group and tenofovir group, with 30 cases in each group” <i>Comment:</i> the study did not describe the exact random component in the sequence generation process	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> “The control group received liver protecting treatment” “The observation group received antiviral treatment with tenofovir” <i>Comment:</i> the study did not address this outcome and no use of placebo	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Only congenital abnormality reported. Other key adverse events not addressed.	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Women considered until late pregnancy. Only elevated bile acid level and amniotic fluid turbidity reported. Other key adverse events of interest in this review not addressed (e.g. hepatitis flare after treatment discontinuation, antiviral resistance)	<b>Low risk</b> <i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol.
Liu MH, (2017b), Chinese	<b>Low risk/Unclear</b> <i>Quotes:</i> “participants were randomly	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> “The control group received no antiviral treatment” “The observation group	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Low risk</b> <i>Comment:</i> 100% follow-up in both treated and control group	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Only	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT	<b>Low risk</b> <i>Comment:</i> the protocol is available in the method

<b>Journal of Woman and Child Health Research, 26</b>	assigned in a 1:1 ratio” <i>Comment:</i> the study did not describe the exact random component in the sequence generation process		received antiviral treatment with TDF” <i>Comment:</i> the study did not address this outcome and no mention of placebo			Apgar score, premature labor, congenital abnormality and retarded development reported. Other key adverse events not addressed.	outcome. Women considered until delivery. Only postpartum hemorrhage reported. Other key adverse events not addressed.	section of the article. The current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol.
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**A. English language studies**

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

## B. Chinese language studies

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

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

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

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

Use , 47	and 40 cases in the control group” <i>Comment:</i> the study did not describe the exact random component in the sequence generation process; importantly, there’s a huge disparity between the numbers of cases in observation and control groups		mention of placebo					analysis is recording were pre-specified in that protocol.
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LDT 600 mg

**A. English language studies**

None

**B. Chinese language studies**

Study (year), journal, No.	Selection bias		Performance bias	Detection bias	Attrition bias			Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data addressed			Selective reporting
					MTCT	Infant Safety	Mother safety	
Wang HY (2018), <b>Contemporary Medicine, 99</b>	<b>Low risk/Unclear</b> <i>Quotes:</i> “80 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 40 cases in each group” <i>Comment:</i> the study did not describe the exact random component in the sequence generation process	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> “The experimental group received LdT” “The control individuals did not receive antiviral treatment and were given supportive treatment or observation” <i>Comment:</i> the study did not address this outcome and no mention of placebo	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Some key adverse events not addressed (e.g. prematurity, neonatal death, sub-optimal bone density)	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>High risk</b> <i>Comment:</i> the protocol is available in the method section of the article. But not all of the study’s pre-specified primary outcomes have been reported (i.e. maternal ALT). One or more reported primary outcomes were not pre-specified (body length, birth weight, gestational

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



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

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

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

<b>Journal of Eugenics and Genetics, 94</b>	group 1, 2, 3 and the control group, with 30 cases in each group”		telbivudine at 20, 24 and 28 weeks, respectively” <i>Comment:</i> the study did not address this outcome and no mention of placebo		clearly that there were no cases LFU)			current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol.
<b>Xie PY (2016), Psychologist, 100</b>	<b>Low risk</b> <i>Quotes:</i> “Referring to random number table, the patients were divided into the observation group and the control group, with 60 cases in each group”	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> “The control group received no antiviral treatment” “The observation group received antiviral treatment with telbivudine” <i>Comment:</i> the study did not address this outcome and no mention of placebo	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Low risk</b> <i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol
<b>Lu QY (2016), Henan J Prev Med, 96</b>	<b>Low risk/Unclear</b> <i>Quotes:</i> “The patients were randomly divided into the observation group and the control group, with 152 cases in the observation group and 132 cases in the control group” <i>Comment:</i> the study did not describe the exact	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> “The control group received HBIG” “The observation group received telbivudine on the basis of HBIG for the control group” <i>Comment:</i> the study did not address this outcome and no mention of placebo	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<b>High risk</b> <i>Comment:</i> Though all the infants were included in this analysis, some key adverse events including Apgar and bone density were not reported.	<b>High risk</b> <i>Comment:</i> Though all women were included in this analysis, some key adverse events, were not addressed (e.g. antiviral resistance, postpartum hemorrhage)	<b>High risk</b> <i>Comment:</i> the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre-specified (mainly maternal and infantile

	random component in the sequence generation process; and importantly, there's a huge disparity between the number of cases in the observation group and that of the control group							adverse reactions)
<b>Ji YY (2015), Chin J Postgrad Med, 50</b>	<b>Low risk</b> <i>Quotes:</i> "Referring to random number table, the patients were divided into telbivudine group, lamivudine group and control group, with 65 cases in each group"	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine or lamivudine" <i>Comment:</i> the study did not address this outcome and no mention of placebo	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>High risk</b> <i>Comment:</i> the protocol is available in the method section of the article. But not all of the study's pre-specified primary outcomes have been reported (e.g. maternal liver function after antiviral treatment).
<b>Li SF. (2015), World of Mother and</b>	<b>Low risk/Unclear</b> <i>Quotes:</i> "The patients were randomly divided into the observation group and the control	<b>Unclear</b> <i>Comment:</i> the method of concealment not described	<b>High risk</b> <i>Quotes:</i> "The control group received no antiviral treatment" "The observation group received antiviral treatment with telbivudine"	<b>Unclear</b> <i>Comment:</i> the study did not address this outcome	<b>Unclear</b> <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Only Apgar score reported. Other key adverse	<b>High risk</b> <i>Comment:</i> same numbers used as for MTCT outcome. Women considered	<b>High risk</b> <i>Comment:</i> the protocol is available in the method section of the article. But one or more

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

<p><b>Peng ML (2014), Chin J Nosocomiol, 97</b></p>	<p><b>Low risk/Unclear</b>  <i>Quotes:</i> “60 cases of pregnant women with chronic hepatitis B were randomly divided into experimental group and control group, 30 cases in each group”  <i>Comment:</i> the study did not describe the exact random component in the sequence generation process</p>	<p><b>Unclear</b>  <i>Comment:</i> the method of concealment not described</p>	<p><b>High risk</b>  <i>Quotes:</i> “The control group received HBIG”  “The observation group received telbivudine on the basis of HBIG for the control group”  <i>Comment:</i> the study did not address this outcome and no mention of placebo</p>	<p><b>Unclear</b>  <i>Comment:</i> the study did not address this outcome</p>	<p><b>Unclear</b>  <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)</p>	<p><b>Unclear</b>  <i>Comment:</i> the study did not address this outcome</p>	<p><b>Unclear</b>  <i>Comment:</i> the study did not address this outcome</p>	<p><b>Low risk</b>  <i>Comment:</i> the protocol is available in the method section of the article. The current outcomes of interest that this meta-analysis is recording were pre-specified in that protocol.</p>
<p><b>Zhu LP (2014), Chin J Mod Drug Appl, 108</b></p>	<p><b>Low risk/Unclear</b>  <i>Quotes:</i> “The patients were randomly divided into the observation group and the control group, with 30 cases in each group”  <i>Comment:</i> the study did not describe the exact random component in the sequence generation process</p>	<p><b>Unclear</b>  <i>Comment:</i> the method of concealment not described</p>	<p><b>High risk</b>  <i>Quotes:</i> “The control group received no antiviral treatment”  “The observation group received antiviral treatment with telbivudine”  <i>Comment:</i> the study did not address this outcome and no mention of placebo</p>	<p><b>Unclear</b>  <i>Comment:</i> the study did not address this outcome</p>	<p><b>Unclear</b>  <i>Comment:</i> No statement about LFU (not reporting any LFU, and also not mentioning clearly that there were no cases LFU)</p>	<p><b>Unclear</b>  <i>Comment:</i> the study did not address this outcome</p>	<p><b>High risk</b>  <i>Comment:</i> same numbers used as for MTCT outcome. Women considered until delivery. Only adverse reactions, renal function despair, and CK elevation reported. Other key adverse events not addressed.</p>	<p><b>High risk</b>  <i>Comment:</i> the protocol is available in the method section of the article. But one or more reported primary outcomes were not pre-specified (e.g. maternal adverse effects)</p>

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



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

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

TDF 300 mg

### A. English Language Observational Studies

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

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

<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.				
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<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

## B. Chinese Language Observational Studies

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

Wang HB, (2018), Chin J Exp Clin Infect Dis, 41	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same threshold for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	★Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	7 (low)
Zhang BF, (2018), Chin J Hepatol, 43	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same HBeAg sero-status but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)
Zhou Y, (2018), New Medical Science, 44	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory	★ Yes	No statement of LFU	8 (low)

						and/or record linkage.			
Chen WJ, (2017), Shandong Medicine, 30	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Gong Q, (2017), China Continuing Medical Education, 31	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Both HBeAg sero-status and threshold for HBV DNA level not described. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)
Huang Q, (2017), Qinghai Medical Journal, 38	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)



			subsequent to the treatment)		at birth				
Wan JY, (2017), China Tropical Medicine, 40	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same thresholds for HBV DNA level but HBeAg sero-status not described. Regimen for infant immunoprophylaxis at birth not described	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	6 (high)
Xiao XH, (2017), Maternal and Child Health Care of China, 42	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same thresholds for HBV DNA level but HBeAg sero-status not described. Regimen for infant immunoprophylaxis at birth not clearly described	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	There is a description of LFU for the exposed but not for the control group	6 (high)

<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

**A. English Language Observational Studies**

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

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

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

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

<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

## B. Chinese Language Observational Studies

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

	infected pregnant woman	and exclusion criteria also)	antiviral therapy (decrease in viral load levels subsequent to the treatment)		regimen for infant immunoprophylaxis at birth	detail (which assay used), indicating use of a central laboratory and/or record linkage.			
Shen ML (2016), WCJD, 76	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same thresholds for HBV DNA level but HBeAg sero-status not described. Regimen for infant immunoprophylaxis at birth not clearly described	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	6 (high)
Wang DM (2016), Chinese Hepatology, 79	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)

Ge YL (2015), Chin J Clin Pharmacol, 60	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)
Han YP (2014), Hebei Medical Journal, 62	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)
Wang W (2014), Hebei Medical Journal, 82	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable for HBV DNA levels but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record	★ Yes	No statement of LFU	7 (low)



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

					at birth	of a central laboratory and/or record linkage.			
Jiang HX (2012), Chin J Hepatol, 68	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Wang EJ (2012), Chinese General Practice, 80	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Yuan QF (2012),	★ At least	★ Drawn from	Adherence/compliance not mentioned and no	★ Always the case	★ Comparable for HBeAg sero-status	★ Indication of	★ Yes (always)	No statement of LFU	6 (high)

Chinese Manipulation & Rehabilitation Medicine, 83	somewhat representative of the average HBV infected pregnant woman	the same community (same inclusion and exclusion criteria also)	data presented on decrease in HBV DNA levels		but HBV DNA level not described. Same regimen for infant immunoprophylaxis.	record linkage	the case)		
Cheng YC (2011), Zhejiang Practical Medicine, 57	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Ren YJ (2011), Hebei Medical Journal, 75	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable for HBeAg sero-status but not for HBV DNA level. Same regimen for infant immunoprophylaxis.	★ Laboratory assays described	★ Yes (always the case)	No statement of LFU	7 (low)
Zhang YF (2010a),	★ At least somewhat	★ Drawn from the same	★ Valid method was used to	★ Always the case	★★★ Same HBeAg sero-status and same	No description	★ Yes	No statement of LFU	7 (low)

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

58	the average HBV infected pregnant woman	(same inclusion and exclusion criteria also)	adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)		DNA level. Same regimen for infant immunoprophylaxis at birth	described in detail (which assay used), indicating use of a central laboratory and/or record linkage.			
Li G (2006), Journal of Wenzhou Medical College, 69	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable HBeAg sero-status but HBV DNA levels not described. Same regimen for infant immunoprophylaxis.	★ Laboratory assays described	★ Yes (always the case)	★ LFU reported and <20% LFU in both treatment group and control group	8 (low)
Li WF (2006), Chinese Hepatology, 71	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)

Ma J (2006), China Practical Medical, 72	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Comparable HBeAg sero-status but HBV DNA levels not described. Regimen for infant immunoprophylaxis not described	★ Laboratory assays described	★ Yes (always the case)	No statement of LFU	6 (high)
Han ZH (2005), Chin J Intern Med, 63	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Wang TM (2005), Chinese Journal of Eugenics and Genetics, 81	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same HBeAg sero-status but HBV DNA level not described. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)

<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

**A. English Language Observational Studies**

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



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

<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, (2016), Hepatology Research, 139	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	Some limited data presented on decrease of maternal viral load, but no mention of linking this with compliance/adherence/time on treatment, and no detailed results provided.	★ Always the case	★ HBV DNA level and HBeAg comparable between treated and non treated groups. Infant immunoprophylaxis not described clearly (no timing of HBIg).	★ Laboratory assays described in detail with indication that testing (and viewing of medical records, was done by study personnel)	★ Yes	Loss to follow-up not mentioned and flow-chart of patients not given. This may indicate omitting of loss to follow-up details rather than perfect (100%) retention, and does not allow one to assume the latter.	6 (high)
Tan Z, (2016), Medicine, 152	★ Truly representative of the average HBV infected pregnant woman	None (Arm 1) ★ (Arm 2) For arm 2 it is drawn from the same community (same inclusion and exclusion criteria also). However, arm 1 is not comparable with the control group.	Adherence or compliance to treatment not examined, little data on tracking of viral load decrease.	★ Always the case	★(Arm 1) ★★(Arm 2) Comparable for HBV DNA level and comparable HBeAg positive for the second treatment arm compared to the control arm. For the first arm of the study they are not comparable. Same regimen for infant immunoprophylaxis.	★ Lab testing done centrally as part of the study, laboratory assays for defining infant outcome described.	★ Yes	★ >80% follow-up in across all treatment arms and control groups.	6 (high) (Arm 1) 8 (low) (Arm 2)
Chen ZX, (2017), J	★ At least	★ Drawn from the	Adherence/compliance not mentioned and no	★ Always the case	★ Comparable for HBV	★ Lab testing done	★ Yes	Loss to follow-up not mentioned and flow-chart of	6 (high)

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

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

			DNA level for treated cohort.		regimen for infant immunoprophylaxis				
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<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

## B. Chinese Language Observational Studies

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

	representative of the average HBV infected pregnant woman	community (same inclusion and exclusion criteria also)	ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)		and comparable HBV DNA levels at baseline. Same regimen for infant immunoprophylaxis at birth				
Li ZY, (2018), Drug Evaluation Research, 135	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Comparable for HBeAg sero-status and HBV DNA level. Same regimen for infant immunoprophylaxis.	★ Indication of record linkage (results viewed retrospectively in medical records)	★ Yes (always the case)	None reported (retrospective)	8 (low)
Tian JH, (2018), China & Foreign Medical Treatment, 153	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	No description	★ Always the case	★★★ Same threshold for HBV DNA level and same HBeAg sero-status used. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	7 (low)
Zhang BF,	★ At least	★ Drawn	★ Valid method	★ Always the	★ Same HBeAg	No description	★ Yes	No statement	6 (high)

(2018), Chin J Hepatol, 43	somewhat representative of the average HBV infected pregnant woman	from the same community (same inclusion and exclusion criteria also)	was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	case	sero-status but different thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth			of LFU	
Zhang GH, (2018), China Health Care & Nutrition, 166	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)
Zheng JC, (2018), China Rural Medicine, 171	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	No description	★ Always the case	★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	7 (low)



Chen WJ, (2017), Shandong Medicine, 30	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Feng XM, (2017), Clinical Research and Practice, 118	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Huang Q, (2017), Qinghai Medical Journal, 38	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant	No description	★ Yes	No statement of LFU	7 (low)

			load levels subsequent to the treatment)		immunoprophylaxis at birth				
Jiang S, (2017), Diet Health, 130	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	No description a	★ Yes	No statement of LFU	6 (high)
Li CM, (2017), Northern Pharmacy, 132	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis.	Laboratory assays used not well described	★ Yes (always the case)	No statement of LFU	6 (high)
Li YH, (2017), Northern Pharmacy, 134	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis	★ Laboratory methods described in detail (which assay used), indicating use	★ Yes	No statement of LFU	8 (low)

			subsequent to the treatment)		at birth	of a central laboratory and/or record linkage.			
Liu J, (2017), Maternal and Child Health Care of China, 137	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and comparable for HBV DNA levels. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	There is a description of LFU for the exposed but not for the control group	7 (low)
Luo DX, (2017) <sup>4</sup>	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Comparable for HBV DNA levels but HBeAg sero-status not described. Regimen for infant immunoprophylaxis at birth not clearly described	No description	★ Yes	No statement of LFU	5 (high)
Pan YC, (2017), J Clin Hepatol, 141	★ At least somewhat representative of	★ Drawn from the same community	No description	★ Always the case	★★★ Same HBeAg sero-status and same thresholds	★ Laboratory methods	★ Yes	★ Subjects lost to	8 (low)

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

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

			load levels subsequent to the treatment)		immunoprophylaxis at birth	indicating use of a central laboratory and/or record linkage.			
Li N, (2016), Medical Innovation of China, 133	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Comparable for HBV DNA levels but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)
Liu XB, (2016), Journal of Contemporary Clinical Medicine, 138	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)
Qiu B, (2016), J Prac Hepatol, 143	★ At least somewhat representative of the average HBV infected pregnant	★ Drawn from the same community (same inclusion and exclusion	★ Valid method was used to ascertain adherence to the antiviral therapy	★ Always the case	★ Same thresholds for HBV DNA level but HBeAg sero-status not described. Same regimen for	★ Laboratory methods described in detail (which	★ Yes	No statement of LFU	7 (low)

	woman	criteria also)	(decrease in viral load levels subsequent to the treatment)		infant immunoprophylaxis at birth	assay used), indicating use of a central laboratory and/or record linkage.			
Shen ML, (2016), WCJD, 76	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	Same thresholds for HBV DNA level but HBeAg sero-status not described. Regimen for infant immunoprophylaxis at birth not clearly described	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	6 (high)
Tian RH, (2016), Chinese Journal of Clinical Research, 154	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	No description	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)
Wang B, (2016), Chinese Remedies &	★ At least somewhat representative of	★ Drawn from the same community	★ Valid method was used to ascertain adherence to the	★ Always the case	★★★ Comparable for HBeAg sero-status and HBV DNA level. Same	★ Laboratory assays described	★ Yes (always the case)	No statement of LFU	8 (low)

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



Zhang R, (2016) <sup>5</sup>	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	No description	★ Always the case	HBeAg sero-status and threshold for HBV DNA level not described. Regimen for infant immunoprophylaxis at birth not clearly described	No description	★ Yes	No statement of LFU	4 (high)
Chen CY, (2015), Chin J Hepatol, 109	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same HBeAg sero-status and same thresholds for HBV DNA level. Regimen for infant immunoprophylaxis at birth not clearly described	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	7 (low)
Cui ZL, (2015), IMHGN, 114	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use	★ Yes	No statement of LFU	8 (low)

<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 treatment)			of a central laboratory and/or record linkage.			
Deng Y, (2015), Chin J Hepatol, 115	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same thresholds for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	6 (high)
Ge YL, (2015), Chin J Clin Pharmacol, 60	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)
Lou JJ, (2015), Chinese Journal of Microecology, 140	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis	★ Laboratory methods described in detail (which assay used),	★ Yes	No statement of LFU	8 (low)

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

(2015), China Pharmaceutica ls, 158	somewhat representative of the average HBV infected pregnant woman	from the same community (same inclusion and exclusion criteria also)	was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	case	sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage.		of LFU	
Zhang X, (2015), J Prac Hepatol, 168	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboaratory and/or record linkage.	★ Yes	No statement of LFU	8 (low)
Chen YL, (2014) <sup>6</sup>	No description of the derivation of the cohort	No description of the derivation of the non exposed cohort	★ Valid method was used to ascertain adherence to the antiviral therapy	★ Always the case	★ Comparable for HBV DNA levels but HBeAg sero- status not described. Same regimen for	No description	★ Yes	No statement of LFU	4 (high)

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

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

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

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

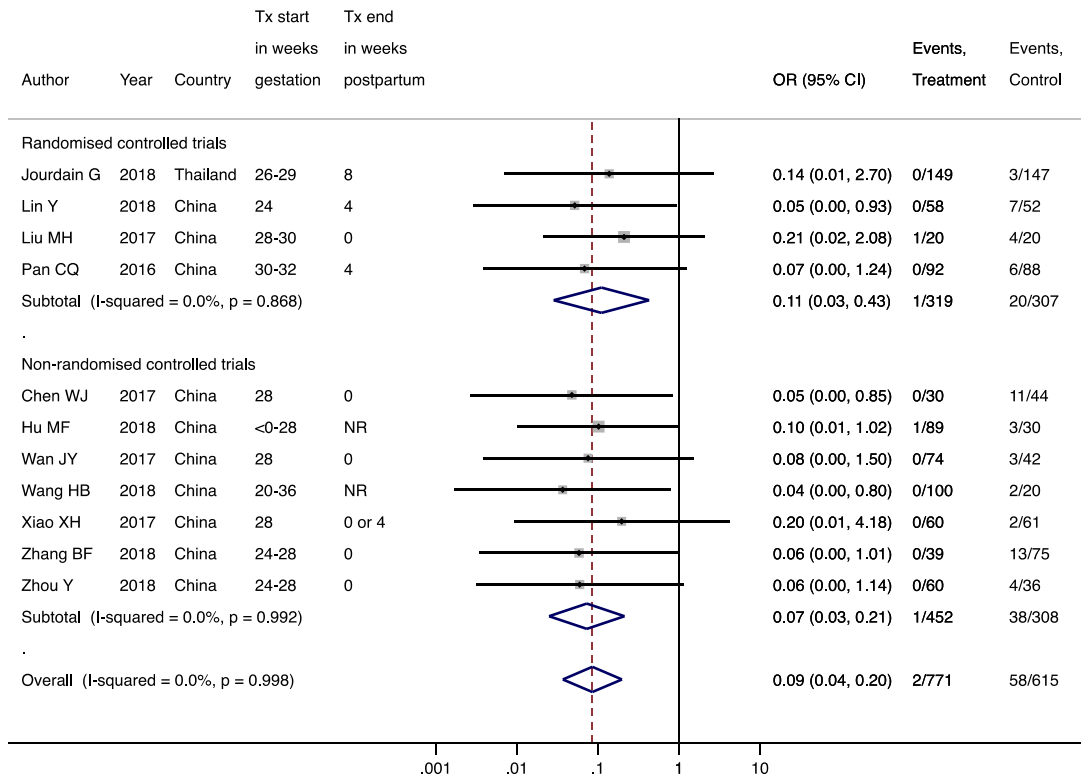


			treatment)			laboratory and/or record linkage.			
Yao ZC, (2011), J Clin Hepatol, 163	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★ Same thresholds for HBV DNA level but HBeAg sero-status not described. Same regimen for infant immunoprophylaxis at birth	★ Laboratory methods described in detail (which assay used), indicating use of a central laboratory and/or record linkage.	★ Yes	No statement of LFU	7 (low)
Zhang YF, (2010b), ADRJ, 169	★ At least somewhat representative of the average HBV infected pregnant woman	★ Drawn from the same community (same inclusion and exclusion criteria also)	★ Valid method was used to ascertain adherence to the antiviral therapy (decrease in viral load levels subsequent to the treatment)	★ Always the case	★★★ Same HBeAg sero-status and same thresholds for HBV DNA level. Same regimen for infant immunoprophylaxis at birth	No description	★ Yes	No statement of LFU	7 (low)

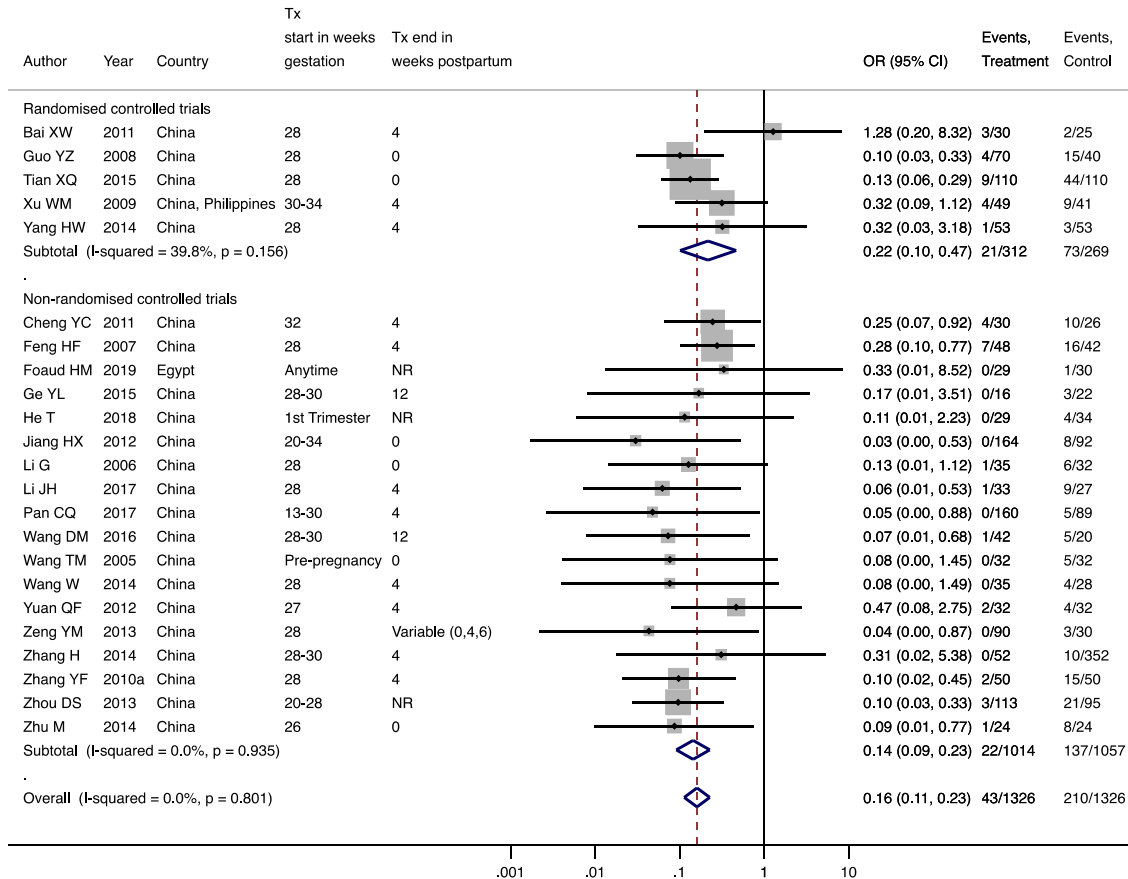
<sup>a</sup>Risk of bias assessments should be classified as being either low ( $\geq 7$ ) or high ( $< 7$ ) by the Newcastle-Ottawa scale

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

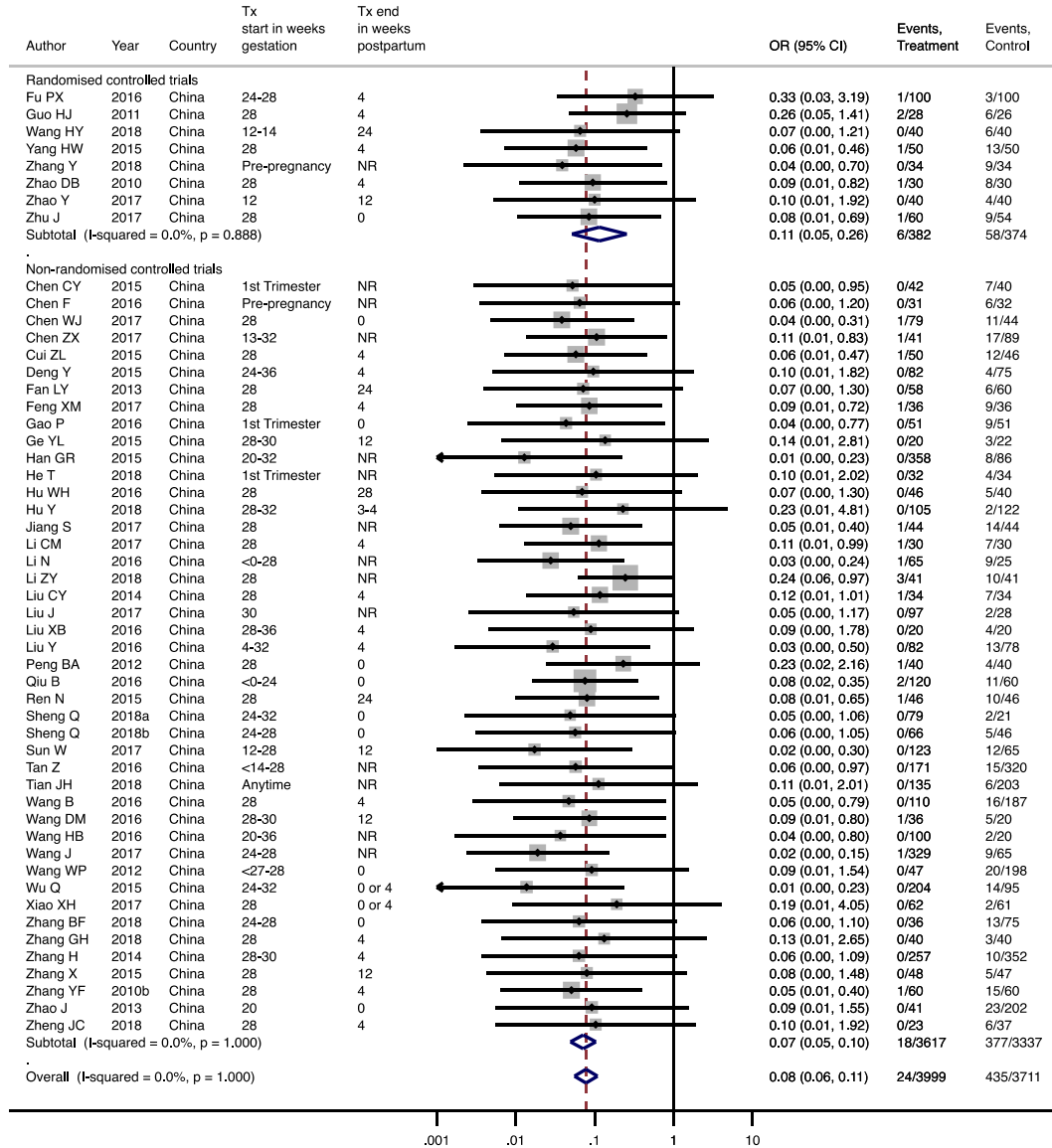
- **TDF 300 mg (infants' HBV DNA positivity)**
  - Overall pooled OR= 0.09 (95% CI: 0.04-0.20),  $p < 0.001$ ,  $I^2 = 0\%$
- RCTs only (n=4): pooled OR=0.11 (95% CI: 0.03-0.43),  $p = 0.001$ ,  $I^2 = 0\%$
- Non-RCTs only (n=7): pooled OR=0.07 (95% CI: 0.03-0.21),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value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



- **LAM 100-150 mg (infants' HBV DNA positivity)**
  - Overall pooled OR= 0.16 (95%CI: 0.11-0.23),  $p < 0.001$ ,  $I^2 = 0.0\%$
- RCTs only: pooled OR= 0.22 (95%CI: 0.10-0.47),  $p < 0.001$ ,  $I^2 = 39.8\%$
- Non-RCTs only: pooled OR=0.14 (95%CI: 0.09-0.23),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between RCTs and non-RCTs was 0.47



- **LdT 600 mg (infants' HBV DNA positivity)**
  - Overall pooled OR= 0.08 (95%CI: 0.06-0.11),  $p < 0.001$ ,  $I^2 = 0.0\%$
- 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),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between RCTs and non-RCTs was 0.29



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

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

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

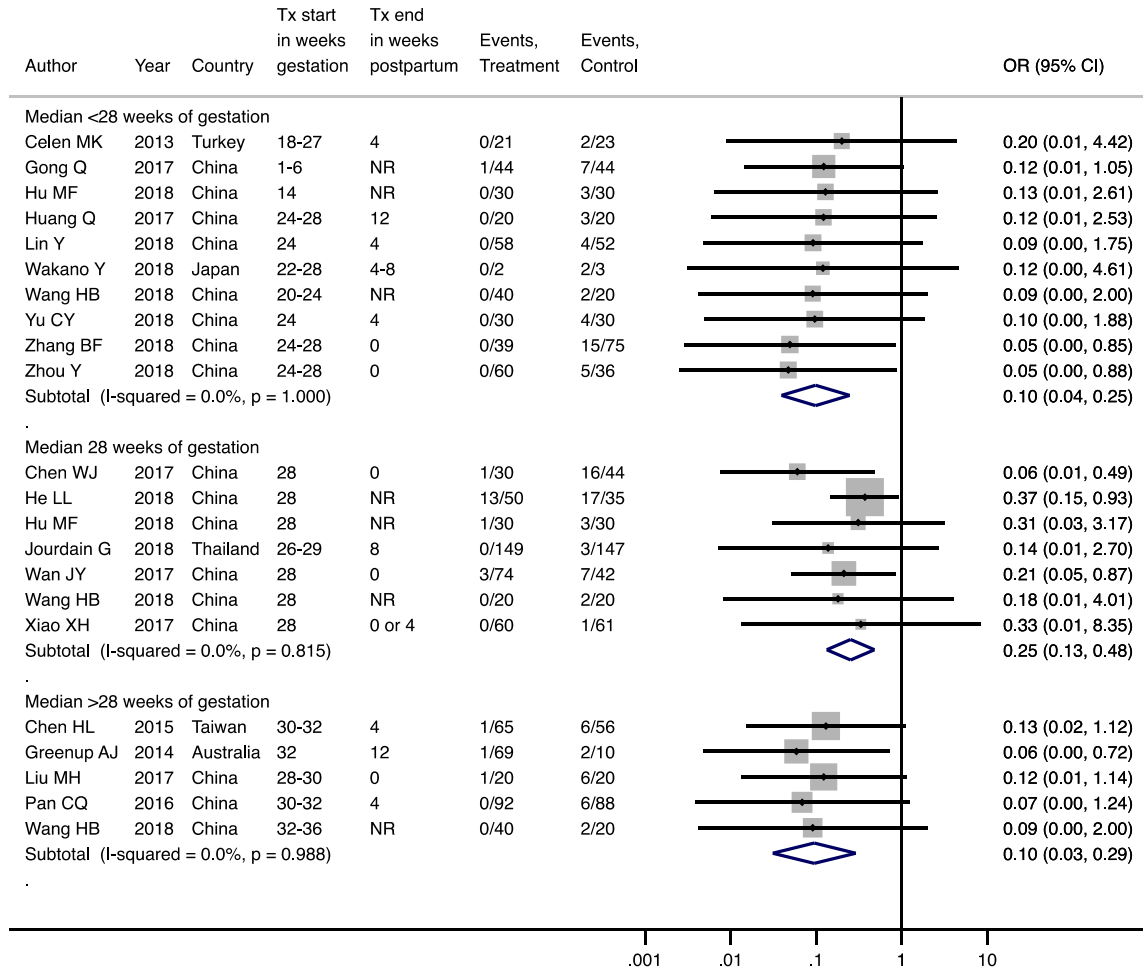
Abbreviations: N/R, not reported

Sex of infant was not reported in any of the MTCT cases.

## Appendix J: Efficacy by timing of PAP initiation

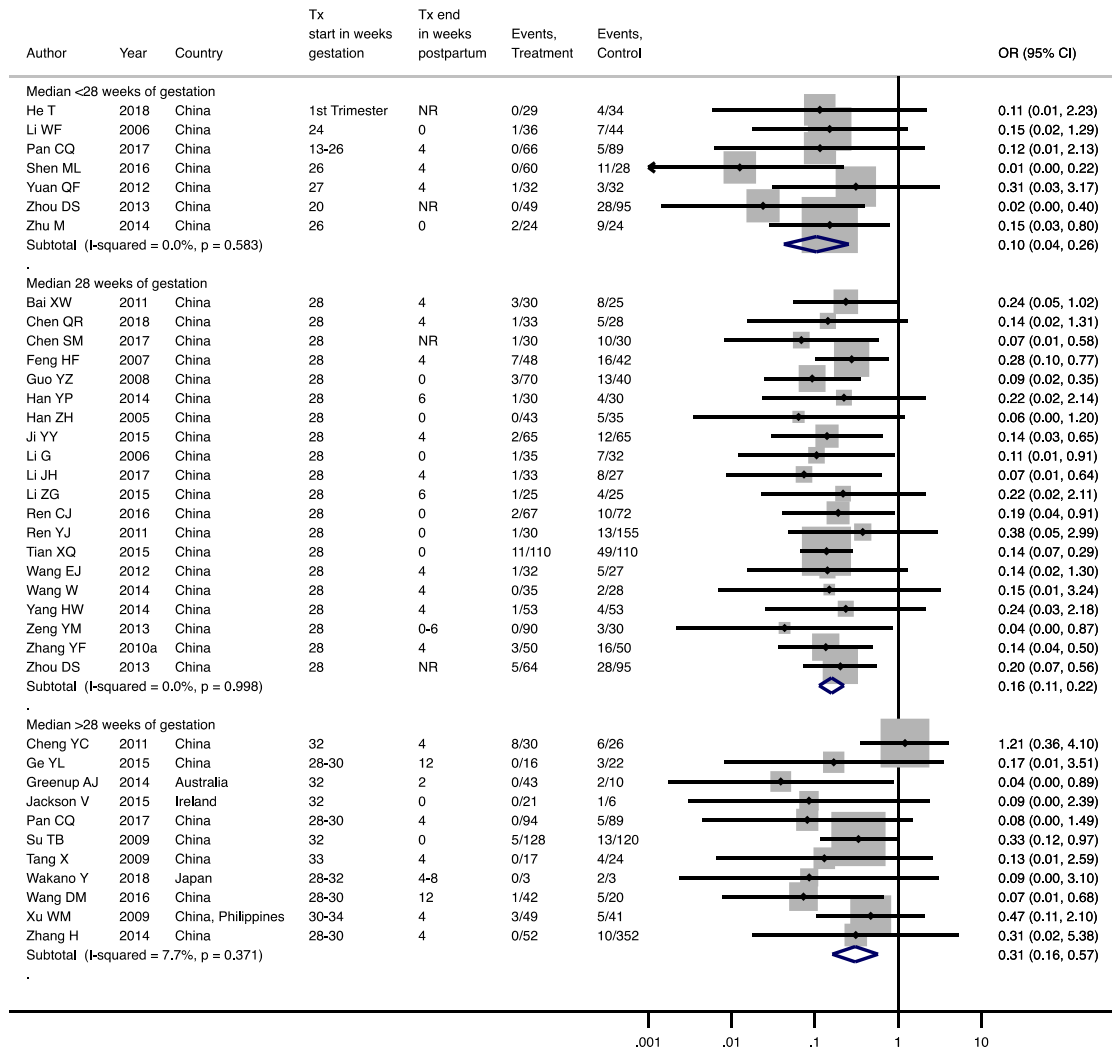
- **TDF 300 mg by timing of PAP initiation**

- <28 weeks gestation (n=10): pooled OR= 0.10 (95%CI: 0.04-0.25), p<0.001, I<sup>2</sup>=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



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

- <28 weeks gestation (n=7): pooled OR= 0.10 (95%CI: 0.04-0.26),  $p < 0.001$ ,  $I^2 = 0\%$
- 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



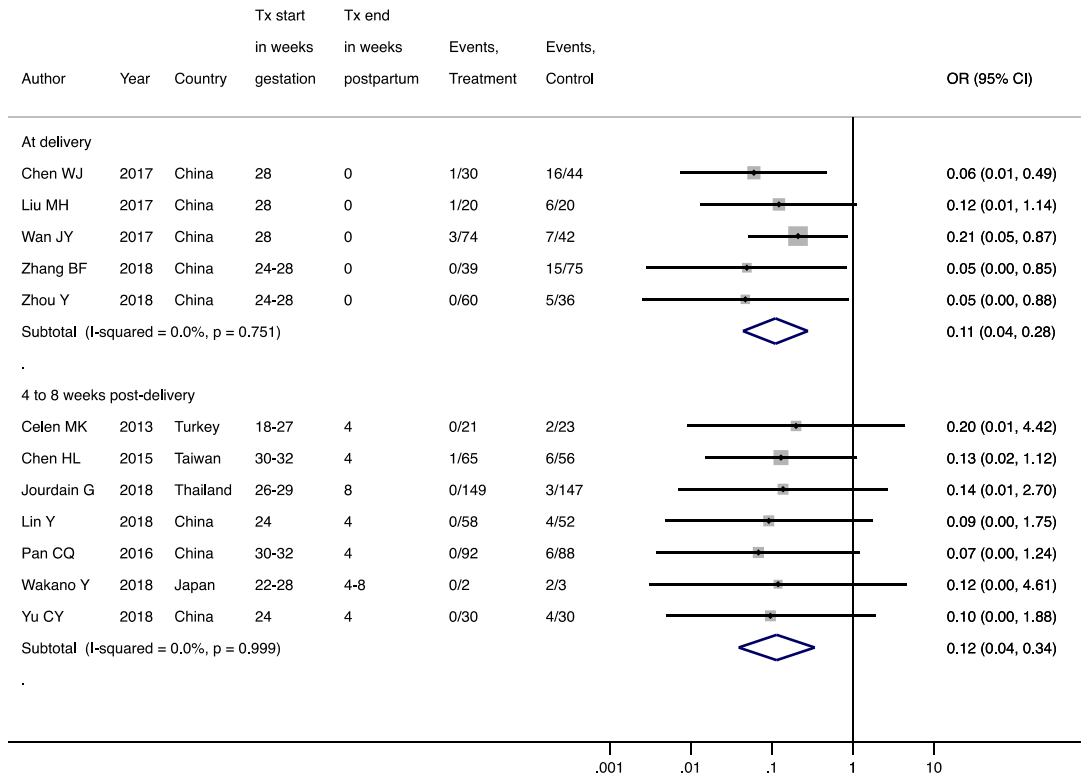




## Appendix K: Efficacy by timing of PAP discontinuation

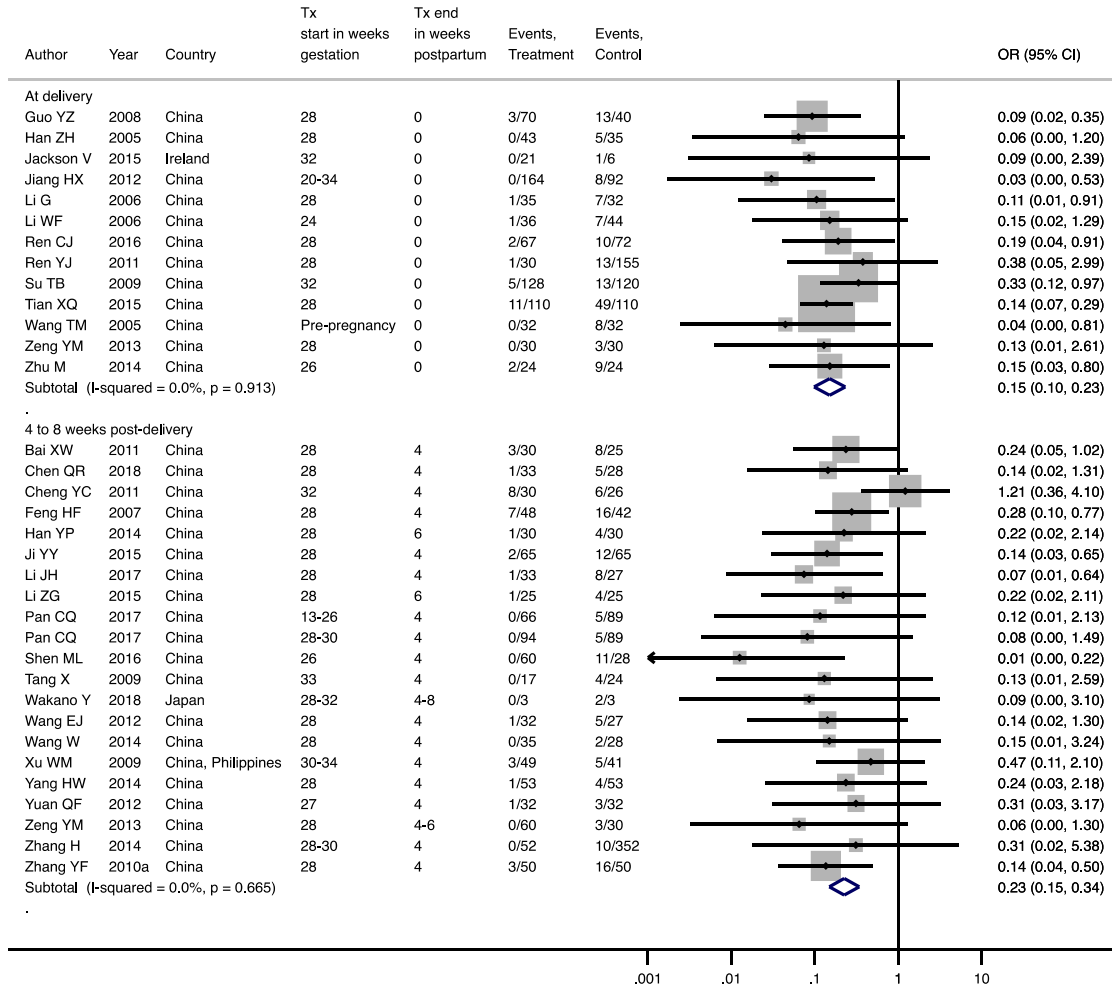
- **TDF 300 mg by timing of PAP discontinuation**

- At delivery (n=5): pooled OR= 0.11 (95% CI: 0.04-0.28),  $p < 0.001$ ,  $I^2 = 0\%$
- 4-8 weeks after delivery (n=7): pooled OR=0.12 (95% CI: 0.04-0.34),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.96



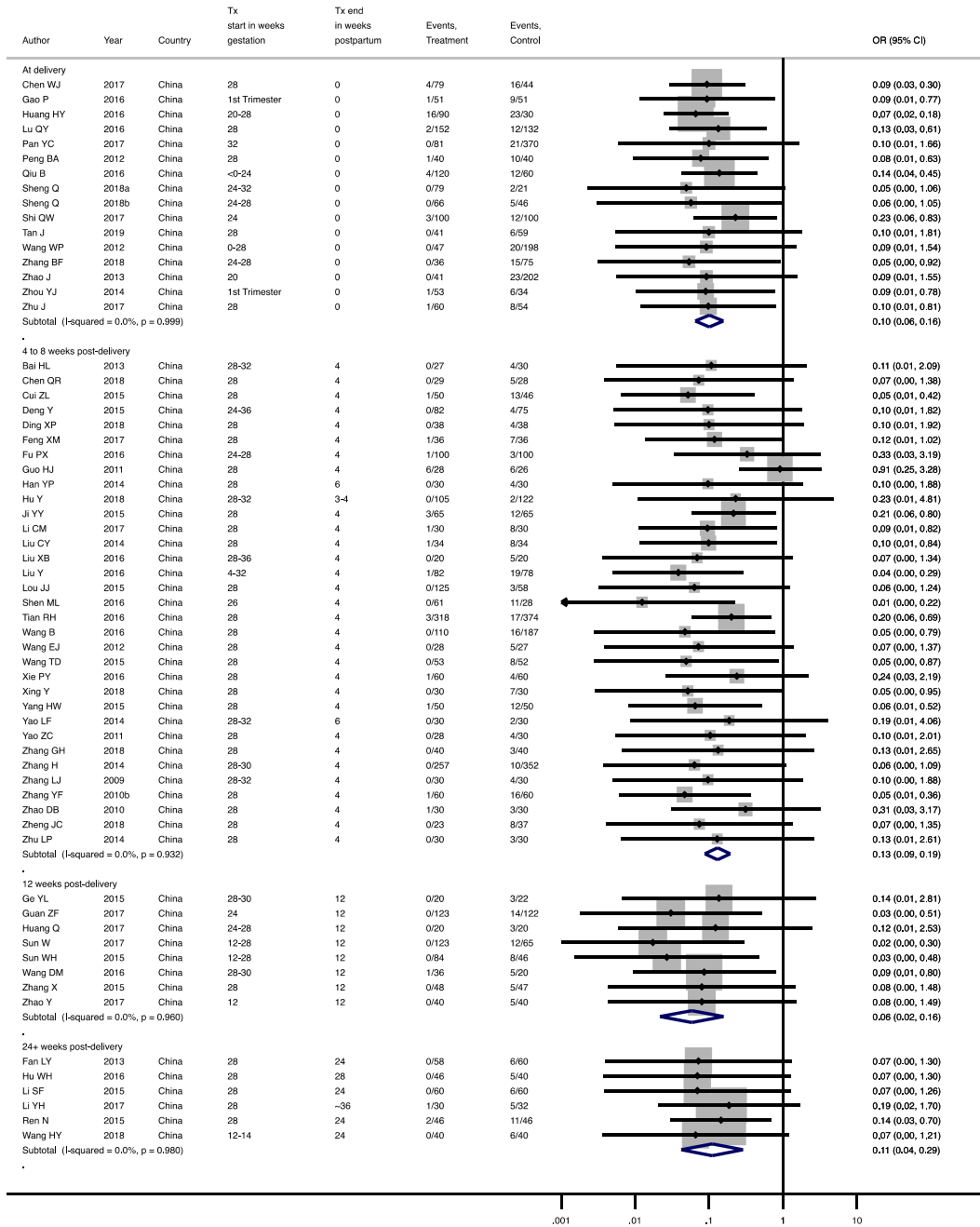
- **LAM 100-150 mg by timing of PAP discontinuation**

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



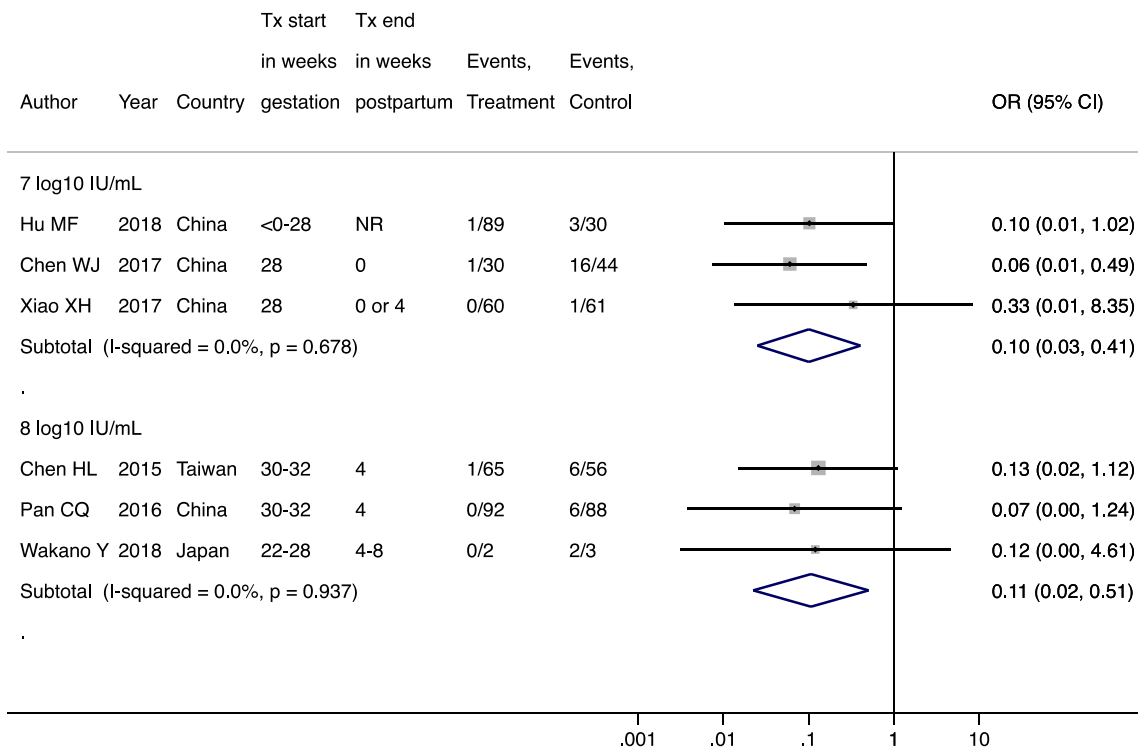
- **LdT 600 mg by timing of PAP discontinuation**

- 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),  $p < 0.001$ ,  $I^2 = 0\%$
- 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



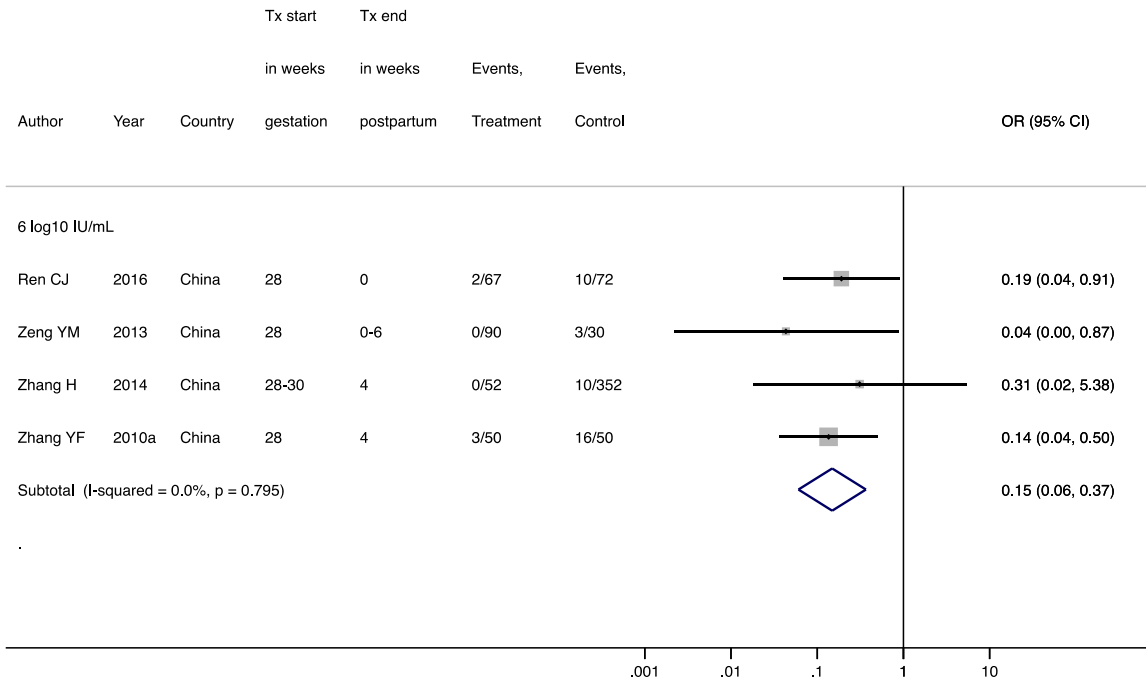
## Appendix L: Efficacy by mean maternal viral load at baseline

- **TDF 300 mg by mean maternal viral load at baseline**
  - 7.0-7.9 log<sub>10</sub> IU/mL (n=3): pooled OR= 0.10 (95%CI: 0.03-0.41), p=0.001, I<sup>2</sup>=0%
  - 8.0-8.9 log<sub>10</sub> IU/mL (n=3): pooled OR= 0.11 (95%CI: 0.02-0.51), p<0.001, I<sup>2</sup>=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



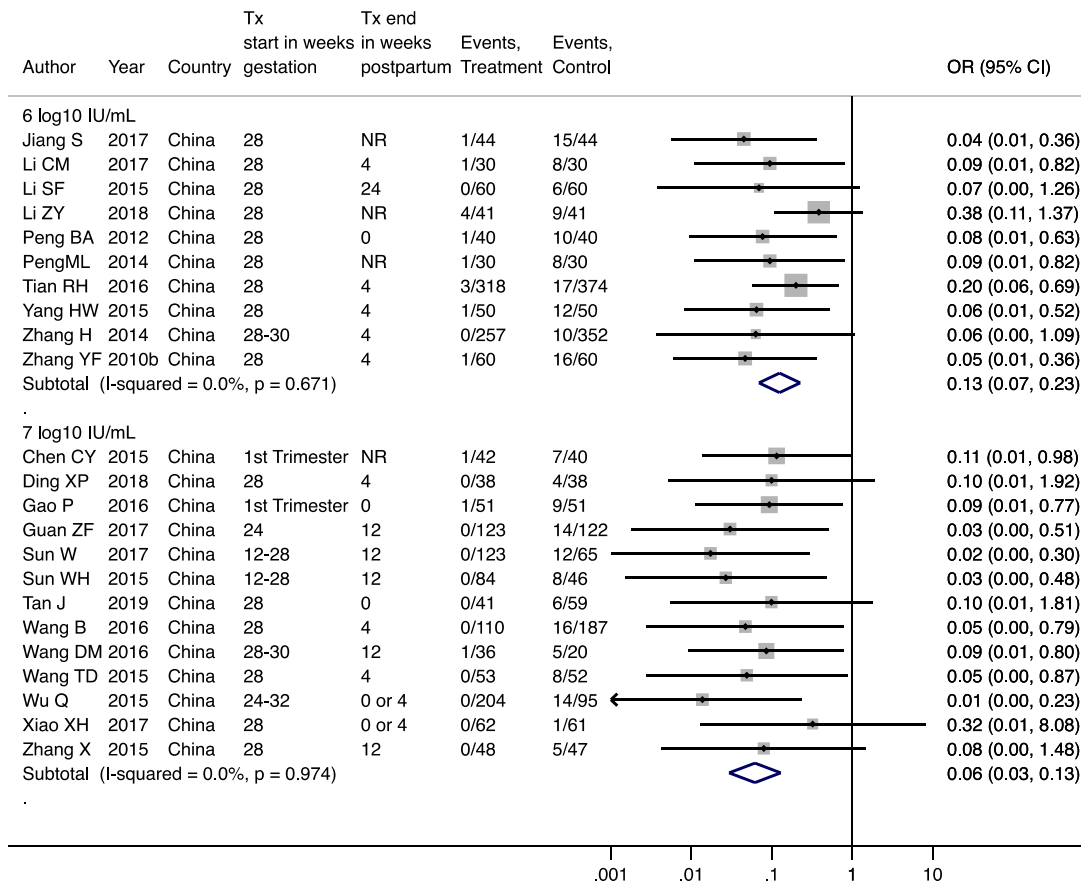
- **LAM 100-150 mg by mean maternal viral load at baseline**

- 6.0-6.9 log<sub>10</sub> IU/mL (n=4): pooled OR= 0.15 (95%CI: 0.06-0.37), p=0.001, I<sup>2</sup>=0%



- **LdT 600 mg by mean maternal viral load at baseline**

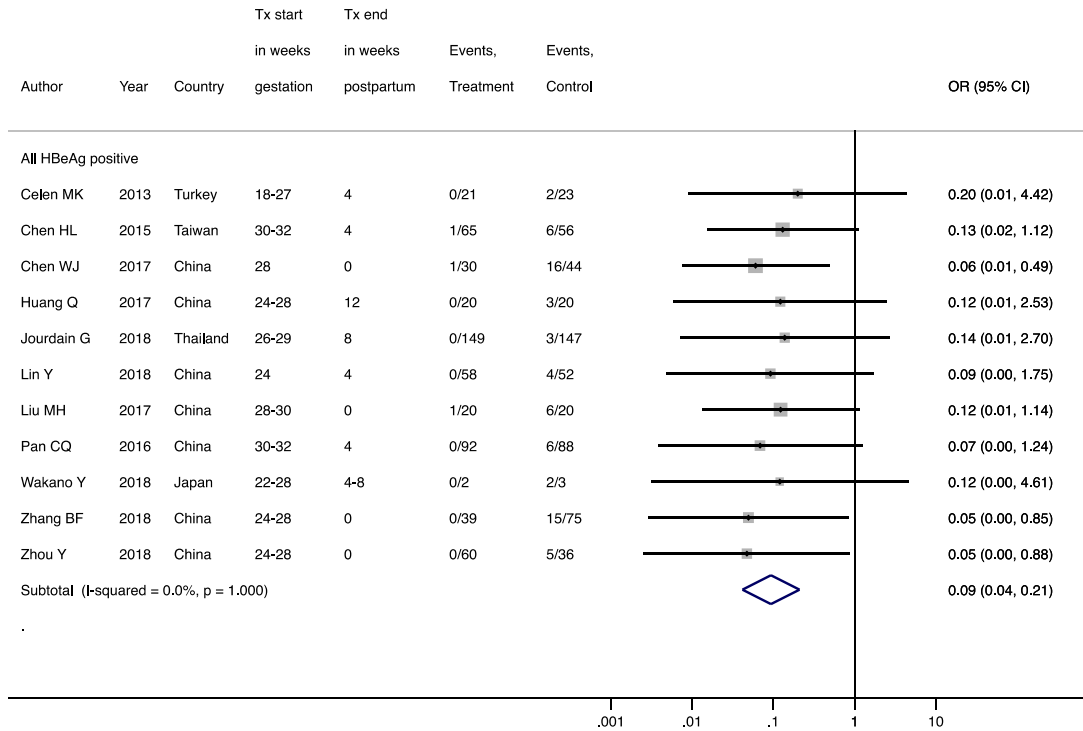
- 6.0-6.9 log<sub>10</sub> IU/mL (n=10): pooled OR= 0.13 (95%CI: 0.07-0.23), p<0.001, I<sup>2</sup>=0%
- 7.0-7.9 log<sub>10</sub> IU/mL (n=13): pooled OR= 0.06 (95%CI: 0.03-0.13), p<0.001, I<sup>2</sup>=0%
- The p-value for heterogeneity between subgroups was 0.14



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

- **TDF 300 mg by maternal HBeAg status at baseline**

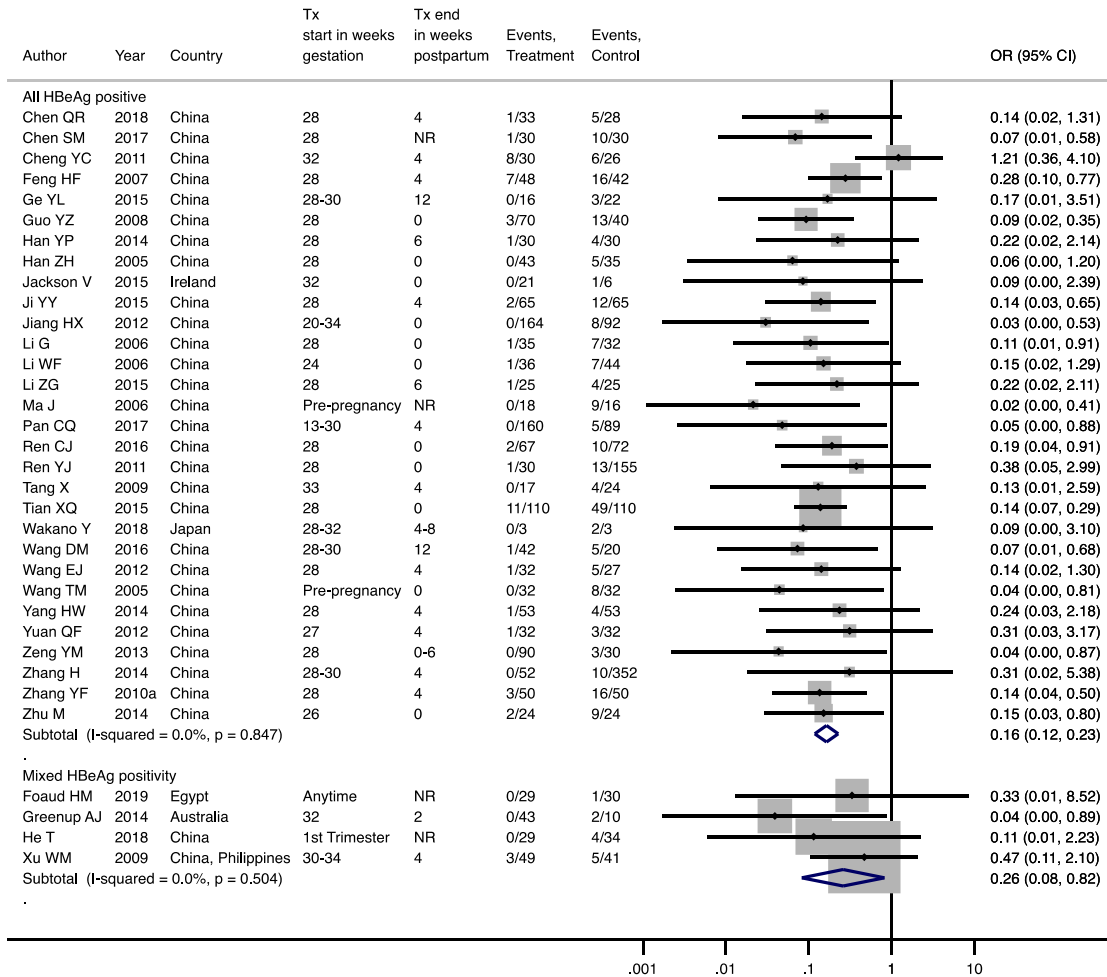
- HBeAg positive only (n=11): pooled OR= 0.09 (95% CI: 0.04-0.21), p<0.001, I<sup>2</sup>=0%



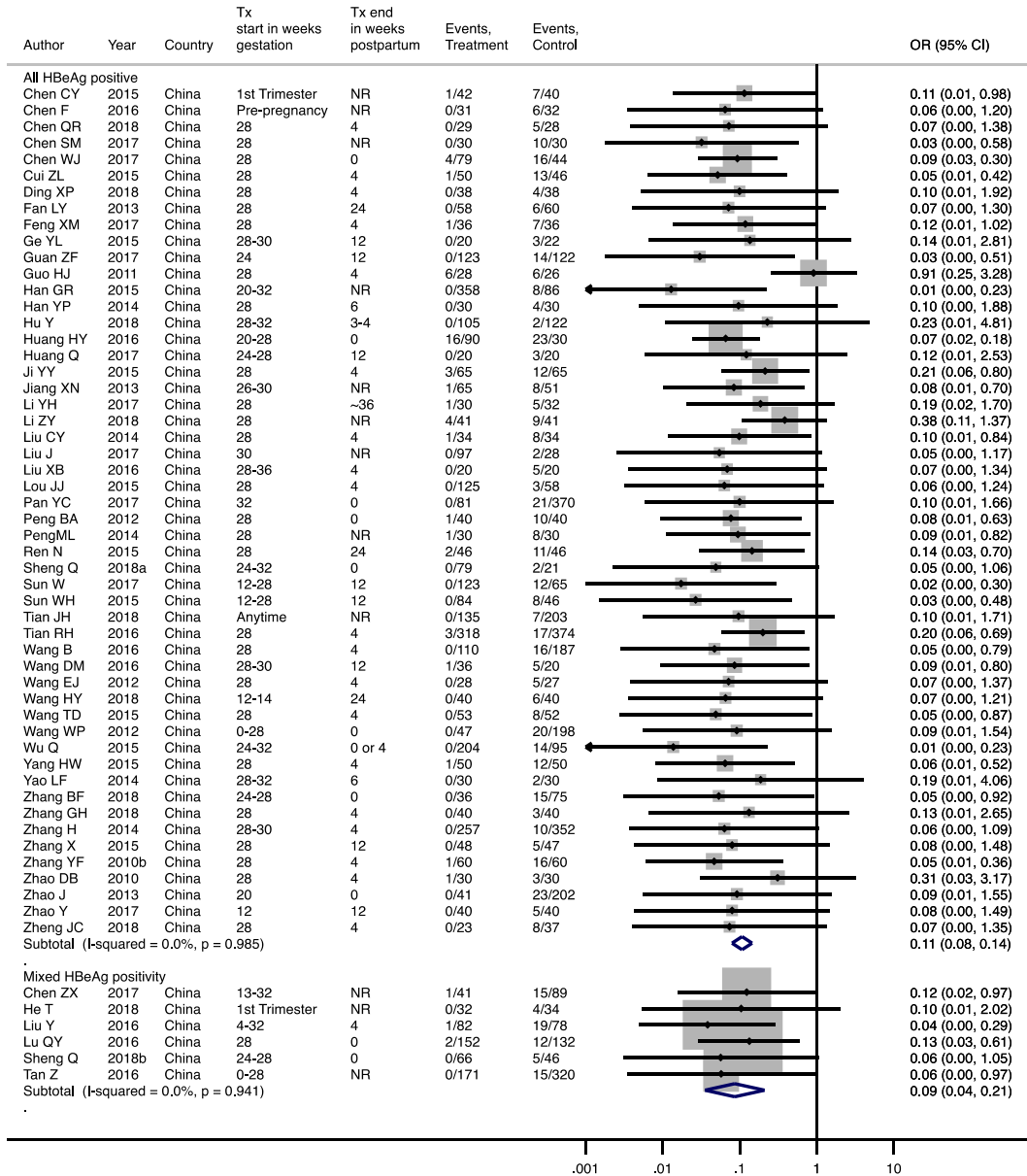


- **LAM 100-150 mg by maternal HBeAg status at baseline**

- HBeAg positive only (n=30): pooled OR= 0.16 (95% CI: 0.12-0.23), p<0.001, I<sup>2</sup>=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

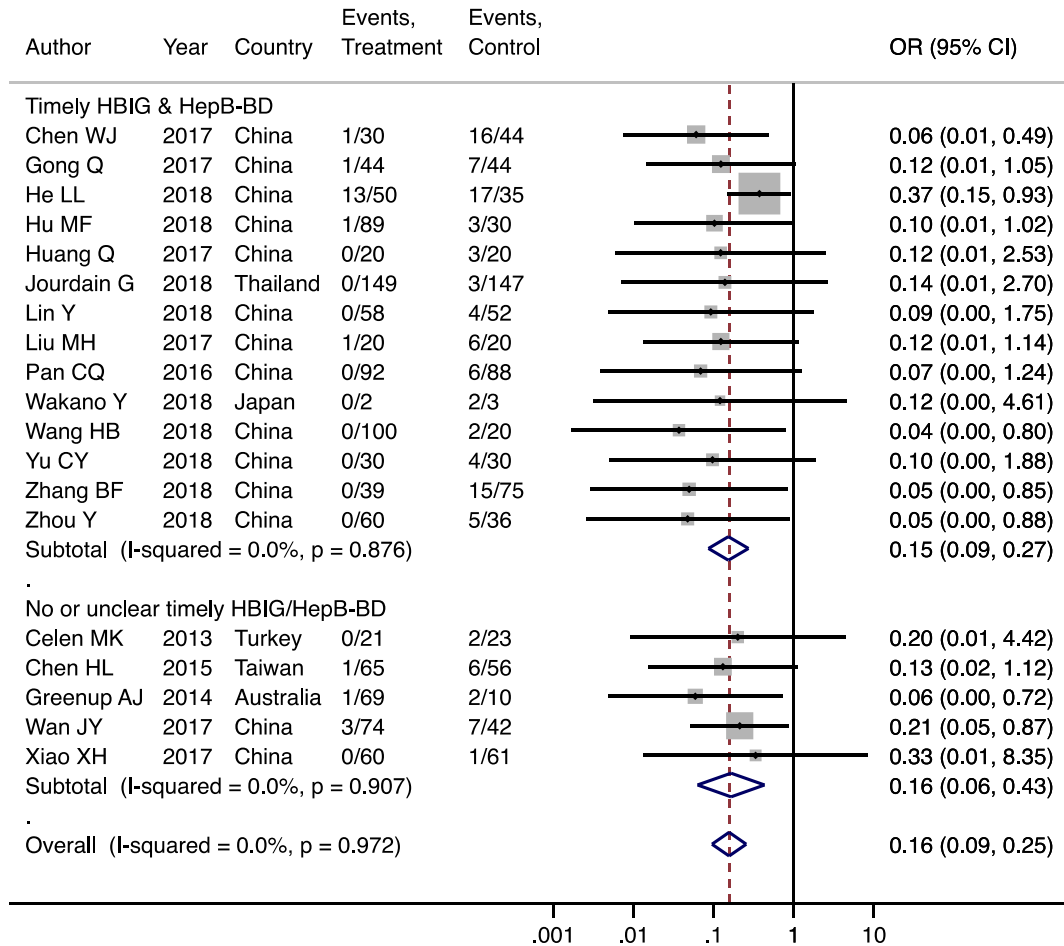


- **LdT 600 mg by maternal HBeAg status at baseline**
- HBeAg positive only (n=52): pooled OR= 0.11 (95%CI: 0.08-0.14),  $p < 0.001$ ,  $I^2 = 0\%$
- Mixed HBeAg positivity (n=6): pooled OR=0.09 (95%CI: 0.04-0.21),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.65



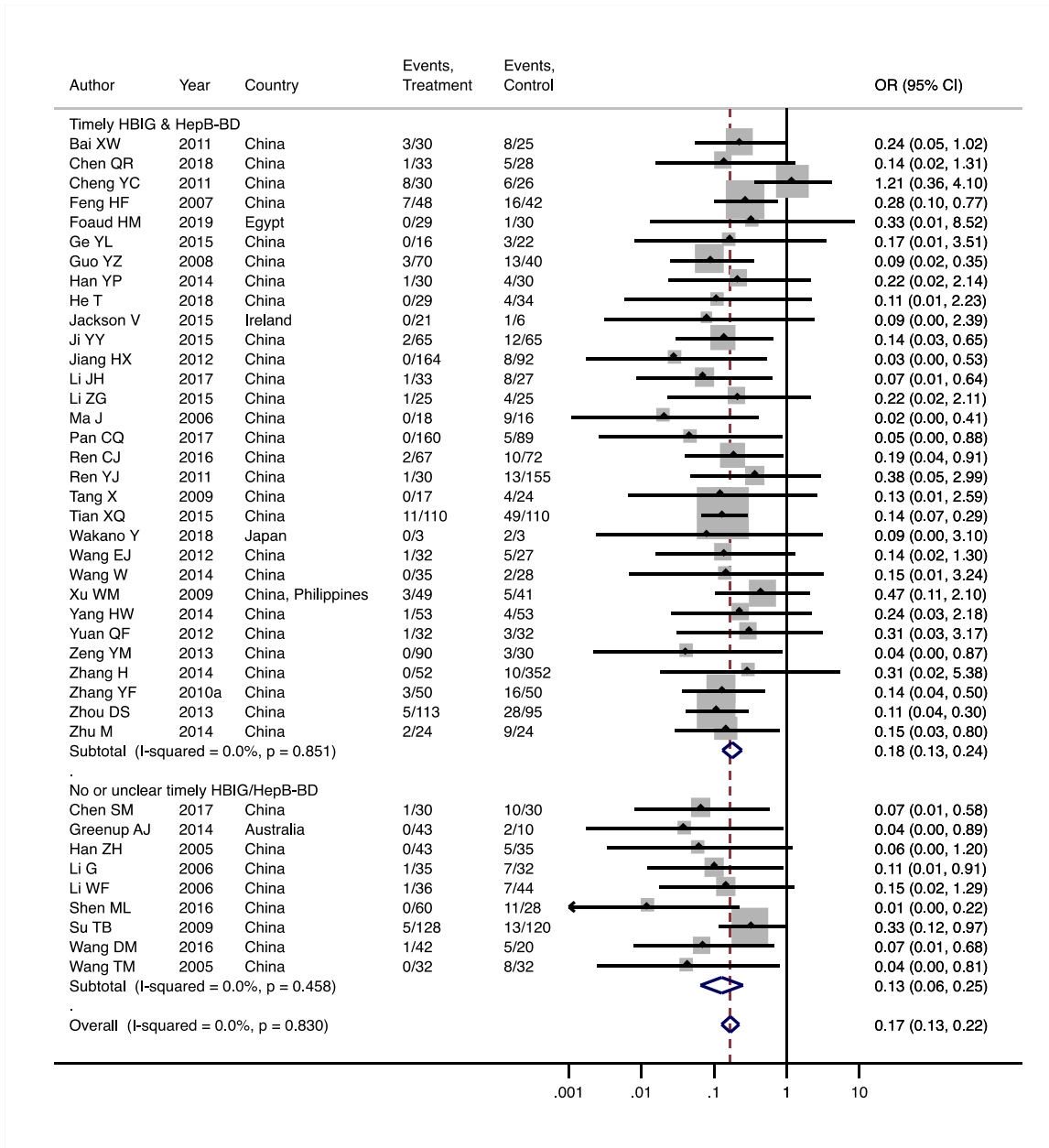
## Appendix N: Efficacy by infant immunoprophylaxis regimen

- **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),  $p < 0.001$ ,  $I^2 = 0\%$
  - The p-value for heterogeneity between subgroups was 0.89



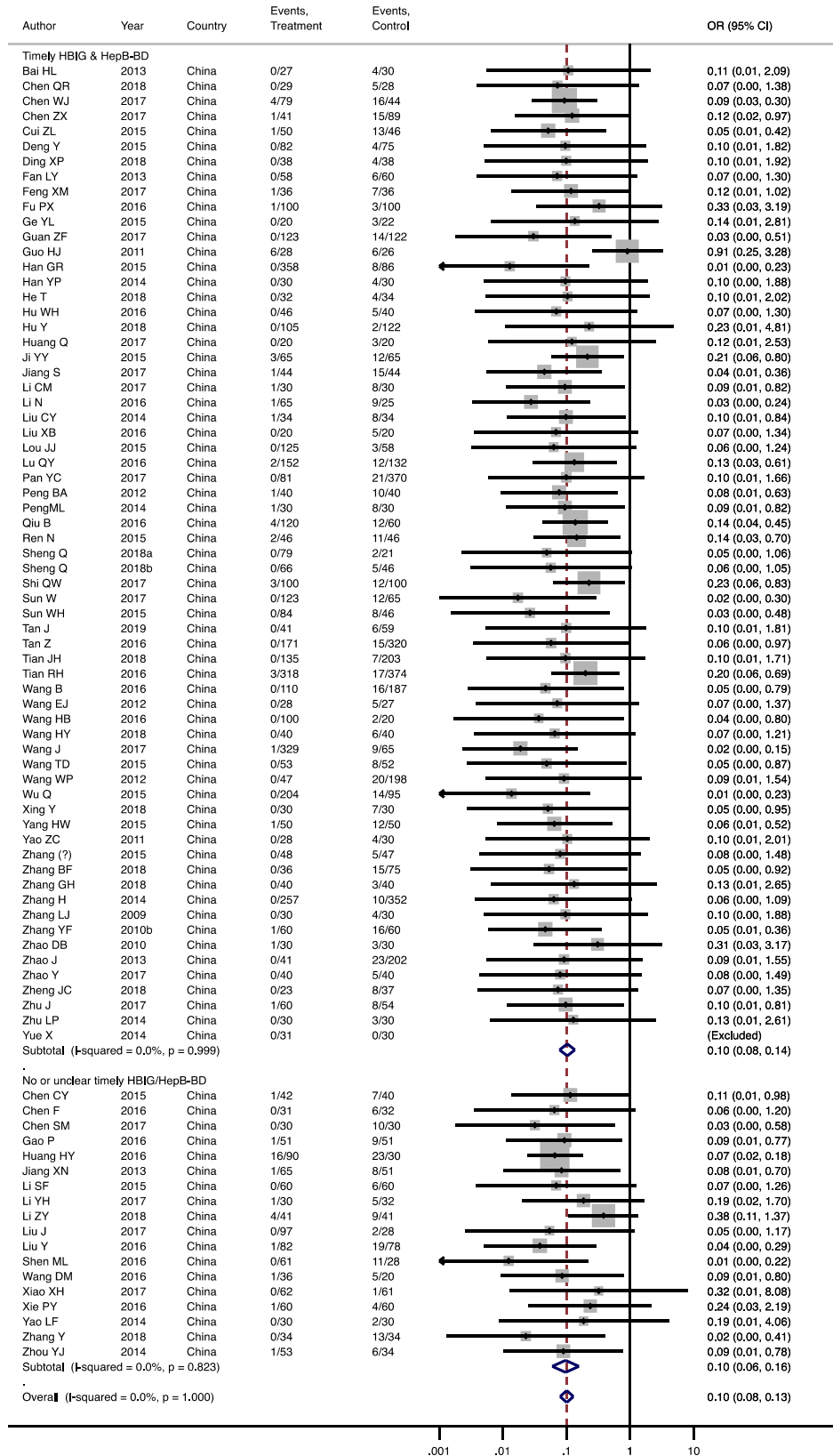
- **LAM 100-150 mg by infant immunoprophylaxis regimens**

- 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),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.38



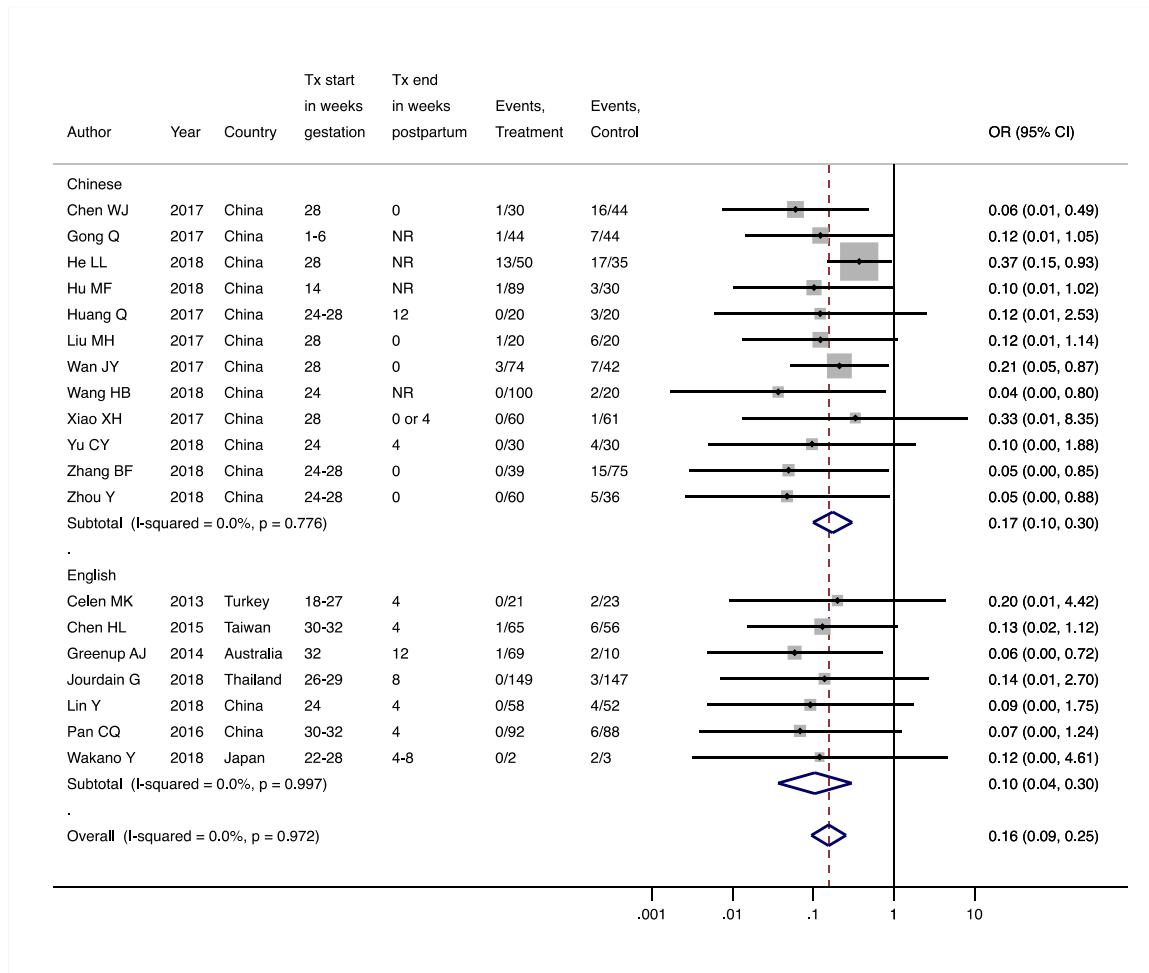
• **LdT 100-150 mg by infant immunoprophylaxis regimens**

- 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),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.83

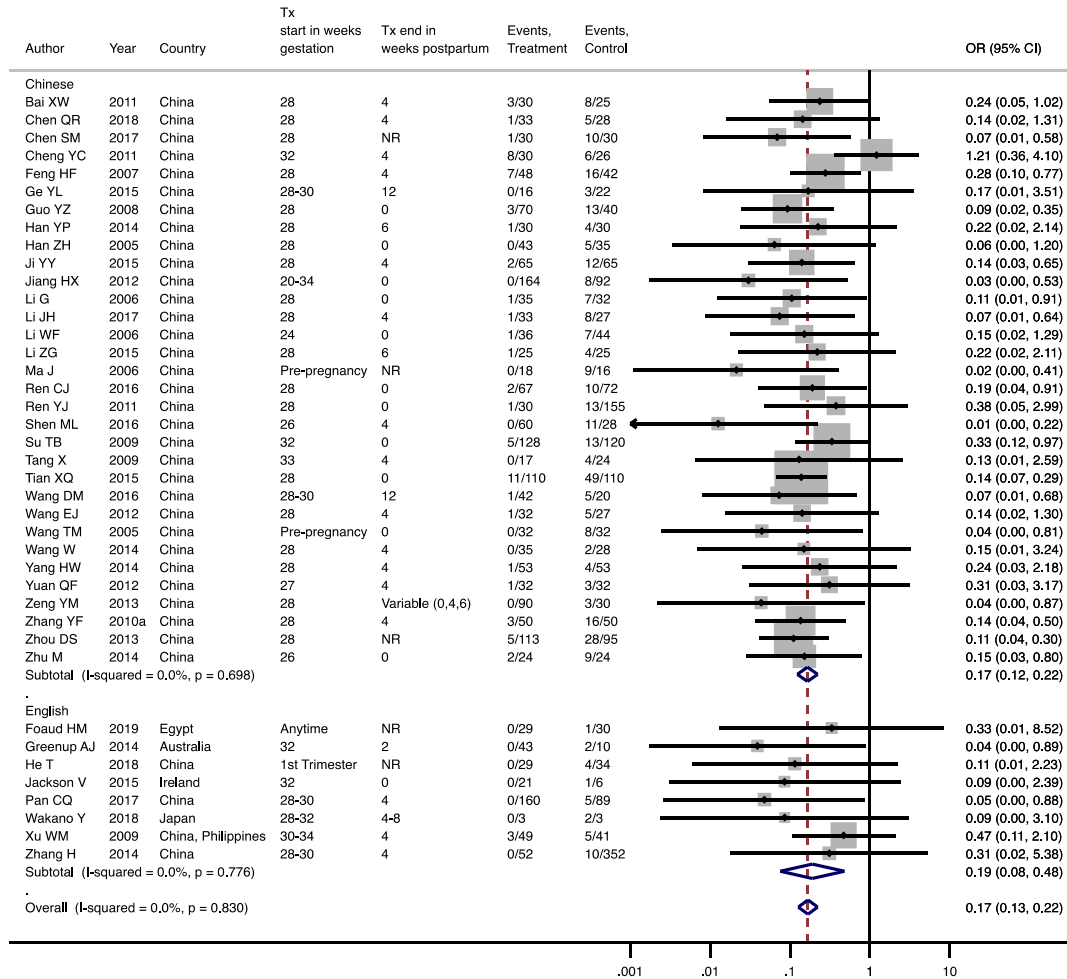


## Appendix O: Efficacy by language used for reporting (Chinese versus English)

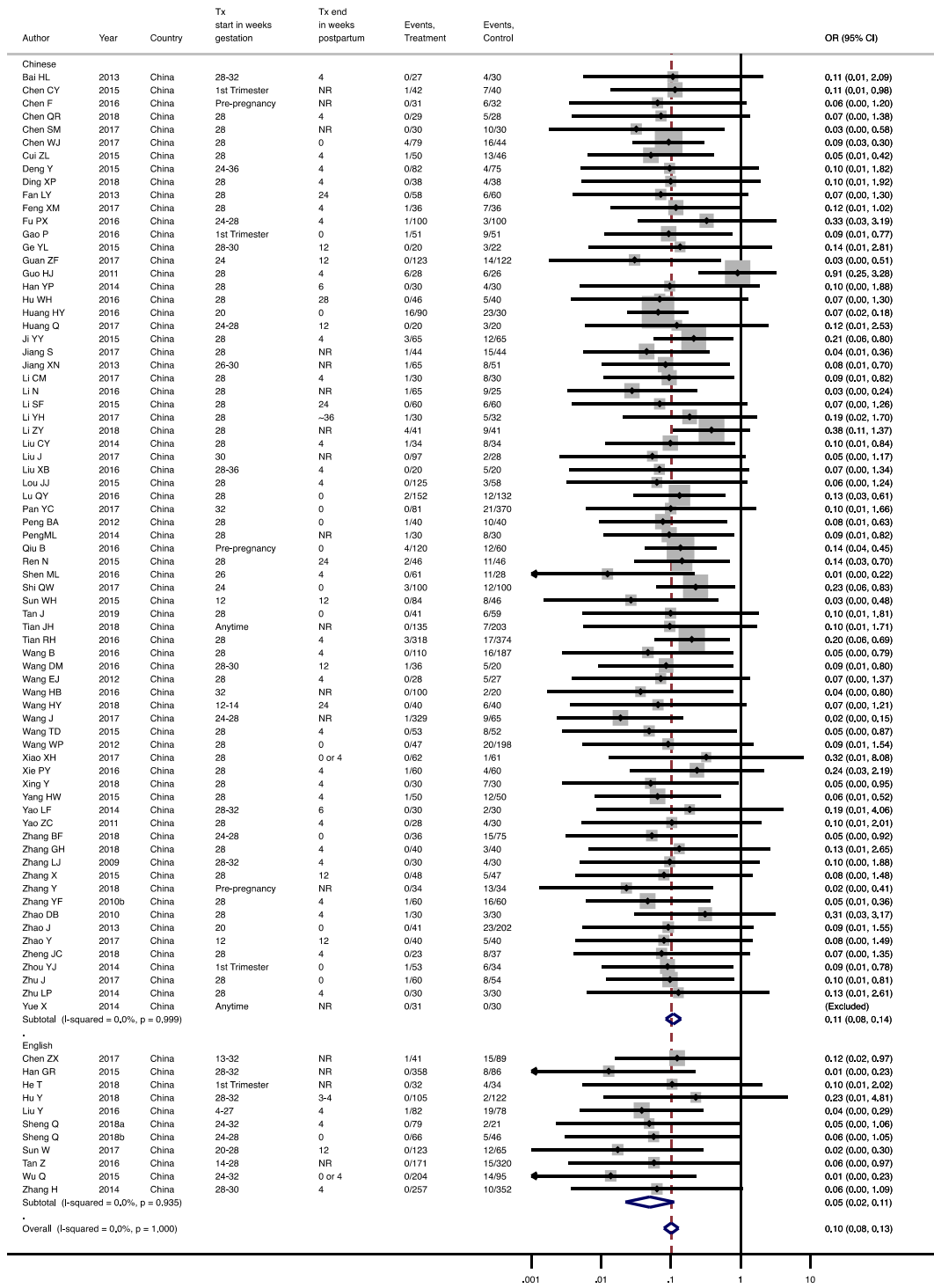
- **TDF 300 mg by language used for reporting (Chinese versus English)**
- Chinese language (n=12): pooled OR= 0.17 (95% CI: 0.10-0.30),  $p < 0.001$ ,  $I^2 = 0\%$
- English language (n=7): pooled OR=0.10 (95% CI: 0.04-0.30),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups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



- **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),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.78



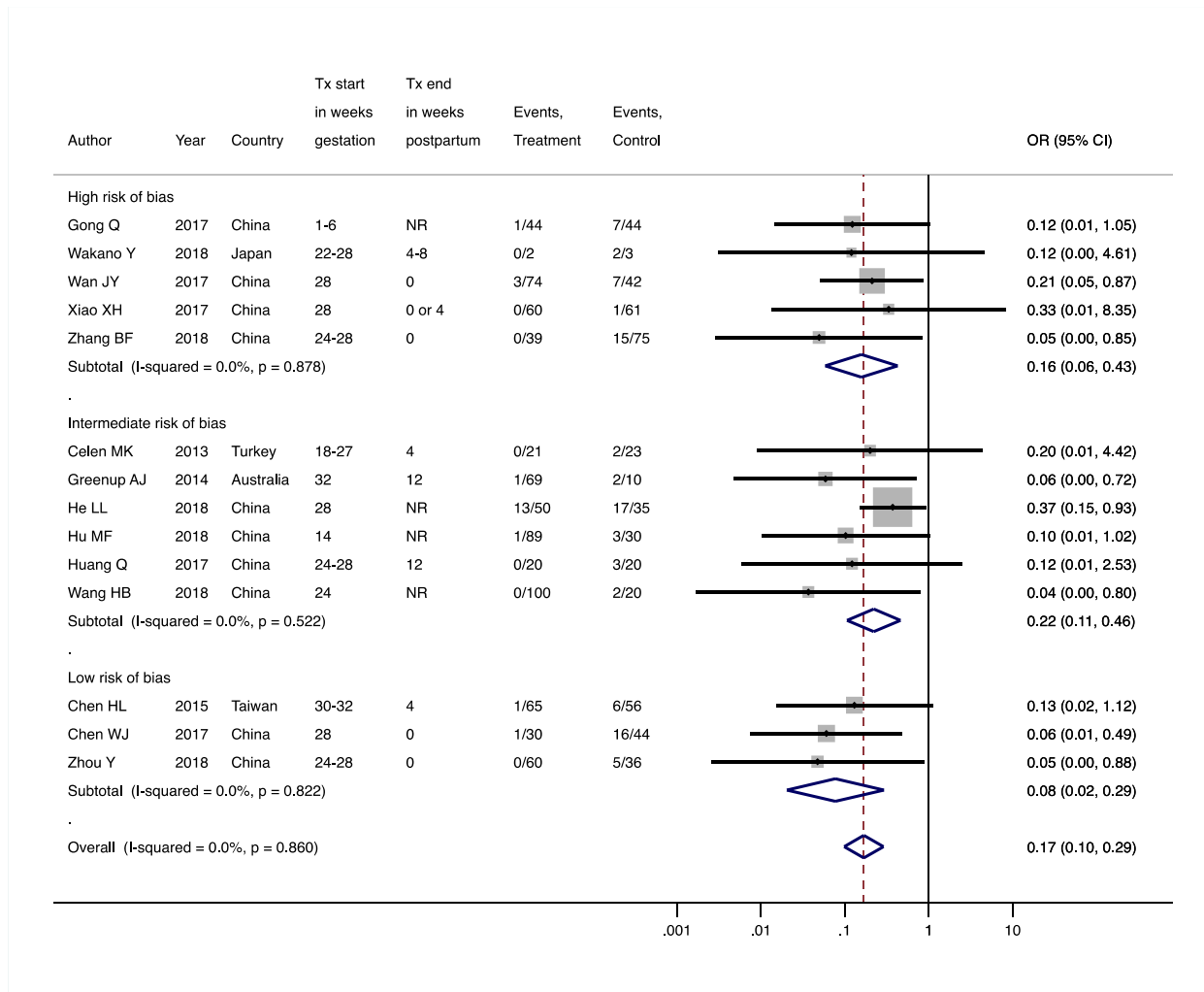
- **LdT 600 mg by language used for reporting (Chinese versus English)**
- Chinese language (n=72): pooled OR= 0.11 (95% CI: 0.08-0.14),  $p < 0.001$ ,  $I^2 = 0\%$
- English language (n=11): pooled OR=0.05 (95% CI: 0.02-0.11),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups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



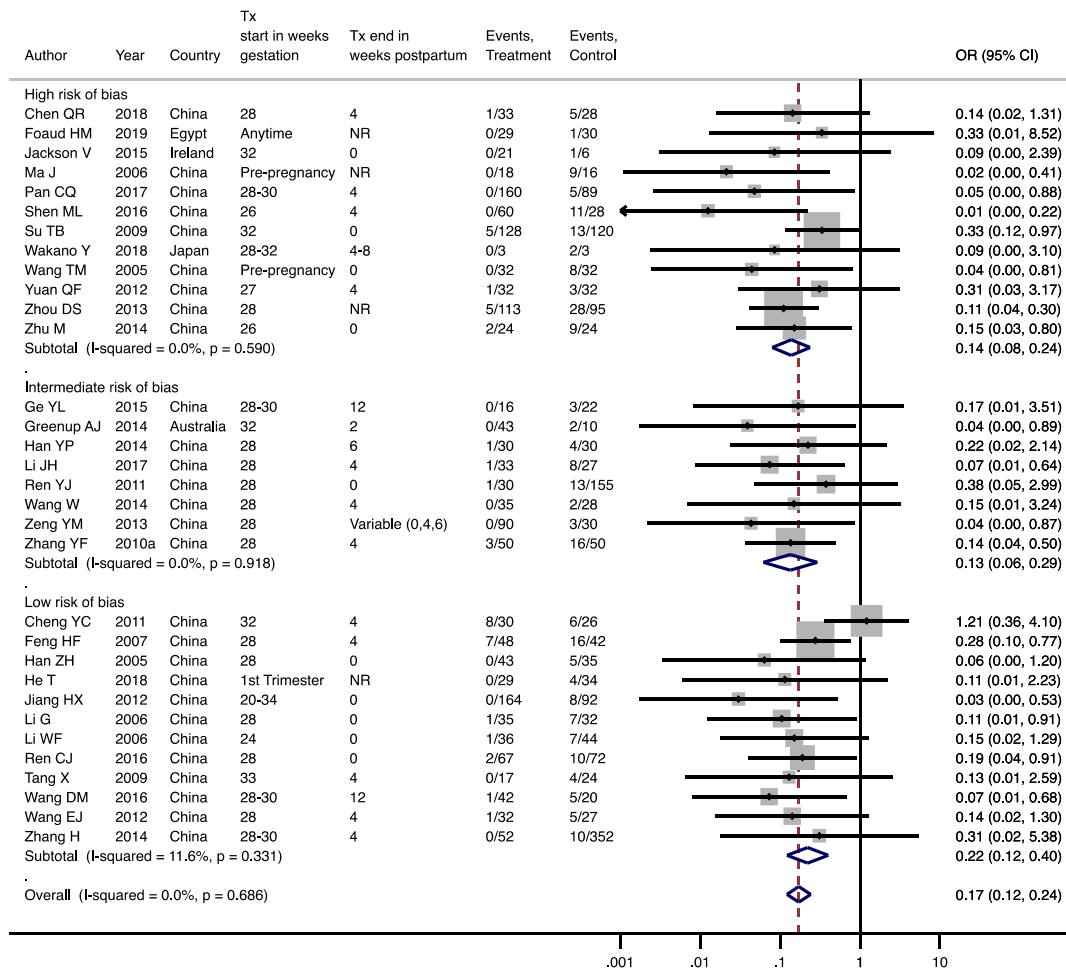


## Appendix P: Efficacy by risk of bias score for non-RCTs

- **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),  $p < 0.001$ ,  $I^2 = 0\%$
  - Low risk (score of 8-9) (n=3): pooled OR=0.08 (95% CI: 0.02-0.29),  $p < 0.001$ ,  $I^2 = 0\%$
  - The p-value for heterogeneity between subgroups was 0.39

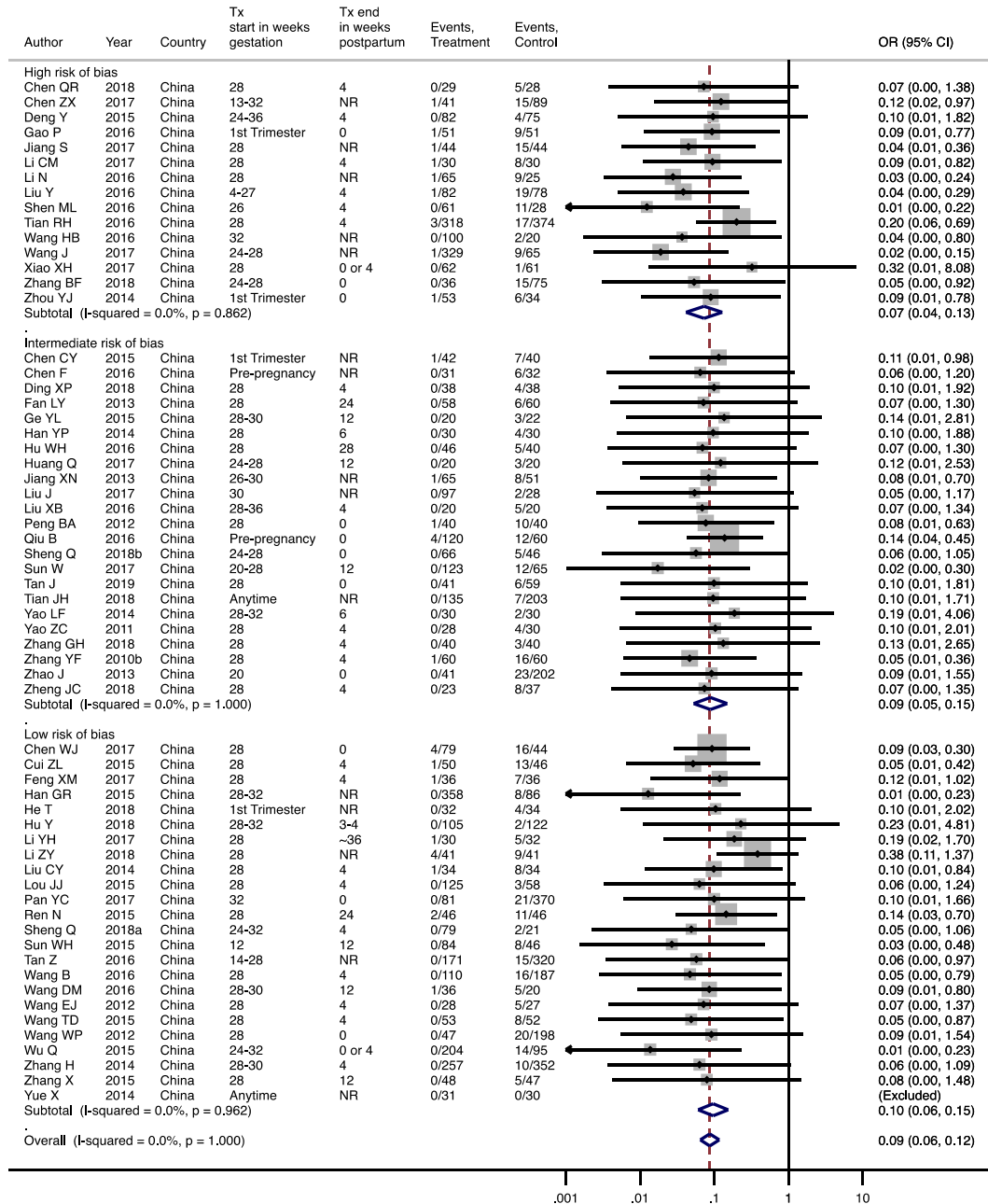


- **LAM 100-150 mg by risk of bias for non-RCTs**
- High risk (score of 6) (n=12): pooled OR= 0.14 (95%CI: 0.08-0.24),  $p < 0.001$ ,  $I^2 = 0\%$
- Intermediate risk (score of 8) (n=8): pooled OR=0.13 (95%CI: 0.06-0.29),  $p < 0.001$ ,  $I^2 = 0\%$
- Low risk (score of 8-9) (n=12): pooled OR=0.22 (95%CI: 0.12-0.40),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.29



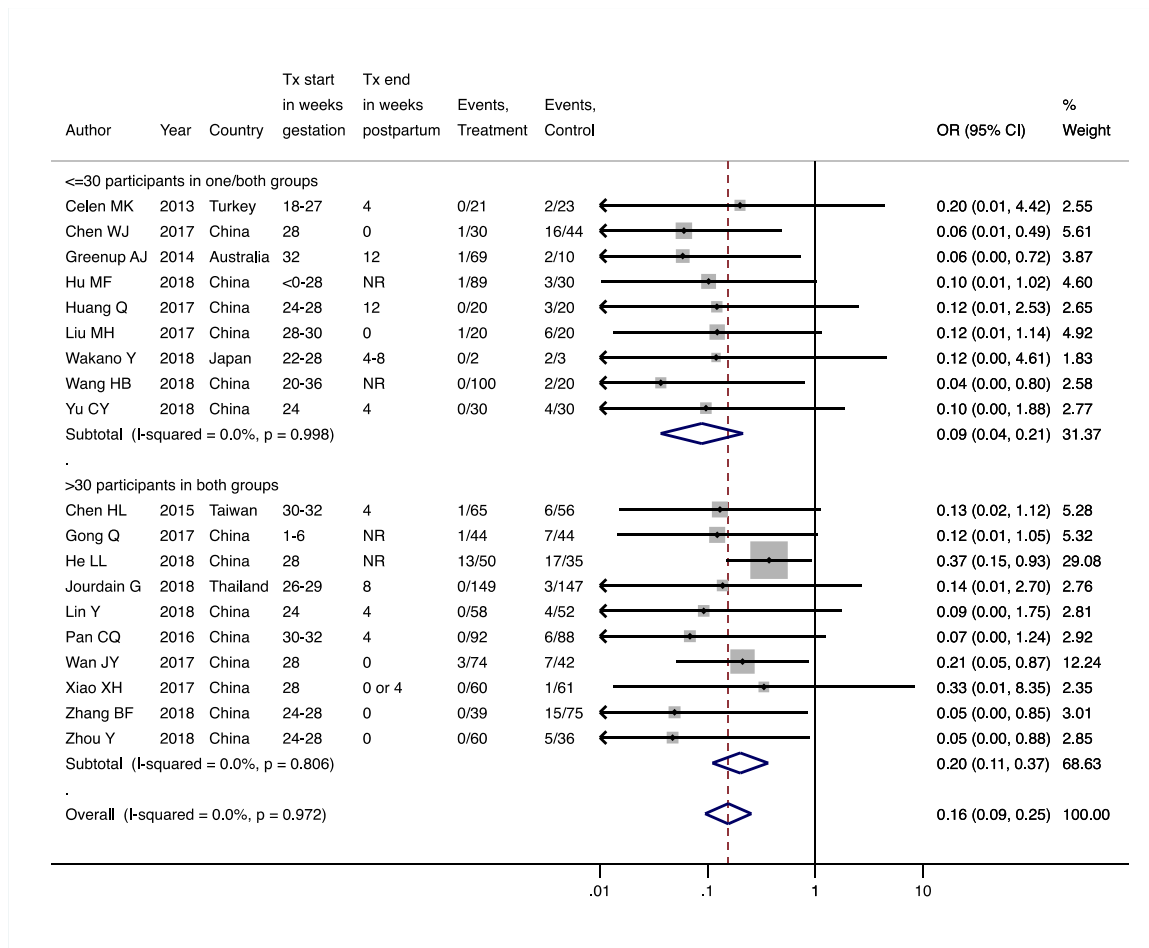
- **LdT 600 mg by risk of bias for non-RCTs**

- High risk (score of 6) (n=15): pooled OR= 0.07 (95%CI: 0.04-0.13),  $p < 0.001$ ,  $I^2 = 0\%$
- 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),  $p < 0.001$ ,  $I^2 = 0\%$
- The p-value for heterogeneity between subgroups was 0.75

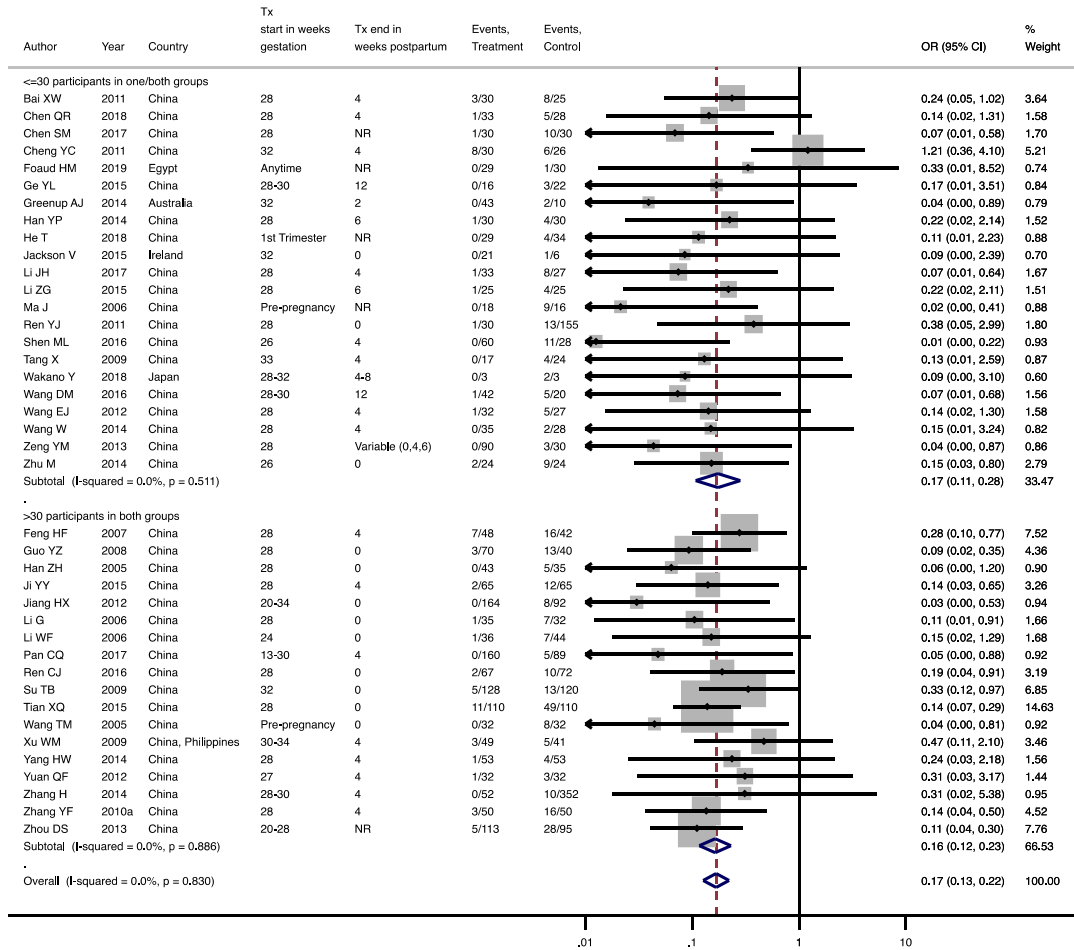


## Appendix Q: Efficacy by study sample size

- **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



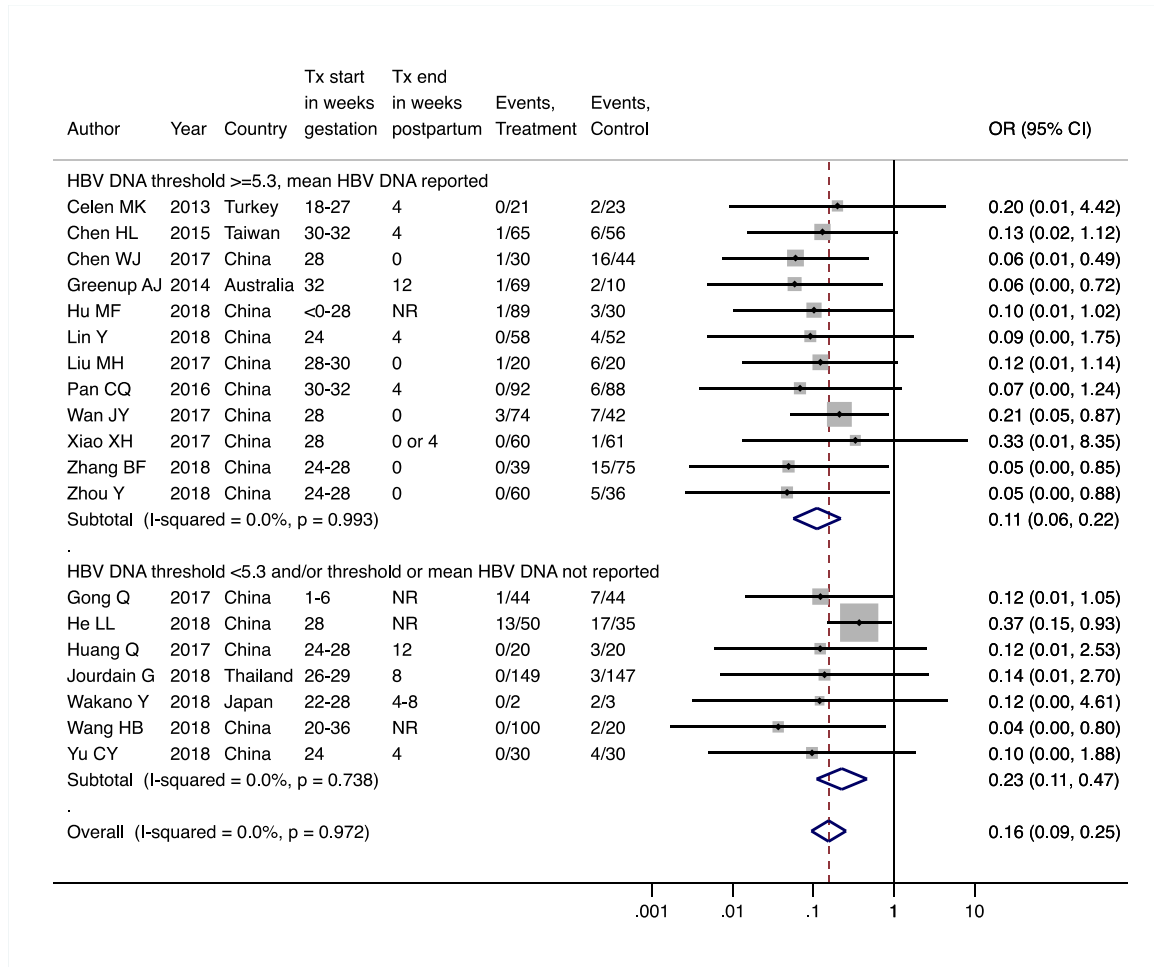
- LAM 100-150 mg by study sample size ( $\leq 30$  participants in either group versus  $>30$  participants in both groups)
- The p-value for heterogeneity between subgroups was 0.838



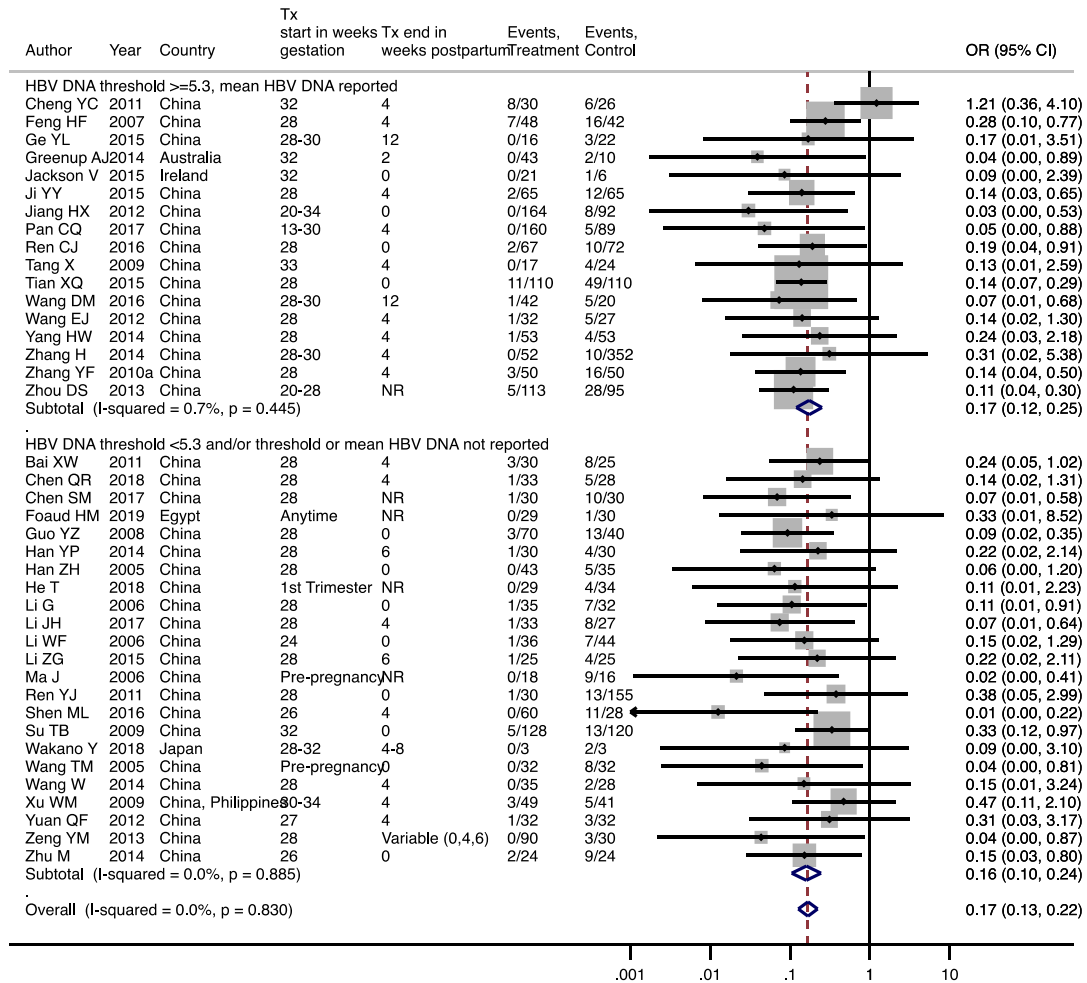


## Appendix R: Efficacy by maternal viral load criteria

- **TDF 300 mg by maternal viral load criteria (Pre-specified viral load threshold of  $\geq 5.3 \log_{10}$  IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low ( $< 5.3 \log_{10}$  IU/ml) and/or HBV DNA level of participating women not reported)**
- The p-value for heterogeneity between subgroups was 0.161



- **LAM 100-150 mg by maternal viral load criteria (Pre-specified viral load threshold of  $\geq 5.3$  log<sub>10</sub> IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low ( $< 5.3$  log<sub>10</sub> IU/ml) and/or HBV DNA level of participating women not reported)**
- The p-value for heterogeneity between subgroups was 0.781



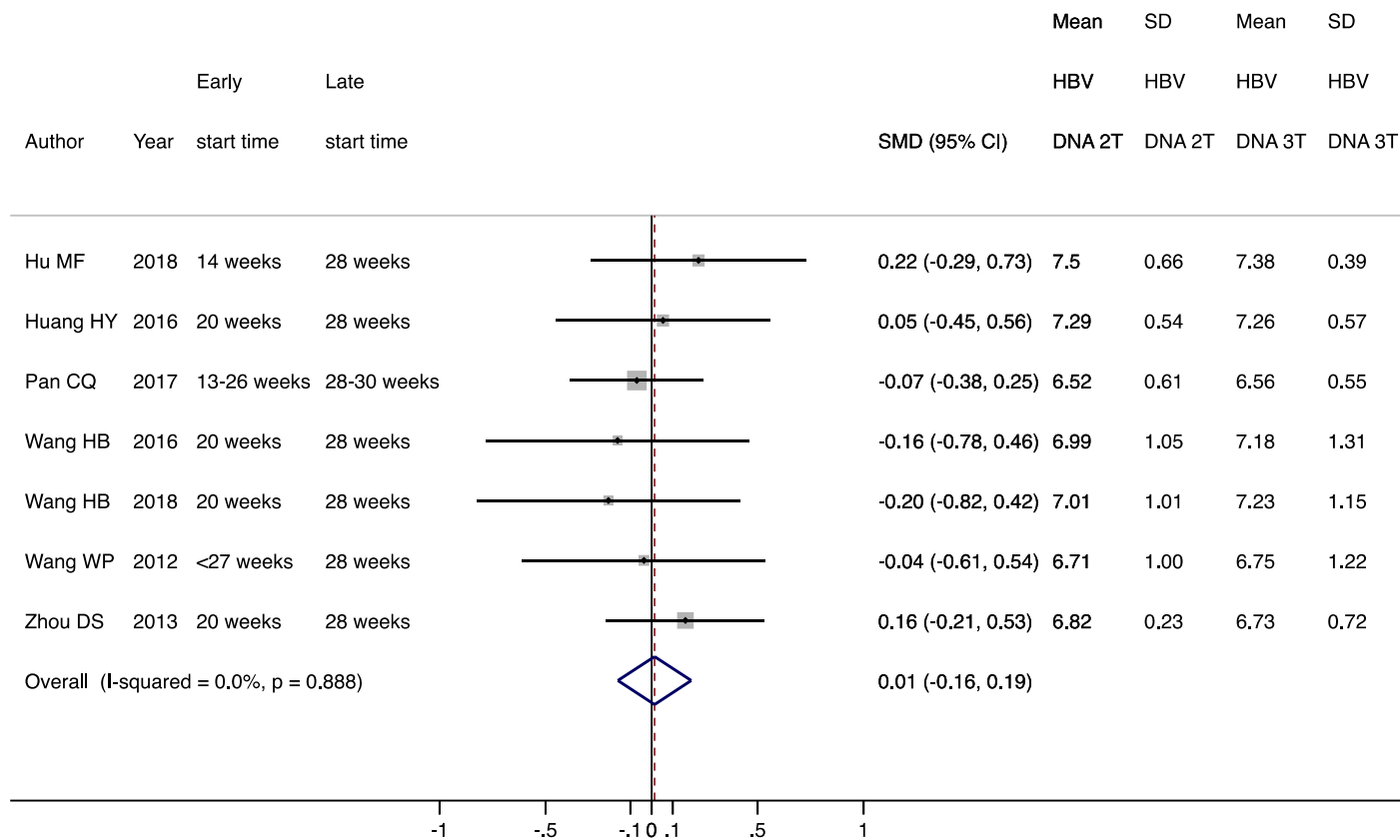


- **LdT 600 mg by maternal viral load criteria (Pre-specified viral load threshold of  $\geq 5.3$  log<sub>10</sub> IU/mL and mean HBV DNA level reported for participating women *versus* viral load threshold not specified or threshold was low ( $< 5.3$  log<sub>10</sub> IU/ml) and/or HBV DNA level of participating women not reported)**
- The p-value for heterogeneity between subgroups was 0.546

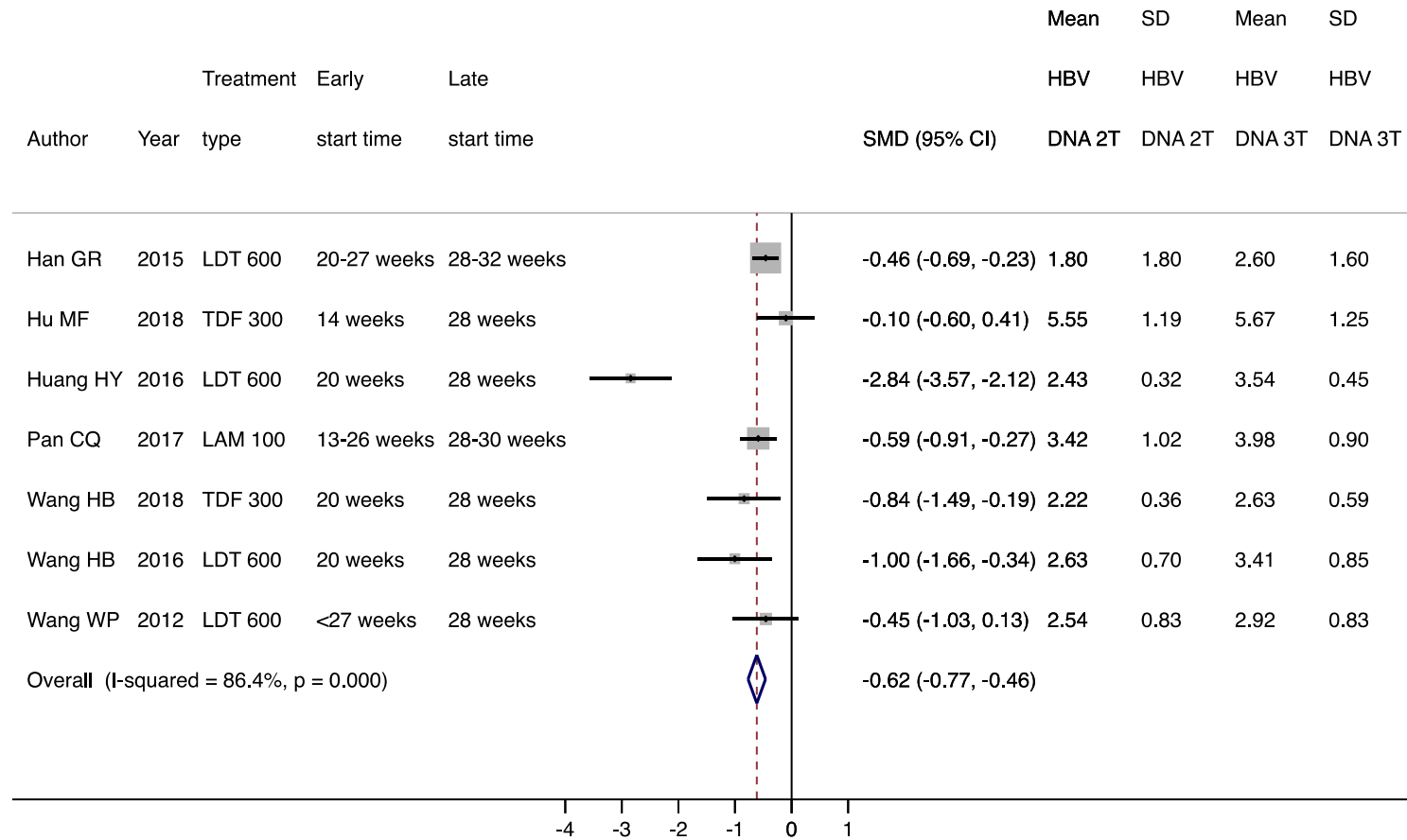


## Appendix S: Viral load prior to treatment and prior to delivery in studies comparing second versus third trimester PAP initiation

- 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

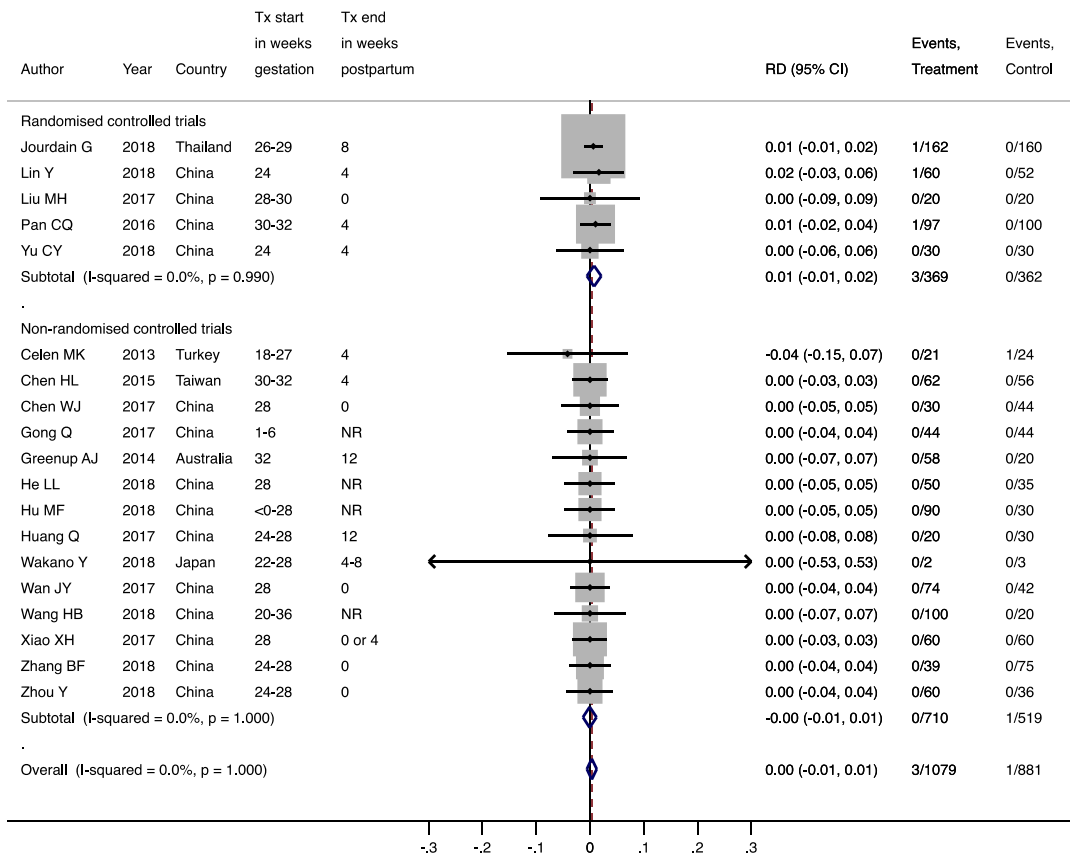


- **Standardized mean difference (SMD) of viral load AT TIME OF DELIVERY comparing participants starting PAP in the second (“experimental/treatment”) versus third trimester (“control”)**
  - 7/9 studies contributing (not Liu Y, 2016 or Zhou DS 2013), SMD= -0.62 (95%CI: -0.77- -0.46) p<0.001

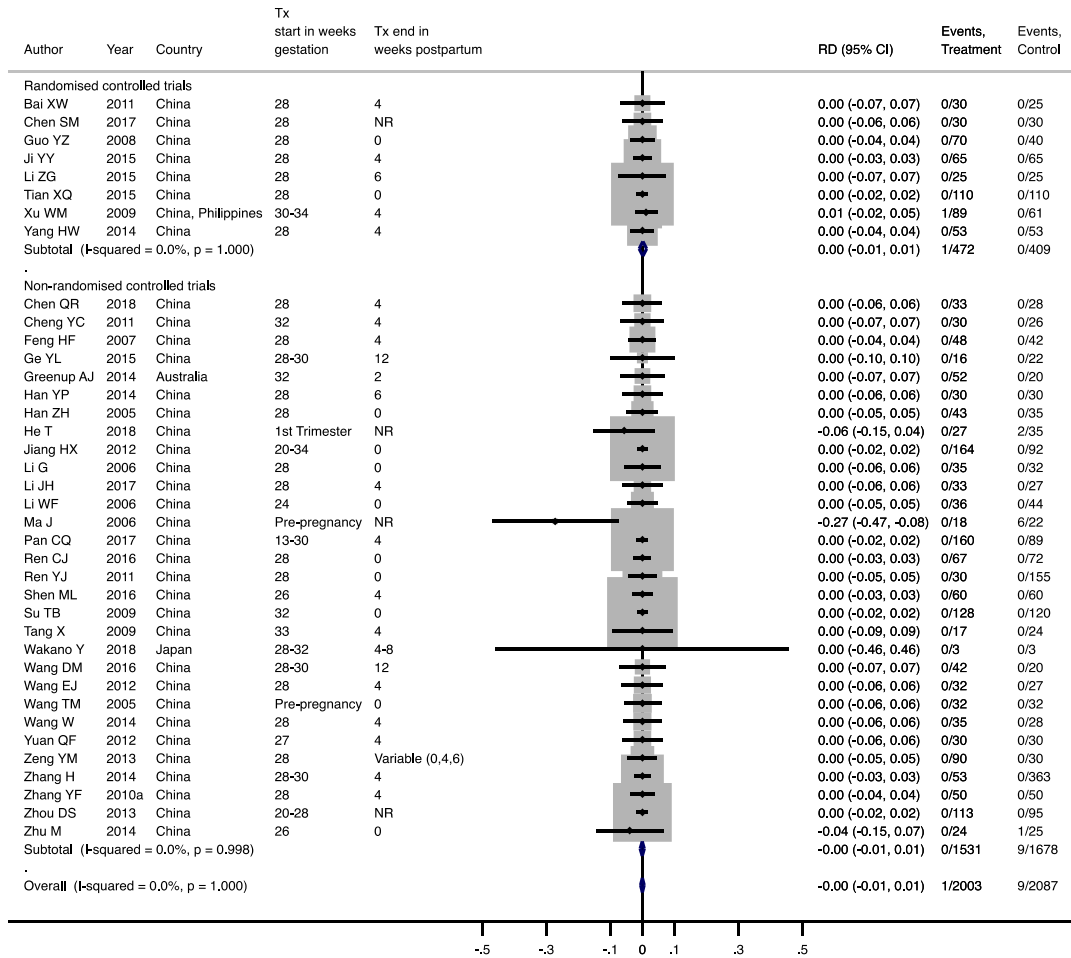


## Appendix T: Maternal safety 1. Fetal deaths

- **TDF 300 mg risk difference for fetal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0%
    - $I^2$  statistic RCTs = 0%
    - $I^2$  statistic non-RCTs = 0%



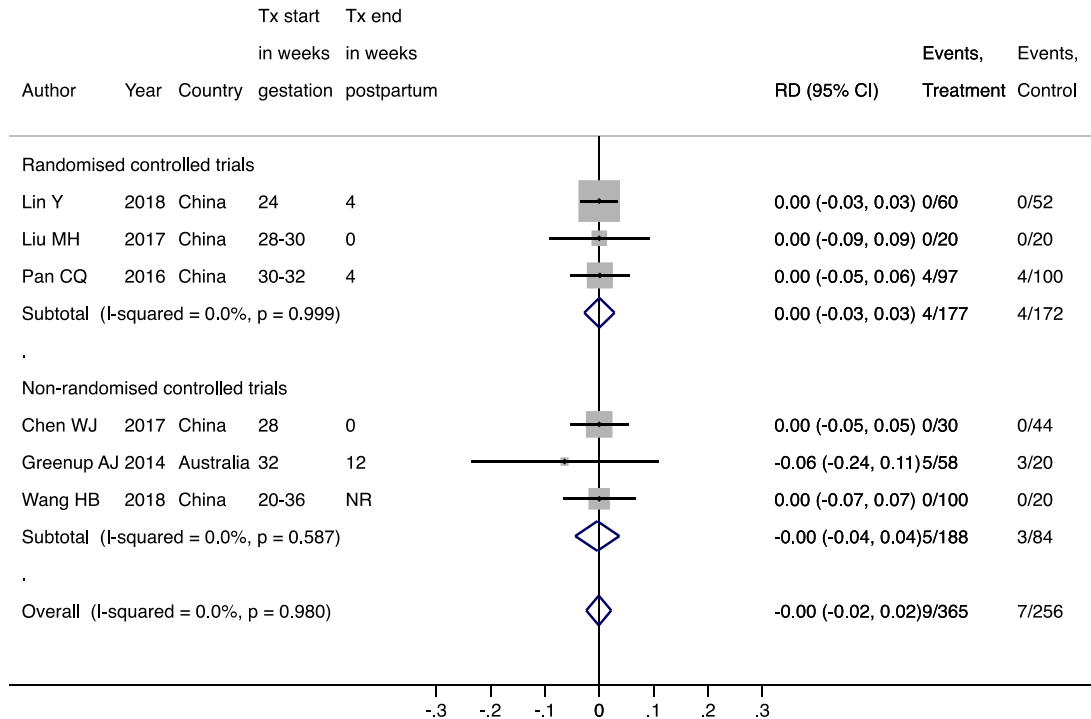
- **LAM 100-150 mg risk difference for fetal death**
  - Weighted pooled risk difference: 0.00 (95% CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%





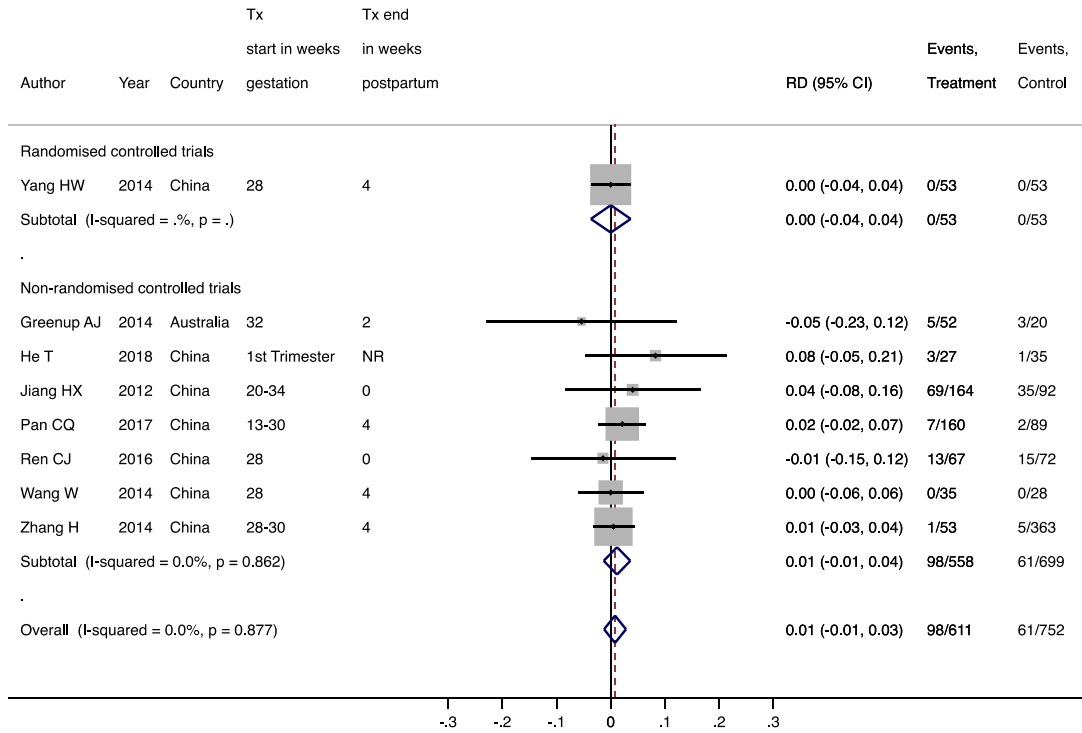
## Appendix U: Maternal safety 2. Postpartum hemorrhage

- **TDF 300 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.02 – 0.02).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%

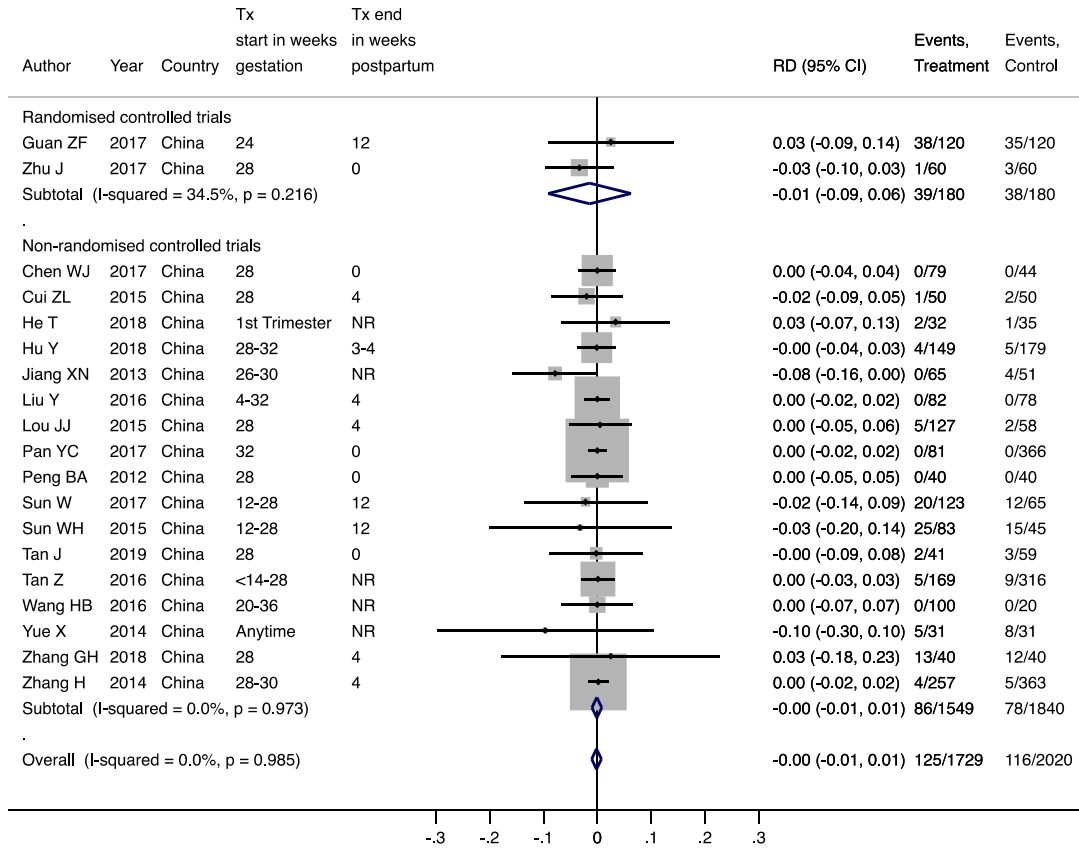




- **LAM 100-150 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: 0.01 (95%CI: -0.01 – 0.03).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = not enough studies
    - $I^2$  statistic non-RCTs = 0.0%



- **LdT 600 mg risk difference for postpartum hemorrhage**
  - Weighted pooled risk difference: -0.001 (95% CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = not enough studies
    - $I^2$  statistic non-RCTs = 0.0%



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

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

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

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

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

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



		available.				
Chen WJ, 2017	Hepatic insufficiency (no time-point specified)	At delivery	0/79 in treated, 0/44 in control	No (no time- point specified)	No hepatic insufficiency	N/A
Chen QR, 2018	ALT elevation (during pregnancy)	4 weeks	1/29 in treated, 1/28 in control	No (not post- partum)	Unknown (not mentioned)	Both cases resolved spontaneously
Deng Y, 2015	Obvious abnormality for liver biochemical indicators (during treatment)	1 month	0/82 in treated group. No data reported for control group.	No (no control)	No	N/A
Ding XP, 2018	Impairment of liver function (during intervention)	1 month	0/38 in treated, 0/38 in control	No (no time- point specified)	No	N/A
Ge YL, 2015	Obvious abnormality for liver function (during treatment)	3 months	0/20 in treated group. No data reported for control group.	No (no control)	No	N/A
Fan LY, 2013	Severe impairment of liver function (after PAP discontinuation)	At least 6 months (9 in 60 pregnant women discontinued treatment 1 month after delivery)	0/9 pregnant women who discontinued antiviral treatment at 1 month after delivery. No data reported for control group.	No (no control 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 (after discontinuation of PAP). Severe: ALT >10 x ULN (after discontinuation of PAP).	(236 stopped at 4 weeks and 126 continued after 4 weeks)	had >5 x ULN, 0/236 with >10 x ULN. 126 mothers in treated group who continued treatment beyond postpartum week 4 were excluded from above. No data reported for control group.	control)		ALT elevation had clinical therapies to reduce ALT levels and by 7-12 months post-partum, ALT of all mothers had returned to normal.
He T, 2018	ALT > 2 x baseline (after child delivery)	All women continued treatment after child delivery.	0/32 in treated, 6/35 in control. However, all women in treated group continued antiviral therapy after child delivery, so this is not used for the meta-analysis of flare.	No (treatment continued)	Unknown (not mentioned)	All flare cases spontaneously resolved without antiviral therapy.
Hu Y, 2018	ALT > 40 U/L (by the 7-14 months postpartum)	3-4 weeks	22/103 in treated, 25/124 in control	Yes	No case of elevated bilirubin or fulminant hepatitis.	ALT normalized within 2-4 weeks.
Jiang S, 2017	Abnormal liver function (no time-point specified)	None given	0/44 in treated group. No data reported for control group.	No (no control)	No	N/A
Jiang XN, 2013	Abnormal ALT (7 months after delivery)	All women continued treatment	0/65 in treated, 4/51 in control.	No (treatment)	3/51 in control group	Unknown (not mentioned)

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

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

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

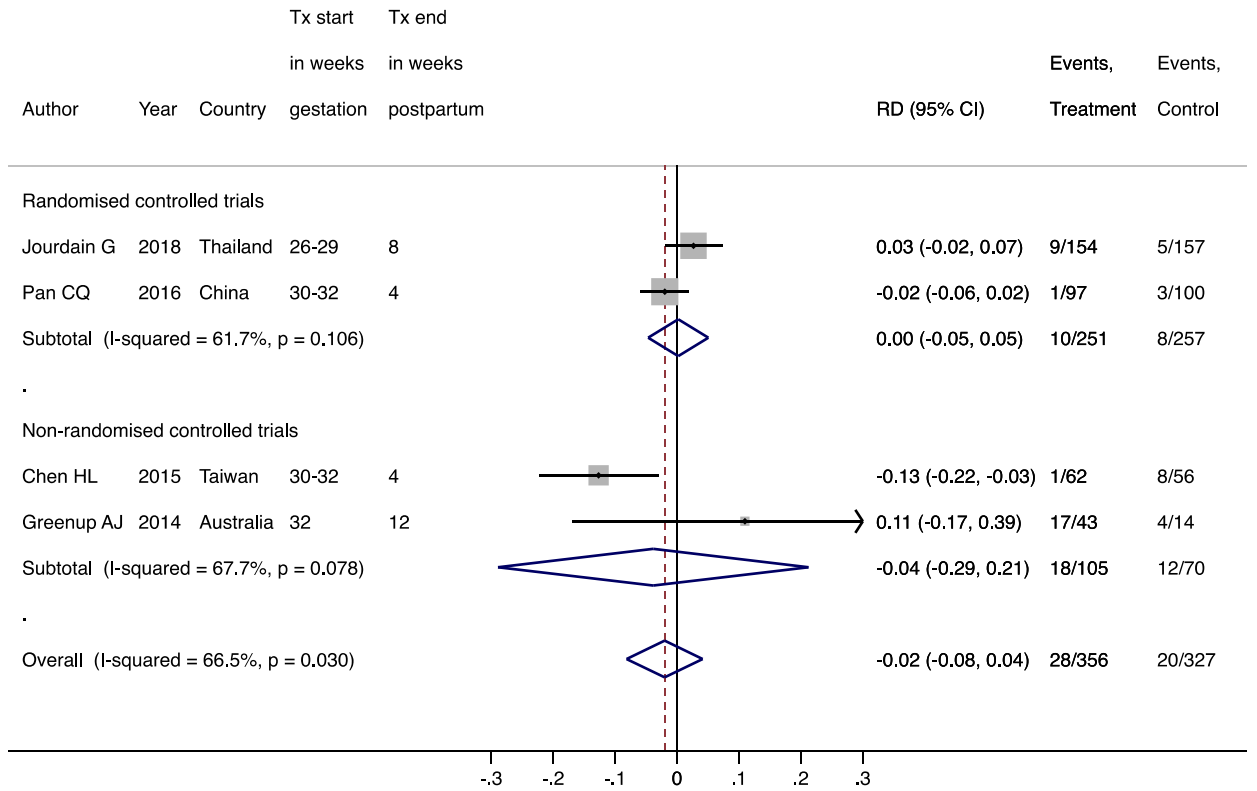
	discontinuation of PAP)		group who continued treatment after child delivery were excluded from the analysis. No data reported for control group.		decompensation	restarted antiviral and resolved.
Shi QW, 2017	Elevation in ALT levels (during treatment)	At delivery	3/100 in treated group. No data reported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

Zhou YJ, 2014	Abnormal liver biochemical indicators (17 weeks of gestation)	Treatment continued after delivery, unless discontinuation criteria met (disaggregated numbers not available)	5/39 in control group. No data reported for treated group.	No (no data for treated group)	1 case of death (this woman received treatment from 17 weeks to delivery, she died of large hemorrhage (unspecified type) at delivery)	4 cases stopped pregnancy; 1 case of death (continuing pregnancy and receiving treatment from 17 weeks to delivery, die of massive hemorrhage at delivery)
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\* In Nguyen V, 2014, 12% (5/43) in the intervention group received LAM.

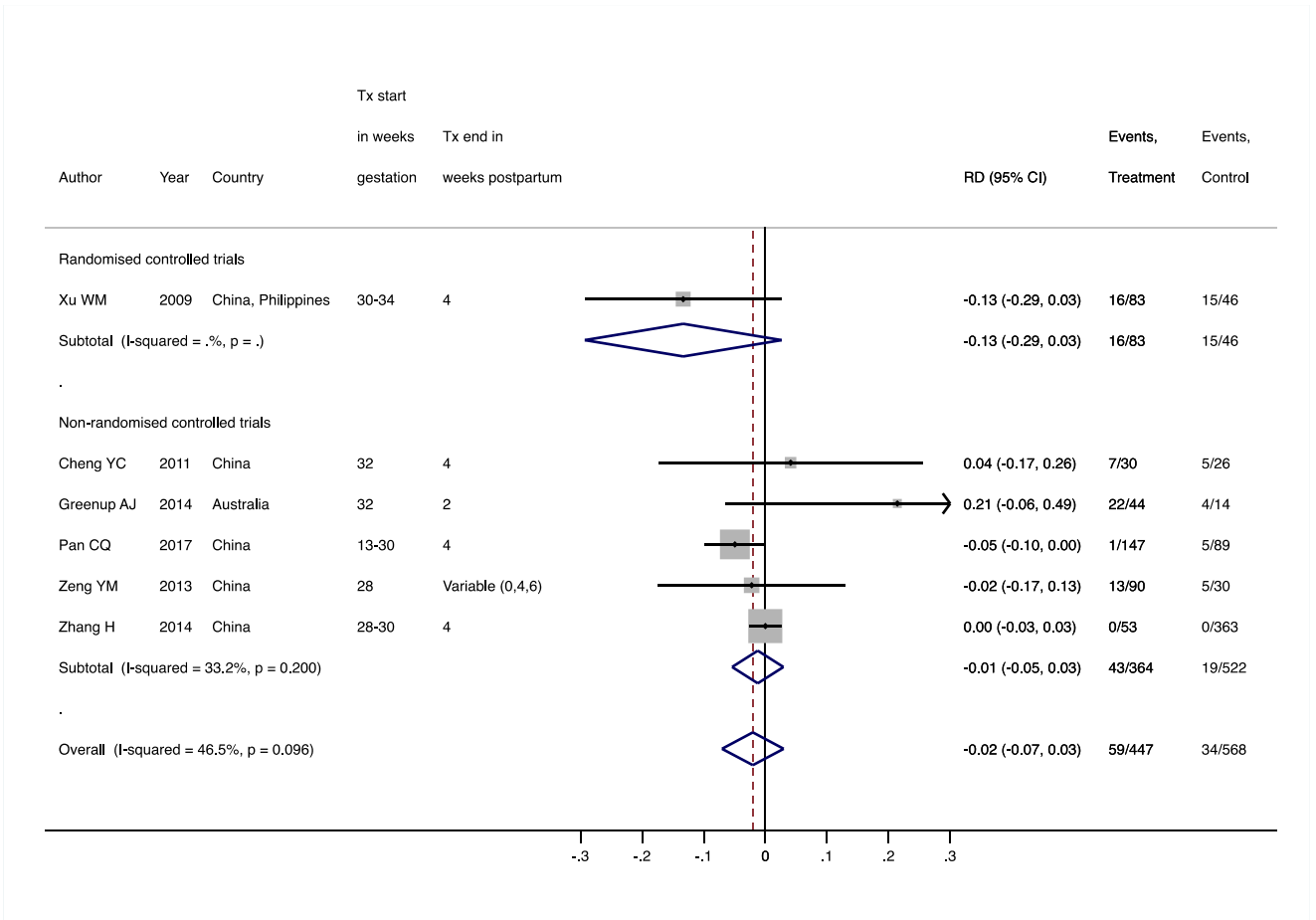
\*\* In Nguyen V, 2014, 18% (8/44) in the intervention group received TDF.

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

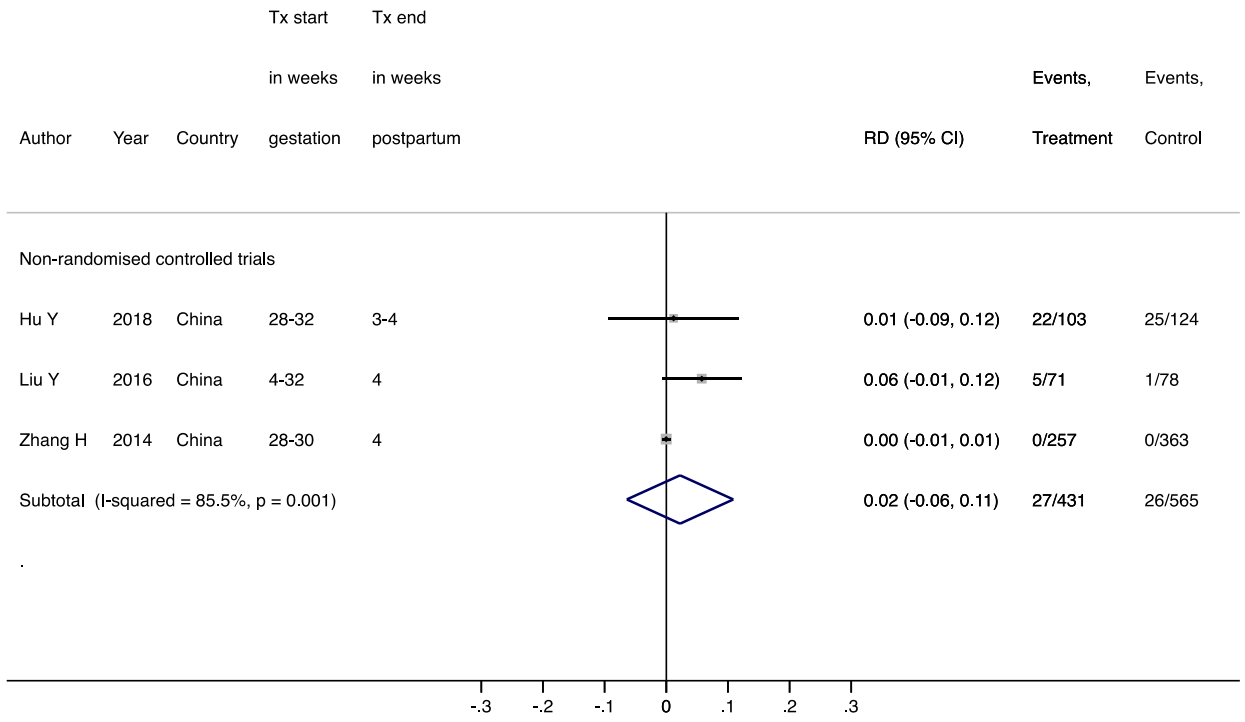




- **Figure: Forest plot for LAM 100-150 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation**



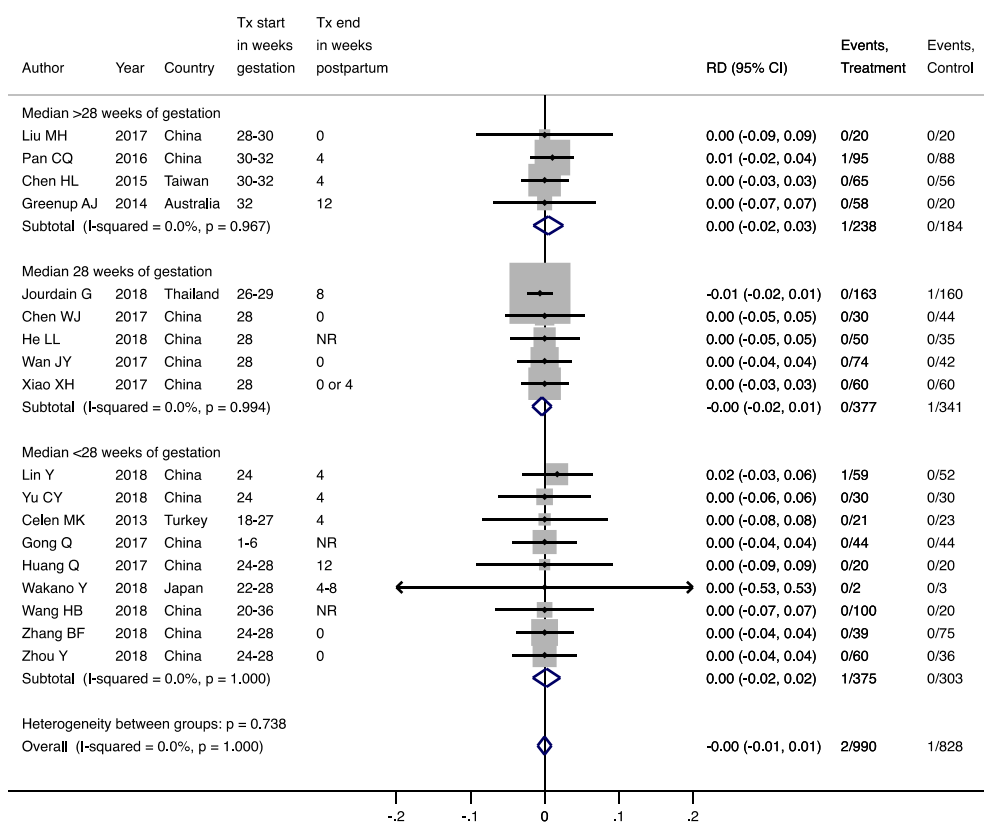
- **Figure: Forest plot for LdT 600 mg weighted risk difference of postpartum hepatitis flare after treatment discontinuation**



## Appendix W: Maternal and Infant Safety Subgroup Analysis

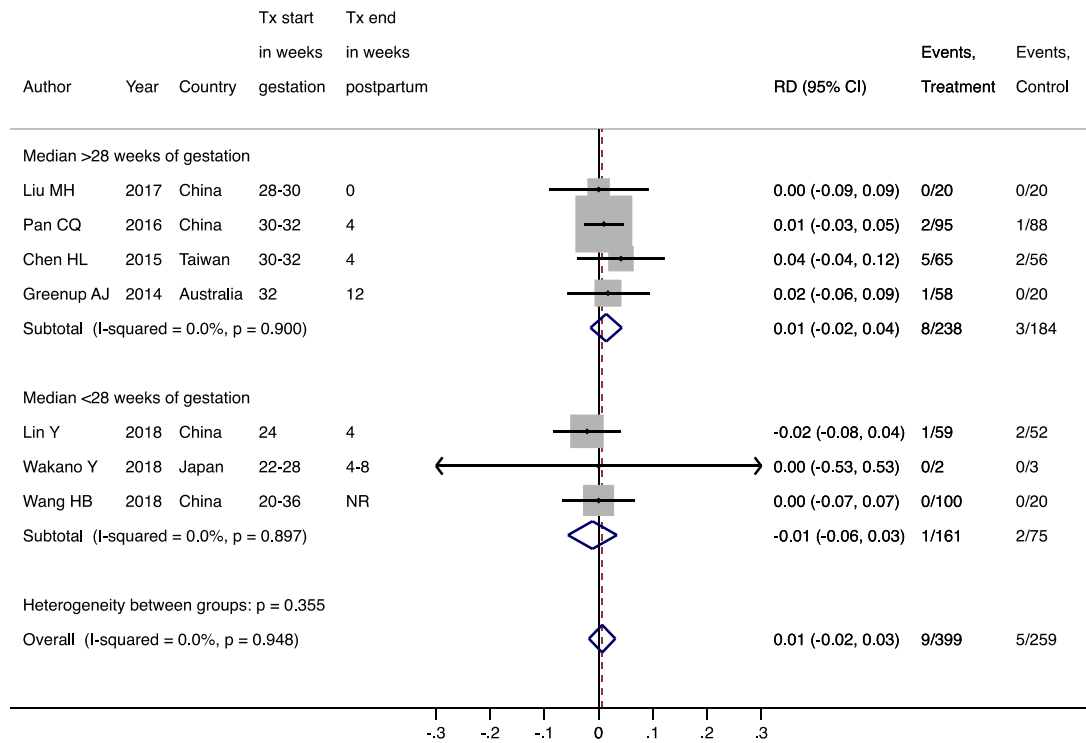
- **TDF 300 mg risk difference of neonatal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.738



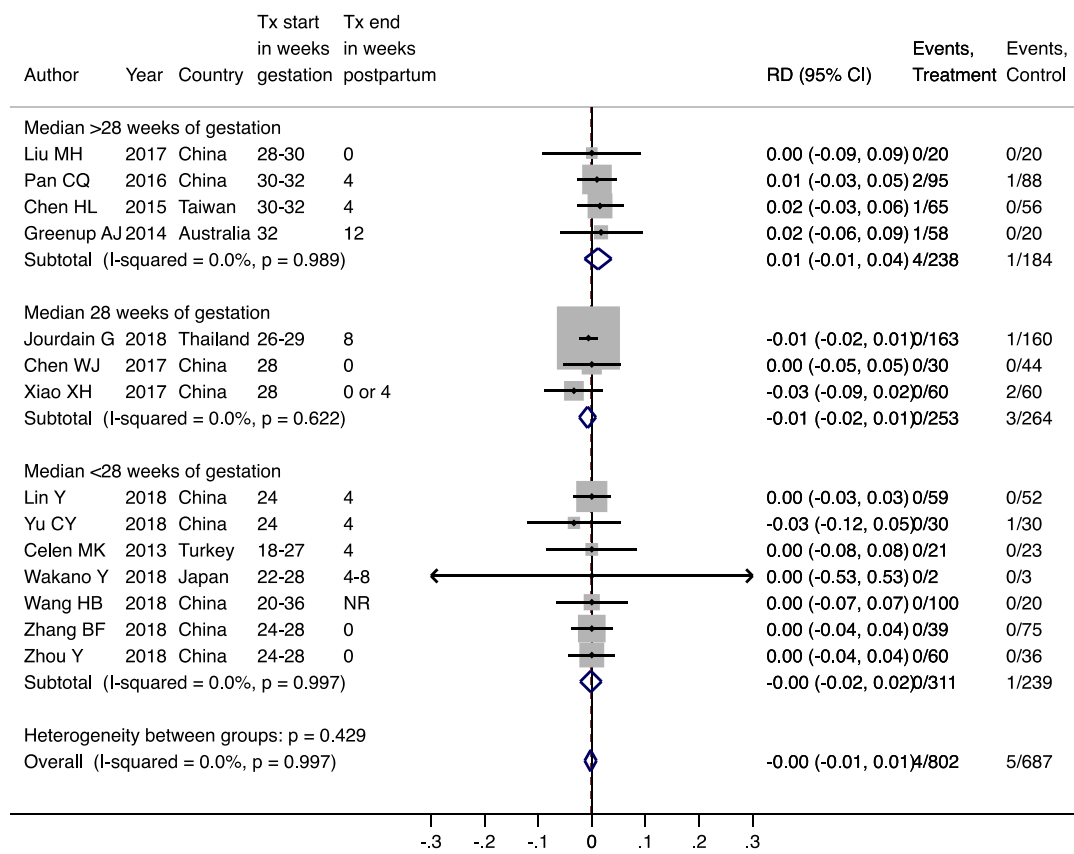
- **TDF 300 mg risk difference of preterm birth by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.355



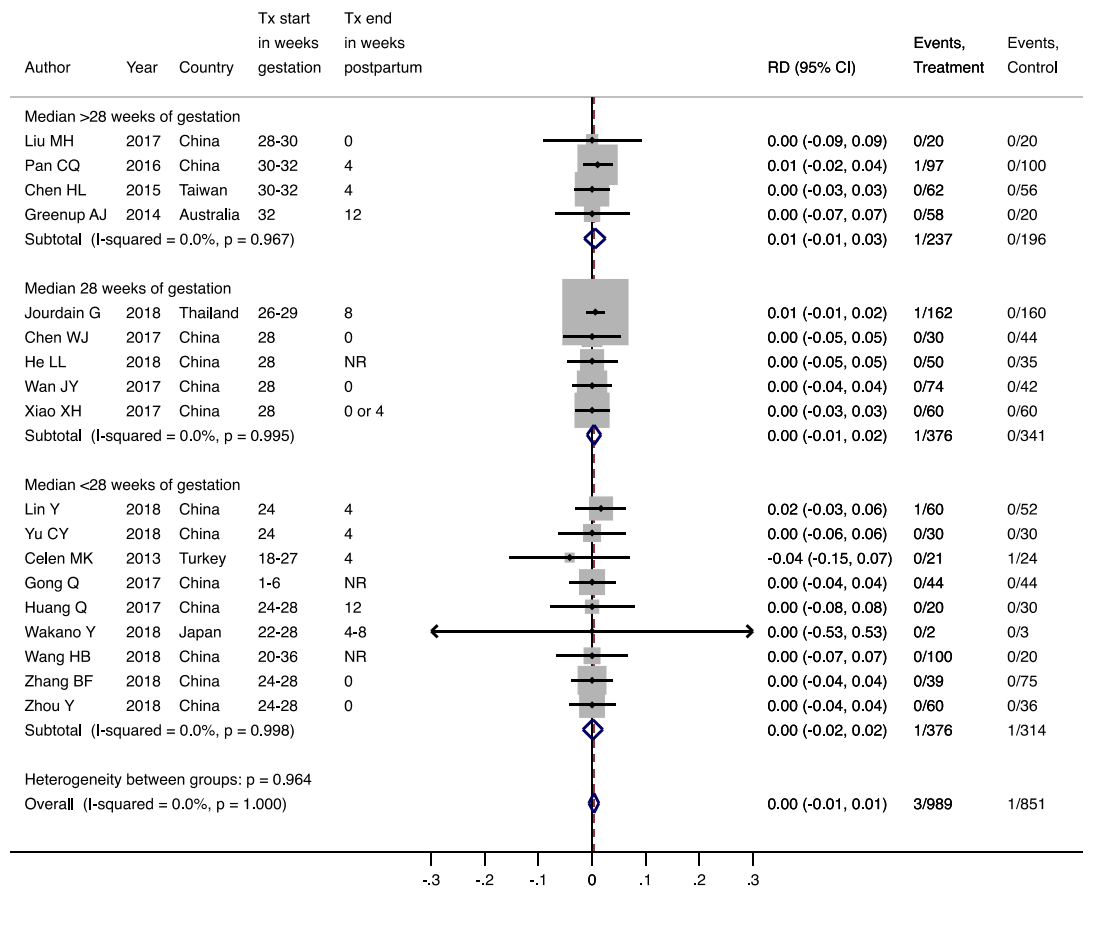
- **TDF 300 mg risk difference of congenital abnormalities by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.429



- **TDF 300 mg risk difference of foetal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.964



- **TDF 300 mg risk difference of postpartum hemorrhage by timing of treatment initiation**

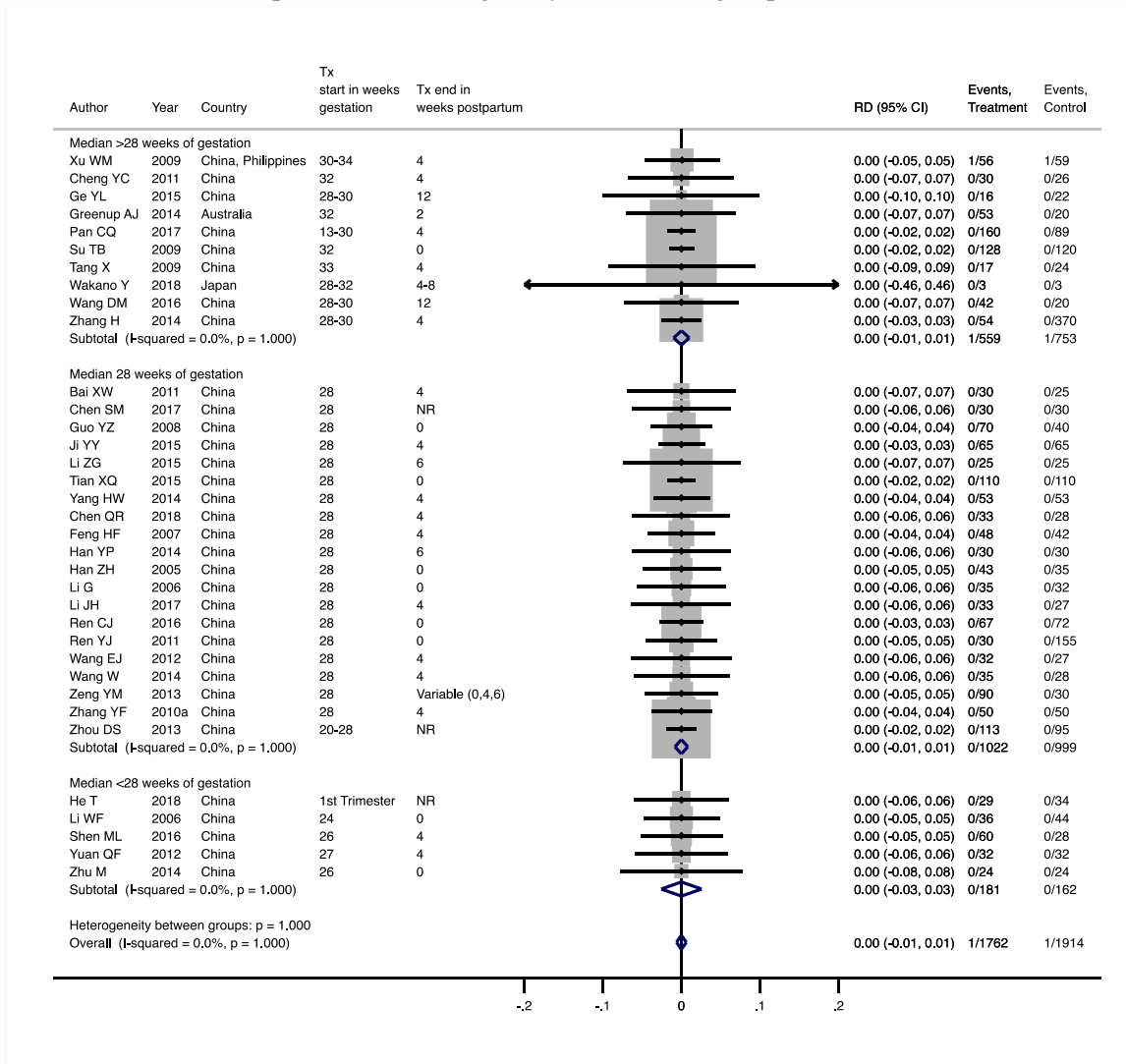
- Too few studies for subgroup analysis

- **TDF 300 mg risk difference of postpartum hepatitis flare by timing of treatment initiation**

- Too few studies for subgroup analysis

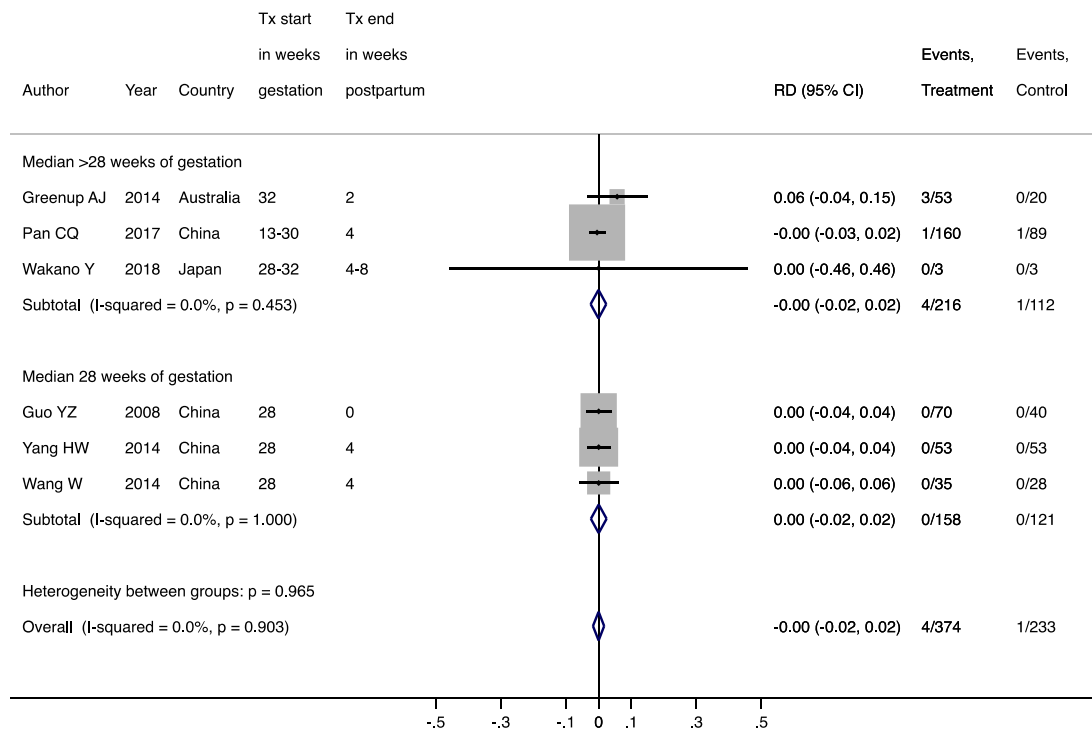
- **LAM 100-150 mg risk difference of neonatal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 1.000



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

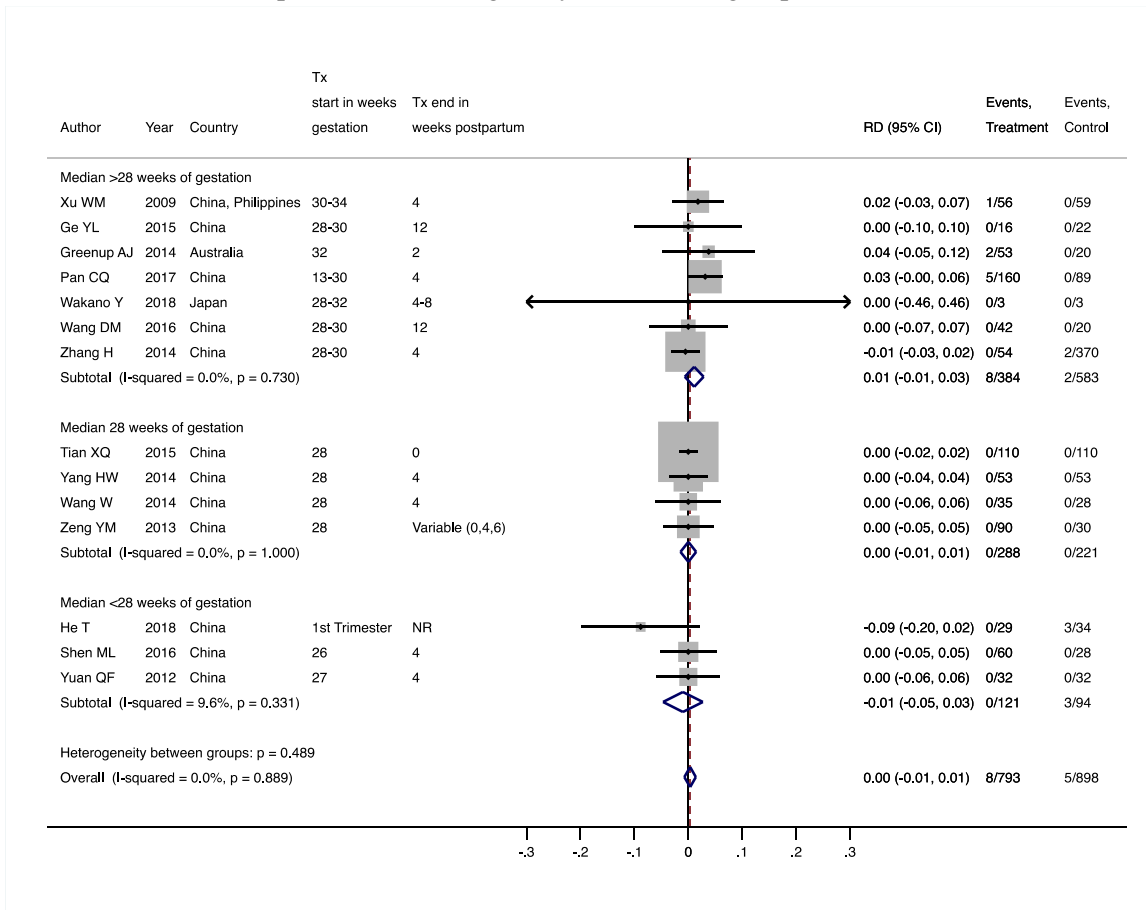
- The p-value for heterogeneity between subgroups was 0.965





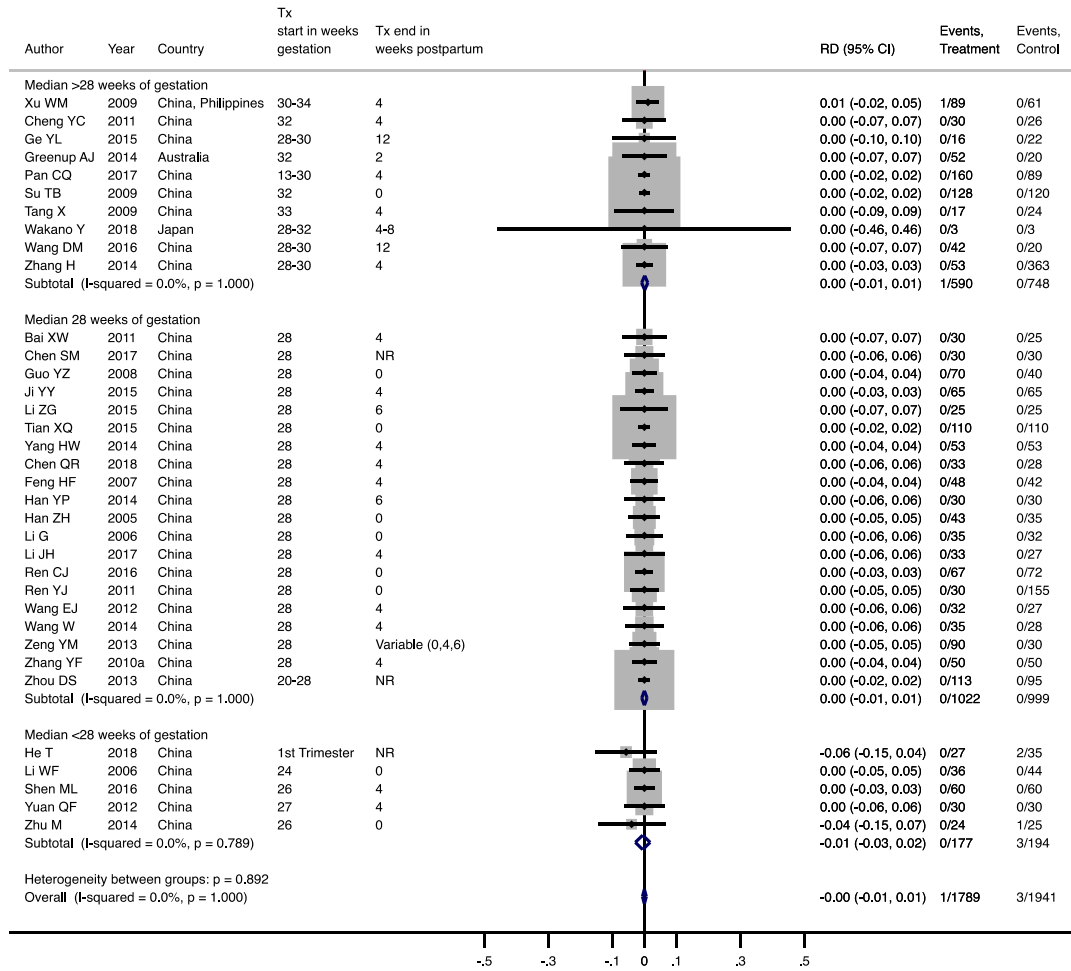
- **LAM 100-150 mg risk difference of congenital abnormalities by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.489



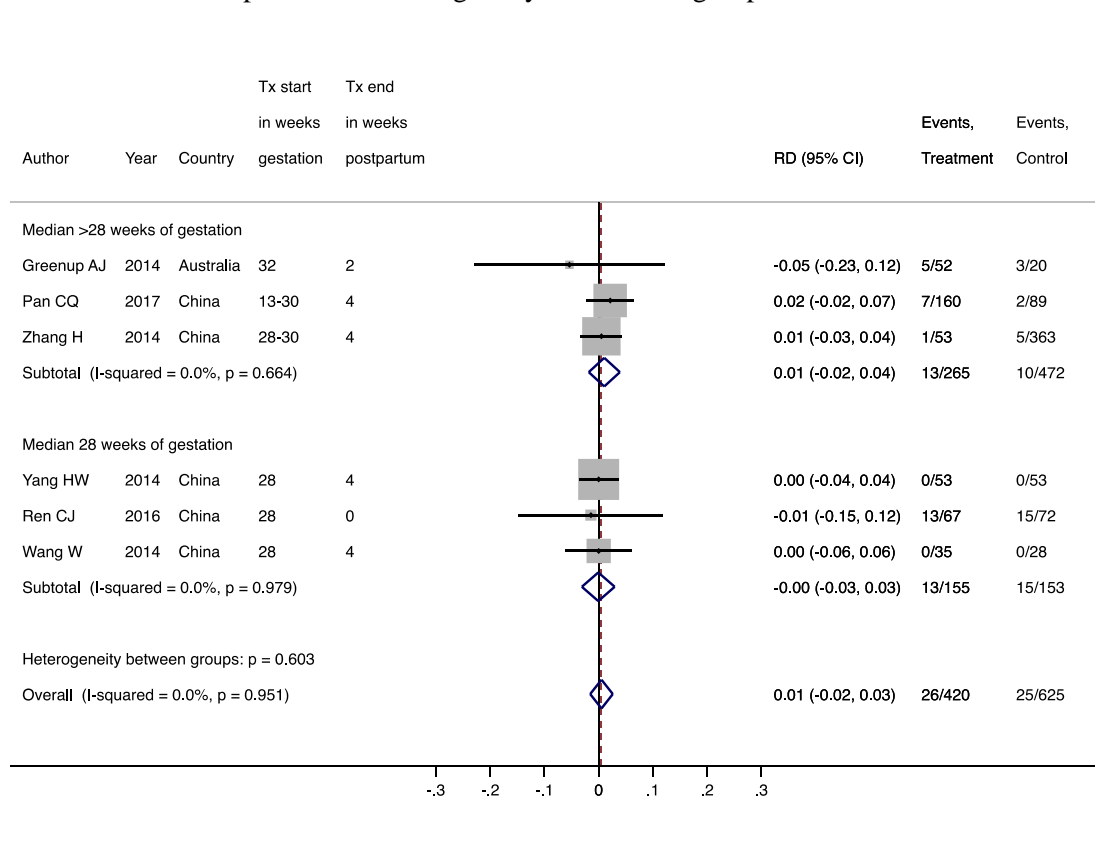
- **LAM 100-150 mg risk difference of foetal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.892



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

- The p-value for heterogeneity between subgroups was 0.603

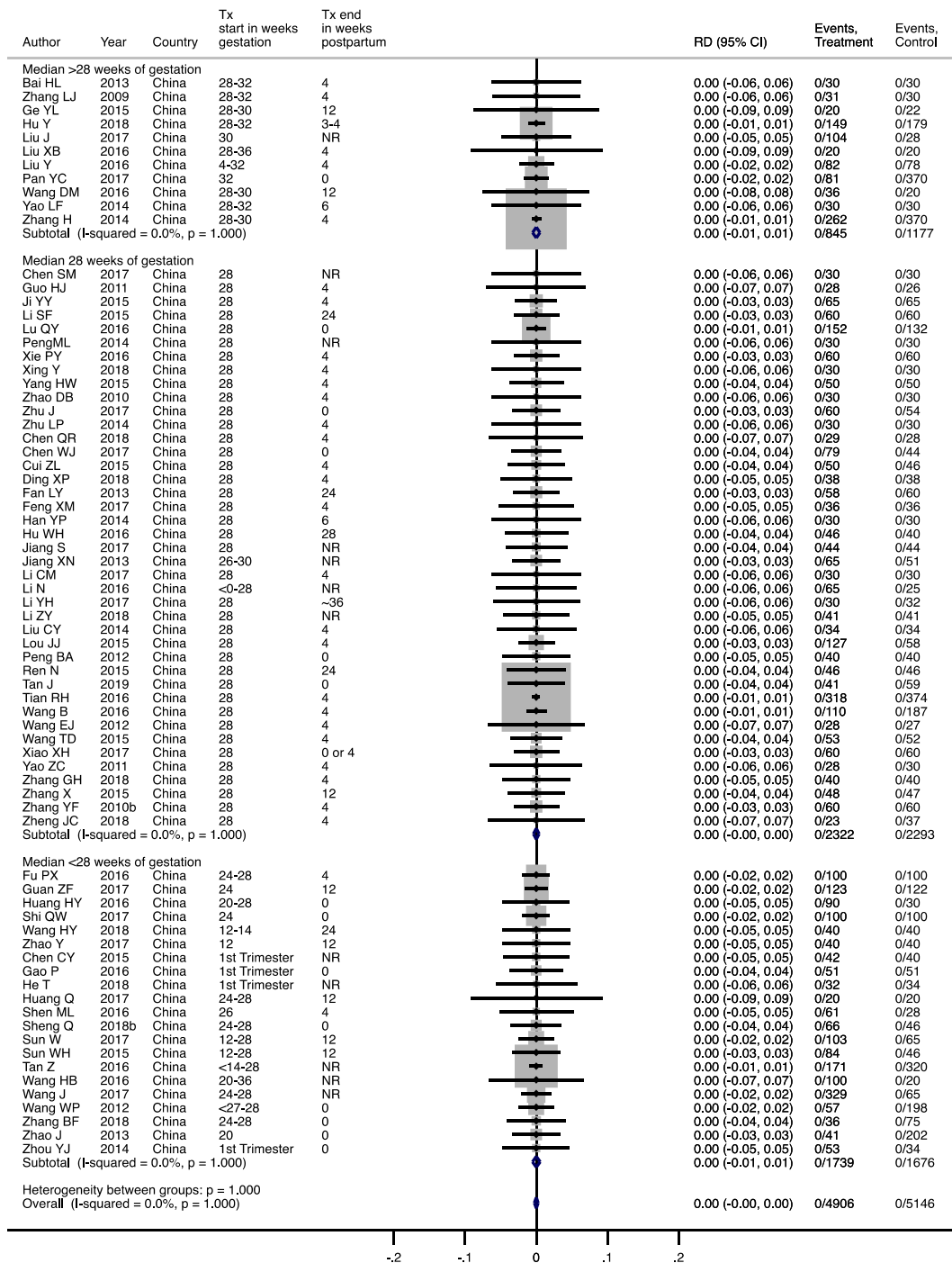


- **LAM 100-150 mg risk difference of postpartum flare by timing of treatment initiation**

- Too few studies for subgroup analysis

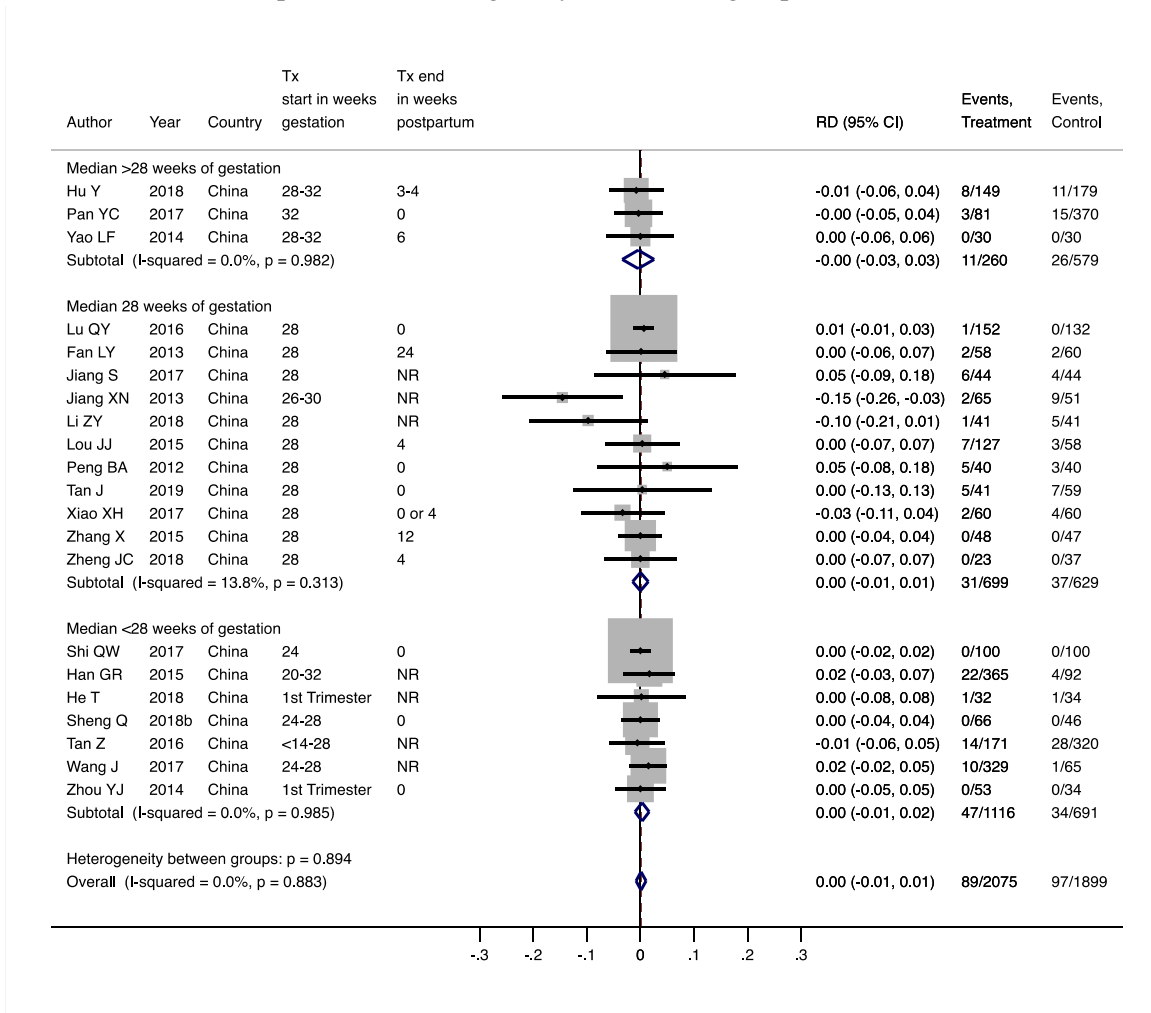
- **LdT 600 mg risk difference of neonatal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 1.000



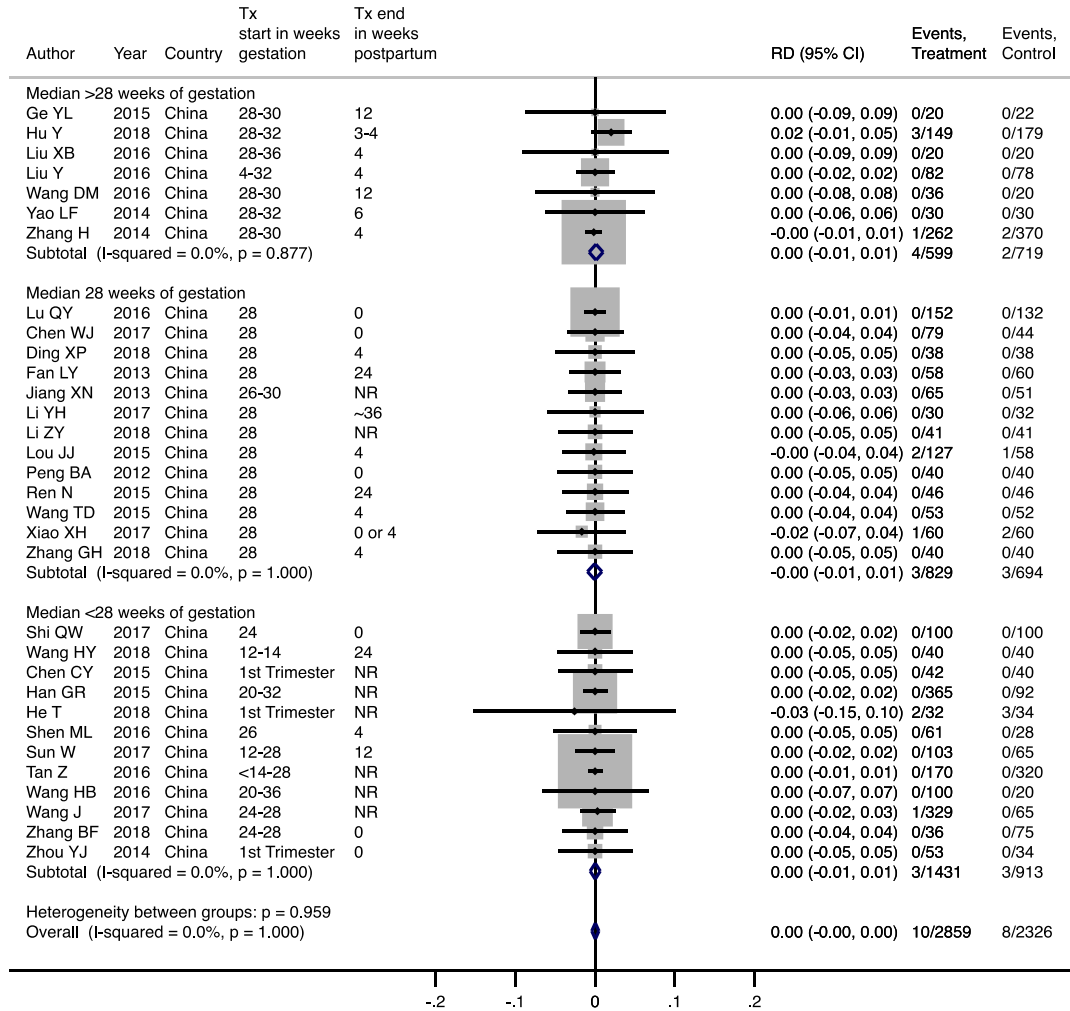
- **LdT 600 mg risk difference of preterm birth by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.894



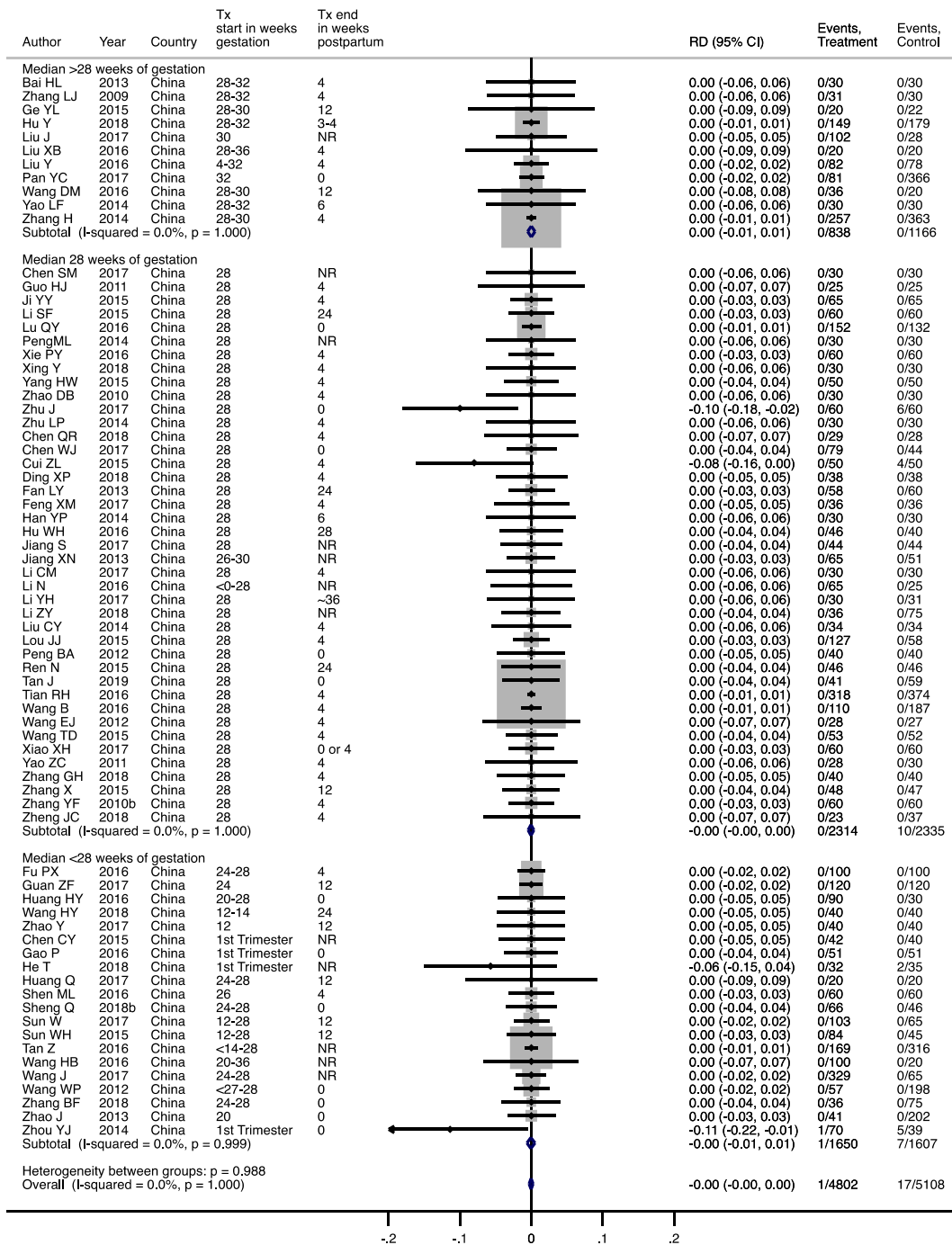
- **LdT 600 mg risk difference of congenital abnormalities by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.959



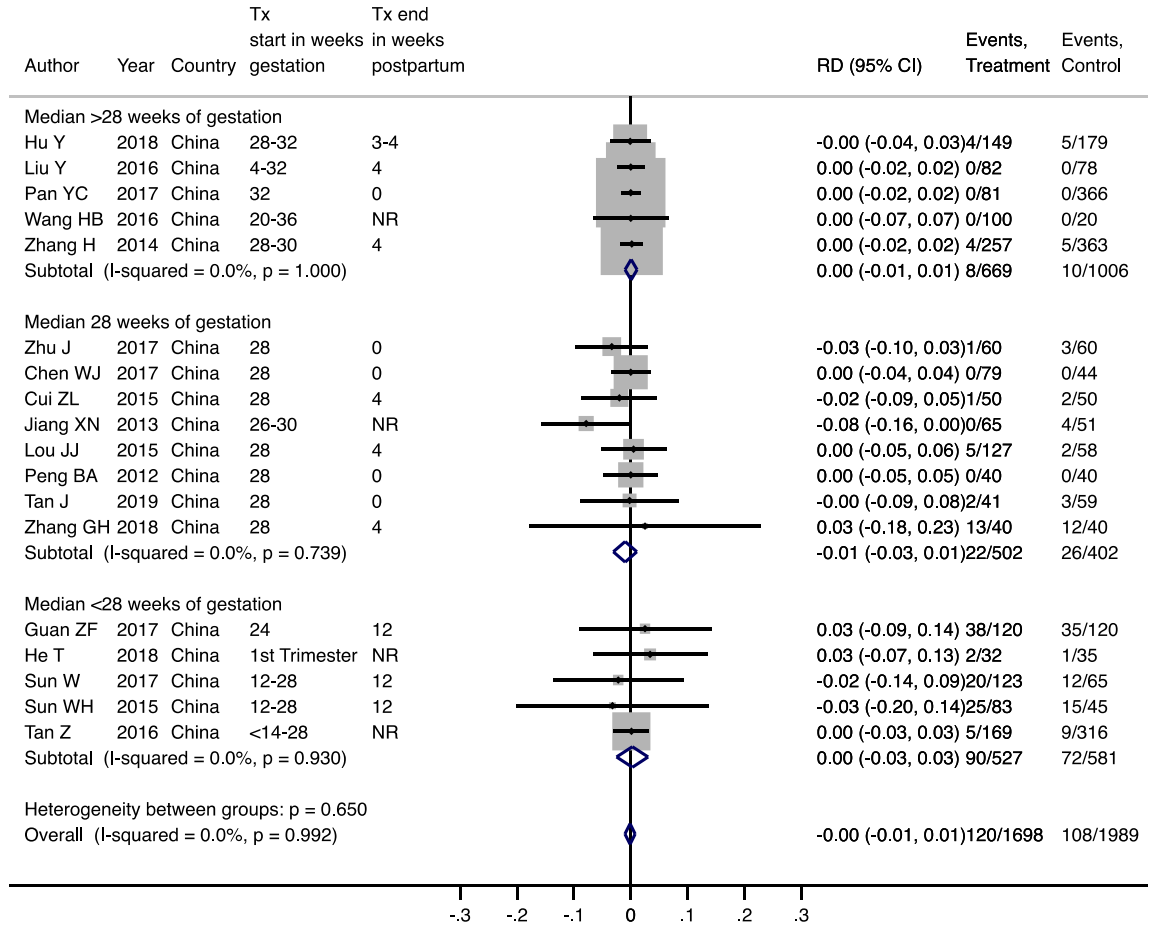
• **LdT 600 mg risk difference of foetal death by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.988



- **LdT 600 mg risk difference of postpartum hemorrhage by timing of treatment initiation**

- The p-value for heterogeneity between subgroups was 0.650



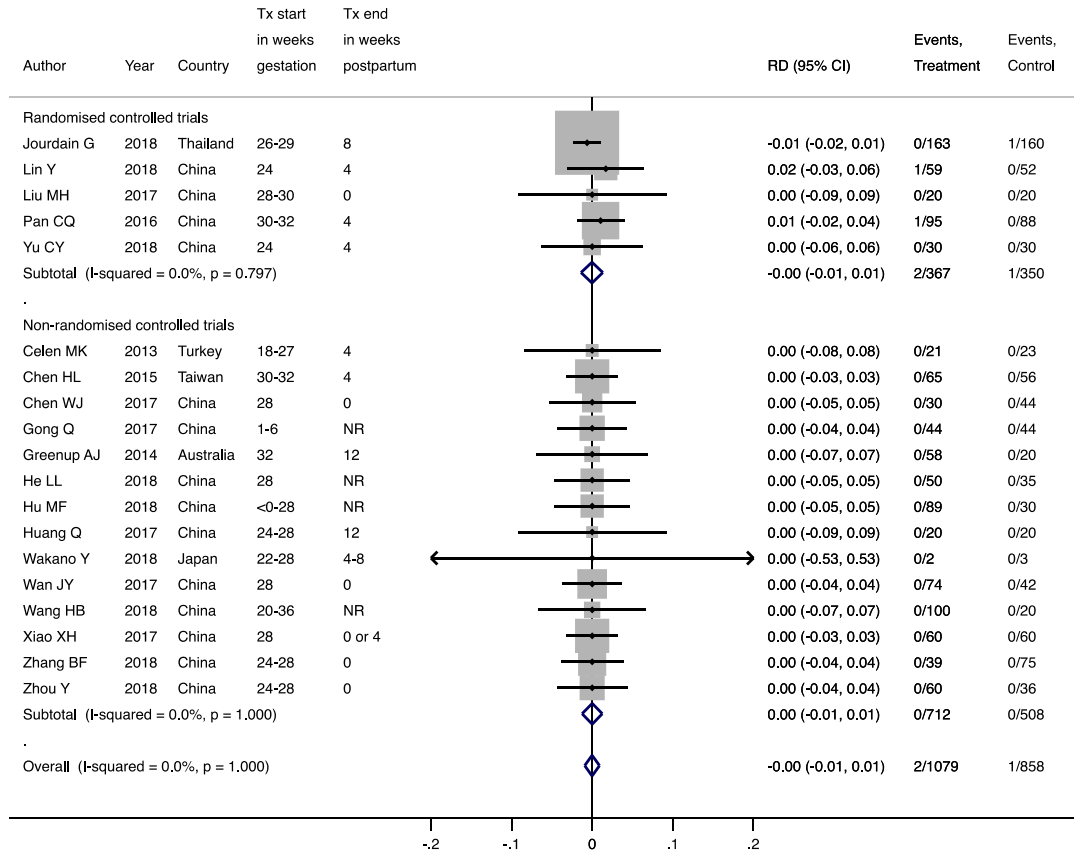
- **LdT 600 mg risk difference of postpartum flare by timing of treatment initiation**

- Not enough studies for subgroup analysis

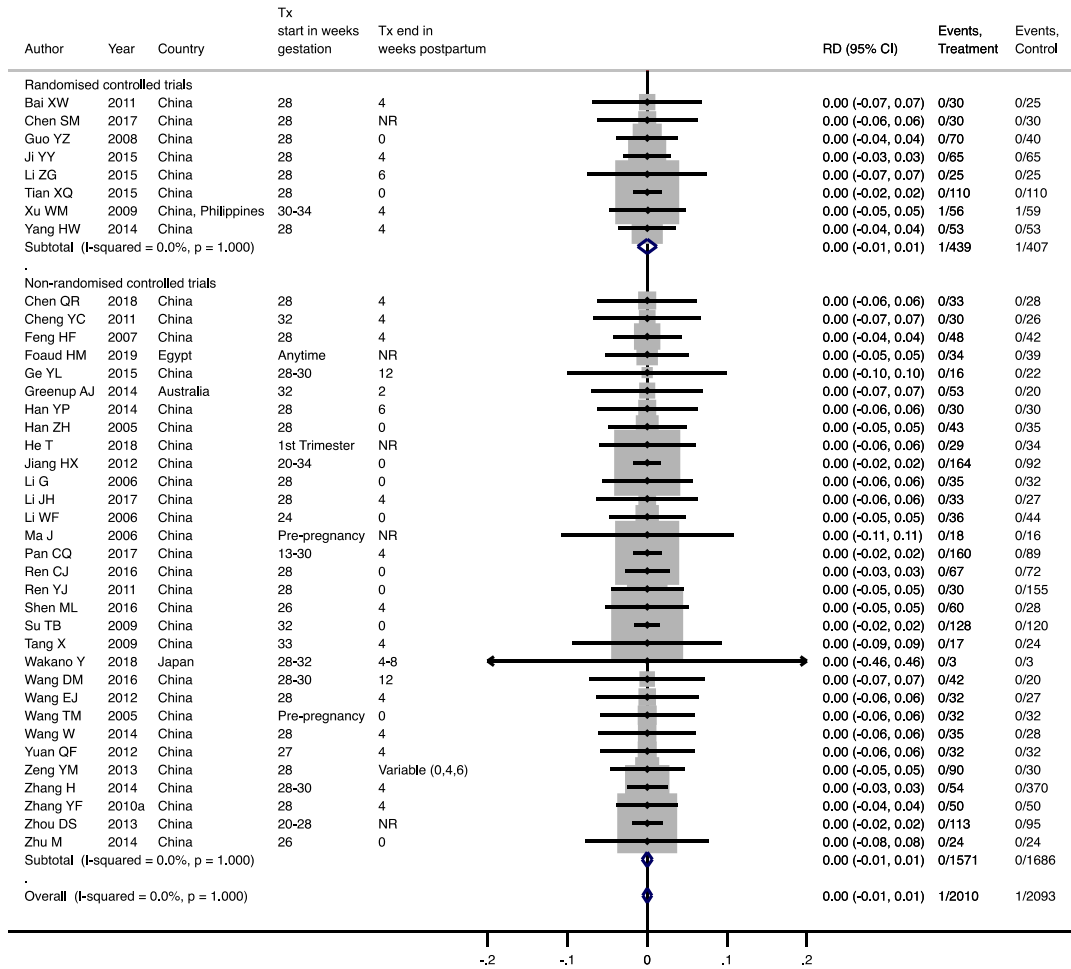


## Appendix X: Infant safety 1. Neonatal deaths

- **TDF 300 mg risk difference for neonatal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%



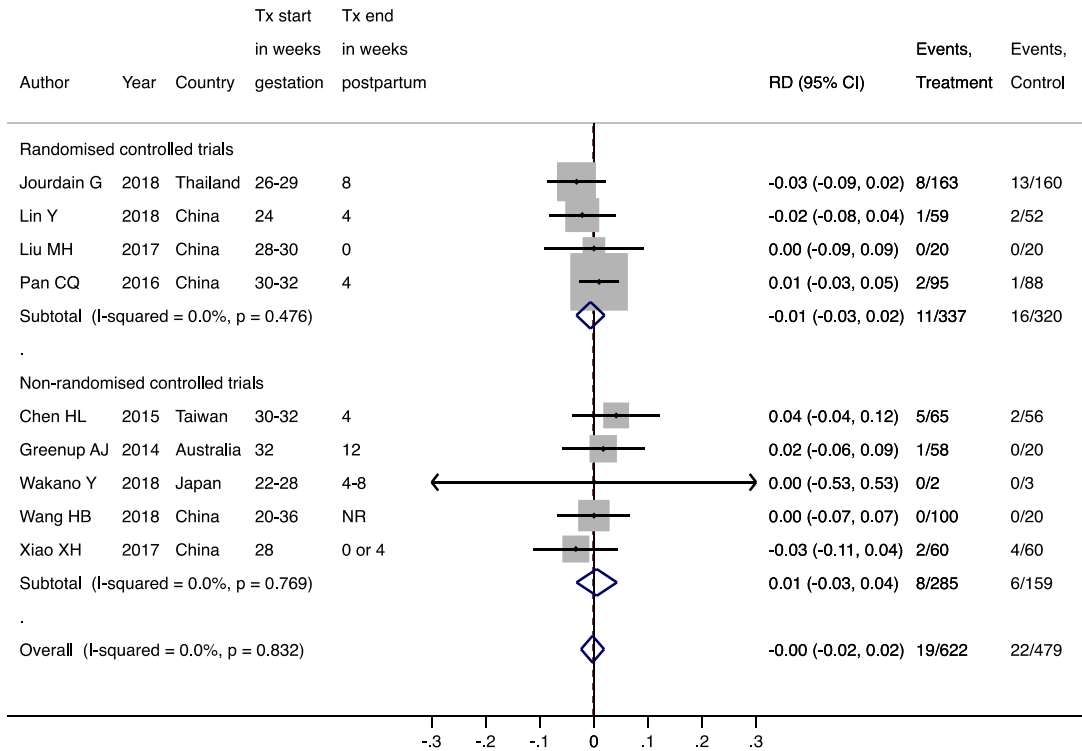
- **LAM 100-150 mg risk difference for neonatal death**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%





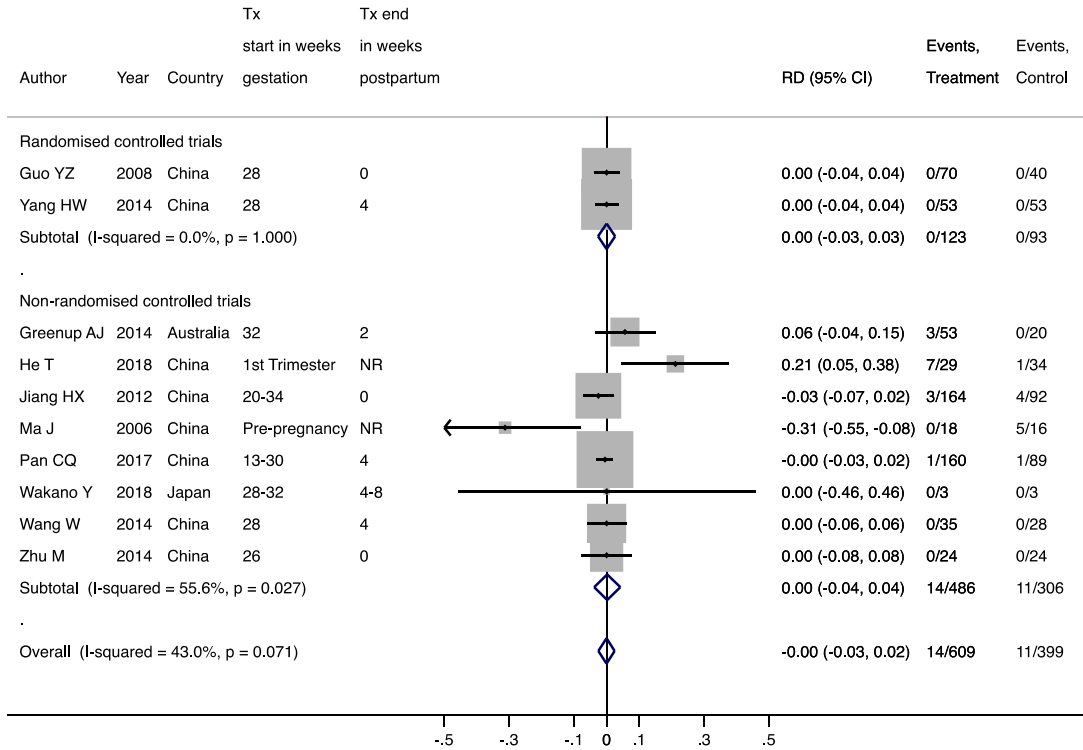
## Appendix Y: Infant safety 2. Preterm birth

- **TDF 300 mg risk difference for preterm birth**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.02 – 0.02).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%



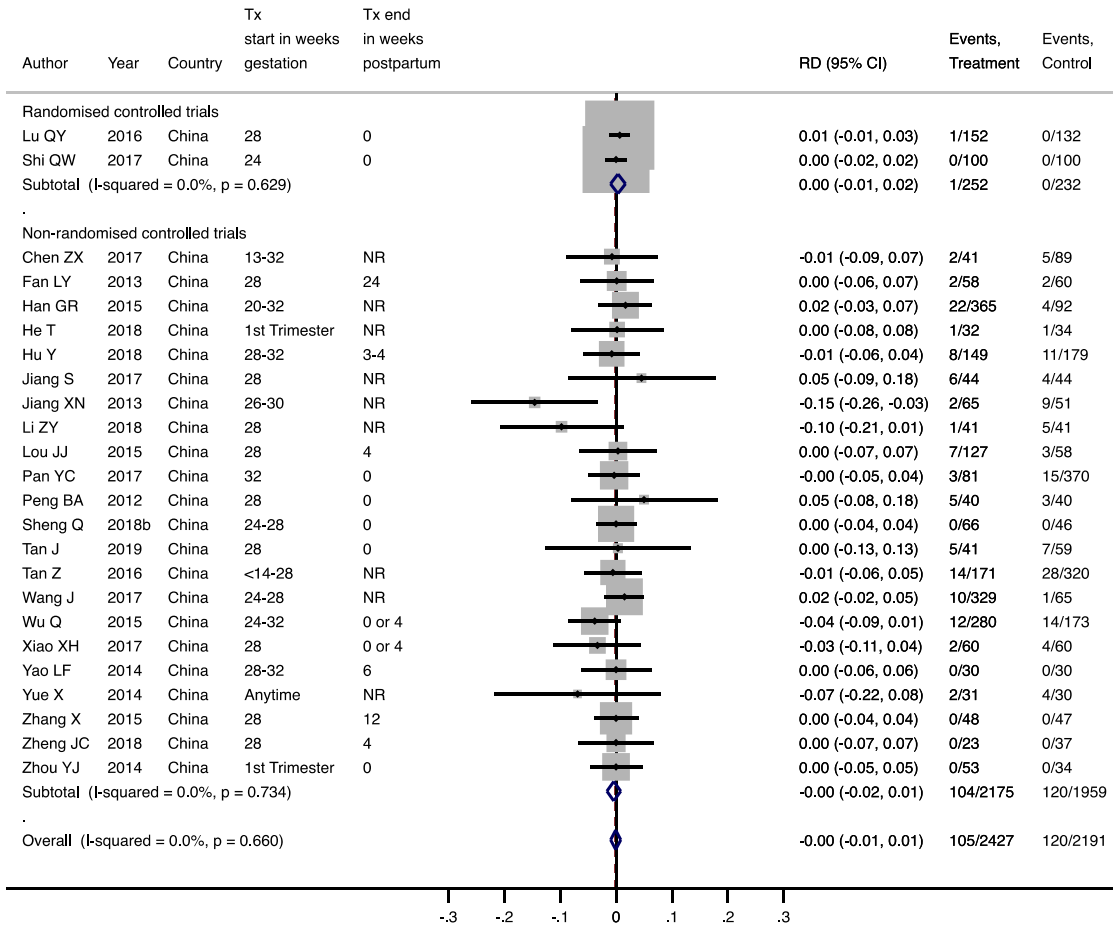
- **LAM 100-150 mg risk difference for preterm birth**

- Weighted pooled risk difference: 0.00 (95%CI: -0.03 – 0.02).
- $I^2$  statistic overall = 43.0%
  - $I^2$  statistic RCTs = not enough studies
  - $I^2$  statistic non-RCTs = 55.6%



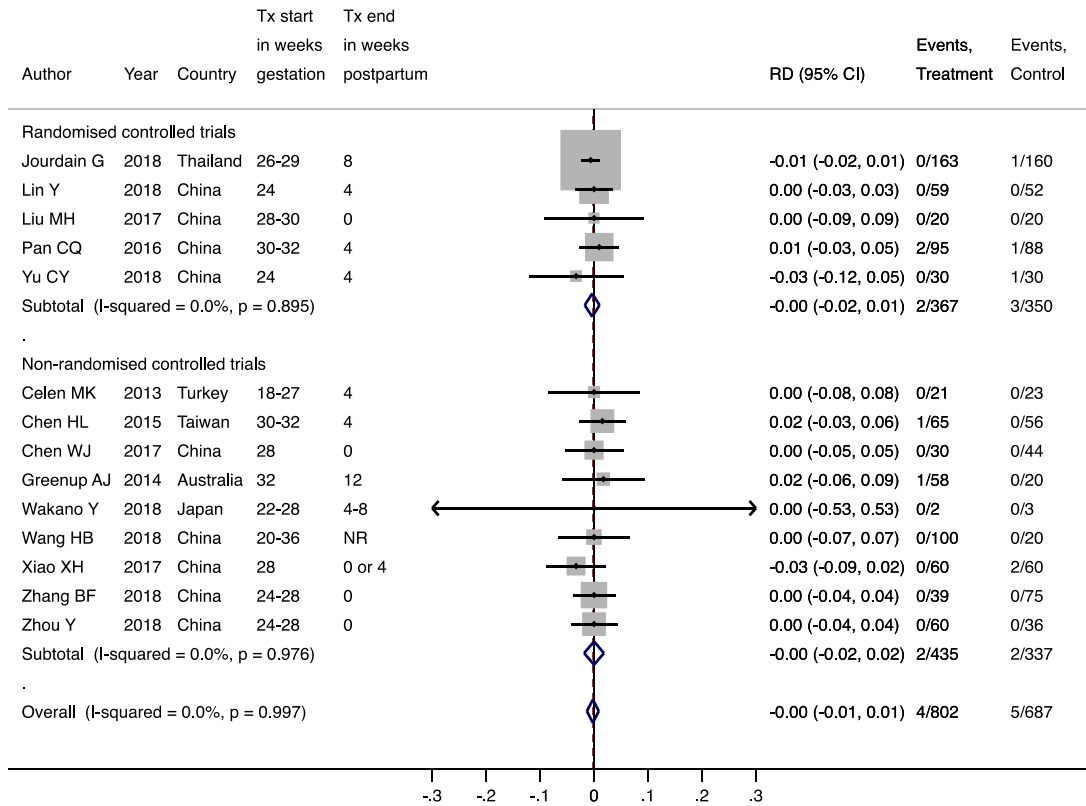
- **LdT 600 mg risk difference for preterm birth**

- Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
- $I^2$  statistic overall = 0.0%
  - $I^2$  statistic RCTs = not enough studies
  - $I^2$  statistic non-RCTs = 0.0%

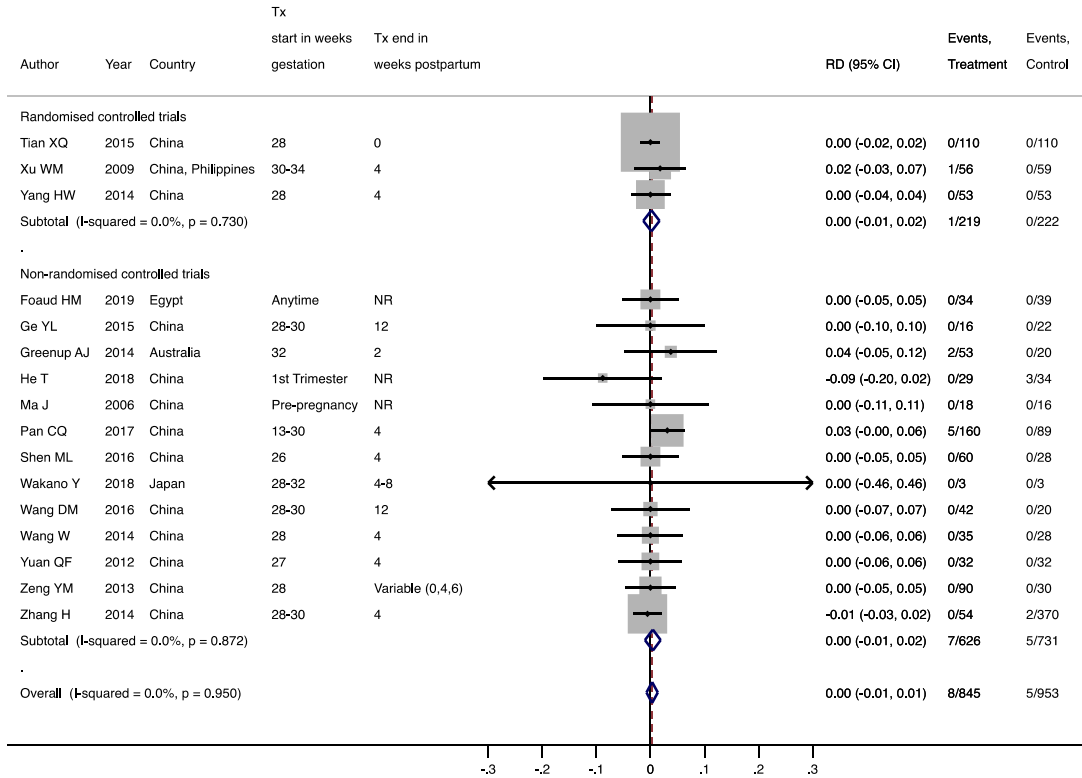


## Appendix Z: Infant safety 3. Congenital abnormalities

- **TDF 300 mg risk difference for congenital abnormalities**
  - Weighted pooled risk difference: -0.00 (95% CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%

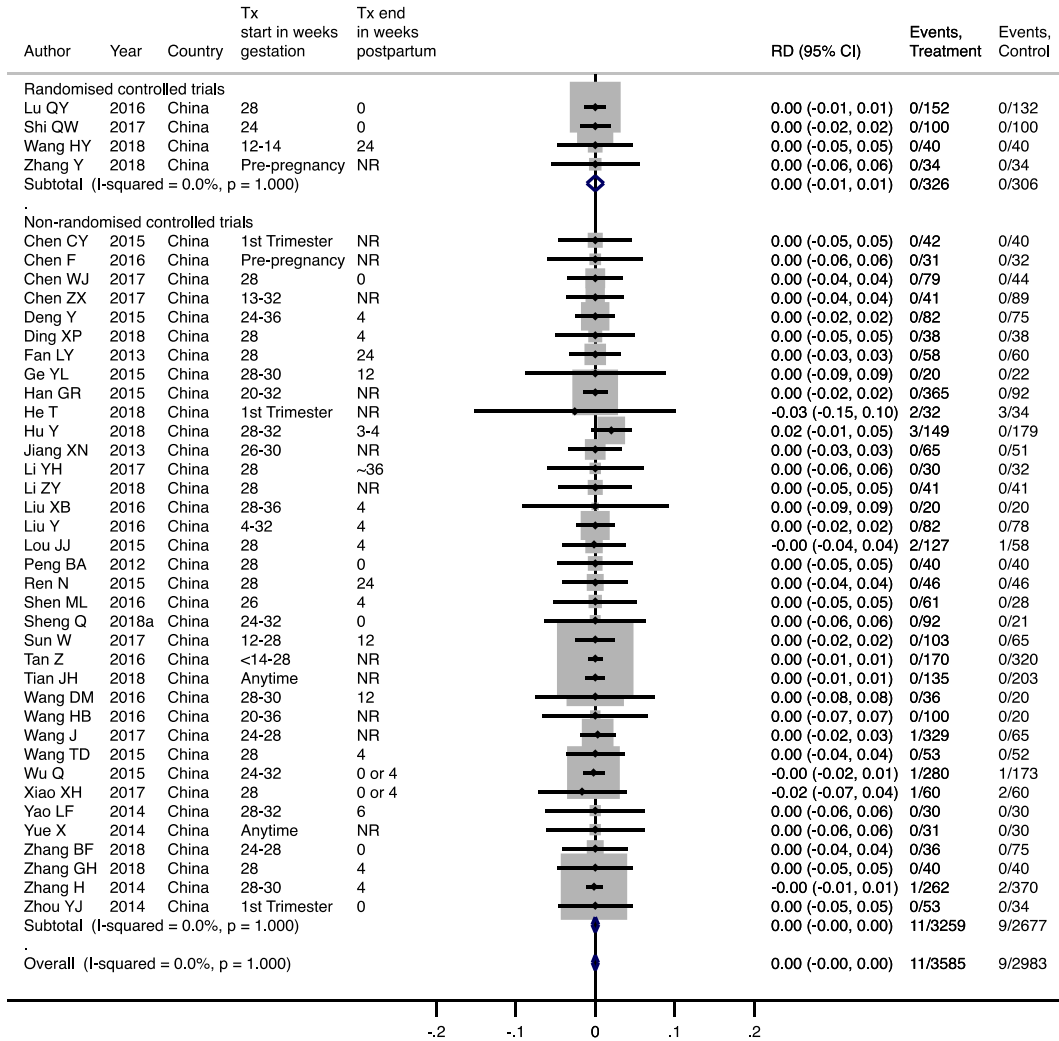


- **LAM 100-150 mg risk difference for congenital abnormalities**
  - Weighted pooled risk difference: 0.00 (95%CI: -0.01 – 0.01).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%





- **LdT 600 mg risk difference of congenital abnormalities**
  - Weighted pooled risk difference: 0.00 (95% CI: -0.00 – 0.00).
  - $I^2$  statistic overall = 0.0%
    - $I^2$  statistic RCTs = 0.0%
    - $I^2$  statistic non-RCTs = 0.0%



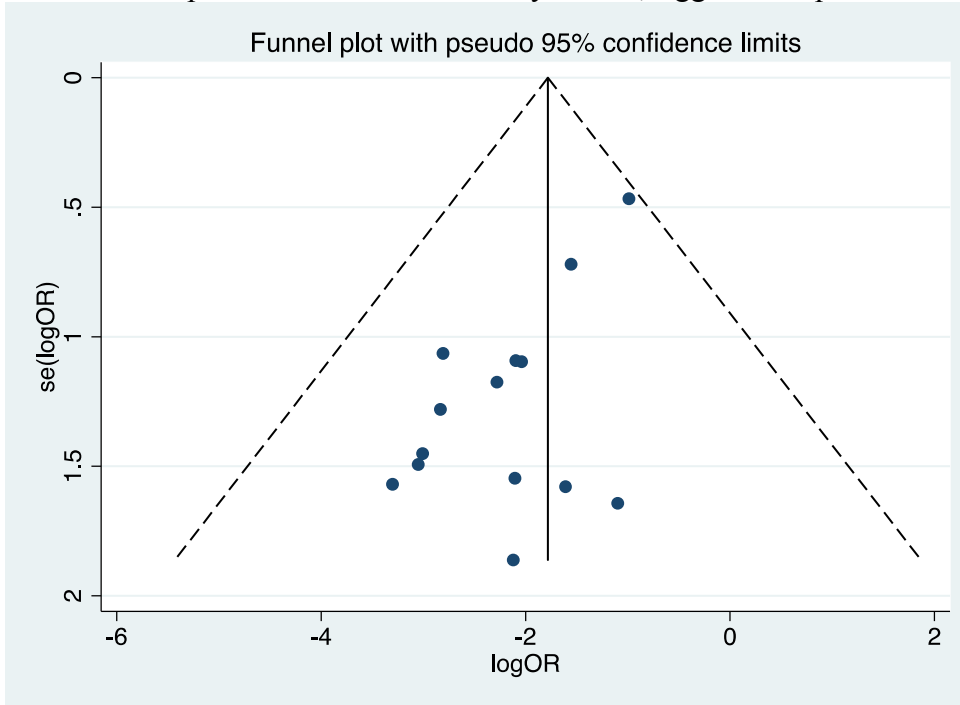
## Appendix AA: Publication Bias Assessment (Funnel Plots)

Efficacy (HBsAg)

TDF 300 mg

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

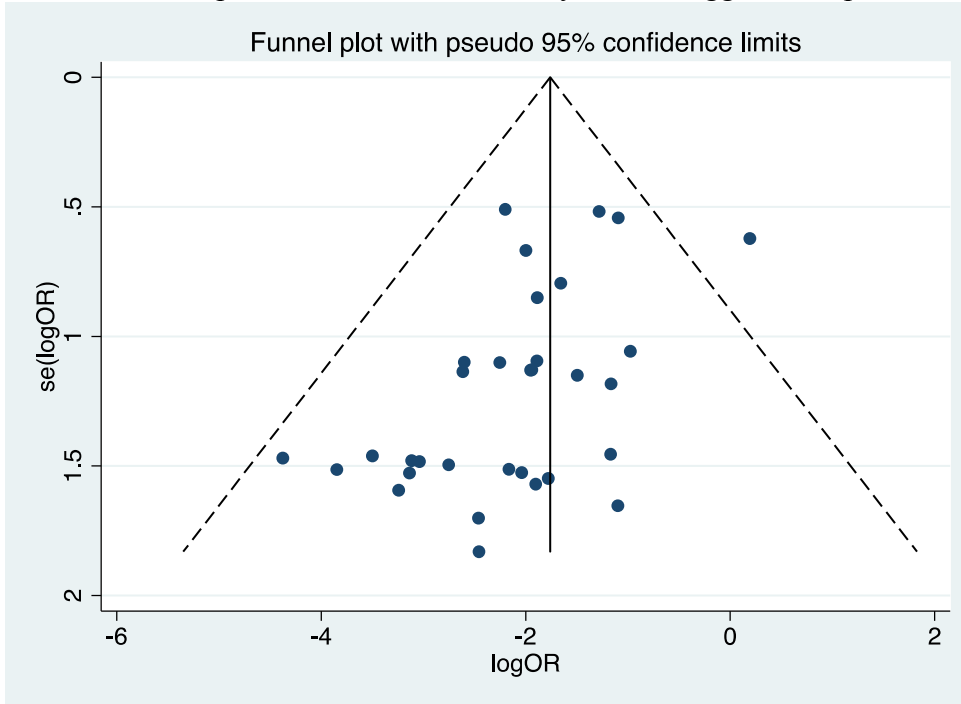
- Possible publication bias/small study effects, Egger's test p-value=0.002



LAM 100-150 mg

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

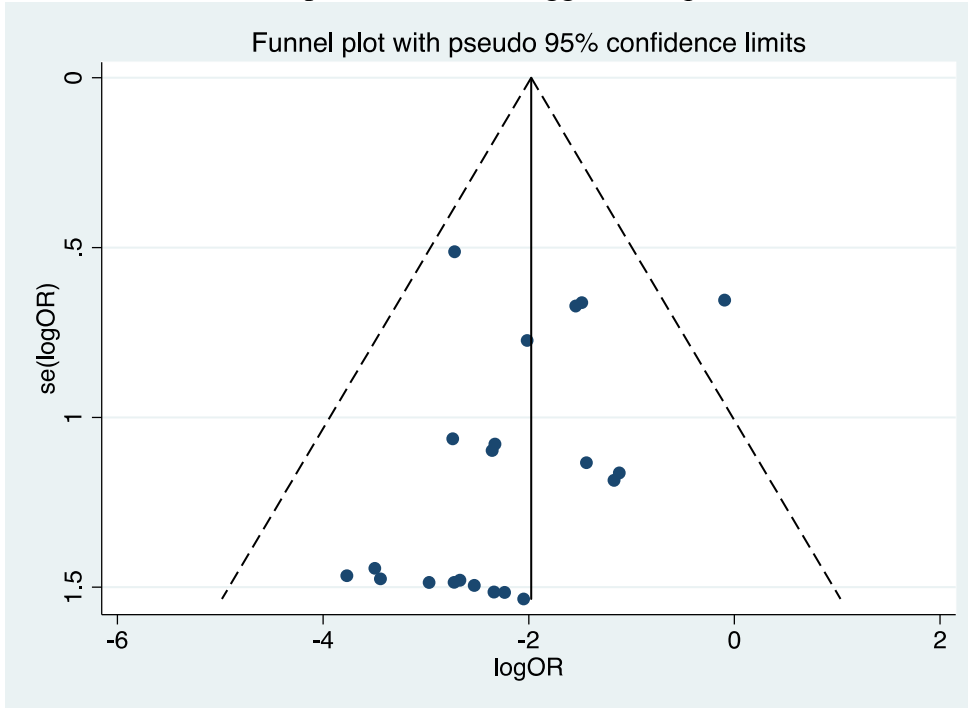
- Possible publication bias/small study effects, Egger's test p-value=0.002



LdT 600 mg

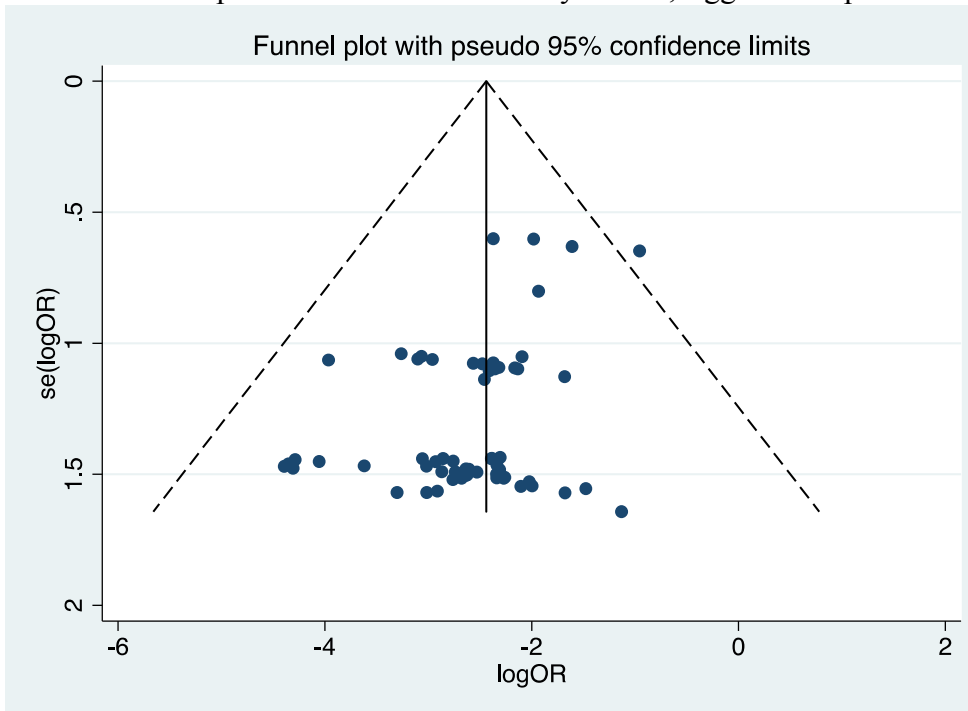
**MTCT indicated by HBsAg positivity at 6-12 months, RCTs**

- 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

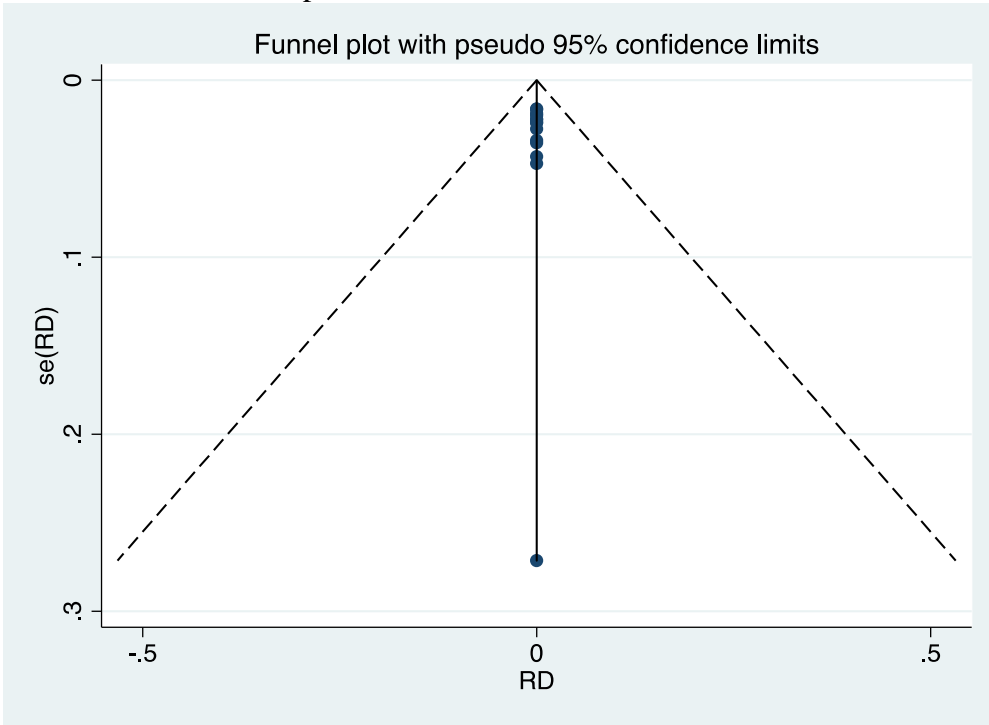


Safety outcomes

TDF 300 mg

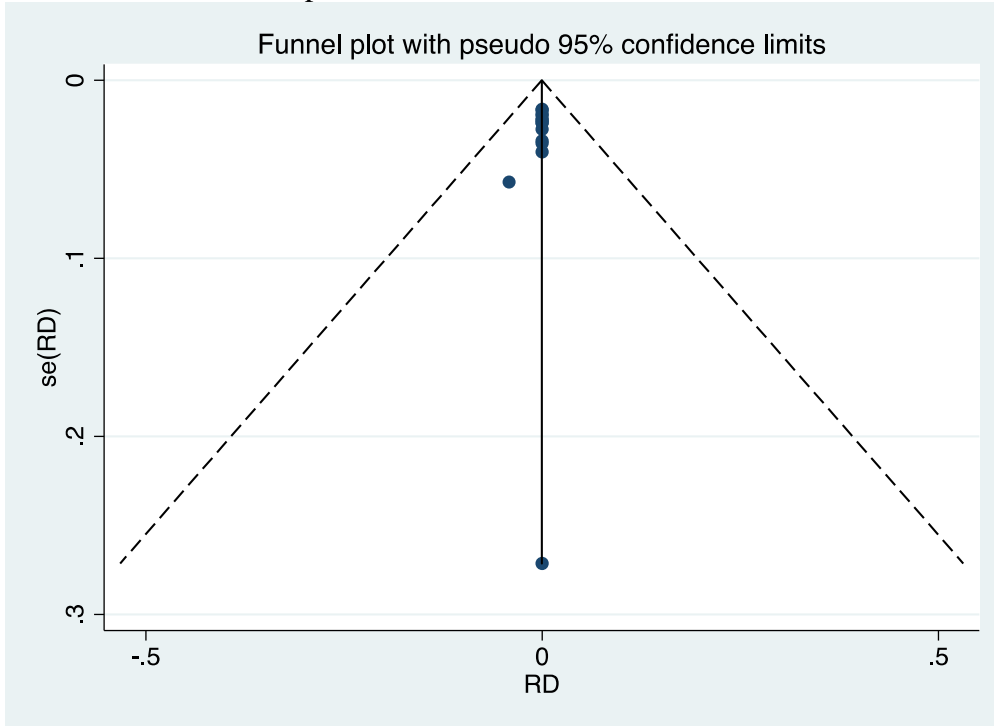
***Neonatal deaths, non-RCTs***

- No evidence of publication bias



***Fetal deaths, non-RCTs***

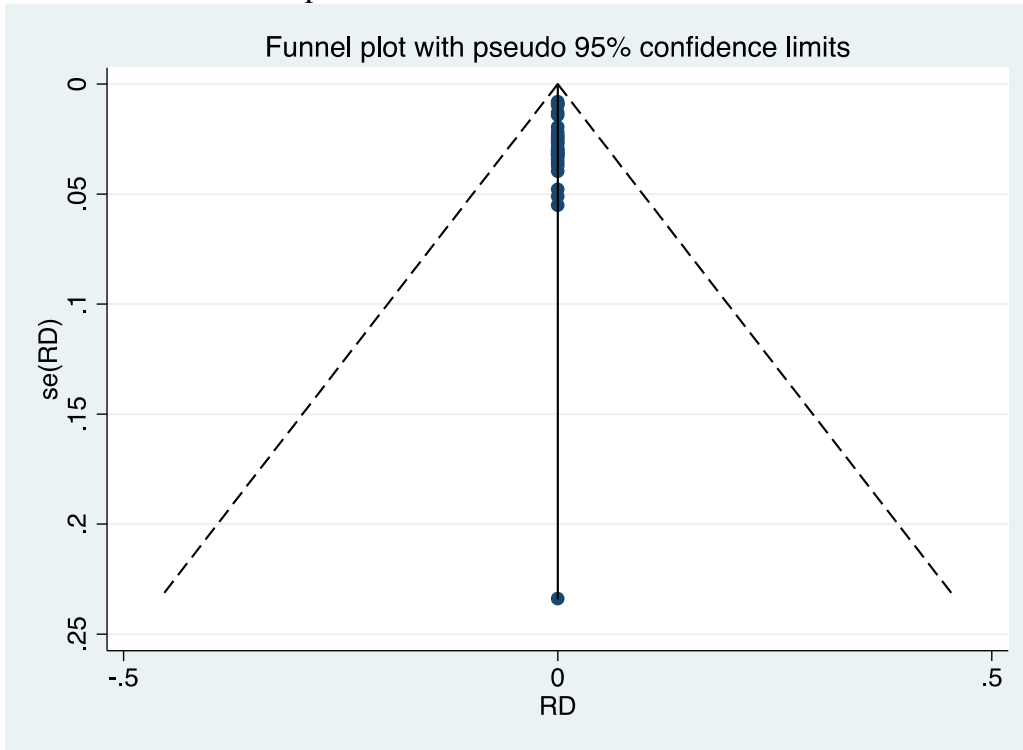
- No evidence of publication bias



LAM 100-150 mg

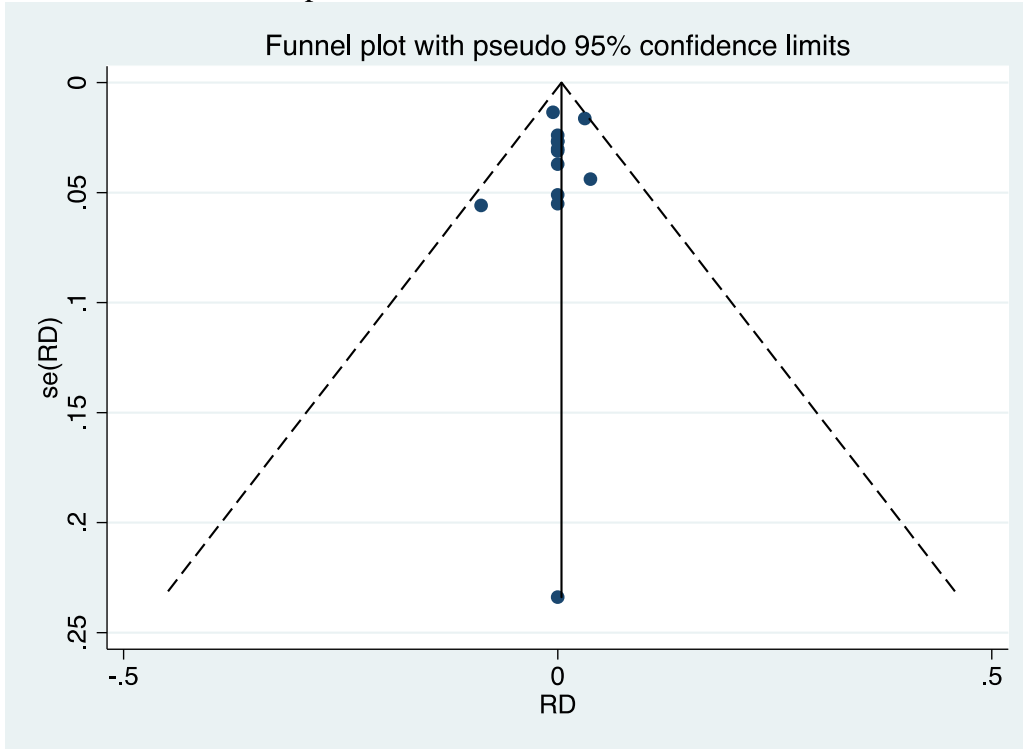
***Neonatal deaths, non-RCTs***

- No evidence of publication bias



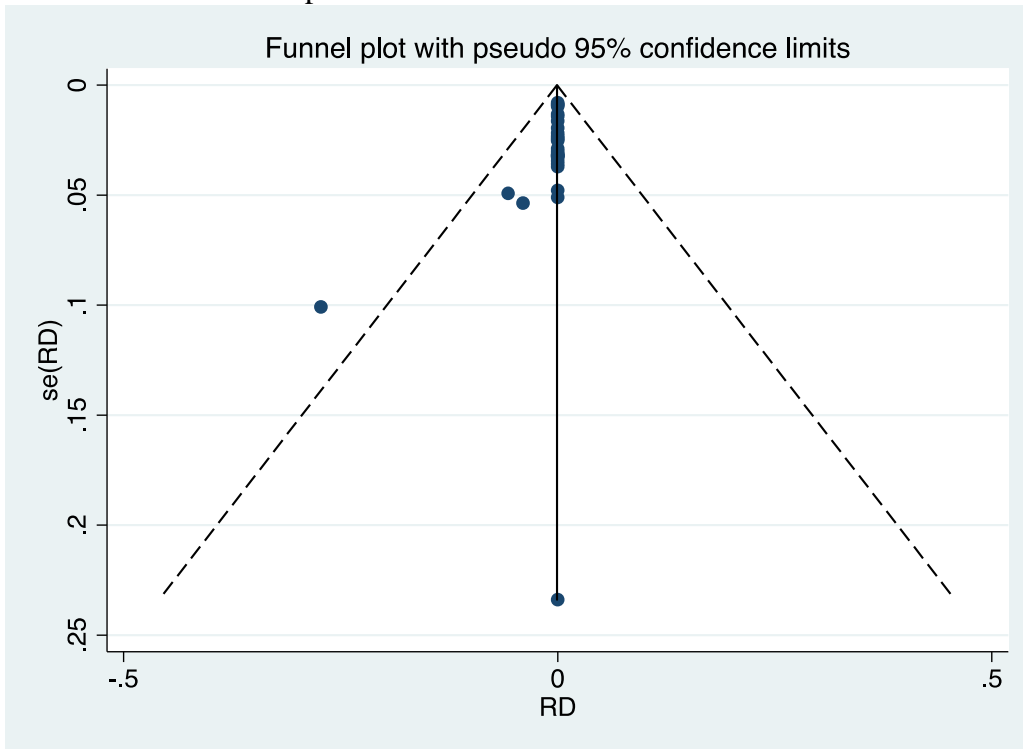
***Congenital abnormalities, non-RCTs***

- No evidence of publication bias



***Fetal deaths, non-RCTs***

- No evidence of publication bias

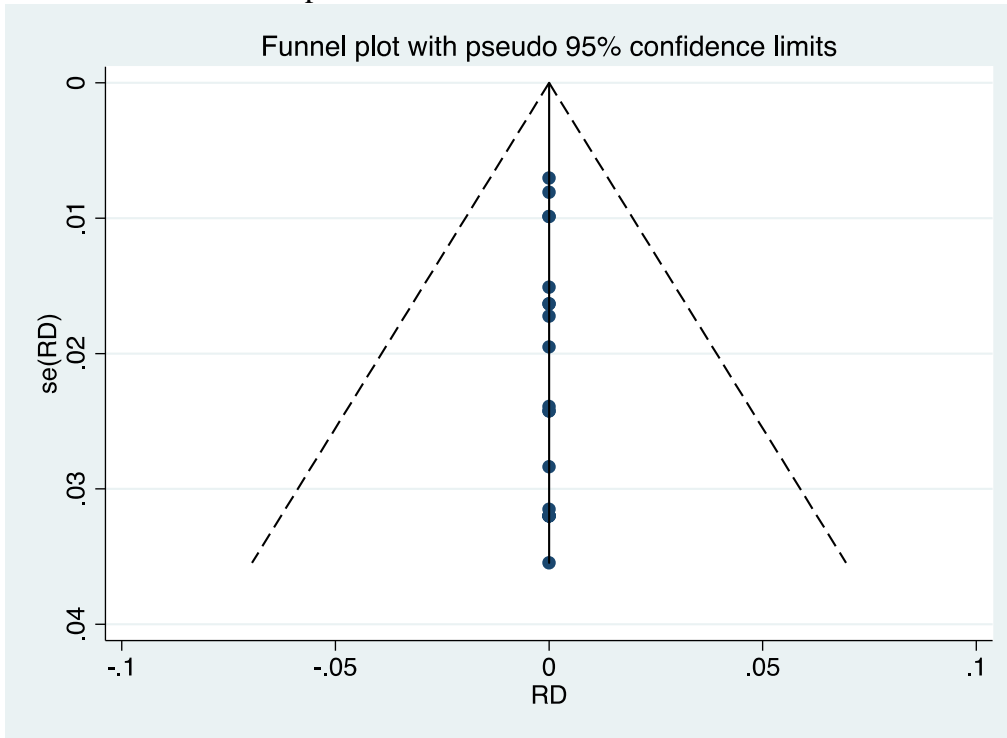




LdT 600 mg

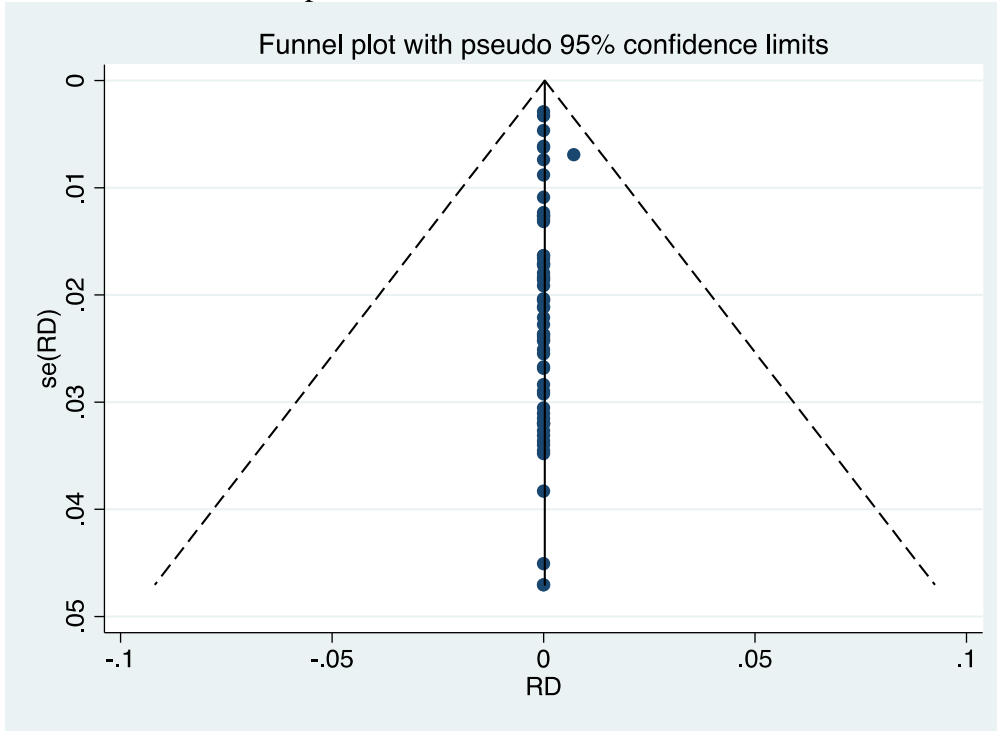
**Neonatal deaths, RCTs**

- No evidence of publication bias



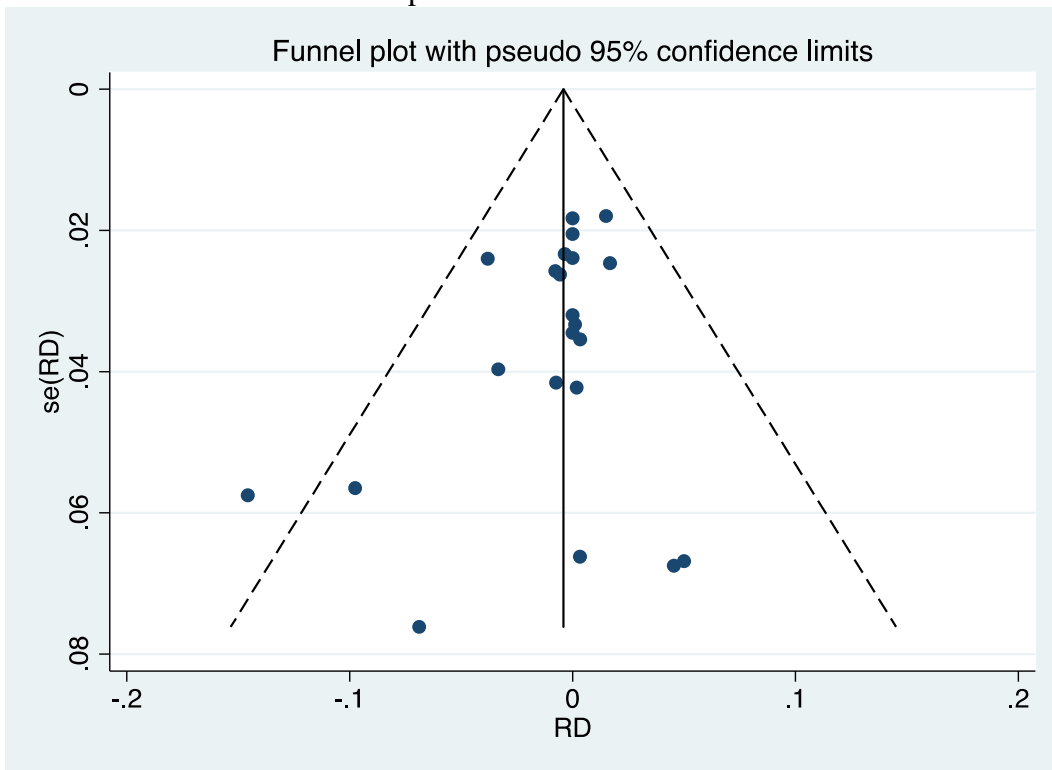
**Neonatal deaths, non-RCTs**

- No evidence of publication bias



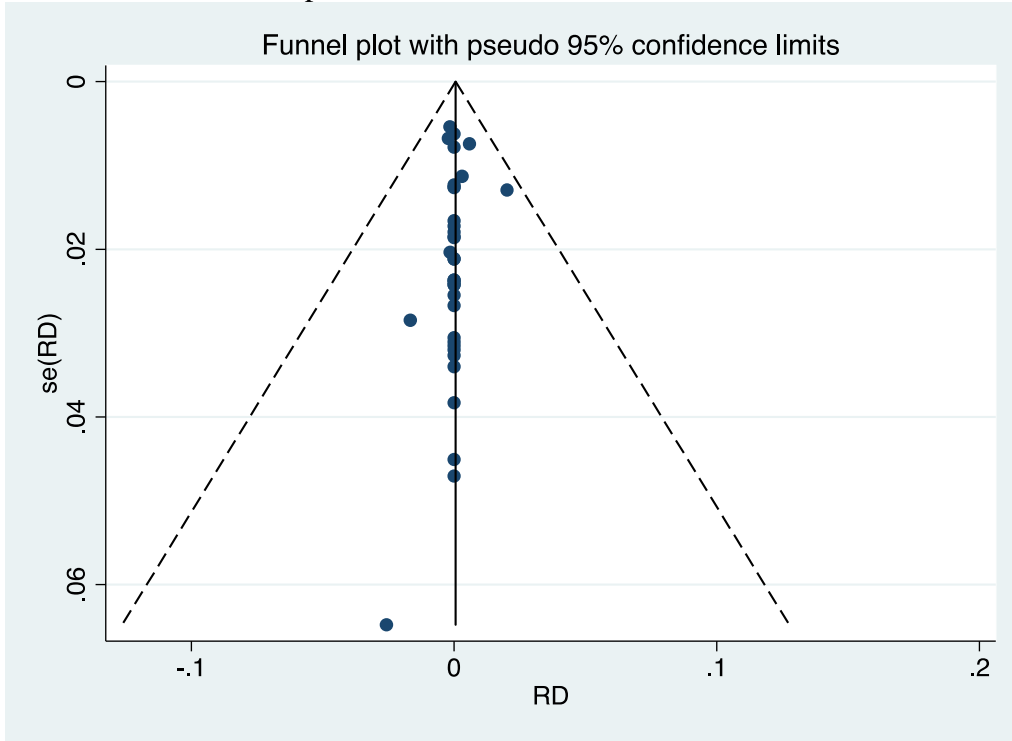
**Prematurity, non-RCTs**

- Unclear/no evidence of publication bias



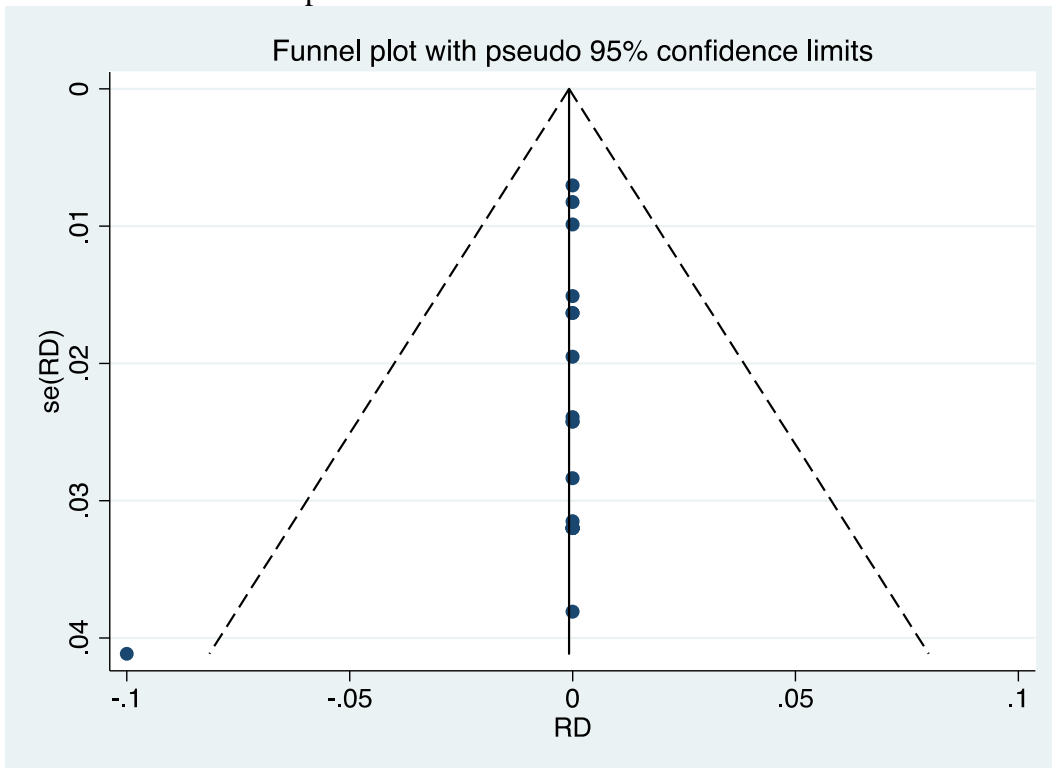
***Congenital abnormalities, non-RCTs***

- No evidence of publication bias



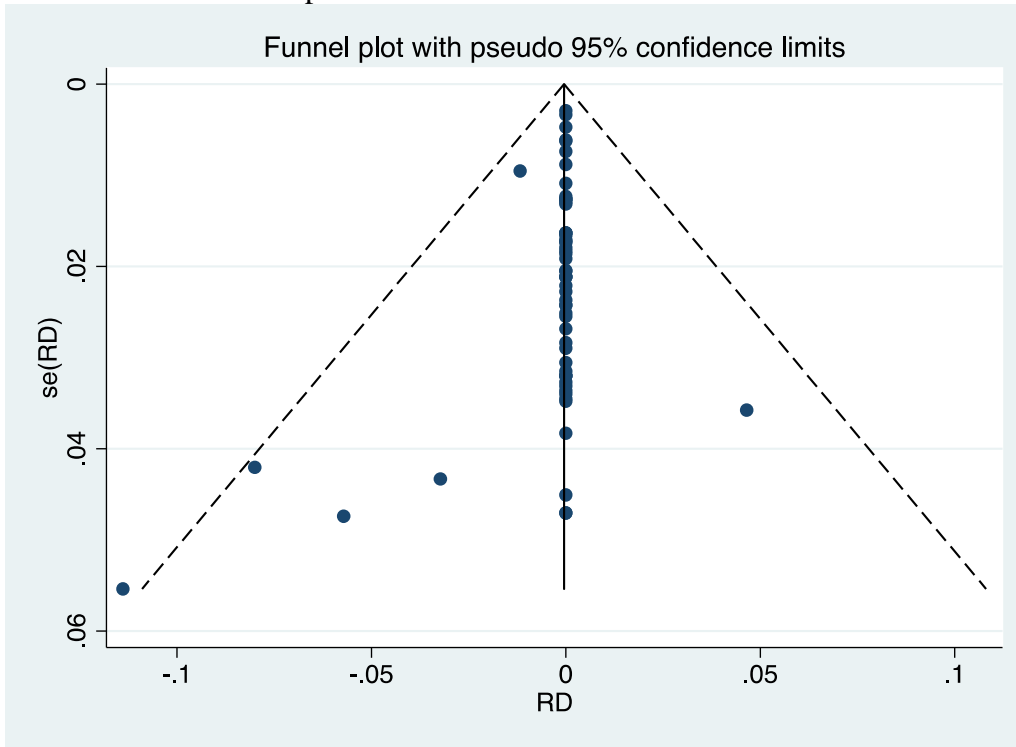
***Fetal deaths, RCTs***

- No evidence of publication bias



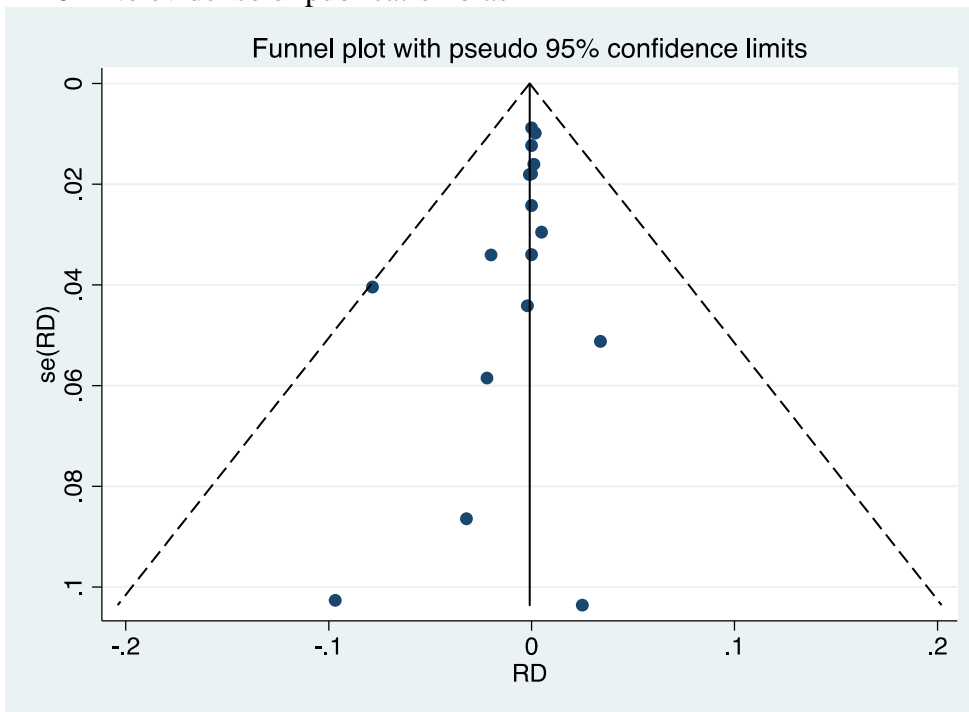
***Fetal deaths, non-RCTs***

- 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 meta-analysis, 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  $>50\%$  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’,  $I^2 \geq 30\% & < 60\%$  = ‘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  $\geq 0.01$  and  $< 0.1$  then it was considered as having ‘serious’ limitations, and if it was  $\geq 0.1$  (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

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

	<i>controlled trials</i>					bias.					fewer - 10 more)	
14	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	No evidence of publication bias	None	0/712 (0.0)	0/508 (0.0)	-	<b>0</b> (10 fewer - 10 more)	Very low <sup>f</sup>
<b>Infant safety: prematurity</b>												
4	<i>Randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	N/A	11/337 (3.3)	16/320 (5.0)	-	<b>10 fewer</b> (30 fewer - 20 more)	Moderate <sup>g</sup>
4	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	None	8/285 (2.8)	6/159 (3.8)	-	<b>10 more</b> (30 fewer to 40 more)	Very low <sup>h</sup>
<b>Infant safety: congenital abnormalities</b>												
5	<i>Randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	N/A	2/367 (0.5)	3/350 (0.9)	-	<b>0</b> (20 fewer - 10 more)	Moderate <sup>i</sup>
9	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	None	2/435 (0.5)	2/337 (0.6)	-	<b>0</b> (20 fewer - 20 more)	Very low <sup>j</sup>
<b>Infant safety: bone mineral density</b>												
1	<i>Randomized controlled trials</i>	No serious	N/A	No serious	Serious	Not able to examine publication bias.	N/A	N/A	N/A	-	<b>-0.006 g/cm<sup>2</sup></b> (-0.019 to 0.007 g/cm <sup>2</sup> ); P = 0.38)	Low <sup>k</sup>
<b>Maternal safety: miscarriage and stillbirth</b>												



5	<i>Randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	N/A	3/372 (0.8)	0/362 (0.0)	-	<b>10 more</b> (10 fewer - 20 more)	Moderate <sup>e1</sup>
14	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	No evidence of publication bias	None	0/570 (0.0)	1/520 (0.2)	-	<b>0</b> (10 fewer - 10 more)	Very low <sup>m</sup>
<b>Maternal safety: postpartum hemorrhage</b>												
3	<i>Randomized controlled trials</i>	Serious	No serious	No serious	Serious	Not able to examine publication bias.	N/A	4/177 (2.3)	5/172 (2.9)	-	<b>0</b> (30 fewer - 30 more)	Low <sup>n</sup>
3	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not able to examine publication bias.	None	5/188 (2.7)	3/84 (3.6)	-	<b>0</b> (40 fewer - 40 more)	Very low <sup>o</sup>
<b>Maternal safety: postpartum hepatitis flare after treatment discontinuation</b>												
2	<i>Randomized controlled trials</i>	No serious	Serious I <sup>2</sup> =43.7%	No serious	Serious	Not able to examine publication bias.	N/A	10/251 (4.0)	8/257 (3.1)	-	<b>2 more</b> (47 fewer - 51 more)	Low <sup>p</sup>
2	<i>Non-randomized controlled trials</i>	No serious	Very serious I <sup>2</sup> =80.6%	No serious	Very serious	Not able to examine publication bias.	None	18/105 (17.1)	12/70 (17.1)	-	<b>38 fewer</b> (289 fewer - 212 more)	Very 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>l</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  $\leq 4$  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 of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	AVT (%)	No AVT (%)	OR (95%CI)	Absolute (95%CI)	
<b>HBsAg positivity at 6-12 months</b>												
8	<i>Randomized controlled trials</i>	Serious	No serious	No serious	No serious	Not possible to examine publication bias.	N/A	25/432 (5.8)	105/389 (27.0)	<b>0.16</b> (0.10-0.26)	<b>190 fewer</b> per 1000 (90-280 fewer)	Moderate <sup>a</sup>
32	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	41/1575 (2.6)	233/1655 (14.1)	<b>0.17</b> (0.12-0.24)	<b>140 fewer</b> per 1000 (110-180 fewer)	Low <sup>b</sup>
<b>HBV DNA positivity at 6-12 months</b>												
5	<i>Randomized controlled trials</i>	Serious	Serious I <sup>2</sup> =39.8%	No serious	No serious	Not possible to examine publication bias.	N/A	21/312 (6.7)	73/269 (27.1)	<b>0.22</b> (0.10-0.47)	<b>160 fewer</b> per 1000 (320 fewer to 4 more)	Low <sup>c</sup>
18	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	No serious	No evidence of publication bias.	Magnitude of the effect.	22/1014 (2.2)	137/1057 (13.0)	<b>0.14</b> (0.09-0.23)	<b>140 fewer</b> per 1000 (90 - 190 fewer)	Moderate <sup>d</sup>
<b>Infant safety: neonatal deaths</b>												

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

											more)	
31	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	No evidence of publication bias.	None	0/1531 (0.0)	9/1678 (0.5)	-	<b>0</b> (10 fewer - 10 more)	Very low <sup>l</sup>
<b>Maternal safety: postpartum hemorrhage</b>												
1	<i>Randomized controlled trials</i>	Serious	Not applicable	No serious	Serious	Not possible to examine publication bias.	N/A	0/53 (0.0)	0/53 (0.0)	-	<b>0</b> (40 fewer - 40 more)	Very low <sup>m</sup>
7	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	Not possible to examine publication bias.	None	98/558 (17.6)	61/699 (8.7)	-	<b>10 more</b> (10 less - 40 more)	Very low <sup>n</sup>
<b>Maternal safety: postpartum hepatitis flare after treatment discontinuation</b>												
1	<i>Randomized controlled trials</i>	Serious	Not applicable	No serious	Very serious	Not possible to examine publication bias.	N/A	16/83 (19.3)	15/46 (32.6)	-	<b>130 less</b> (290 fewer - 30 more)	Very low <sup>o</sup>
5	<i>Non-randomized controlled trials</i>	No serious	Serious I <sup>2</sup> = 33.2%	No serious	Serious	Not possible to examine publication bias.	None	43/364 (11.8)	19/522 (3.6)	-	<b>10 fewer</b> (50 fewer - 30 more)	Very 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  $\leq 4$  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  $\leq 4$  of 8 criteria with low risk of bias, the rest being unclear or high).

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

<sup>m</sup>Downgrading due to 'serious' study design limitations (all RCTs had  $\leq 4$  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  $\leq 4$  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

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	AVT (%)	No AVT (%)	OR (95%CI)	Absolute (95%CI)	
<b>HBsAg positivity at 6-12 months</b>												
21	<i>Randomized controlled trials</i>	Serious	No serious	No serious	No serious	No evidence of publication bias	N/A	36/1209 (3.0)	175/1123 (15.6)	<b>0.14</b> (0.09-0.21)	<b>150 fewer</b> per 1000 (100-200 fewer)	Moderate <sup>a</sup>
62	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	34/4762 (0.7)	521/4674 (11.1)	<b>0.09</b> (0.06-0.12)	<b>130 fewer</b> per 1000 (110-150 fewer)	Low <sup>b</sup>
<b>HBV DNA positivity at 6-12 months</b>												
8	<i>Randomized controlled trials</i>	Serious	No serious	No serious	No serious	Not possible to examine publication bias.	N/A	6/382 (1.6)	58/374 (15.5)	<b>0.12</b> (0.05-0.26)	<b>160 fewer</b> per 1000 (60 to 250 fewer)	Moderate <sup>c</sup>
45	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	18/3648 (0.5)	377/3367 (11.2)	<b>0.07</b> (0.05-0.10)	<b>130 fewer</b> per 1000 (100 - 150 fewer)	Low <sup>d</sup>
<b>Infant safety: neonatal deaths</b>												
21	<i>Randomized controlled trials</i>	Serious	No serious	No serious	Serious	No evidence of publication bias	N/A	0/1213 (0.0)	0/1123 (0.0)	-	<b>0 per 1000</b> (10 fewer - 10 more)	Low <sup>e</sup>
61	<i>Non-</i>	No	No	No	No	No evidence of publication	None	2/4539	0/4740	-	<b>0 per</b>	Low <sup>f</sup>

	<i>randomized controlled trials</i>	serious	serious	serious	serious	bias		(0.0)	(0.0)		<b>1000</b> (2 fewer - 3 more)	
<b>Infant safety: prematurity</b>												
2	<i>Randomized controlled trials</i>	Serious	No serious	No serious	Serious	Not possible to examine publication bias.	N/A	1/252 (0.4)	0/232 (0.0)	-	<b>0 per 1000</b> (10 fewer - 20 more)	Low <sup>g</sup>
22	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	No evidence of publication bias	None	104/2175 (4.8)	120/1959 (6.1)	-	<b>0 per 1000</b> (20 fewer - 10 more)	Very low <sup>h</sup>
<b>Infant safety: congenital abnormalities</b>												
4	<i>Randomized controlled trials</i>	Serious	No serious	No serious	Serious	Not possible to examine publication bias.	N/A	0/326 (0.0)	0/306 (0.0)	-	<b>0 per 1000</b> (10 fewer - 10 more)	Low <sup>i</sup>
36	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	No serious	No evidence of publication bias	None	11/3529 (0.3)	9/2677 (0.3)	-	<b>0 per 1000</b> (4 fewer - 4 more)	Low <sup>j</sup>
<b>Maternal safety: miscarriage and stillbirth</b>												
20	<i>Randomized controlled trials</i>	Serious	No serious	No serious	Serious	No evidence of publication bias	N/A	0/1107 (0.0)	6/1026 (0.6)	-	<b>1 fewer per 1000</b> (8 fewer - 6 more)	Low <sup>k</sup>
61	<i>Non-randomized controlled</i>	No serious	No serious	No serious	No serious	No evidence of publication bias	None	3/4538 (0.1)	14/4797 (0.3)	-	<b>0 per 1000</b> (3 fewer -	Low <sup>l</sup>



	<i>trials</i>										2 more)	
<b>Maternal safety: postpartum hemorrhage</b>												
2	<i>Randomized controlled trials</i>	Serious	Serious I <sup>2</sup> =34.5%	No serious	Serious	Not possible to examine publication bias.	N/A	39/180 (21.7)	38/180 (21.1)	-	<b>10 fewer</b> (90 fewer - 60 more)	Very low <sup>m</sup>
17	<i>Non-randomized controlled trials</i>	No serious	No serious	No serious	Serious	No evidence of publication bias	None	86/1549 (5.6)	78/1840 (4.2)	-	<b>1 fewer</b> (10 less - 8 more)	Very low <sup>n</sup>
<b>Maternal safety: postpartum hepatitis flare after treatment discontinuation</b>												
3	<i>Non-randomized controlled trials</i>	No serious	Very serious I <sup>2</sup> =85.5%	No serious	Very serious	Not possible to examine publication bias.	N/A	27/431 (6.3)	26/565 (4.6)	-	<b>20 less</b> (60 fewer - 110 more)	Very 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 'serious' 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>l</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<sup>2</sup>>30%), downgrading due to imprecision.

<sup>n</sup>Downgrading due to 'very serious' inconsistency (I<sup>2</sup>>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 (I<sup>2</sup>>60%), downgrading due to imprecision