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Abstract

Background: In 2013, France modified its pertussis vaccination schedule to remove one dose at 3 months of age and change the age of the booster dose from 16 to 11 months. We aimed to assess the subsequent impact on pertussis epidemiology in France.

Methods: We analysed the PCR test results of nasopharyngeal swabs (N=7493) collected from symptomatic outpatients aged 2-20 years old between 2012 and 2019 in France. We developed a negative binomial regression model for the number of pertussis cases by year and age. The linear predictor included the year, the age group, the population size and a proxy of waning immunity that could vary with vaccine schedule. We also compared the anti-pertussis toxin (PT) antibody levels of 315 children born before and after the vaccine schedule change.

Findings: The model that best fitted the 2012-2018 epidemiological data supported a faster waning of immunity following vaccination with the new vaccine schedule. Three years after vaccination, the risk of developing pertussis was 1.7 (95% CI, 1.4-2.0) times higher for children vaccinated according to the new schedule than those vaccinated according to the previous schedule. The model correctly predicted the age distribution of cases in 2019. Anti-PT IgG levels were significantly lower in children born after implementation of the new schedule, compared to children born before.

Interpretation: A shorter-lived protection induced by the 2/4+11 vaccine schedule recommended in France since 2013 is associated with an increase of pertussis cases in 2-5-year olds.

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Research in context

Evidence before this study

On September 1st, 2020 we searched PubMed for English-language articles (from database inception onwards) that included comparisons of vaccine effectiveness and immunogenicity between different pertussis vaccination schedules (i.e., primary vaccinations with 2 vs. 3 doses, different ages of vaccination initiation or first booster, different intervals between doses) among children. We also searched for articles that described the impact of vaccine schedule changes on pertussis epidemiology. We included randomized trials and observational studies. We used the research strategy ("whooping cough"[tiab] OR "pertussis"[tiab] OR Tdap[tiab]) AND (vaccin*[tiab] OR immunization[tiab]) AND (dose*[tiab] OR schedule*[tiab]) AND (effectiveness[tiab] OR efficacy[tiab]) NOT pregnan*[ti] NOT adolescen*[ti] NOT maternal*[ti] NOT cocooning[ti]. We also considered the 2014 report of EHESP for WHO SAGE pertussis working group "Comparative efficacy/effectiveness of schedules in infant immunization against pertussis, diphtheria and tetanus: Systematic review and meta-analysis". We identified few studies that have compared the effectiveness and immunogenicity of different vaccine schedules. These studies lacked power to analyze subgroups by age, and most of them did not evaluate effectiveness or immunogenicity more than 2 years after primary vaccination. Epidemiological studies on the impact of changes in vaccine schedules mainly focused on the introduction of boosters, with a subsequent significant reduction of pertussis incidence among older children consistently observed. No previous study has explored the epidemiological impact of removing a vaccine dose.

Added value of this study

In 2013, France modified its pertussis vaccination schedule to remove one dose at 3 months of age and change the age of the booster dose from 16 months to 11 months. We aimed to assess the subsequent impact on pertussis epidemiology in France. We developed a statistical model that was able to reproduce the dynamics of pertussis cases by age in 2012-2018, and predict age distribution of pertussis cases in 2019. The model supported a faster waning of immunity following vaccination with the new vaccine schedule. Three years after vaccination, the risk of developing pertussis was 1.7-fold higher in children vaccinated with the new schedule compared to the previous schedule. We also performed a serological survey and found that the anti-PT IgG levels measured in the 2 and 3-year-old children were significantly lower in those born after the schedule modification compared to children born before it. This study suggests that the recent change of vaccine schedule may have accelerated the waning of vaccine-induced protection against pertussis in young children, which may have led to an increase of pertussis cases in 2-5-year-olds.

Implication of all available evidence

Pertussis vaccines have greatly reduced the burden of whooping cough in children, but the benefit of acellular vaccines is limited by their rapid waning of vaccine-induced protection in young children. Our work suggests that the speed of this waning is affected by vaccine schedules, implying that schedule choice is a key component of the strategy of prophylactic protection against *Bordetella pertussis*.

Introduction

Whooping cough, or pertussis, is an acute respiratory illness mainly caused by *Bordetella pertussis* (Bp).[1] Despite widespread vaccine implementation, the World Health Organization (WHO) still estimated pertussis as the cause of 160,700 deaths in children aged <5 years in 2014, and that half of infected infants younger than 12 months needed hospital care.[2] During the last decade, a resurgence in pertussis cases has been observed worldwide, including in highly vaccinated populations.[3] It has been attributed to a multitude of factors including aging of under-vaccinated cohorts, more sensitive laboratory testing methods, strain evolution towards escape of acellular pertussis (aP) vaccines-induced immunity, lack of natural boosters by infection, as well as limited aP vaccine efficacy against Bp carriage.[4,5] Furthermore, it is widely documented that rapid waning of immunity after vaccination with aP vaccines contributes to disease burden.[6] Indeed, whole-cell pertussis (wP) vaccines have progressively been replaced by the less reactogenic aP vaccines in all but one EU/EEA countries since the 1990s.[7] Compared to natural infection or wP vaccination, several studies have revealed a shorter duration of protection after vaccination with aP vaccines, mostly in children who received aP vaccines as infants.[8-10] The lower effectiveness of aP vaccines after a certain time may be attributable to its failure to induce appropriate cellular immune responses, especially those induced by Th1 cells.[11]

The schedules used in national immunization programs vary greatly between countries.[12,13] Based on the WHO expanded program on immunization, most high-income countries initially applied an accelerated schedule consisting of three primary doses during the first 6 months of life, and some added a booster during the second year of life ("3+1" schedule). A few countries such as Sweden have applied a schedule with two primary doses and an early booster during the second year of life ("2+1" schedule). Few studies have compared the efficacy of different vaccines schedules.[14] One cohort study in Sweden compared vaccine effectiveness between regions with a "3+0" vs. a "3+1" schedule, and did not find any significant difference of outcome with a follow-up to 28th months of age. However, the study lacked the power to analyze subgroups of patients by age.[15] The same study found higher serological responses after the third dose in a group of patients vaccinated with the "2+1" vs. the "3+1". Another study revealed a better immunogenicity of a 2/4/6 months vs. 2/5 months primary doses, and that a fourth dose at 15 months induced higher antibodies than a third dose at 12 months.[16] Despite the absence of clear scientific evidence for higher effectiveness, European countries have recently tended to move from a "3+1" to a "2+1" schedule, driven mainly by sociological and pragmatic factors.[13]

In April 2013, France changed from a "3+1" schedule with three primary doses at 2, 3 and 4 months, and a first booster at 16-18 months, to a "2+1" schedule with two primary doses at 2 and 4 months, and a first booster at 11 months, to simplify the immunization program.[17] A childhood booster dose was also added at 6 years of age as suggested by the Swedish experience.[18] Changes in national vaccine policies might have consequences on pertussis epidemiology. In France, in 2017-2018, there was a 2.4-

fold increase in the overall annual incidence of confirmed pertussis cases, compared to 2014-2016.[19] This increase was not unusual in itself, given that pertussis typically follows a cyclical pattern of 3-7 years and the last recrudescence in France had been in 2012-2013.[20] More surprising was the change in the age distribution of cases: the largest increase in incidence occurred in the 2-5-year-old population, whose proportion doubled, from 7% of all cases in 2014-2016 to 14% in 2017-2018,[21] despite an estimated national vaccine coverage of >95% at the age of two years.[22,23] The main objective of this study was to better understand this change in the age distribution of pertussis cases and to assess whether the immunization schedule modification in 2013 was likely to have affected pertussis epidemiology in France. We conducted a regression analysis using national surveillance data between 2012 and 2019, complemented by a retrospective serological survey.

Methods

Data sources and definitions

Every month, Santé publique France (SpF) and the National Reference Center (NRC) of whooping cough and other *Bordetella* infections collect data on pertussis cases in the general population from the two main outpatient laboratories (Cerba and Eurofins-Biomnis) (Appendix, Text S1). We analysed laboratory results from nasopharyngeal swabs that were collected from symptomatic outpatients suspected of whooping cough between January 1, 2012 and December 31, 2019 in France, and tested for *Bordetella spp* (*B. bronchiseptica* or *B. pertussis* or *B. holmesii*) using PCR targeting insertion sequences *IS481*. A pertussis confirmed case was defined as a patient with a positive PCR result. We restricted our analysis to the 2-20-year-old population. The lower limit of 2 years old was chosen to only include children who were expected to have completed their initial immunization series (primary vaccination and first booster, Appendix, Text S2).

We also performed a serological survey based on a random sample of retrospective collections of leftover sera from children aged 2 to 5 years old, not tested for pertussis or a recent respiratory infection, from two different time periods (2008-2009 and 2017-2019). The serological assay is described in Appendix (Text S3).

We use the terminology “new vaccine schedule” or “2/4+11” to describe the schedule implemented after April 2013, and “former vaccine schedule” or “2/3/4+16” the schedule implemented before April 2013. Following an official statement by the French High Council for Public Health in December 2012,[17] the new recommendations were published on April 19, 2013; we therefore considered for our analyses that the new vaccine schedule was effective from May 2013, as corroborated by health insurance data (Figure S1).

Statistical analyses

Model

In order to study the potential impact of vaccine schedule changes on the epidemiology of pertussis, we developed a negative binomial regression model for the number of pertussis cases by age and year. We included in the linear predictor the population size of each age group, a year effect, the age group, and a waning function to capture reducing immunity over time following vaccination (Text S4). This model allowed us to account for potential variations in demography, annual epidemic size, and disease risk by age. The waning function was a proxy of waning immunity and was meant to represent the mean effect of waning immunity on the number of pertussis cases, in the whole cohort of children of a given age, in a given year. This function could vary with the vaccine schedule (2/3/4+16 or 2/4+11) and the type of the last vaccination theoretically received by the individuals (first booster, childhood booster or adolescent booster). We tested four different models, in which the waning functions could be either identical or different between the new and former vaccine schedules, and could vary or not with the type of vaccine received for primary vaccination (whole cell before 2002 or acellular since 2002, Appendix, Text S2). More details about the methodology are given in the Appendix, Text S4.

The models were fitted to the 2012-2018 data, and the 2019 data were left out for external model validation. We computed relative risks of pertussis (corresponding to incidence rate ratios) by exponentiating the regression coefficients. This allowed us to compare the risk of developing pertussis between children theoretically vaccinated according to the new vaccine schedule and those theoretically vaccinated according to the former vaccine schedule. We used the best model to predict the expected proportions of cases by age for 2019, and compared these out-of-sample predictions to the observed proportions.

We performed several sensitivity analyses to assess the robustness of our best model: we fitted the model to data from each laboratory separately, we included the total number of negative samples and we used several definitions for the age groups or no age effect at all (Appendix, Text S5).

Statistical analyses of serological data

The levels of antibody titres by age were compared between 2-5-year-old children born before February 1st, 2013 (supposed to be vaccinated with the 2/3/4+16 schedule) and 2-5-year-old children born after February 2013 (supposed to be vaccinated with the 2/4+11 schedule). Results are presented as geometric mean concentrations with 95% CI. We used independent samples t tests for comparisons between groups for log10-transformed antibody concentrations. Results with p-values <0.05 were considered significant.

Ethical approval

The data collection received approval by French supervisory ethics authority (CNIL, n°1474593), and was approved by the local Institutional Review board (N° 2020 1028160733). All data processing and

storage comply with the General Data Protection Regulation (GDPR) and ethical standards of the National Research Committee. This study was conducted in accordance with the Helsinki Declaration, with informed consent obtained from each patient's guardians.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Description of the data

Between January 1, 2012 and December 31, 2019, we collected data on 7493 pertussis confirmed cases aged 2 to 20 years (Appendix, Table S1). Over the study period, two epidemic cycles of pertussis were observed in 2012-2013 and 2017-2019, with a lower circulation of the bacteria in intermediate years (Figure 1A). Age distributions by year revealed two phenomena: from 2017 onwards, a new peak appeared at 4-5 years old, and from 2014 onwards, the peak between 6-10 years old shifted towards older ages (Figure 1B and 1C). Children aged 2-5 years accounted for 36% of the cases observed among the 2-20-year-olds during 2017-2019, versus only 21% during 2012-2016 (Table S1).

Model

Among the four models that we tested, the two models that provided the best fit to epidemiological data were models where the waning functions of the new and former schedules were different (Figure S2). The two models where the waning functions of the new and former vaccine schedules were identical, were not supported by the data (Deviance Information Criteria (DIC) difference of 25 and 27 compared to the best model, respectively). The best model in terms of DIC assumed that the decay rate of the childhood or adolescent booster was independent of the type of vaccine received for primary vaccination, while the second best model assumed that it varied with the type of vaccine. The difference in DIC between these two models was only 2 units, consistent with no significant difference in performance. Therefore, model comparison indicated that waning was different between the new and former schedules but did not allow to decide whether the waning of the childhood or adolescent booster varied with the type of vaccine received for primary vaccination.

In the best model, the waning function of the new vaccine schedule decayed faster than the waning function of the former schedule, suggesting that protection conferred by the new vaccine schedule was of shorter duration (Figure 2A, Table S2). In terms of relative risk of disease, we estimated that a higher relative risk was associated with the new vaccine schedule, compared to the former schedule (Figure

2B). For instance, three years after vaccination by the first booster, the risk of developing pertussis was 1.7 (95%CI 1.4-2.0) times higher for children vaccinated according to the new schedule than for children vaccinated according to the former schedule. We also estimated that, independently of vaccine schedules and waning of immunity, the relative risk of developing pertussis varied with age, and was higher (1.5 [95%CI 1.4-1.7]) for 6-11-year-old individuals, compared to the reference age group of the 2-5-year-olds (Figure 2C). Similar results were found for the second best model (Figure S3, Table S2). In addition, this model estimated that the decay rate of the childhood or adolescent booster was higher for children who received an aP vaccine for primary vaccination, than for those who received a wP vaccine for primary vaccination (Figure S3A, Table S2), leading to an increased risk of pertussis for the former group of children compared to the latter (Figure S3B). Five years after vaccination by the childhood or adolescent booster, the risk of pertussis was 1.2 (95%CI 1.0-1.5) times higher for children who received an aP vaccine for primary vaccination than for those who received a wP vaccine for primary vaccination.

The best model correctly captured the two main features observed in the data, i.e. the increased proportion of cases among the 2-5-year-olds in 2017 and 2018, and the shift of the second peak towards children aged 11 years (Figure 3A and 3B). In our model, the first feature could be explained by the estimated faster decay of vaccine protection with the new vaccine schedule, while the second feature could be explained by the introduction of the 6-year-old booster in 2013. The correlation between the observed and estimated proportions of cases by age and year was high (Pearson r=0.94) (Figure 3C).

We then used the best model to predict the expected age distribution of cases in 2019. Cases from this year were not included in the model fitting process. The proportions of cases by age predicted by the model showed a high correlation with the proportions observed in 2019 (Pearson r=0.97), with a large first peak at 5 years old and a smaller second peak at 11 years old (Figure 4). The models where the waning functions of the new and former vaccine schedules were identical could not reproduce the large peak at 5 years old in 2019 (Figure S4).

Sensitivity analyses

The estimates found in sensitivity analyses differed slightly from the estimates found in the baseline analysis (best model), but confirmed our main findings. All model variants favored a higher risk of pertussis with the new vaccine schedule than with the former vaccine schedule, explained by a faster decay of the waning function (Table S3 and Figure S5). Among the differences observed, the decay rate of the former schedule was slightly higher than in the baseline analysis when only Biomnis laboratory data were analysed, when age was not included in the model, or when a different age-group definition was used. Among the six sensitivity analyses that we performed, the decay rate of the new schedule was slightly lower in five of them, and similar to the baseline analysis when negative samples were

added in the model. In all sensitivity analyses, the relative risk of pertussis disease three years after vaccination with the new schedule compared to the former schedule was above 1, and ranged from 1.4 to 1.8.

Sero-epidemiology according to vaccination schedules

Sera from 315 children aged from 2 to 5 years were collected. The distribution of anti-PT IgG level is presented by age group in Figure 5A and Table S4. Geometric mean concentrations (GMC) were 50% lower in children vaccinated with the new schedule compared to children vaccinated with the former schedule in 2-year-old children (GMC= 5.85 IU/mL (95%CI 4.08-8.39) vs. GMC = 11.62 IU/mL (95%CI 9.05-14.92), p<0.002), and 43% lower in 3-year-old children (GMC=3.88 IU/mL (95%CI 2.82-5.34) vs. GMC=6.80 IU/mL (95%CI 4.77-9.70), p=0.03). GMC were not statistically different in 4-year-old children. When stratified by time since last vaccination, GMC were significantly lower the first year since last vaccination in children vaccinated with the new vaccine schedule compared to children vaccinated with the former schedule (Figure 5B).

Discussion

Following the modification of the vaccine schedule from a 2/3/4+16 to a 2/4+11 schedule in April 2013, an increase in the proportion of pertussis cases among the 2-5-year-olds have been observed in France since 2017. In this 8-year national population-based study, we investigated whether this increase could be explained by the vaccine schedule modification. We developed a statistical model that was able to accurately capture and reproduce the dynamics of French pertussis epidemiology by age during 2012-2018. The model also correctly predicted the age distribution of pertussis cases in 2019. This analysis suggests that children vaccinated according to the new schedule have a risk of developing pertussis three years after receiving the first booster that is 1.7 times higher than children vaccinated according to the former schedule, potentially due to a faster decay of immunity after the first booster. The results of the serological analyses were consistent with this hypothesis, as the anti-PT IgG levels measured in the 2-3-year-old children were significantly lower in those born after the schedule modification compared to children born before it.

Pertussis epidemiology is typically cyclical.[24] Our data revealed that a new epidemic cycle started in 2017, four years after the previous peak observed in 2012-2013. These long-term trends in pertussis cycles have been attributed to waning in vaccine protection, as well as long-lasting natural immunity, driven by periodic waves of infection and declining vaccine coverage.[3,25] Over the study period, we also observed significant changes in proportions of pertussis cases according to age. These variations could be partly explained by the introduction of the 11-13 years booster dose introduced in 1998, and the 6-year-old booster in 2013. The effect of recent changes in vaccine schedules, mainly by the introduction of boosters, was apparent in the reduction of pertussis incidence among children in several countries

such as England or Australia.[25,26] Pertussis epidemiology should therefore be considered in the context of such changes, together with vaccine coverage trends, enhanced awareness and improved diagnosis methods, and vaccine-escape strains emergence. In addition to the introduction of boosters, changes in initial immunization schedules can also impact pertussis epidemiology; this was observed in Australia when replacement of an 18-month dose with an adolescent dose in 2003 resulted in a 40% increase in infections in the age group 18-47 months.[25]

Our modelling approach allowed us to investigate whether differences in waning immunity following vaccination by two different vaccine schedules could explain the age patterns observed in French surveillance data. As in other studies,[9,10] we found evidence of waning protection after completing an initial immunization series (primary vaccination and first booster) with both types of immunization schedules. Furthermore, our study suggests that the 2/4+11 schedule might lead to a faster decay of vaccine protection, compared to a 2/3/4+16 schedule, and might thus be responsible for increased risk of disease in 2-5-year-olds. To our knowledge, no other study had compared the vaccine schedules in terms of long-term protection and waning. In older ages, we could not conclude whether the waning after the childhood or adolescent booster varied with the type of vaccine received for primary vaccination. Other studies had shown that the odds of pertussis disease after a booster dose were higher if the primary vaccination used aP vaccines compared to wP.[9,27]

We cannot determine whether the accelerated waning of the new schedule is due to the number of primary vaccination doses (2 vs. 3 doses), to the time of first booster (11 months vs. 16-18 months), or to both. Previous studies did not find significant differences between 2 or 3 primary doses, in terms of vaccine effectiveness in infants younger than 11 months.[15,28,29] Whether the effectiveness of a booster dose may be impacted by the number of primary doses, needs to be elucidated. In contrast, Bisgard et *al*. reported a higher risk of pertussis for children who received their first booster before the age of 13 months, compared with children who received it at an older age, which supports the hypothesis that a first booster at 11 months is less effective than a first booster at 16-18 months.[30] This difference in effectiveness could be linked to lower antibody responses in younger ages, due to the immaturity of the immune system. Administering the booster at an older age may be beneficial, as it could elicit a stronger immune response.[16,31] However, the impact of delaying this first booster by a few months on the risk of developing pertussis during the period between the last priming dose and the first booster should be evaluated.

The findings of the statistical model are strengthened by the serological study, as the lower anti-PT antibody levels in patients born after the modification of the vaccine schedule suggest a shorter duration of humoral immune responses following the 2/4+11 vaccine schedule. This suggests, at least, that the booster dose of the 2/4+11 schedule fails to induce persistent high level of anti-PT IgG. Anti-PT antibodies are defined as specific antibodies to assess serological responses to vaccine.[32] However, their

levels decrease rapidly following vaccination, and there is no defined serological correlate of protection for pertussis.[33] Therefore, we cannot ascertain that the lower antibody levels participate to the waning of the new schedule. Further immunological explorations, including cell-mediated immunity, are needed.[34]

Whether the vaccination schedule modification is the only cause of the observed epidemiological changes needs further exploration. Annual variations in epidemic size (due to the oscillation cycle) were accounted for in the model by introducing a year-level effect; it will be important to ensure whether we observe these patterns in intermediate years between cycles. We recently observed an increased number of pertactin-deficient (PRN-) *B. pertussis* strains in France, with a sharp increase of PRN- between 2014 and 2017. However, there has been a relative stability between the 2015-2016 and 2017-2018 periods (Bouchez et al, *in press*).[35] Therefore, the increase in the overall annual incidence of pertussis cases observed in 2017-2018 cannot be due to incidence changes of the PRN- strains. Besides, although pertactin deficiency may participate in disease transmission and resurgence,[36] there is no evidence of any change in aP vaccine effectiveness in areas with high prevalence of PRN- strains.[37] Variations in vaccine coverage could have affected this dynamic too. However, the national vaccine coverage estimated at 2 years old was very high and stable over the study period (>98% for primary vaccination, and >95% for the first booster since 2015),[22,23] and therefore cannot explain the observed patterns. Likewise, as wP vaccines were completely replaced by aP vaccines in 2004, it is very unlikely to explain the change in age distribution among the 2-5-year-olds in 2017. In addition to the 3-antigen aP vaccines, two other aP vaccines with 2 and 5 antigens started to be available for primary vaccination in 2016 and 2018, respectively. Therefore, these new vaccines cannot be responsible for the increase of incidence observed in children aged from 3 to 5 years in 2017-18. Finally, there was no change in sampling or diagnostic practices over the study period, and in a sensitivity analysis, we added the number of negative samples in the model to account for sampling trends by age over the study period, with no impact on the results.

Pertussis disease in the 2-5-year-old group is usually mild. However, the increased incidence in this age group could impact the pathogen spread in the general population, and a fortiori in vulnerable age groups such as infants, who are more at risk of severe disease and death. For instance, it has been shown that siblings were responsible for 17-24% of the infections among 0-5-month-old infants.[24] Here, we focused on the effect of vaccine schedule changes on children over 2 years of age. We did not assess the direct and indirect (through transmission) consequences on pertussis epidemiology in infants. Outpatient laboratories data cannot report pertussis in infants with enough exhaustiveness, as most of them are diagnosed at the hospital. The French Renacoq Network, a hospital-based pediatric surveillance network, monitors hospitalized cases in infants. Through this network, a concomitant increase in the number of pertussis cases in infants was observed in 2012[24] and in 2017-2018

(unpublished report), although this latter peak was smaller. Whether the increased risk in the 2-5-year-olds leads to an increased risk in infants needs further exploration, using a mechanistic transmission model for instance.

Our study has several limitations. First, as we used positive PCR targeting *IS*481 as case-definition, there is potential for false-positive results (misclassified cases). Indeed, *IS*481 has good sensitivity but is not specific of pertussis, as it also detects *B. holmesii*, which can cause pertussis-like symptoms. However, we randomly controlled about 900 samples positive for *IS*481, and found that only 10 (1.2%) were positive for h*IS*1001, a specific marker of *B. holmesii*, and all of them were above 8 years of age,[38] suggesting a very low probability of misclassified cases in our study. Besides, we might miss cases diagnosed purely on the basis of symptoms, even though PCR testing, recommended for diagnosis of pertussis since 2011 and reimbursed by the French Social Security system, is widely used by practitioners. Second, the results of the serological survey must be taken with caution: the study was based on a convenience sample, lacking clear generalizability, the sample size was relatively small, and it was not known whether the children had been vaccinated according to the recommended vaccine schedule. Third, in our model, we assumed that the vaccine schedules were followed precisely, while the true ages at vaccination can deviate from the recommendations. However, the lack of adherence to the recommended vaccine schedule for pertussis does not seem to be a major phenomenon in France (Figure S1).[39] This can contribute to explain the small differences between model estimates and observed data. Finally, it must be noted that our model is a regression model at an aggregated level (age-year level). Contrary to mechanistic models, regression models do not explicitly reproduce the biological processes of pertussis transmission and vaccination. Therefore, the waning function that we use is only a proxy of waning immunity, but cannot be used to infer values of vaccine effectiveness or proportion of immune children over time. Developing a mechanistic model could help to better characterize vaccine effectiveness and duration of immunity, as well as transmission patterns between age groups, and to compare different vaccination strategies.[25,40] In addition, the relative risks that we report here are estimates from the regression model. This is a weaker form of evidence than if relative risks were directly estimated from a clinical trial comparing the two vaccine schedules.

In conclusion, this study suggests that the recent change of immunization schedule may have accelerated the waning of vaccine-induced protection against Bp in young children, which consequently impacted childhood pertussis epidemiology in France. More studies, such as clinical trials aiming at comparing the two schedules, are required to fully confirm our findings.

Figure Legends

Figure 1: Pertussis cases diagnosed by PCR in two outpatient laboratories (Cerba and Eurofins-Biomnis) among the 2-20-year-olds, in 2012-2019, France. (A) Time-series of number of cases by month and laboratory. (B) Number of cases by age and year. (C) Proportion of cases by age and year.

Figure 2: Parameters estimated by the best model (mean and 95% credible interval). (A) Waning function after vaccination by the former vaccine schedule (2/3/4+16), by the new vaccine schedule (2/4+11), and by the childhood (6 years) or adolescent (11 years) booster. (B) Relative risk of pertussis after vaccination by the new vaccine schedule compared to the former schedule. (C) Relative risk of pertussis by age group, after accounting for vaccination schedule.

Figure 3: Model fit for 2012-2018. (A) Observed proportions of cases by age and year. (B) Estimated proportions of cases by age and year. (C) Correlation between estimated and observed proportions of cases by age and year.

Figure 4: Model predictions for 2019. (A) Observed proportions of cases by age (2012-2019) and predicted proportions of cases by age (2019). (B) Correlation between the observed and predicted proportions in 2019.

Figure 5. Anti-PT IgG levels by age for children born before or after the implementation of the new vaccine schedule (2/4+11). Box plot, geometric mean concentrations and 95% confidence intervals.

Additional statements

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Contributors

JT conceived the study, and JT, SC, JP, DLB and SB designed the study. JT, JP and FAB collected the data, and JT and JP were responsible for the data. SG, HS and SM participated to data analysis. STP and VJ performed the microbiology analyses, and participated to the serum and data collection. JP, SC and JT performed the statistical analyses. JP, JT and SC wrote the first draft of the manuscript. JP, SC, and JT have access and verified the source data, and were responsible for the decision to submit the manuscript. All authors drafted the manuscript for important intellectual content, contributed to the revision of the final version of the manuscript, and approved the final version submitted.

Conflict of interest

We declare no competing interests.

Data sharing agreement

Data are available upon reasonable request, after approval of a proposal.

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Figure 1

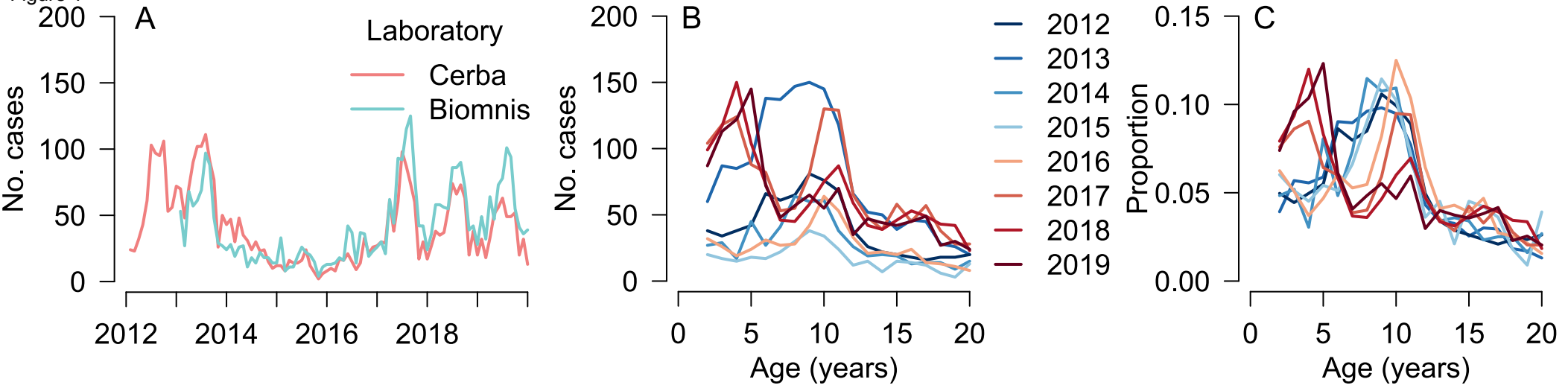

A
Laboratory
Cerba
Biomnis
No. cases
200
150
100
50
0
2012
2014
2016
2018
B
No. cases
200
150
100
50
0
0
5
10
15
20
Age (years)
2012
2013
2014
2015
2016
2017
2018
2019
C
Proportion
0.15
0.10
0.05
0.00
0
5
10
15
20
Age (years)

Figure 2

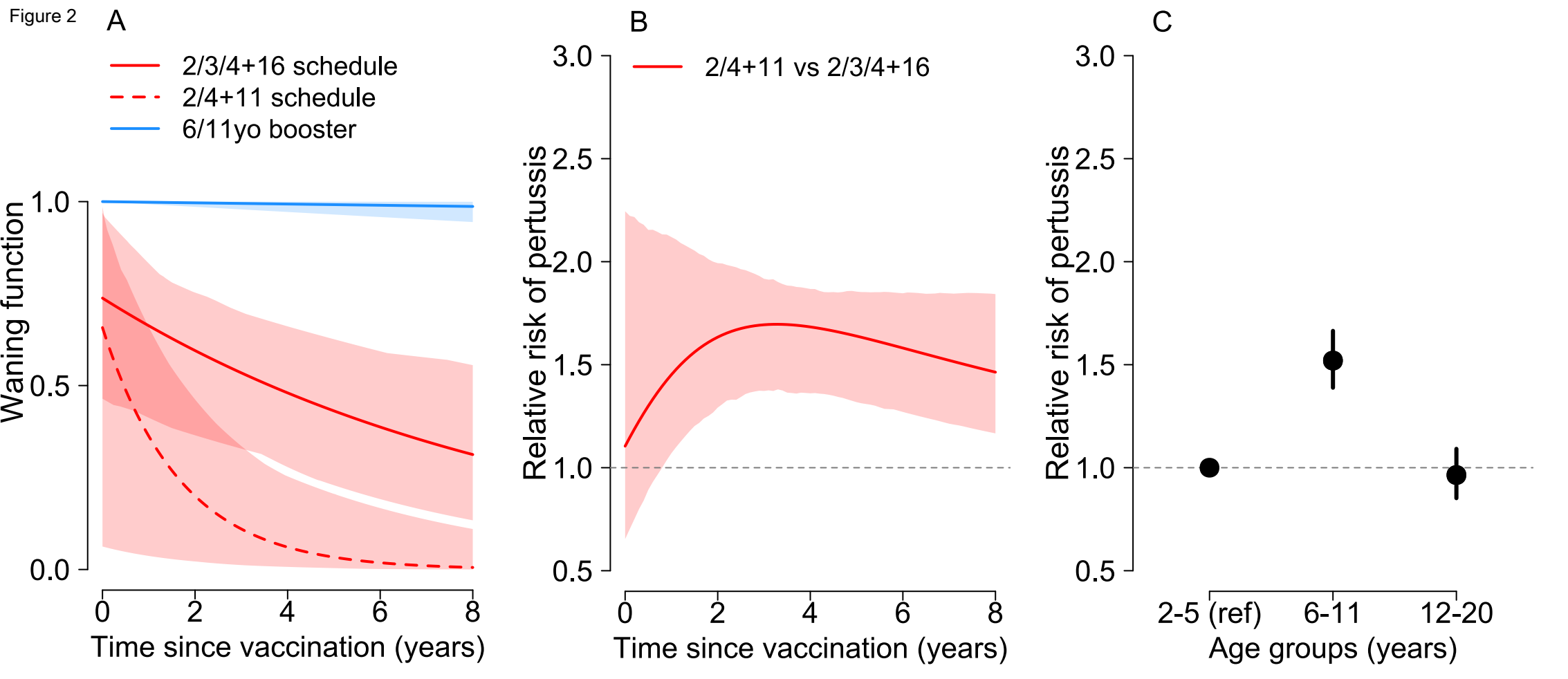

A
2/3/4+16 schedule
2/4+11 schedule
6/11yo booster
Waning function
1.0
0.5
0.0
0
2
4
6
8
Time since vaccination (years)
B
2/4+11 vs 2/3/4+16
Relative risk of pertussis
3.0
2.5
2.0
1.5
1.0
0.5
0
2
4
6
8
Time since vaccination (years)
C
Relative risk of pertussis
3.0
2.5
2.0
1.5
1.0
0.5
2-5 (ref)
6-11
12-20
Age groups (years)

Figure 3

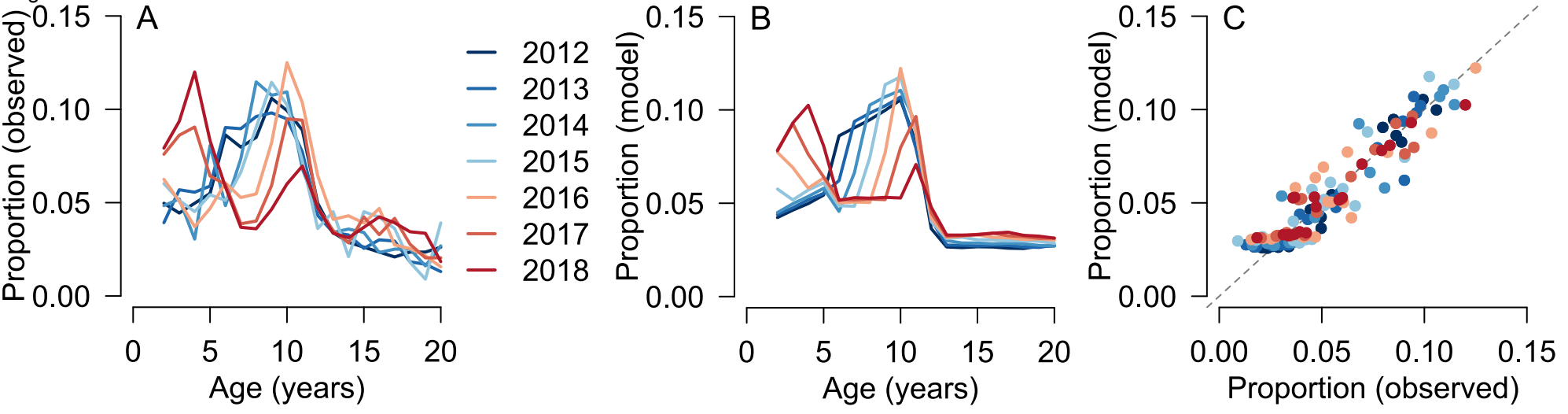

A
B
C
Proportion (observed)
Proportion (model)
Age (years)
Proportion (observed)
Proportion (model)
0.00
0.05
0.10
0.15
0
5
10
15
20
2012
2013
2014
2015
2016
2017
2018

Figure 4

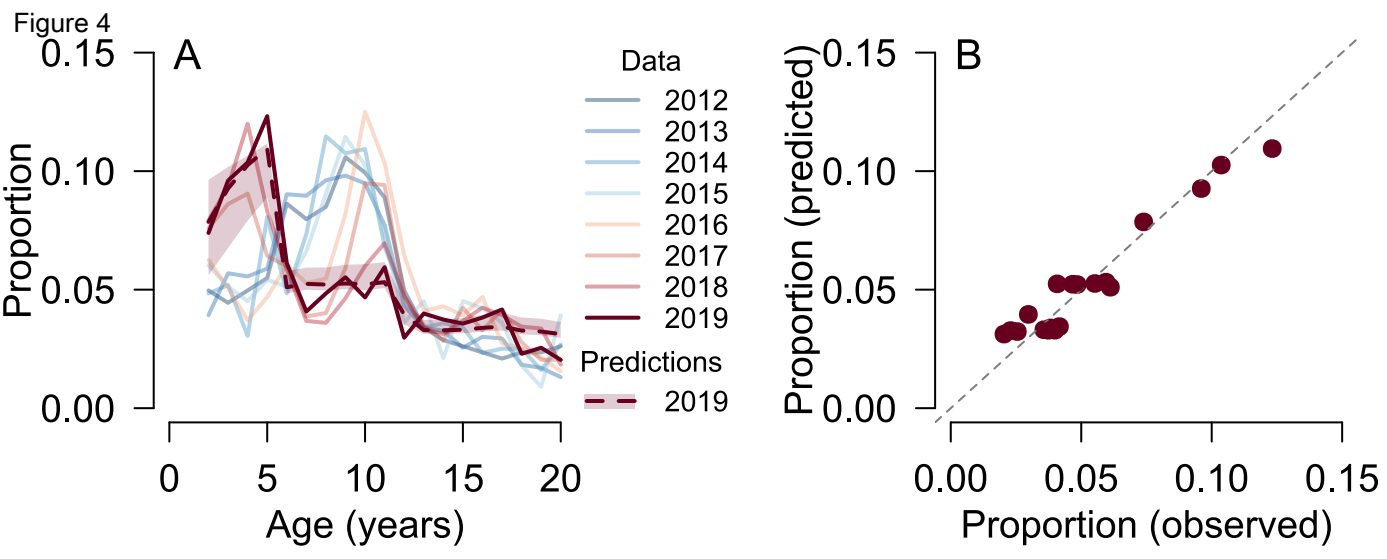
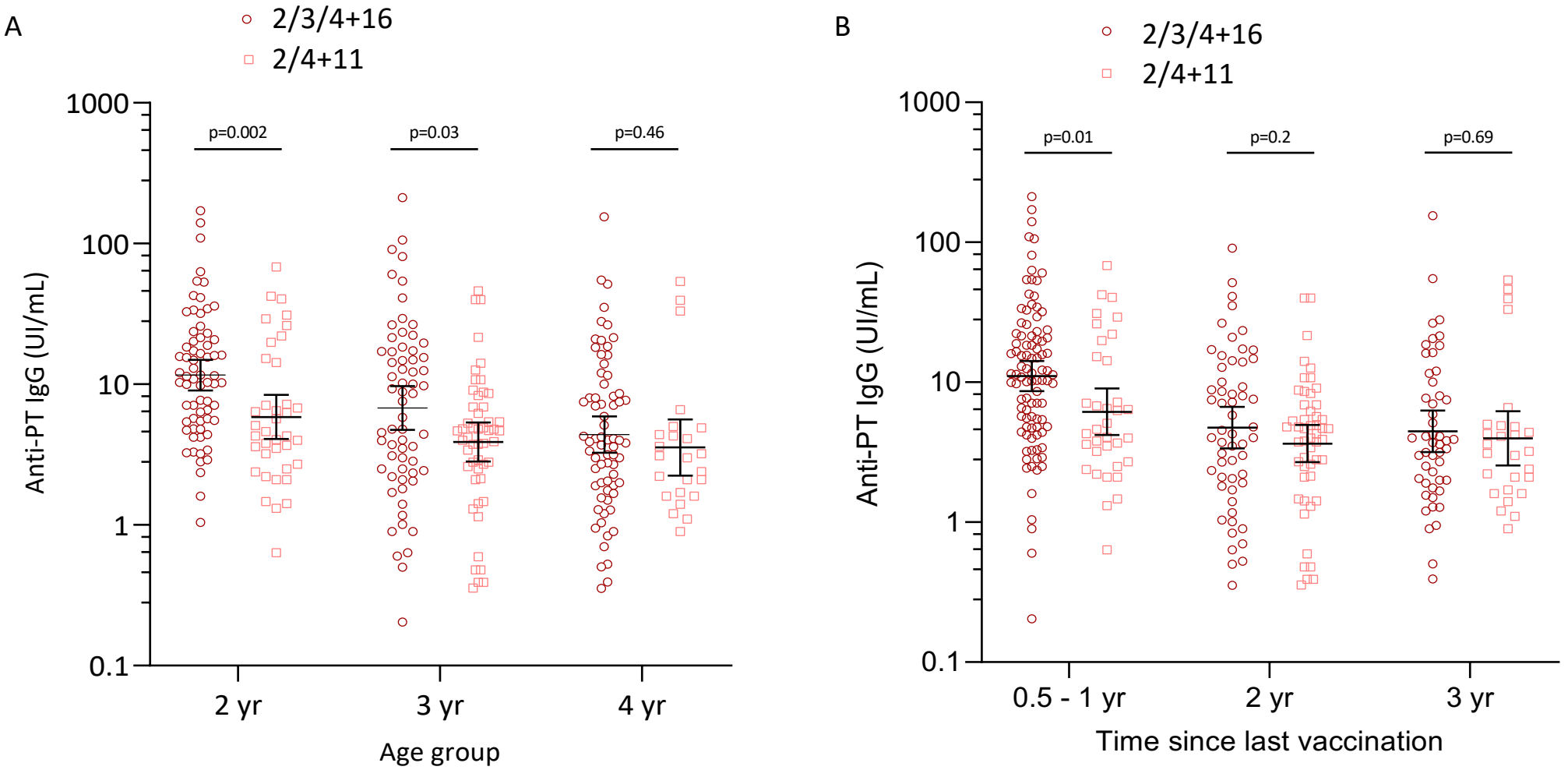

A
B
Proportion
Age (years)
Proportion (predicted)
Proportion (observed)
0.00
0.05
0.10
0.15
0
5
10
15
20
Data
2012
2013
2014
2015
2016
2017
2018
2019
Predictions
2019

Figure 5


A
2/3/4+16
2/4+11
Anti-PT IgG (UI/mL)
1000
100
10
1
0.1
p=0.002
p=0.03
p=0.46
2 yr
3 yr
4 yr
Age group
B
2/3/4+16
2/4+11
Anti-PT IgG (UI/mL)
1000
100
10
1
0.1
p=0.01
p=0.2
p=0.69
0.5 - 1 yr
2 yr
3 yr
Time since last vaccination

Supplementary appendix

1. Supplementary Material

Text S1: Case data

Santé publique France (SpF), with the support of the National Reference Center (NRC) of whooping cough and other *Bordetella* infections, is responsible for pertussis surveillance in France. Alongside monitoring hospital pediatric cases through a network of voluntary hospitals,[1] SpF and the NRC collect every month data on cases in the general population from two outpatient laboratories (Cerba and Eurofins-Biomnis). These laboratories carry out more than 90% of the biological diagnostic tests of outpatient pertussis cases in France. Briefly, biologists list and send results for all polymerase chain reaction (PCR) targeting insertion sequences IS*481* and IS*1001* to SpF and the NRC. The NRC regularly assists the laboratories to assess the specificity for *B. pertussis* in a selected panel of IS*481* positive samples using complementary PCRs such as hIS*1001* which detect *B. holmesii,* or a specific PCR targeting the promoter region of the pertussis toxin gene (named ptxA–Pr).[2] PCR methods from these two laboratories were quality assessed by the NRC.[3] We analysed laboratory results from nasopharyngeal swabs collected from symptomatic patients between January 1, 2012 and December 31, 2019 in all France. Samples included in the study were all tested for *Bordetella spp* (*B. bronchiseptica* or *B. pertussis* or *B. holmesii*) using PCR targeting insertion sequences *IS481*. A pertussis confirmed case was defined as a patient with a positive PCR result.

Text S2: Vaccine schedules and coverage

In France, aP vaccines were first introduced in 1998 as a booster for teenagers (at 11-13 years of age). They progressively replaced wP vaccines for primary vaccination since 2000, and became predominantly administered since 2002. wP vaccines were discontinued in 2004 for primary vaccination, and in 2006 for all vaccinations (primary and booster).[4] Formulations of aP vaccine now available in France contain 2,3 or 5 antigens. In April 2013, France changed from a "3+1" schedule with three primary doses at 2, 3 and 4 months, and a first booster at 16-18 months, to a "2+1" schedule with two primary doses at 2 and 4 months, and a first booster at 11 months, to simplify the immunization program.[5] The national vaccine coverage was estimated >98% for primary vaccination, and >95% for the first booster since 2015.[6,7]

Text S3: Serological assay

The serological survey was based on a random sample of retrospective collections of completely anonymized leftover serum samples from persons throughout mainland France. For the purpose of this study, two collections from different time periods were used: i) Sera from the first collection were residual sera from subjects aged 2 to 5 years submitted for diagnostic testing other than respiratory infection (mostly for allergy -specific IgE- testing) in 2017-2019 by Cerba laboratories. No individual information of the donors was collected except age and date of sampling. Sera were identified by a unique identifier to ensure that only one sample from any subject was tested; ii) The second collection was used as a comparator, and was composed of historical specimens collected in 2008-2009 from patients aged 2 to 5 years without any severe disease. The samples were initially collected in the context of a prospective study to determine the blood lead level (BLL) distribution in children**,** and stored in

a biobank owned by Santé Publique France; parents of participating children had given their written consent after receiving information from the investigators.[8,9] The birth year of the oldest child included in this analysis was 2004.

For both biocollections, all patients have been informed for the potential anonymous use of their serum for biomedical research.

Sera were stored in – 80°C until used in assays. Serum IgG specific for pertussis toxin (PT) were used for this serosurvey.[10] They were measured in February 2020 using the Savyon® SeroPertussis Toxin IgG ELISA Kit (Ashdod, Israel) according to manufacturer's instructions. The good performance of this kit was validated previously, with a low variance between duplicates on different days.[11]

Text S4: Model

In order to study the potential impact of vaccine schedule changes on the epidemiology of pertussis, we developed a regression model for Y_{ay}, the number of pertussis cases by age *a* and year *y*:

$$Y_{ay} \sim NegBin(\mu_{ay}, k)$$

$$\log(\mu_{ay}) = \alpha + \log(P_{ay}) + \theta_y + \theta_a + \beta W_{ay}$$

where μ_{ay} is the mean of the negative binomial distribution, k is the overdispersion parameter, α is an intercept, P_{ay} is the population of age *a* in year *y* (offset), θ_y is the year effect (with 2012 as reference), θ_a is the age-group effect (three categories: 2-5, 6-11 and 12-20 years old, with 2-5 years old as reference), W_{ay} is a waning function that is described below and β is the regression coefficient associated to this function. This model allowed us to consider potential variations in demography, annual epidemic size, and transmission risk by age.

The waning function W_{ay} is a proxy of waning immunity and is meant to represent the mean effect of waning immunity on the number of pertussis cases, in the whole cohort of children of a given age *a* in year *y*. First, we built a dataset of children born between February 1991 and December 2016 (i.e. the oldest individuals were aged 20 years in January 2012 and the youngest ones were aged 2 years in December 2018). We followed these cohorts of children at monthly time step from 2 to 20 years old, until December 2018. For each individual *i* of age *a* and each month of the study period, we computed the expected time elapsed since the last recommended vaccination (difference between age *a* and age of the last recommended vaccination, a_{vacc}). We then defined a waning function $w_i(a)$ of an individual *i* as a negative exponential function, decaying with the expected time $t_{i,a}$ since last vaccination:

$$w_i(a) = Me^{-\lambda t_{i,a}} = Me^{-\lambda(a-a_{vacc})}$$

where λ is the decay rate (in years^{-1}) and M corresponds to the maximum of the function when $t = 0$ (M lies in the interval [0-1]). We then computed W_{ay} as the mean of w_i over all the individuals aged [a,a-1[years in year *y*.

In our model, the two parameters M and λ were allowed to vary with the vaccine schedule and the type of the last vaccination theoretically received by the individuals. Thus, we defined 4 waning functions:

- The waning function after vaccination with the 2/3/4+16-18 schedule, with parameters M_1 and λ_1 (applied before May 2013).

- The waning function after vaccination with the 2/4+11 schedule, with parameters M_2 and λ_2 (applied from May 2013).
- The waning function after the childhood (at 6 years old from May 2013) or adolescent (at 11-13 years old) booster, for children who received a wP vaccine for primary vaccination, with parameters M_3 and λ_3 (before 2002).
- The waning function after the childhood or adolescent booster, for children who received an aP vaccine for primary vaccination, with parameters M_4 and λ_4 (from 2002).

In order to decrease the number of parameters to estimate and thus avoid over-fitting the data, we fixed $M_3 = M_4 = 1$, and estimated the two other M relatively to M_3 and M_4.

We tested four different models:

- Models 1A and 1B: The waning functions of the new and former vaccine schedule are identical (no impact of the changes in vaccine schedule): $M_1 = M_2$ and $\lambda_1 = \lambda_2$.
    - Model 1A: The decay rate of the childhood or adolescent booster is independent of the type of vaccine received for primary vaccination: $\lambda_3 = \lambda_4$.
    - Model 1B: The decay rate of the childhood or adolescent booster can vary with the type of vaccine received for primary vaccination: $\lambda_3 \neq \lambda_4$.
- Models 2A and 2B: The waning functions of the new and former vaccine schedule can be different: $M_1 \neq M_2$ and $\lambda_1 \neq \lambda_2$.
    - Model 2A: The decay rate of the childhood or adolescent booster is independent of the type of vaccine received for primary vaccination: $\lambda_3 = \lambda_4$.
    - Model 2B: The decay rate of the childhood or adolescent booster can vary with the type of vaccine received for primary vaccination: $\lambda_3 \neq \lambda_4$.

The models were fitted via Bayesian Markov Chain Monte Carlo sampling. We used uniform priors for all parameters. We report the posterior mean and 95% credible interval (CI) of the parameters. We compared the models' performance by computing the deviance information criterion (DIC), with the lowest DIC value corresponding to the best fit.[12] A difference of 4 in DIC units was considered substantial.[13] Convergence was assessed by visual examination of trace plots (Figure S6). The analysis was performed in R. We used functions from the *fitR* and *coda* packages.

Text S5: Sensitivity analyses

We performed several sensitivity analyses (SA) to assess the robustness of our best model. The data came from two different laboratories. We fitted the model to data from each laboratory separately, to assess whether there was a laboratory effect (SA1 and SA2). We also included in the regression equation the total number of negative samples received by age and year (as an offset, in logarithmic form), in order to account for potential variations in sampling (SA3). Finally, in the baseline analysis, we defined 3 age groups (2-5, 6-11 and 12-20 years old). We also considered one model with no age effect (SA4) and two models with different age groups (2-6, 7-12 and 13-20 years old (SA5), or 2-4, 5-10 and 11-20 years old (SA6)).

2. Supplementary Tables and Figures

Parameter	Description	Model 2A	Model 2B
Parameters of the waning function			
λ_1	Decay rate of the waning function for the 2/3/4/16-18 schedule (years^{-1})	0.11 (0.02, 0.24)	0.11 (0.02, 0.24)
λ_2	Decay rate of the waning function for the 2/4/11 schedule (years^{-1})	0.60 (0.16, 0.98)	0.63 (0.18, 0.98)
λ_3	Decay rate of the waning function for the 6/11-year-old booster for all children (model 2A) or for children who received a wP vaccine for primary vaccination (model 2A) (years^{-1})	0.002 (2e^{-05}, 0.006)	0.002 (4e^{-05}, 0.007)
λ_4	Decay rate of the waning function for the 6/11-year-old booster for children who received an aP vaccine for primary vaccination (years^{-1})	NA	0.03 (0.003, 0.08)
M_1	Maximum value of the waning function for the 2/3/4/16-18 schedule	0.74 (0.47, 0.98)	0.75 (0.48, 0.98)
M_2	Maximum value of the waning function for the 2/4/11 schedule	0.66 (0.11, 0.98)	0.65 (0.09, 0.98)
M_3, M_4	Maximum value of the waning function for the 6/11-year-old booster	1 (fixed)	1 (fixed)
Parameters of the regression			
α	Intercept	-9.3 (-9.4, -9.1)	-9.2 (-9.3, -9.1)
β	Coefficient associated to the waning function	-1.2 (-1.4, -1.1)	-1.3 (-1.5, -1.1)
θ_a	Age-group effect		
	2-5 years old (reference)	0	0
	6-11 years old	0.42 (0.33, 0.51)	0.39 (0.30, 0.48)
	12-20 years old	-0.03 (-0.15, 0.10)	-0.01 (-0.14, 0.11)
θ_y	Year effect		
	2012 (reference)	0	0
	2013	0.71 (0.59, 0.82)	0.71 (0.60, 0.82)
	2014	-0.25 (-0.39, -0.12)	-0.25 (-0.38, -0.12)
	2015	-0.73 (-0.88, -0.58)	-0.73 (-0.88, -0.58)
	2016	-0.27 (-0.40, -0.13)	-0.28 (-0.41, -0.14)
	2017	0.75 (0.55, 0.79)	0.71 (0.59, 0.83)
	2018	0.67 (0.55, 0.79)	0.63 (0.51, 0.74)
k	Overdispersion parameter	79.7 (65.4, 90.9)	77.9 (62.2, 91.6)

Table S1: Estimated parameters (posterior mean and 95% credible interval) obtained for the best model (model 2A) and the second best model (model 2B).

Parameter	Description	Baseline analysis	SA1	SA2	SA3	SA4	SA5	SA6
λ_1	Decay rate of the waning function for the 2/3/4/16-18 schedule (years-1)	0.11 (0.02, 0.24)	0.11 (0.04, 0.20)	0.16 (0.06, 0.32)	0.10 (0.01, 0.22)	0.15 (0.06, 0.26)	0.16 (0.06, 0.29)	0.10 (0.04, 0.19)
λ_2	Decay rate of the waning function for the 2/4/11 schedule (years-1)	0.60 (0.16, 0.98)	0.35 (0.05, 0.90)	0.42 (0.03, 0.94)	0.60 (0.18, 0.97)	0.23 (0.02, 0.56)	0.45 (0.07, 0.93)	0.26 (0.01, 0.85)
λ_3	Decay rate of the waning function for the 6/11-year-old booster for children who received a wP vaccine for primary vaccination (years-1)	0.002 ($2e^{-05}$, 0.006)	0.002 ($1e^{-04}$, 0.007)	0.003 ($1e^{-04}$, 0.012)	0.002 ($4e^{-05}$, 0.006)	0.001 ($3e^{-05}$, 0.005)	0.003 ($1e^{-04}$, 0.014)	0.001 ($3e^{-05}$, 0.005)
M_1	Maximum value of the waning function for the 2/3/4/16-18 schedule	0.74 (0.47, 0.98)	0.92 (0.73, 1.00)	0.89 (0.64, 1.00)	0.72 (0.46, 0.97)	0.94 (0.83, 1.00)	0.94 (0.80, 1.00)	0.94 (0.79, 1.00)
M_2	Maximum value of the waning function for the 2/4/11 schedule	0.66 (0.11, 0.98)	0.75 (0.28, 0.99)	0.61 (0.10, 0.98)	0.69 (0.16, 0.99)	0.75 (0.41, 0.99)	0.70 (0.15, 0.99)	0.75 (0.31, 0.98)
M_3, M_4	Maximum value of the waning function for the 6/11-year-old booster	1 (fixed)	1 (fixed)	1 (fixed)	1 (fixed)	1 (fixed)	1 (fixed)	1 (fixed)
	DIC	*928*			*928*	*1006*	*969*	*974*

Table S2: Parameters of the waning function (posterior mean and 95% credible interval) estimated in the baseline analysis (model 2A) and sensitivity analyses (SA1: using data from Cerba laboratory only ; SA2: using data from Eurofins-Biomnis laboratory only ; SA3: adding the number of negative samples in the model ; SA4: removing the age-group effect in the model ; SA5: changing the definition of the age groups to 2-6, 7-12 and 13-20 years old ; SA6: changing the definition of the age groups to 2-4, 5-10 and 11-20 years old). Deviance information criteria (DIC) are only given for models that are fitted to the full dataset.

Age group	Former vaccine schedule		New vaccine schedule		Comparison	
	Patients (n)	GMC, UI/mL (95%IC)	Patients (n)	GMC, IU/mL (95%IC)	GM ratio (95%IC)	p-value
2 years	68	11.62 (9.05-14.92)	38	5.85 (4.08-8.39)	0.50 (0.45-0.56)	0.0016
3 years	64	6.80 (4.77-9.70)	51	3.88 (2.82-5.34)	0.57 (0.55-0.59)	0.026
4 years	70	4.39 (3.26-5.91)	24	3.56 (2.56-5.62)	0.77 (0.69-0.95)	0.46

Table S3: Results of the serological assay: geometric mean concentrations (GMC) by age group and vaccine schedule. Comparisons between groups are expressed as geometric mean (GM) ratios, calculated from the back-transformed log mean difference between groups.

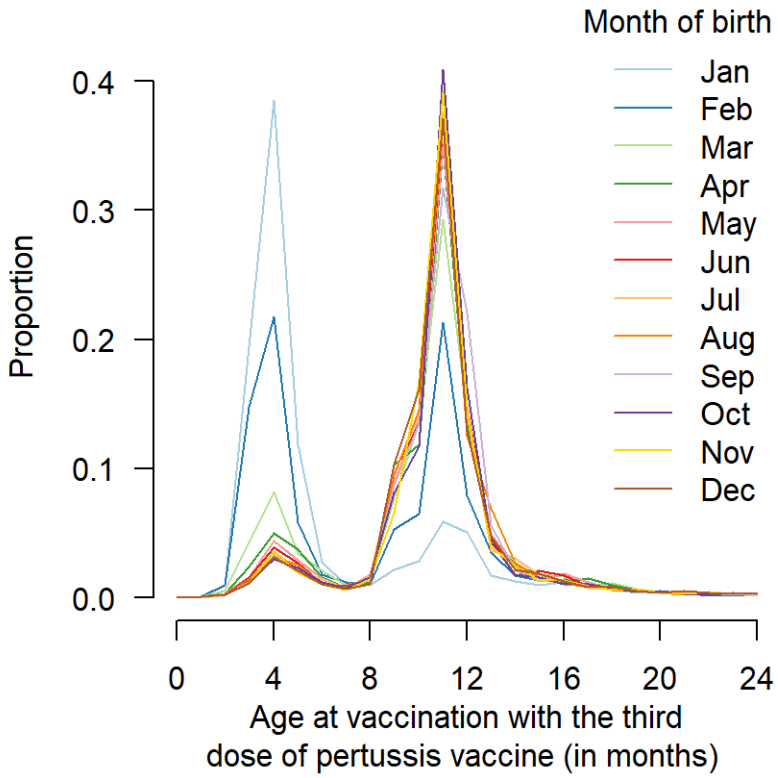


Figure S1: Distribution of the age at vaccination with the third dose of pertussis vaccine for children born in 2013, by month of birth. Data were extracted from the comprehensive social health insurance database ("Datamart de consommation inter-régimes", DCIR). The switch in the age at vaccination with the third dose of pertussis vaccine (from 4 months to 11 months) clearly occurred in children born in February 2013, confirming that the new vaccine schedule was quickly implemented after its publication on April 19, 2013.

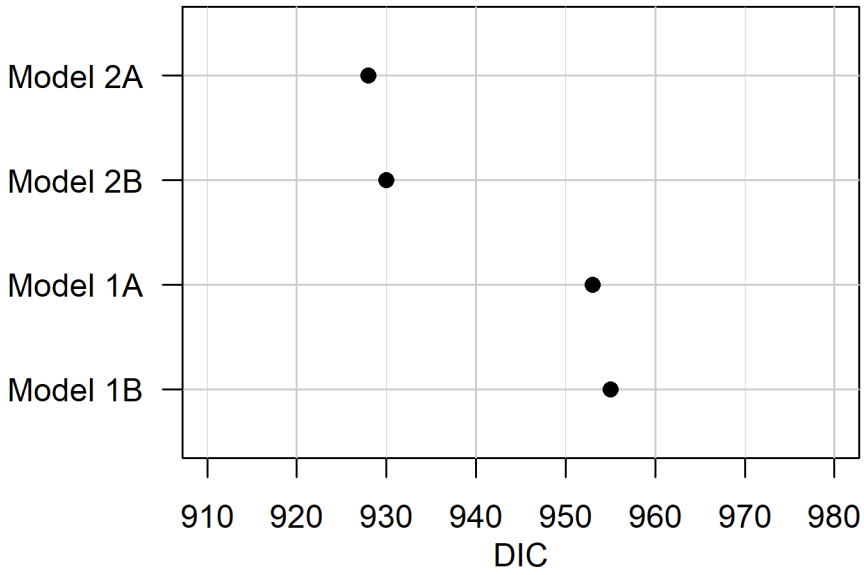


Figure S2: Models' comparison using the deviance information criterion (DIC). Models 1A/1B: The waning functions of the former and new vaccine schedules are identical (no impact of the changes in vaccine schedule). Models 2A/2B: The waning functions of the former and new vaccine schedules can be different. Models 1A/2A: The decay rate of the childhood or adolescent booster is independent of the type of vaccine (wP/aP) received for primary vaccination. Models 1B/2B: The decay rate of the childhood or adolescent booster can vary with the type of vaccine (wP/aP) received for primary vaccination.

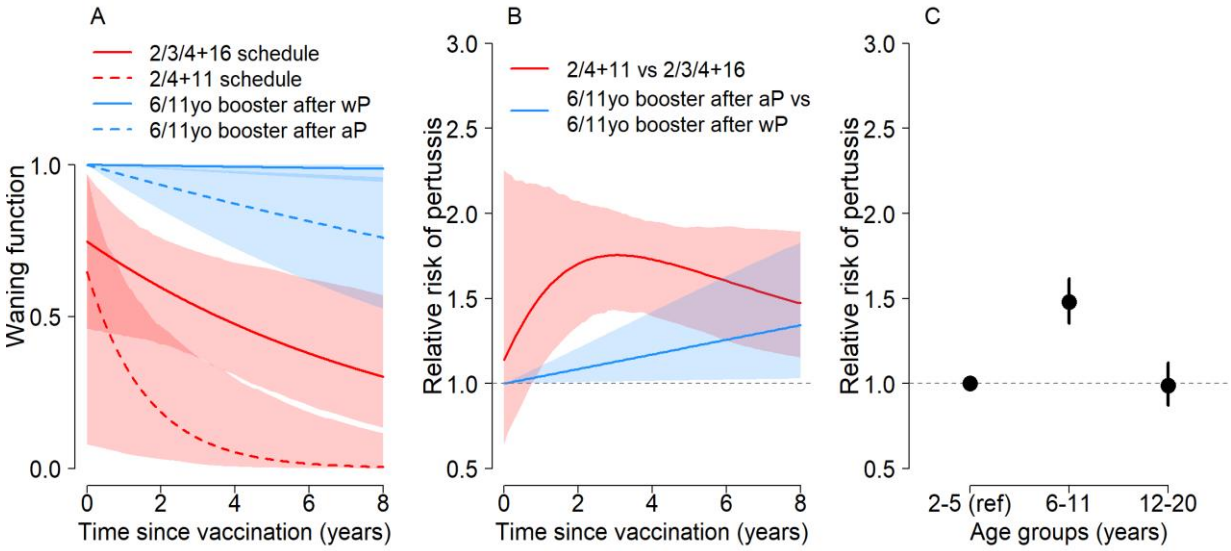


Figure S3: Parameters estimated by the second best model (model 2B) (mean and 95% credible interval). (A) Waning function after vaccination by the former vaccine schedule (2/3/4+16), by the new vaccine schedule (2/4+11), by the childhood (6 years) or adolescent (11 years) booster after primary vaccination with a wP vaccine, and by the childhood or adolescent booster after primary vaccination with an aP vaccine. (B) Relative risk of pertussis after vaccination by the new vaccine schedule compared to the former schedule, and relative risk of pertussis after vaccination by the childhood/adolescent booster for children who received an aP vaccine for primary vaccination compared to children who received a wP vaccine for primary vaccination. (C) Relative risk of pertussis by age group, after accounting for vaccination schedule.

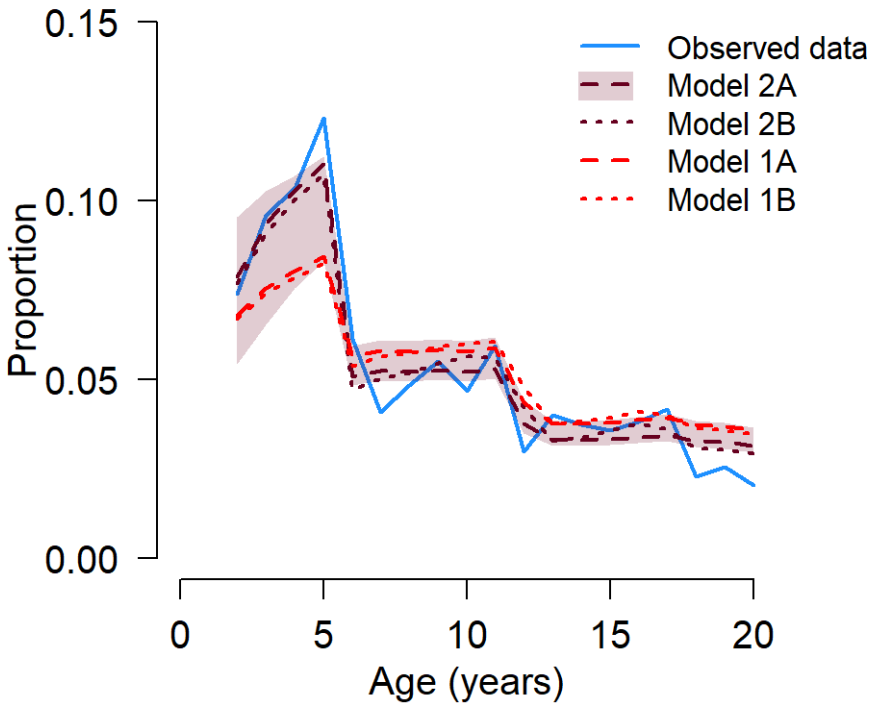


Figure S4: Proportions of cases by age in 2019, observed and predicted by the different models. Models 1A/1B: The waning functions of the former and new vaccine schedules are identical (no impact of the changes in vaccine schedule). Models 2A/2B: The waning functions of the former and new vaccine schedules can be different. Models 1A/2A: The decay rate of the childhood or adolescent booster is independent of the type of vaccine (wP/aP) received for primary vaccination. Models 1B/2B: The decay rate of the childhood or adolescent booster can vary with the type of vaccine (wP/aP) received for primary vaccination.

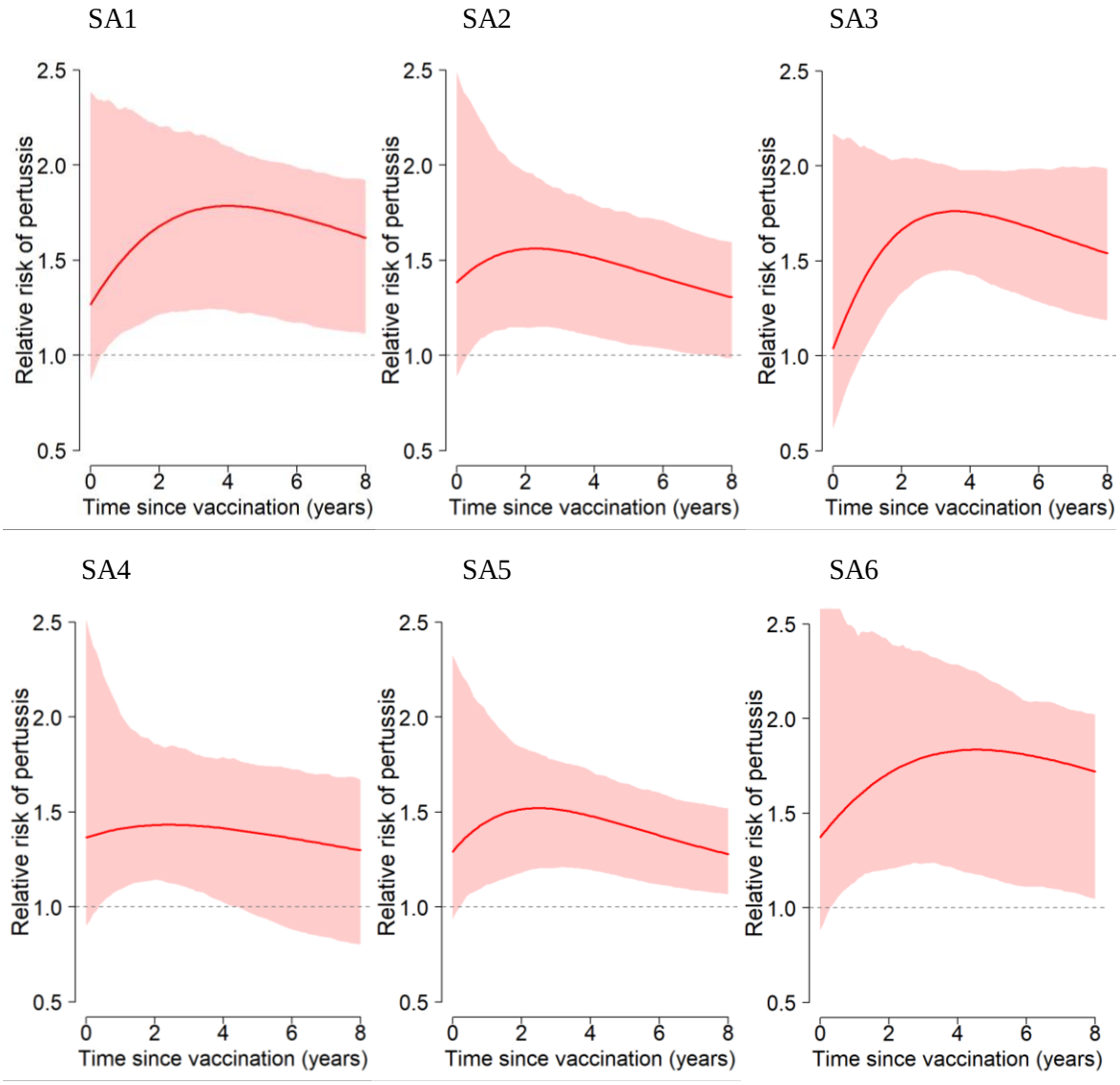


Figure S5: Estimated relative risk of pertussis after vaccination by the new vaccine schedule compared to the former vaccine schedule, in the six sensitivity analyses (SA1: using data from Cerba laboratory only ; SA2: using data from Eurofins-Biomnis laboratory only ; SA3: adding the number of negative samples in the model ; SA4: removing the age-group effect in the model ; SA5: changing the definition of the age groups to 2-6, 7-12 and 13-20 years old; SA6: changing the definition of the age groups to 2-4, 5-10 and 11-20 years old). Three years after vaccination, the relative risk of disease with the new vaccine schedule compared to the former schedule was 1.8 (1.2-2.2) for SA1, 1.6 (1.1-1.9) for SA2, 1.7 (1.4-2.0) for SA3, 1.4 (1.1-1.8) for SA4, 1.6 (1.2-1.9) for SA5 and 1.7 (1.2-2.1) for SA6.

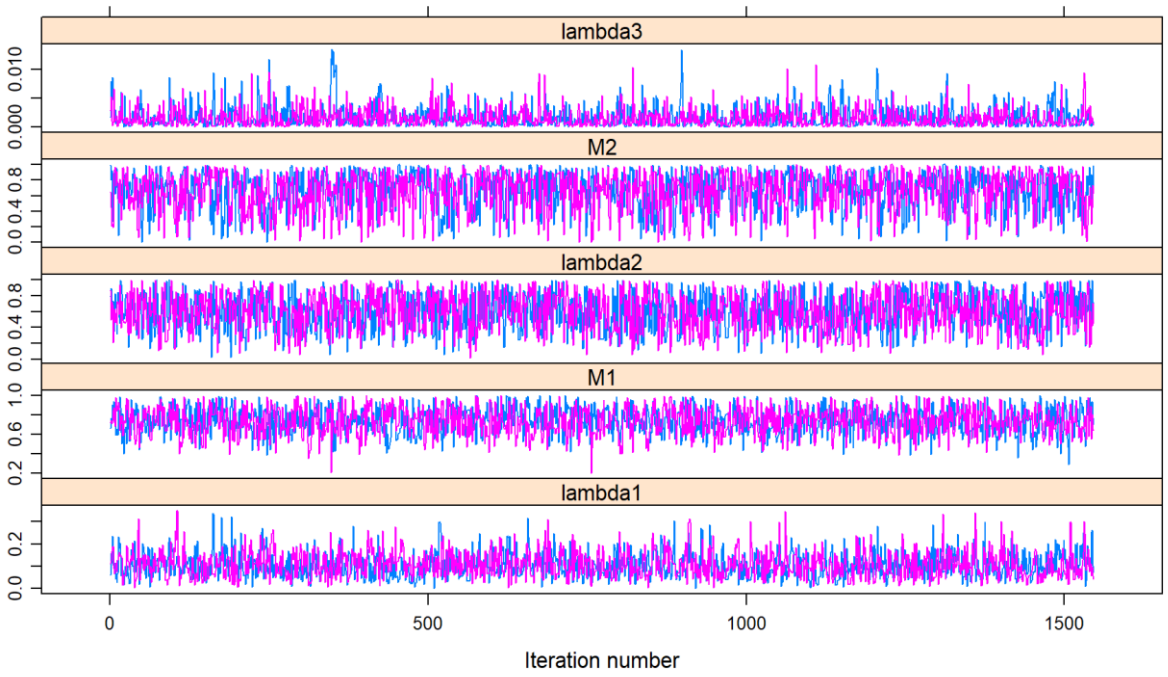


Figure S6. Trace plots of MCMC chains after burn-in. Two parallel MCMC chains were run starting from different initial values. Each chain was run for 25000 iterations, discarding the first 8000 samples of each simulation as burn-in, with a thinning of 10.

1. References

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