# The optimal strategy for pertussis vaccination: a systematic review and meta-analysis of randomized control trials and real-world data

Hung Song Nguyen, MD; Nguyen-Phong Vo, MD; Shih-Yen Chen, MD, PhD; Ka-Wai Tam, MD, PhD

**OBJECTIVE:** Severe pertussis infection has been reported in infants before receiving routine immunization series. This problem could be solved by vaccinating mothers during pregnancy or children at birth. This study aimed to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) and real-world evidence to evaluate the optimal strategy for pertussis vaccination.

**DATA SOURCES:** PubMed, Embase, and the Cochrane Library databases were searched until December 2020.

**STUDY ELIGIBILITY CRITERIA:** RCTs, cohort studies, case-control studies, and case series were included if they investigated the efficacy, immunogenicity, and safety of acellular pertussis vaccine during pregnancy and at birth.

**METHODS:** Number of pertussis cases, severe adverse events (SAEs), and pertussis antibody concentration in infants before and after they receive routine vaccination series were extracted and random-effect model was used to pool the analyses.

**RESULTS:** Overall, 29 studies were included. Our meta-analysis revealed that pertussis immunization during pregnancy significantly increased the concentrations of 3 pertussis antibodies and reduced the incidence rates of infected infants below 3 months of age (odds ratio, 0.22; 95% confidence interval, 0.14—0.33). Similarly, infants vaccinated at birth had higher levels of pertussis antibody than those who were not. No significant difference in rates of severe adverse events was seen in all vaccination groups (during pregnancy [risk ratio, 1.18; 95% confidence interval, 0.76—1.82] and at birth [risk ratio, 0.72; 95% confidence interval, 0.34—1.54]).

**CONCLUSION:** Pertussis vaccination during pregnancy could protect infants against pertussis disease before the routine vaccination. Pertussis immunization at birth would be an alternative for infants whose mothers did not receive pertussis vaccines during pregnancy.

**Key words:** meta-analysis, pertussis vaccination, systematic review, vaccine at birth, vaccine during pregnancy

## Introduction

Pertussis is a highly contagious disease caused by *Bordetella pertussis*. It is endemic worldwide, especially in developing countries.[1] Unfortunately, despite routine immunization programs considerably reducing the number of cases and mortality rates,[2] the incidence rates and number of severe cases remain high in infants who are yet to receive the primary vaccination series—more than 1000 cases per 100,000 infants during outbreaks.[3] According to the Global Burden of Disease Study, approximately 400 pertussis-associated deaths per million live births occurred among infants aged <1 year in 2013.[4] Furthermore, during the 2010 pertussis outbreak in the United States, 10 deaths among 9000 pertussis infections occurred in infants <3 months of age.[5]

Several strategies, such as cocooning or vaccination during pregnancy, during the postpartum period, or at birth, have been introduced to prevent pertussis in infants before they receive their first doses of routine vaccines. The efficacy of cocooning immunization remains uncertain because of the lack of cost-effectiveness and need to vaccinate several caregivers around the vulnerable infant.[6] Furthermore, postpartum vaccination only protects the mother and fails to induce the infant's immunity.[7] Earlier implementation of vaccine, that is, during pregnancy, could increase the child's level of antibodies and reduce hospitalizations,[8] but many controversies surrounding the optimal timing, safety, and interference of maternal antibodies, have remained.[9] Finally, little evidence exists for the efficacy and safety of vaccination at birth.[10] Although Provenzano et al[11] and Halsey et al[12] have

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## AJOG at a Glance

### Why was this study conducted?

Severe pertussis infection has been reported in infants before receiving routine immunization series. This study aimed to evaluate the efficacy, immunogenicity, and safety of pertussis vaccination during pregnancy and at birth.

### Key findings

Administering the pertussis vaccine during pregnancy and at birth was safe and significantly increased pertussis antibody concentration in infants before the primary vaccination schedule. Maternal immunization significantly reduced the incidence of pertussis in infants aged <3 months.

### What does this add to what is known?

A national maternal immunization program could be considered to protect infants against pertussis before routine vaccinations. Furthermore, neonatal immunization could be an alternative for infants of mothers who did not receive a pertussis vaccine during pregnancy.

suggested using whole-cell vaccines to induce immune tolerance and limit maternal immunologic responses, other studies have demonstrated adequate immunogenicity among infants receiving the acellular vaccines.[13–16]

Nevertheless, vaccinating mothers and their children at birth could potentially prevent early severe pertussis cases and was the focus of this study. Although a randomized controlled trial (RCT) is generally considered to be the most reliable study design to report intervention effectiveness, it lacks the ability to represent the wider and more heterogeneous population of pertussis cases, whose evidence is found in real-world data, such as cohort studies and case-control studies. Therefore, we conducted a systematic review, a meta-analysis of RCTs, and real-world data study to investigate the efficacy, immunogenicity, and safety of acellular pertussis vaccine during pregnancy and at birth.

## Methods

### Search strategy

PubMed or MEDLINE, Embase, and the Cochrane Library databases were searched using a combination of medical subject headings and key words (Methods in Supplemental data). In addition, we searched ClinicalTrials.gov and relevant papers manually for further studies. The search started from the inception of the study to December 2020. This study was registered a priori in the online International Prospective Register of Systematic Reviews (registration number: CRD42020160746).

### Selection criteria

RCTs, cohort studies, case-control studies, and case series were included in this analysis when (1) efficacy, (2) immunogenicity, or (3) severe adverse events (SAEs) of pertussis vaccination were evaluated in either of the 2 following scenarios. First, they were compared between infants whose mothers received pertussis vaccines during pregnancy and infants whose mothers did not (comparison number 1). Second, they were compared between infants vaccinated at birth and those who were not (comparison number 2). All infants received pertussis vaccines from 2 or 3 months of age according to the routine immunization program. Non-English studies were included in our analysis. We excluded studies on nonhuman cases, preterm newborns, or those that did not report on the 3 aforementioned measurements.

### Data extraction

Here, 2 researchers (H.S.N. and N.P.V.) screened the papers identified and then extracted the baseline and outcome data independently. A third author (K.W.T.) made the final decision in case of any disagreements. The following data were extracted: author, year of publication, period of study, inclusion criteria, primary vaccination schedule, number of participants, intervention, outcome data, and vaccine manufacturer. We contacted the authors for additional information if necessary.

### Methodological quality appraisal

Quality appraisal was independently performed by 2 reviewers (H.S.N. and N.P.V.) using the recommendations from the Cochrane Collaboration. The risk of bias for RCTs was assessed using the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[17] For nonrandomized studies, the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool was used.[18] The third author (K.W.T.) resolved all disagreements.

### Outcomes

The primary outcomes were (1) the immunogenicity of the pertussis vaccine, (2) incidence rates of pertussis, or (3) SAEs between the intervention and control groups. Immunogenicity was defined as the child's plasma concentrations of antigen-specific antibodies: antipertussis toxin (anti-PT), antifilamentous hemagglutinin (anti-FHA), and antipertactin (anti-PRN) immunoglobulin G (IgG) measured at 3 time points (umbilical cord blood and before and after the primary vaccination schedules). SAEs were defined and classified according to the World Health Organization (WHO) definition.[19] Secondary outcomes were to assess whether antibody concentration in umbilical cord arterial serum varies according to different gestational ages at vaccination (early vs late in the third trimester of pregnancy).

### Statistical analyses

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The Review Manager software package (RevMan version 5.3, Cochrane Collaboration) was used to analyze the extracted data.[21] The incidence of pertussis was presented as odds ratios (ORs) and 95% confidence intervals (CIs), calculated using the

Mantel-Haenszel method. Vaccine efficacy was calculated as 1 minus OR based on the definition from the WHO.[22] As most studies reported the geometric mean concentration for levels of antibodies, we converted these to natural logarithm and, hence, from log-normal to normal distributions for all studies.[23] Moreover, as the studies used different assays to measure antibody levels, the immunogenicity of the pertussis vaccine was reported as standardized mean differences (SMDs) and 95% CIs, calculated using the inverse variance method. Risk ratios (RRs) with 95% CIs were used to evaluate SAEs. The random effect model was used for the pooled estimate of effect sizes.

Heterogeneity among studies was evaluated using both the Cochrane Q tests and $I^2$ statistics. When $I^2$ statistics were higher than 50% or the *P* value was lower than .10, heterogeneity was considered significant.[24] In addition, subgroup analyses were performed for different study designs: RCTs, cohort studies, or case-control studies.

## Results

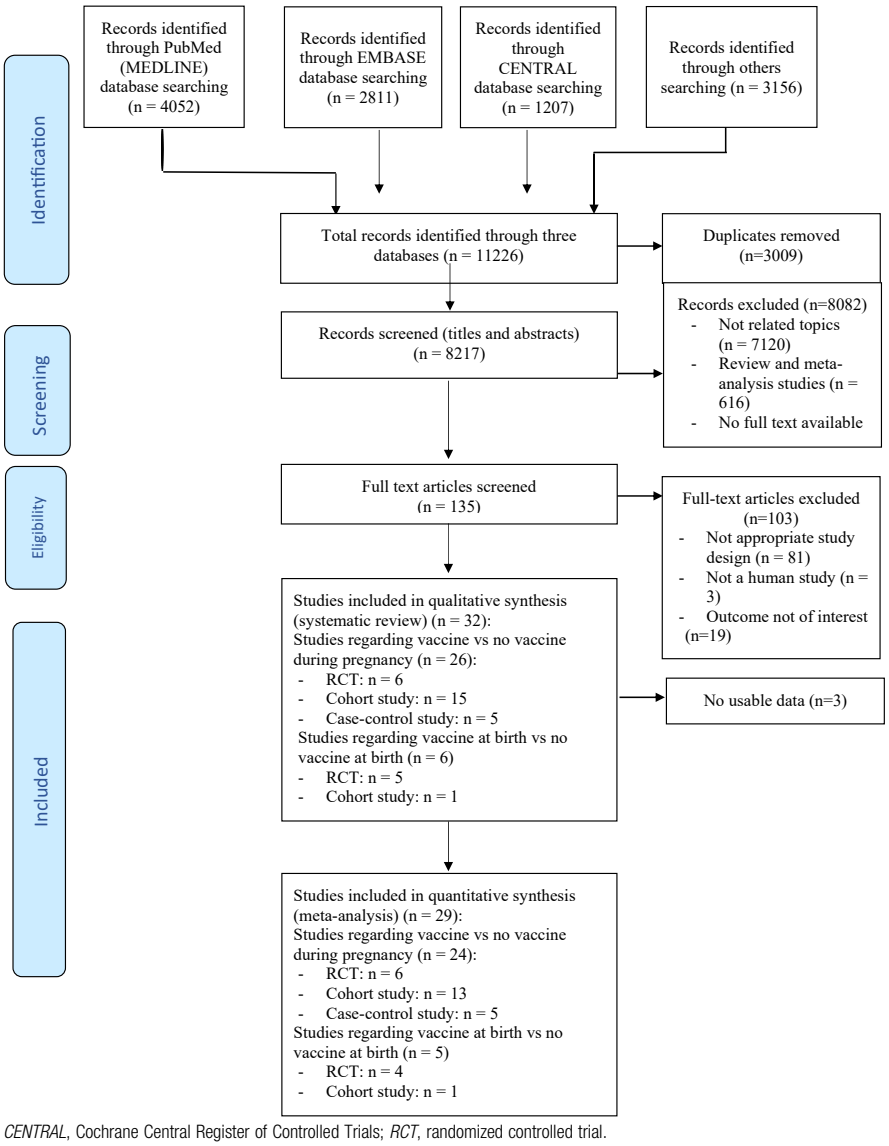
### Study selection

The selection procedure and screened studies are presented in a PRISMA flowchart (Figure 1). Overall, the systematic review included 26 studies[13,25–50] comparing pertussis vaccination with no vaccination during pregnancy (Table 1) and 6 studies[10,13–16,51] comparing infants vaccinated at birth with those who were not (Table 2). Furthermore, meta-analysis was performed on 29 studies,[10,14–16,25–31,33,34,36–51] of which 24 studies were carried out in pregnant women[25–31,33,34,36–50] and 5 studies in neonates.[10,14–16,51] Acellular pertussis vaccine was used for both the intervention and the routine vaccination series groups.

### Vaccination during pregnancy: study characteristics

The results are presented in Table 1. All studies were published from 2008 to 2020. Children received their doses of routine vaccination at 2, 4, and 6 months of age in 14 studies[27,28,30–32,34–38,41,43,45,49]; at 2, 3, and 4 months in 5 studies[39,40,42,45,46]; and at 3 and 5 months in 2 studies.[26,45] The vaccines used in the intervention group were from GlaxoSmithKline (GSK) in 10 studies[26,27,31,33,41,42,45–47] and from Sanofi Pasteur in 13 studies.[27,32,34–40,43,46,48,49] All RCTs[26,34,39,43,45,49] and prospective studies[25,30,32,35–38,40–42,44,46] investigated the immunogenicity outcome, and all case-control studies[28,29,31,47,48] investigated the incidence rate of pertussis.

**FIGURE 1**
**Flowchart of the study selection process**




*CENTRAL*, Cochrane Central Register of Controlled Trials; *RCT*, randomized controlled trial.

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### Quality of the studies

In general, 6 RCTs[26,34,39,43,45,49] were assessed for bias using RoB 2 (Supplemental Figure 1, A). Moreover, 13 cohorts (Supplemental Figure 1, B)[25,27,30,33,36–38,40–42,44,46,50] and 5 case-control studies[28,29,31,47,48] were assessed for bias using ROBINS-I (Supplemental Figure 1, C). The quality of each study in the meta-analysis is summarized in detail in Supplemental Figure 1, A, B, and C.

**TABLE 1**
**Characteristic of studies on vaccines during pregnancy vs no vaccines during pregnancy**

| Author (year) | Place | Inclusion criteria | Primary pertussis vaccination schedule | Number of participants | Intervention | Period of study | Vaccine manufacturer applied in the intervention |
|---|---|---|---|---|---|---|---|
| Randomized control trial study | | | | | | | |
| Barug et al (2019)[26] | The Netherlands | Mother: no pregnancy abnormalities, no pertussis vaccination <5 y, no Td vaccine <2 y, no vaccine <2 wk. Infant: healthy and >37 wk of gestation | 3 and 5 mo | T1: 53<br>T2: 50 | T1: Tdap vaccination at 30–32 wk<br>T2: Tdap vaccination within 48 h after delivery | January 2014 to March 2016 | GSK |
| Halperin et al (2018)[34] | Canada | Mother: no pregnancy abnormalities, no pertussis <5 y, no Td or Tdap vaccine <5 y, no vaccine <2 wk. Infants: healthy with no medical condition | 2, 4, and 6 mo | T: 135<br>C: 138 | T: Tdap vaccination at 30.0–35.7 wk<br>C: Td vaccination at 30.0–35.7 wk | March 2012 to April 2014 | Sanofi Pasteur |
| Hoang et al (2016)[39] | Vietnam | Mother: no Tdap <10 y, no Td <1 mo, no fever <72 h. Infant: healthy with no medical condition | 2, 3, and 4 mo | T: 52<br>C: 51 | T: Tdap vaccination at 18–32 wk<br>C: vaccinated only Tetanus at 18–32 wk | December 2012 to December 2014 | Sanofi Pasteur |
| Munoz et al (2014)[43] | United States | Mother: no pregnancy abnormalities, no Tdap or Td <2 y, no vaccines <4 wk, no influenza vaccine <2 wk, no fever <72 h | 2, 4, and 6 mo | T1: 33<br>T2: 15 | T1: Tdap vaccination at 30–32 wk<br>T2: Tdap vaccination after birth | October 2008 to May 2012 | Sanofi Pasteur |
| Perrett et al (2020)[45] | Australia, Canada, Czech Republic, Finland, Italy, Spain | Mother: no pregnancy abnormalities, no Tdap during pregnancy, no pertussis <5 y, no vaccine <30 d, no fever <72 h | 2 and 4 mo in Spain<br>3 and 5 mo in Finland and Italy<br>2, 3, and 4 mo in the Czech Republic<br>2, 4, and 6 mo in Australia, Canada, and Spain | T: 341<br>C: 346 | T: Tdap vaccination at 27–36 wk<br>C: no aP vaccine during pregnancy | October 2015 to October 2017 | GSK |
| Villarreal Pérez et al (2017)[49] | Mexico | Mother: no pregnancy abnormalities, no Tdap or Td vaccine <2 y, no fever <72 h | 2, 4, and 6 mo | T: 90<br>C: 81 | T: Tdap vaccination at 30–32 wk<br>C: no aP vaccine during pregnancy | September 2011 to August 2014 | Sanofi Pasteur |
| Prospective cohort study | | | | | | | |

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*(continued)*

**TABLE 1**
**Characteristic of studies on vaccines during pregnancy vs no vaccines during pregnancy** *(continued)*

| Author (year) | Place | Inclusion criteria | Primary pertussis vaccination schedule | Number of participants | Intervention | Period of study | Vaccine manufacturer applied in the intervention |
|---|---|---|---|---|---|---|---|
| Abu Raya et al (2014)[25] | Israel | Mother: no pregnancy abnormalities, no pertussis <5 y, no Td or Tdap vaccine <5 y, no vaccine <2 wk. Infants: weight >2000 g | NA | T: 51<br>C: 20 | T: Tdap vaccination at 23–36 wk<br>C: no aP vaccine during pregnancy | November 2013 to May 2014 | GSK |
| Fallo et al (2018)[30] | Argentina | Mother: no pregnancy abnormalities and no cough that lasted >2 wk. Infants: weight >2000 g | 2, 4, and 6 mo | T: 105<br>C: 99 | T: Tdap vaccination at 13.2–36.6 wk<br>C: no aP vaccine during pregnancy | 2011 to 2014 | NA |
| Gall et al (2011)[32] | United States | NA | 2, 4, and 6 mo | T: 52<br>C: 52 | T: Tdap during the second trimester of pregnancy<br>C: no aP vaccine during pregnancy | October 2008 to December 2009 | Sanofi Pasteur |
| Hardy-Fairbanks et al (2013)[35] | United States | Mother: no pregnancy abnormalities<br>Infants: healthy and >37 wk of gestation | 2, 4, and 6 mo | T: 16<br>C: 54 | T: Tdap vaccination at 16–36 wk<br>C: no aP vaccine during pregnancy | March 2008 to February 2009 | Sanofi Pasteur |
| Healy et al (2018)[37] | United States | Infants: healthy and >37 wk of gestation | 2, 4, and 6 mo | T: 312<br>C: 314 | T: Tdap vaccination at 27–36 wk and ≥14 d before birth<br>C: no aP vaccine during pregnancy | December 2013 to March 2014 | Sanofi Pasteur |
| Healy et al (2013)[36] | United States | Mother: no pregnancy abnormalities, Tdap vaccine <2 y. Infants: >37 wk of gestation | 2, 4, and 6 mo | T1: 19<br>T2: 86 | T1: Tdap vaccination at 1–28 wk<br>T2: Tdap vaccination before pregnancy within the prior 2 y | June 2009 to May 2011 | Sanofi Pasteur |
| Hincapié-Palacio et al (2018)[38] | Colombia | Mother: no pregnancy abnormalities, no fever <72 h. Infants: >37 wk of gestation. Pertussis cases: confirmation by PCR or laboratory test + epidemiology or clinical criteria and occurring <6 mo | 2, 4, and 6 mo | T: 745<br>C: 260 | T: Tdap vaccination at 30–36 wk<br>C: no aP vaccine during pregnancy | December 2015 to April 2016 | Sanofi Pasteur |

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**TABLE 1**
**Characteristic of studies on vaccines during pregnancy vs no vaccines during pregnancy** *(continued)*

| Author (year) | Place | Inclusion criteria | Primary pertussis vaccination schedule | Number of participants | Intervention | Period of study | Vaccine manufacturer applied in the intervention |
|---|---|---|---|---|---|---|---|
| Ladhani et al (2015)[40] | England | Infant: ≥37 wk of gestation | 2, 3, and 4 mo | T: 141<br>C: 246 | T: Tdap vaccination at 28–38 wk<br>C: no aP vaccine during pregnancy | December 2012 to July 2014 | Sanofi Pasteur |
| Lima et al (2019)[41] | Brazil | Mother: no pregnancy abnormalities and no pertussis vaccination. Infants: healthy with adequate weight for the gestational age | 2, 4, and 6 mo | T: 66<br>C: 101 | T: Tdap vaccination at 30–36 wk<br>C: no aP vaccine during pregnancy | NA | GSK |
| Maertens et al (2016)[42] | Belgium | Mother: no pregnancy abnormalities, no Tdap vaccine <10 y, no vaccine <4 wk, no fever <72 h. Infants: healthy with no medical condition | 2, 3, and 4 mo | T: 57<br>C: 42 | T: Tdap vaccination at 22–33 wk<br>C: Tdap vaccination after birth | February 2012 to December 2016 | GSK |
| Naidu et al (2016)[44] | Australia | Mother: no pregnancy abnormalities, no Tdap in pregnancy. Infants: >37 wk of gestation | NA | T1: 53<br>T2: 62<br>C: 39 | T1: Tdap vaccination at 28–32 wk<br>T2: Tdap vaccination at 32–36 wk<br>C: no aP vaccine during pregnancy | April 2014 to September 2014 | NA |
| Rice et al (2019)[46] | United Kingdom | Mother: no pregnancy abnormalities | 2, 3, and 4 mo | T: 16<br>C: 15 | T: vaccinated at 30–32 wk<br>C: no aP vaccine during pregnancy | May 2014 to September 2016 | Sanofi Pasteur or GSK |
| Retrospective cohort study | | | | | | | |
| Baxter et al (2017)[27] | United States | Mothers: born <1996 g. Infants: >37 wk of gestation. Pertussis case: confirmation by PCR and occurring <8 wk and <1 y | 2, 4, and 6 mo | T: 68,168<br>C: 79,292 | T: Tdap vaccination during pregnancy until ≥8 d before birth<br>C: no aP vaccine during pregnancy | 2006 to 2015 | Sanofi Pasteur or GSK |
| Griffin et al (2018)[33] | New Zealand | Mothers: Mother: >20 wk of gestation. Infants: >400 g and >28 wk of gestation | NA | T: 8178<br>C: 60,372 | T: Tdap vaccination at 28–38 wk<br>C: no aP vaccine during pregnancy | 2013 | GSK |

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*(continued)*

**TABLE 1**
**Characteristic of studies on vaccines during pregnancy vs no vaccines during pregnancy** *(continued)*

| Author (year) | Place | Inclusion criteria | Primary pertussis vaccination schedule | Number of participants | Intervention | Period of study | Vaccine manufacturer applied in the intervention |
|---|---|---|---|---|---|---|---|
| Winter et al (2017)[50] | United States | Mother: no pregnancy abnormalities. Infants: >27 wk of gestation and weighted >500 g. Pertussis case: confirmation by PCR or laboratory test or clinical criteria and occurring <8 wk and <1 y | NA | T1: 42,941<br>T2: 31,563 | T1: Tdap vaccination at 27–36 wk<br>T2: Tdap vaccination postpartum | 2013 to 2014 | NA |
| Case-control study | | | | | | | |
| Dabrera et al (2015)[29] | United Kingdom | Pertussis case: confirmation by PCR or laboratory test and occurring <8 wk | NA | T: 49<br>C: 64 | T: Tdap vaccination at 26–38 wk<br>C: no aP vaccine during pregnancy | 2013 to 2014 | NA |
| Bellido-Blasco et al (2017)[28] | Spain | Pertussis case: confirmation by PCR and occurring <12 wk | 2, 4, and 6 mo | T: 46<br>C: 42 | T: Tdap vaccination at 28–36 wk<br>C: no aP vaccine during pregnancy | March 2015 to February. 2016 | NA |
| Fernandes et al (2019)[31] | Brazil | Infants >36 wk of gestation and weighed >2500 g. Pertussis cases: clinical criteria and occurring <8 wk | 2, 4, and 6 mo | T: 151<br>C: 139 | T: Tdap vaccination at 18–37 wk<br>C: no aP vaccine during pregnancy | February 2015 to July 2016 | GSK |
| Saul et al (2018)[47] | Australia | Pertussis case: confirmation by PCR or laboratory test or clinical criteria and occurring <12 wk and <6 mo | NA | T: 48<br>C: 48 | T: Tdap vaccination during pregnancy until ≥8 d before birth<br>C: no aP vaccine during pregnancy | February 2015 to July 2016 | GSK |
| Skoff et al (2017)[48] | Portland | Infants: >37 wk of gestation. Pertussis case: confirmation by PCR or laboratory test or laboratory test + epidemiology or clinical criteria and occurring <8 wk | NA | T: 139<br>C: 636 | T: Tdap vaccination during pregnancy until ≥8 d before birth<br>C: no aP vaccine during pregnancy | January 2011 to December 2014 | Sanofi Pasteur or GSK |

*aP*, acellular pertussis vaccine; *C*, control group; *GSK*, GlaxoSmithKline; *NA*, not applicable; *PCR*, polymerase chain reaction; *T*, intervention group; *Td*, diphtheria and tetanus vaccine; *Tdap*, diphtheria, tetanus, and acellular vaccine.

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**TABLE 2**
**Characteristic of studies regarding vaccine at birth vs no vaccine at birth**

| Author (year) | Place | Inclusion criteria | Primary pertussis vaccination schedule | Number of participants | Intervention | Period of study | Vaccine manufacturer applied in the intervention |
|---|---|---|---|---|---|---|---|
| Randomized control trial study | | | | | | | |
| Belloni et al (2003)[13] | Italy | Mother: no pregnancy abnormalities. Infant: healthy and 36–42 wk of gestation | 3 and 5 mo | T: 45<br>C: 46 | T: vaccinated aP on the fourth d of birth<br>C: no aP at birth | January 1999 to August 1999 | Biocine |
| Halasa et al (2008)[10] | United States | Mother: no pregnancy abnormalities. Infant: healthy and ≥36 wk of gestation | 2, 4, and 6 mo | T: 25<br>C: 25 | T: vaccinated DTaP within 2–14 d of birth<br>C: no aP at birth | February 2004 to August 2004 | Sanofi Pasteur |
| Knuf et al (2008)[14] | Germany | Mother: no pregnancy abnormalities. Infant: healthy and 36–42 wk of gestation | 2, 4, and 6 mo | T: 60<br>C: 61 | T: vaccinated aP within 2–5 d of birth<br>C: no aP at birth | July 2004 to April 2006 | GSK |
| Wood et al (2018)[16] | Australia | Mother: no pregnancy abnormalities, no Tdap vaccine <5 y, and no pertussis <5 y. Infant: healthy and ≥36 wk of gestation | 1.5, 4.0, and 6.0 mo | T: 221<br>C: 219 | T: vaccinated aP within 5 d of birth<br>C: no aP at birth | June 2010 to March 2013 | GSK |
| Wood et al (2010)[15] | Australia | Mother: no pregnancy abnormalities. Infant: healthy and ≥36 wk of gestation | 2, 4, and 6 mo | T: 27<br>C: 26 | T: vaccinated aP within 5 d of birth<br>C: no aP at birth | February 2005 to March 2007 | GSK |
| Prospective cohort study | | | | | | | |
| White et al (2010)[51] | Australia | Infant: healthy with no medical condition | 2, 4, and 6 mo | T: 11<br>C: 10 | T: vaccinated aP within 5 d of birth<br>C: no aP at birth | NA | GSK |

*aP*, acellular Pertussis vaccine; *C*, control group; *DTaP*, tetanus, diphtheria, and acellular vaccine; *GSK*, GlaxoSmithKline; *NA*, not applicable; *T*, intervention group.

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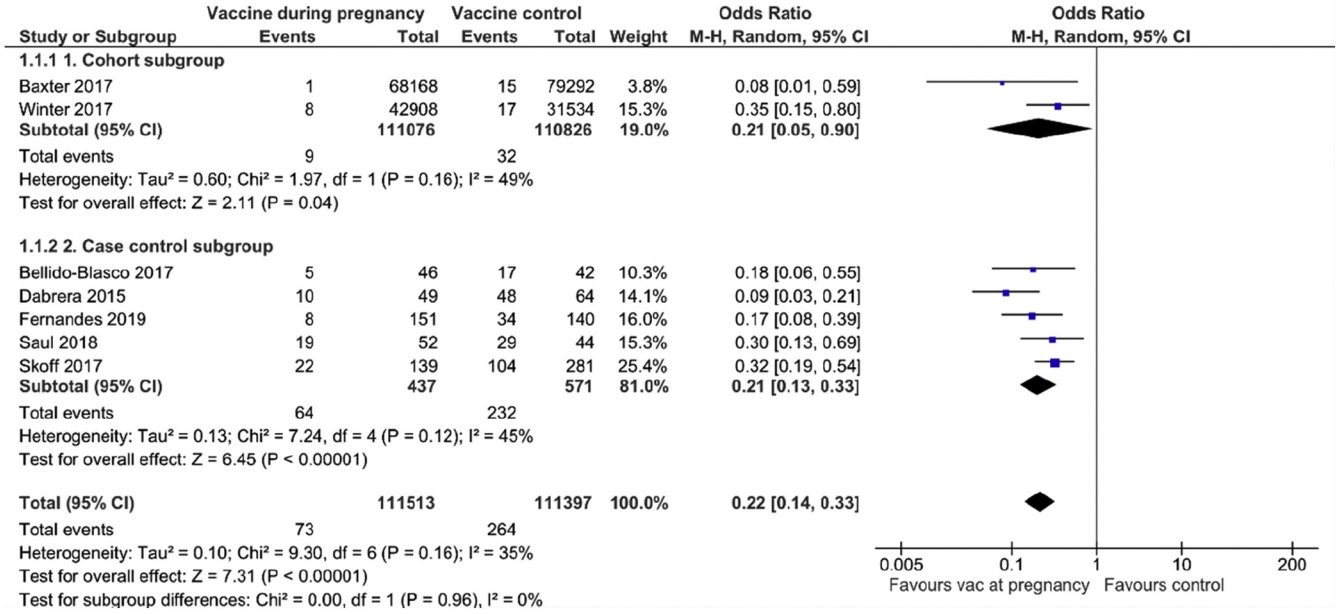
**FIGURE 2**
**Incidence of pertussis in 0 to 3 months infants between vaccine during pregnancy and control groups**




*CI*, confidence interval.

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### Incidence of pertussis

This outcome was reported in 2 retrospective studies[27,50] and 5 case-control studies.[28,29,31,47,48] The pooled data analysis revealed that the pertussis incidence rates were 0.065% (73 of 111,513 cases) in the vaccine during pregnancy group and 0.236% (264 of 111,397 cases) in the control group. The maternal immunization group had a significantly reduced pertussis incidence rate in children aged 0 to 3 months than the control group (OR, 0.22; 95% CI, 0.14−0.33) (Figure 2).

### Vaccine immunogenicity

Pertussis IgG concentrations before the primary immunization in children, born to mothers who either received vaccination during pregnancy or not, were investigated in 6 RCTs[26,34,39,43,45,49] and 3 cohort studies.[37,42,46] Moreover, 6 RCTs[26,34,39,43,45,49] and 3 cohort studies[37,42,46] evaluated the anti-PT concentrations; 5 RCTs[26,34,39,43,45] and 2 cohort studies[42,46] evaluated the anti-FHA concentrations; and 6 RCTs[26,34,39,43,45,49] and 3 cohort studies[37,42,46] evaluated the anti-PRN concentrations. The antibody concentration before the primary vaccination was defined as the antibody level in infants' blood within 1 month before the first dose of the primary vaccination schedule. The pooled estimates indicated that the maternal immunization group had significantly increased levels of anti-PT IgG (SMD, 1.48; 95% CI, 1.15−1.81) (Figure 3, A), anti-FHA IgG (SMD, 2.33; 95% CI, 2.01−2.66) (Figure 3, B), and anti-PRN IgG (SMD, 2.09; 95% CI, 1.81−2.36) compared with the control group (Figure 3, C).

Pertussis IgG antibody concentrations after the primary vaccination schedule were investigated in 2 groups in 6 RCTs[26,34,39,43,45,49] and 3 cohort studies.[40,42,46] Moreover, 6 RCTs[26,34,39,43,45,49] and 3 cohort studies[40,42,46] evaluated the anti-PT concentrations; 5 RCTs[26,34,39,43,45] and 3 cohort studies[40,42,46] evaluated the anti-FHA concentrations; and 6 RCTs[26,34,39,43,45,49] and 2 cohort studies[42,46] evaluated the anti-PRN concentrations. The antibody concentration after the primary vaccination was defined as the level of antibody in infants' blood within 1 month after the final dose of the primary vaccination schedule. The maternal immunization group displayed significantly lower levels of anti-PT IgG (SMD, −0.58; 95% CI, −0.79 to −0.37) (Supplemental Figure 2, A) and anti-FHA (SMD, −0.53; 95% CI, −0.85 to −0.22) (Supplemental Figure 2, B) than the control group. In addition, maternal immunization reduced the concentration of anti-PRN IgG (SMD, −0.21; 95% CI, −0.69 to 0.27) in both groups (Supplemental Figure 2, C).

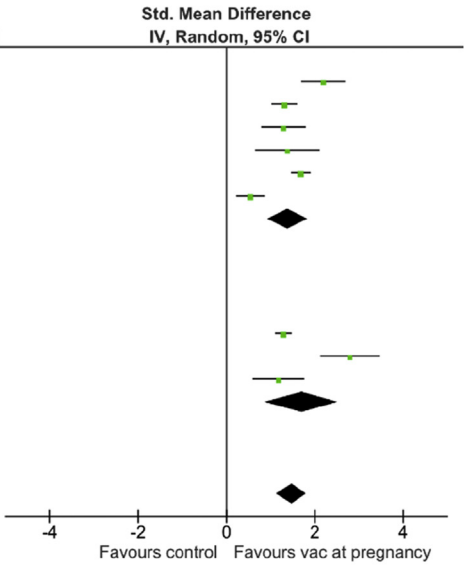
Pertussis IgG antibody concentrations in the umbilical cord were investigated in both groups in 6 RCTs[26,34,39,43,45,49] and 9 cohort studies.[25,30,36−38,41,42,44,46] Moreover, 6 RCTs[26,34,39,43,45,49] and 9 cohort studies[25,30,36−38,41,42,44,46] evaluated the anti-PT concentrations; 5 RCTs[26,34,39,43,45] and 6 cohort studies[25,36,41,42,44,46] evaluated the anti-FHA concentrations; and 6 RCTs[26,34,39,43,45,49] and 6 cohort studies[25,36,41,42,44,46] evaluated the anti-PRN concentrations. The pooled data revealed that groups with maternal immunization had significantly higher levels of anti-PT IgG (SMD, 1.51; 95%

**FIGURE 3**

**IgG concentrations before primary scheduled vaccination between pertussis vaccine during pregnancy and control groups**

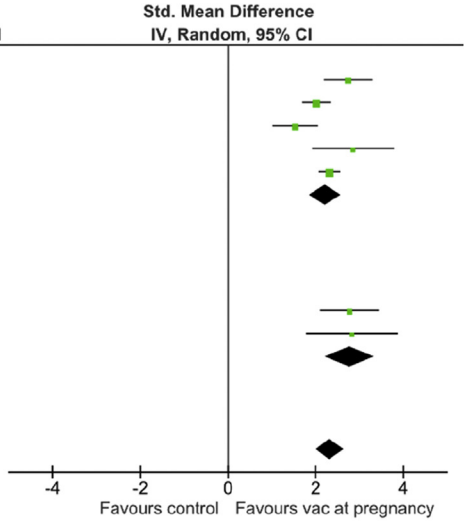
**A**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.1.1 RCT group** | | | | | | | | |
| Baruq 2019 | 3.31 | 1.13 | 55 | 0.59 | 1.33 | 53 | 10.7% | 2.19 [1.71, 2.67] |
| Halperin 2018 | 2.65 | 1.13 | 124 | 1.28 | 0.94 | 123 | 12.6% | 1.31 [1.04, 1.59] |
| Hoang 2016 | 1.44 | 1.18 | 45 | -0.22 | 1.39 | 35 | 10.6% | 1.29 [0.80, 1.78] |
| Munoz 2014 | 3.03 | 0.98 | 31 | 1.67 | 0.94 | 13 | 8.4% | 1.38 [0.66, 2.09] |
| Perrett 2020 | 2.48 | 1.1 | 242 | 0.79 | 0.9 | 253 | 13.1% | 1.68 [1.48, 1.89] |
| Villarreal Pérez 2017 | 2.39 | 1.09 | 90 | 1.82 | 1 | 81 | 12.4% | 0.54 [0.24, 0.85] |
| **Subtotal (95% CI)** | | | **587** | | | **558** | **67.9%** | **1.39 [0.94, 1.84]** |
| Heterogeneity: Tau² = 0.27; Chi² = 48.57, df = 5 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 6.09 (P < 0.00001) | | | | | | | | |
| **2.1.2 Cohort group** | | | | | | | | |
| Healy 2018 | 2.47 | 1.06 | 312 | 1.16 | 0.97 | 314 | 13.3% | 1.29 [1.12, 1.46] |
| Maertens 2016 | 2.74 | 0.89 | 51 | 0.1 | 1.02 | 26 | 9.0% | 2.79 [2.14, 3.45] |
| Rice 2019 | 3.15 | 1.09 | 90 | 1.87 | 1.02 | 15 | 9.8% | 1.18 [0.61, 1.75] |
| **Subtotal (95% CI)** | | | **453** | | | **355** | **32.1%** | **1.71 [0.89, 2.54]** |
| Heterogeneity: Tau² = 0.47; Chi² = 19.51, df = 2 (P < 0.0001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 4.06 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **1040** | | | **913** | **100.0%** | **1.48 [1.15, 1.81]** |
| Heterogeneity: Tau² = 0.21; Chi² = 68.11, df = 8 (P < 0.00001); I² = 88% | | | | | | | | |
| Test for overall effect: Z = 8.78 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0% | | | | | | | | |




**B**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.3.1 RCT group** | | | | | | | | |
| Baruq 2019 | 4.43 | 0.8 | 55 | 1.61 | 1.22 | 50 | 14.7% | 2.74 [2.20, 3.28] |
| Halperin 2018 | 3.93 | 0.83 | 124 | 1.81 | 1.23 | 123 | 20.1% | 2.02 [1.71, 2.32] |
| Hoang 2016 | 4.08 | 0.7 | 45 | 3.14 | 0.46 | 35 | 15.5% | 1.53 [1.03, 2.04] |
| Munoz 2014 | 4.6 | 0.73 | 31 | 1.89 | 1.34 | 12 | 8.3% | 2.85 [1.93, 3.77] |
| Perrett 2020 | 4.48 | 1.01 | 242 | 1.89 | 1.21 | 253 | 21.9% | 2.32 [2.09, 2.54] |
| **Subtotal (95% CI)** | | | **497** | | | **473** | **80.5%** | **2.22 [1.86, 2.59]** |
| Heterogeneity: Tau² = 0.11; Chi² = 14.87, df = 4 (P = 0.005); I² = 73% | | | | | | | | |
| Test for overall effect: Z = 12.00 (P < 0.00001) | | | | | | | | |
| **2.3.2 Cohort group** | | | | | | | | |
| Maertens 2016 | 4.8 | 0.66 | 51 | 3.14 | 0.43 | 26 | 12.4% | 2.77 [2.12, 3.42] |
| Rice 2019 | 4.25 | 0.77 | 16 | 1.7 | 0.98 | 15 | 7.1% | 2.83 [1.80, 3.86] |
| **Subtotal (95% CI)** | | | **67** | | | **41** | **19.5%** | **2.79 [2.24, 3.34]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 9.91 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **564** | | | **514** | **100.0%** | **2.33 [2.01, 2.66]** |
| Heterogeneity: Tau² = 0.11; Chi² = 18.79, df = 6 (P = 0.005); I² = 68% | | | | | | | | |
| Test for overall effect: Z = 14.00 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.80, df = 1 (P = 0.09), I² = 64.3% | | | | | | | | |

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*(continued)*

CI, 1.24−1.78) (Supplemental Figure 3, A), anti-FHA IgG (SMD, 2.23; 95% CI, 1.62−2.84) (Supplemental Figure 3, B), and anti-PRN IgG (SMD, 2.23; 95% CI, 1.67−2.8) (Supplemental Figure 3, C) than the control groups.

The anti-PT IgG concentration in the umbilical cord was compared between early (27−30 weeks' gestation) and late (31−36 weeks' gestation) immunization groups in 2 cohort studies.[25,37] The latter group displayed a decreasing but nonsignificant trend in the level of anti-PT IgG (SMD, 0.33; 95% CI, −0.59 to 1.25) (Supplemental Figure 4).

### Vaccine safety

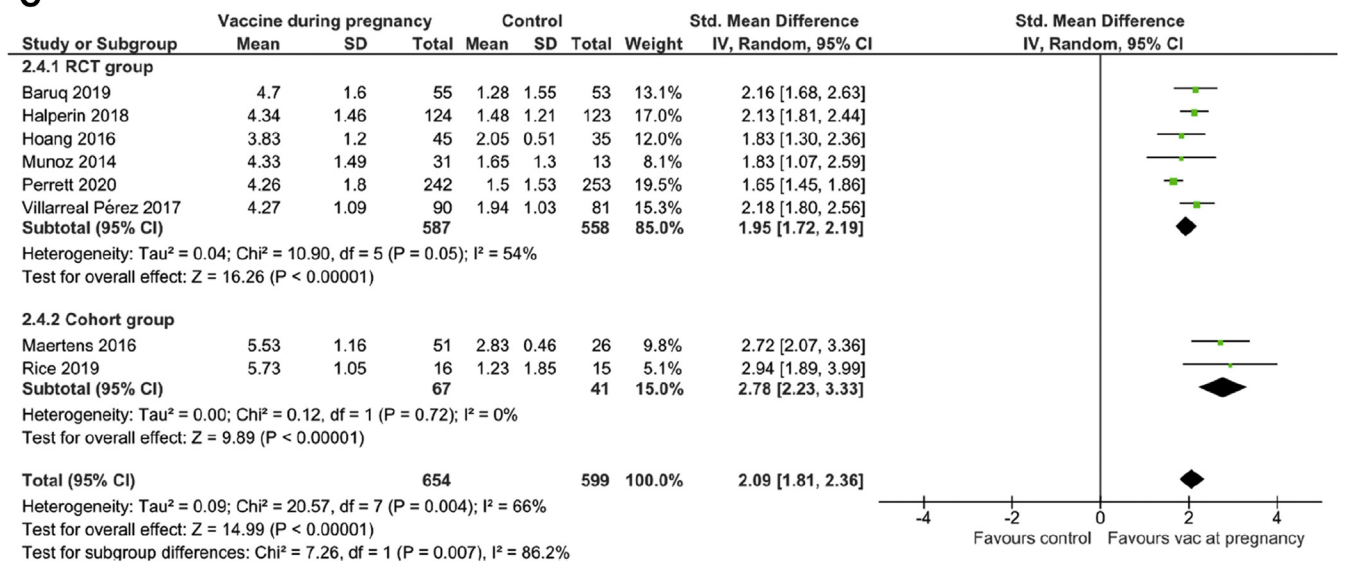
SAEs in mothers were evaluated in 6 studies.[26,34,39,42,43,45] Among these studies, 5 studies[26,34,42,43,45] reported the SAEs in infants in the 2 groups. No statistical difference was observed in the SAE rate of mothers (RR, 1.18; 95% CI, 0.76−1.82) (Figure 4, A) and infants (RR, 0.77; 95% CI, 0.42−1.42) (Figure 4, B) in both groups.

### Vaccination at birth: study characteristics

The results are displayed in Table 2. All studies were published from 2008 to

**FIGURE 3**
**Continued**

**C**




**A,** Level of IgG antibody against pertussis toxin. **B,** Level of IgG antibody against filamentous hemagglutinin. **C,** Level of IgG antibody against pertactin.

*CI*, confidence interval; *IgG*, immunoglobulin G; *RCT*, randomized controlled trial; *SD*, standard deviation.

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2018 and used the acellular pertussis vaccine. The 2-, 4-, and 6-month immunization schedules were used in 4 studies[10,14,15,51] and the 3- and 5-month schedules in 1 study.[13] The GSK vaccines were used in 4 studies,[14–16,51] whereas the Sanofi Pasteur vaccines were used in 1 study.[10] Moreover, 1 RCT on vaccination at birth[10] applied the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine instead of the acellular pertussis vaccine. All studies evaluated the immunogenicity outcome.[10,13–16,51]

### Quality of the studies

Notably, 4 RCTs[10,14–16] in meta-analysis were assessed for bias using RoB 2 (Supplemental Figure 1, D), and 1 cohort[51] was assessed for bias using ROBINS-I (Supplemental Figure 1, E). The quality of each study in the meta-analysis is summarized in detail in Supplemental Figure 1, D and E.

### Vaccine immunogenicity

Pertussis IgG antibody concentrations before the primary vaccination schedule between infants who were and were not vaccinated at birth were reported in 2 RCTs[15,16] and 1 cohort study.[51] The antibody concentration before the primary vaccination schedule was defined as the antibody level in infants' blood within 1 month before the first dose of the primary vaccination schedule. Vaccination at birth significantly increased the concentrations of anti-PT IgG (SMD, 0.55; 95% CI, 0.33–0.77) (Figure 5, A) and anti-FHA IgG (SMD, 0.52; 95% CI, 0.33–0.71) (Figure 5, B) than the control group. In addition, neonatal immunization seemed to increase the anti-PRN IgG concentration (SMD, 0.27; 95% CI, 0.05–0.48) (Figure 5, C).

Pertussis antibody IgG concentrations in the 2 groups after the primary vaccination schedule was reported in 4 RCTs[10,14–16] and 1 cohort study.[51] The antibody concentration after the primary vaccination schedule was defined as the antibody levels in infants' blood within 1 month after the final dose of the primary vaccination series. The pooled data revealed no significant difference in the level of anti-PT IgG (SMD, 0.08; 95% CI, −0.27 to 0.44) (Supplemental Figure 5, A) and anti-PRN IgG (SMD, −0.02; 95% CI, −0.37 to 0.33) (Supplemental Figure 5, C) between the 2 groups. However, the anti-FHA IgG concentration was significantly higher in the vaccine at birth group than in the control group (SMD, 0.69; 95% CI, 0.28–1.10) (Supplemental Figure 5, B).

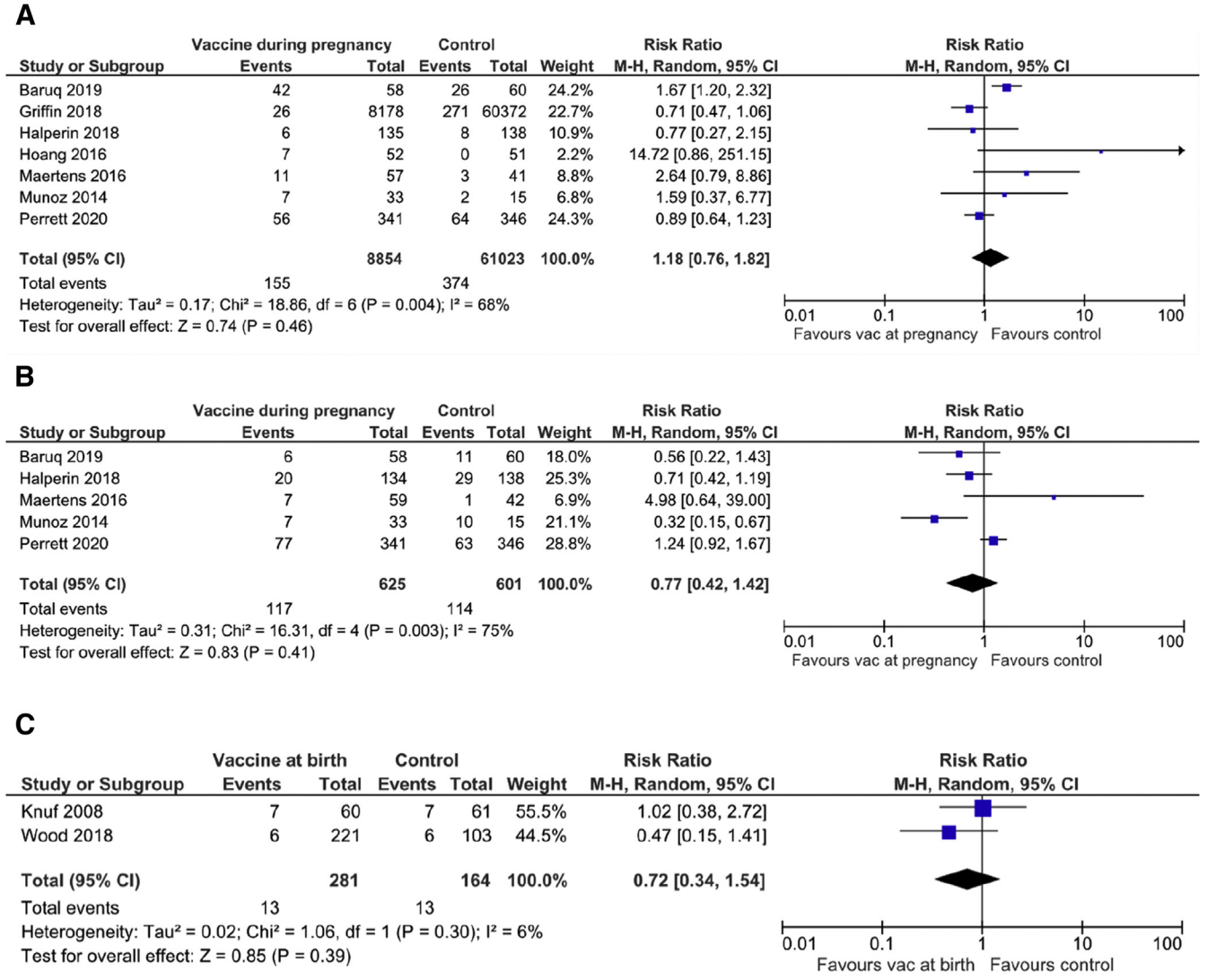
### Vaccine safety

The differences in SAEs rates between the vaccine at birth and control groups were investigated in 2 RCTs.[14,16] The pooled results indicated no significant difference in SAEs between the 2 groups (RR, 0.72; 95% CI, 0.34–1.54) (Figure 4, C).

## Discussion

This meta-analysis investigated the efficacy, immunogenicity, and safety of pertussis vaccination during pregnancy and at birth. The inclusion of real-world data is believed to help move research toward a more comprehensive view. First, our study revealed that vaccination during pregnancy reduced the incidence of pertussis in children before receiving routine immunization series and was

**FIGURE 4**
**SAEs in the intervention and control groups**




**A,** SAEs in mothers in the pertussis vaccine during pregnancy and control groups. **B,** SAEs in infants in the pertussis vaccine during pregnancy and control groups. **C,** SAEs in infants in the pertussis vaccine at birth and control groups.

*CI*, confidence interval; *SAE*, severe adverse event.

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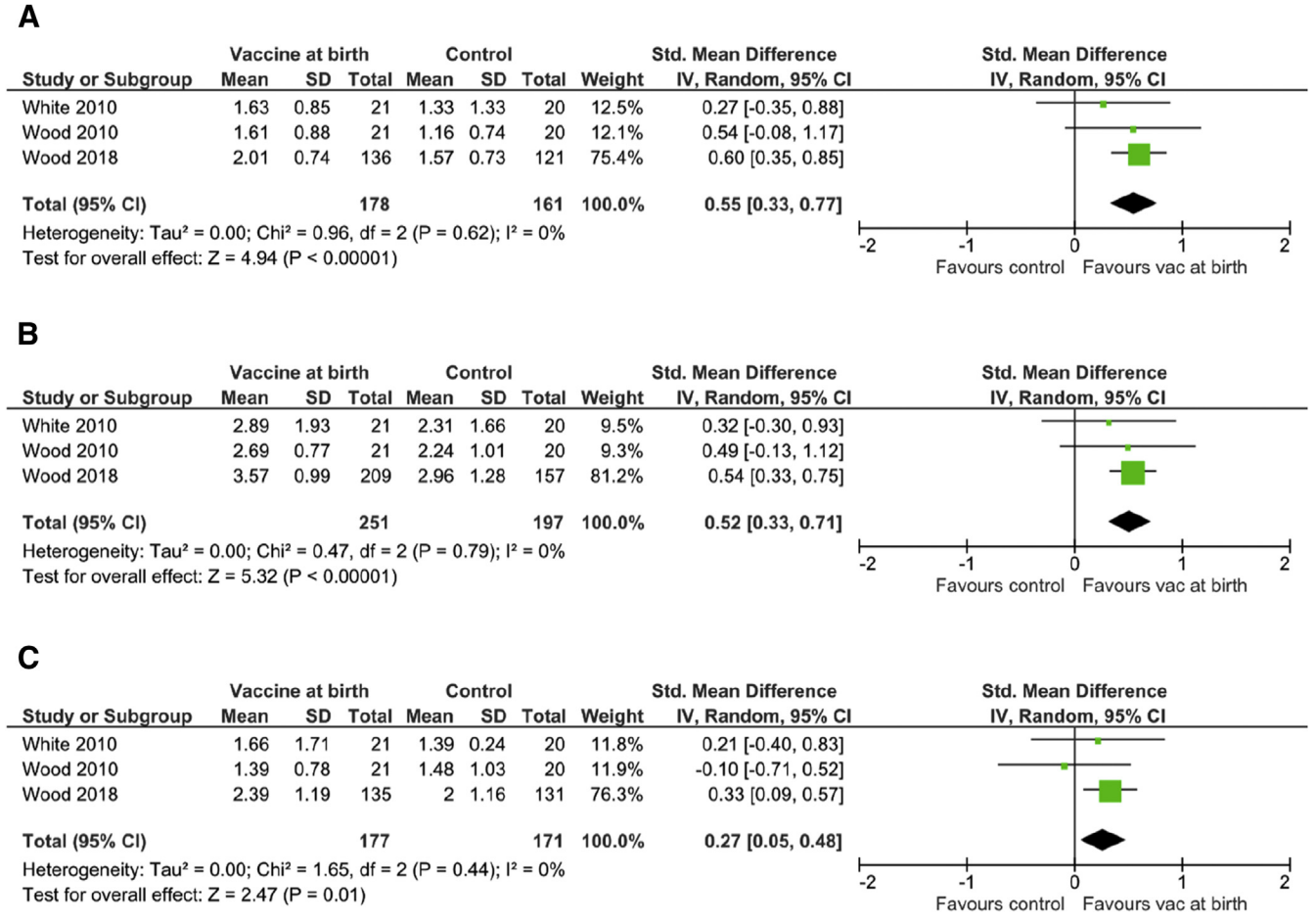
safe for both the mother and child. Moreover, neither gestational vaccination timings (early or late in the third trimester of pregnancy) were identified as optimal. Second, vaccination at birth significantly increased pertussis antibody concentrations and was well tolerated by neonates.

### Vaccination during pregnancy

Several countries have implemented pertussis vaccination during pregnancy. However, the relationship between immunogenicity and protection before primary vaccination remains debatable.[52] Most studies on vaccination during pregnancy have had small sample sizes, lacking sufficient power to present the overall picture of immunogenicity and efficacy of the pertussis vaccine.[26–31,34,36–40,42–50] This meta-analysis combined studies investigating the immunogenicity of 1953 participants and the efficacy of vaccinations among 222,910 participants, revealing that maternal immunization significantly raised the concentration of infants' IgG antibodies. Furthermore, vaccine efficacy among children younger than 3 months was determined to be 78% (95% CI, 67–86). Moreover, 1 case-control study showed that the vaccination during pregnancy group had a significantly reduced incidence rate of severe pertussis in children 0 to 6 months of age than the control group

**FIGURE 5**
**IgG concentrations before primary schedule vaccination between pertussis vaccine at birth and control groups**




**A,** Level of IgG antibody against pertussis toxin. **B,** Level of IgG antibody against filamentous hemagglutinin. **C,** Level of IgG antibody against pertactin.

*CI*, confidence interval; *IgG*, immunoglobulin G; *SD*, standard deviation.

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(OR, 0.15; 95% CI, 0.06−0.43).[47] Therefore, vaccination during pregnancy could induce immunogenicity and protect children against pertussis disease before the primary doses are administered.

The optimal gestational time for maternal vaccination remains controversial. A prospective cohort study with Thai participants comparing the immunogenicity of pertussis vaccination between 26 to 30 and 31 to 36 weeks' gestation suggested that vaccinating at a later time was associated with higher levels of maternal pertussis antibodies; however, cord-to-maternal antibody ratios were significantly higher for the antibodies in the early group than the late group.[53] Although not significant, our findings showed that in the third trimester of pregnancy, early vaccination (27−30 weeks' gestation) was associated with higher levels of pertussis antibody. Therefore, there is still a lack of clarity regarding the adequate gestational time for maternal vaccination because of the lack of studies and power. Further studies are required to identify the optimal vaccination timing during pregnancy.

In addition, the interference of vaccination during pregnancy on the antibody response after the routine immunization series or booster doses remains under debate. One of the mechanisms of this interference was that the maternally derived antibodies might inhibit the B-cell response to vaccine antigens.[54] Unfortunately, infant immunity was likely to be inhibited by transplacental antibody after the child received primary and booster doses of vaccination.[52,55] Furthermore, our meta-analysis proved that maternal vaccination significantly reduced the level of 2 pertussis antibodies after the routine vaccination. However, 2 trials showed that after the booster dose, the pertussis antibodies in infants did not differ between vaccine during pregnancy and control groups at around 13 months of age.[43,56] Regarding the clinical aspect,

1 retrospective cohort study conducted in the United States showed that vaccination during pregnancy reduced the risk of pertussis infection by an estimated 69% in infants during the first year of life.[27] Moreover, the surveillance data from the United Kingdom demonstrated that there was no increase in the incidence of pertussis infection after the introduction of the vaccination during pregnancy.[8] Therefore, further studies are needed to clarify the waning pertussis immunity and clinical effects in children after receiving the primary immunization series, from 6-month-old to 1-year-old children, whose mothers were vaccinated during pregnancy.

### Vaccination at birth

The role of pertussis vaccination at birth on immunogenicity status before and after the primary immunization remains debatable. A prospective cohort study revealed that whole-cell pertussis vaccines induced immune paralysis and significantly reduced the levels of pertussis antibodies in infants before and after the routine vaccination.[11] However, our findings demonstrated that acellular pertussis vaccines at birth dramatically increased pertussis antibody concentrations before the primary vaccination period in the intervention group. Further investigations are required to determine vaccine efficacy in infants before and after receiving the routine immunization series.

### Safety

The safety of pertussis vaccination in the mother and infant is a major concern. A systematic review reported that maternal vaccination was associated with 2 SAEs, namely, postvaccination fever and chorioamnionitis.[57] Our findings indicated that the risk of SAEs, including postvaccination fever and chorioamnionitis, was not significantly higher after maternal vaccination. Similar results were found among at-birth vaccination studies. Therefore, pertussis vaccination during pregnancy and at birth was well tolerated.

### Heterogeneity

Heterogeneity was observed in several aspects of the studies, including different primary schedules, vaccination timing during pregnancy, and pertussis case definition. Furthermore, different components in vaccines from the GSK (3 components) and Sanofi Pasteur (5 components) and tetanus toxoid and diphtheria contained in the vaccine could affect the pertussis vaccine component.[58] In addition, varying follow-up periods might contribute to heterogeneity.

### Cost-effectiveness

It is worth mentioning that some of the studies included were conducted amid local pertussis outbreaks. This, along with public health policies and cost-effectiveness, would help decide whether maternal immunization should be introduced nationwide. However, the cost-effectiveness of maternal and neonatal vaccinations is difficult to predict. A study in the United States suggested that vaccination during pregnancy was a cost-effective intervention than vaccinating a second parent or postpartum vaccination.[59] The current meta-analysis did not investigate the cost-effectiveness of maternal and neonatal pertussis vaccinations because of the lack of studies focusing on cost-effectiveness in different countries, especially developing ones.

### Limitations

Our study has several limitations. We could not reach a consensus on optimal vaccination timing during pregnancy, or assess the effect of concomitant antigens in routine vaccination. The impact of maternal pertussis vaccination within 5 years before pregnancy on immunogenicity was also unknown. Findings from this study might not apply to preterm infants, who reportedly have weaker immune systems. Finally, vaccination during pregnancy and at birth should be directly compared in the future.

### Conclusion

This systematic review and meta-analysis have provided rigorous evidence that vaccination during pregnancy displayed effective immunogenicity, safety, and efficacy in protecting children against pertussis from birth until the first dose of routine vaccinations is administered. Therefore, vaccination during pregnancy is recommended to protect the infants from pertussis infection before receiving routine vaccinations. However, the inclusion of maternal immunization in the national vaccination program would depend on the occurrence of pertussis outbreaks, public health policies, and cost-effectiveness. The administration of acellular vaccines at birth could be an alternative for infants whose mothers were not immunized during pregnancy. ■

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## Supplemental Online Content

**Methods:** Search strategy on PubMed and MEDLINE, Cochrane Central Register of Controlled Trials, Embase, and other.

**Selections:** Detailed selection procedure.

**Supplemental Figure 1.** Risk of bias assessment per study and domain.

- **Supplemental Figure 1A.** Randomized control trials (RCTs) regarding the vaccine during pregnancy
- **Supplemental Figure 1B.** Cohort studies regarding the vaccine during pregnancy.
- **Supplemental Figure 1C.** Case-control studies regarding the vaccine during pregnancy.
- **Supplemental Figure 1D.** RCTs regarding the vaccine at birth.
- **Supplemental Figure 1E.** Non-RCTs regarding the vaccine at birth.

**Supplemental Figure 2.** IgG antibody concentrations after the primary schedule vaccination between vaccine during pregnancy and control groups.

- **Supplemental Figure 2A.** Level of IgG antibody against pertussis toxin (anti-PT IgG).
- **Supplemental Figure 2B.** Level of IgG antibody against filamentous hemagglutinin (anti-FHA IgG).
- **Supplemental Figure 2C.** Level of IgG antibody against pertactin (anti-PRN IgG).

**Supplemental Figure 3.** Immunoglobulin G (IgG) antibody concentrations in cord blood between the vaccine during pregnancy and control groups.

- **Supplemental Figure 3A.** Level of anti-PT IgG.
- **Supplemental Figure 3B.** Level of anti-FHA IgG.
- **Supplemental Figure 3C.** Level of anti-PRN IgG.

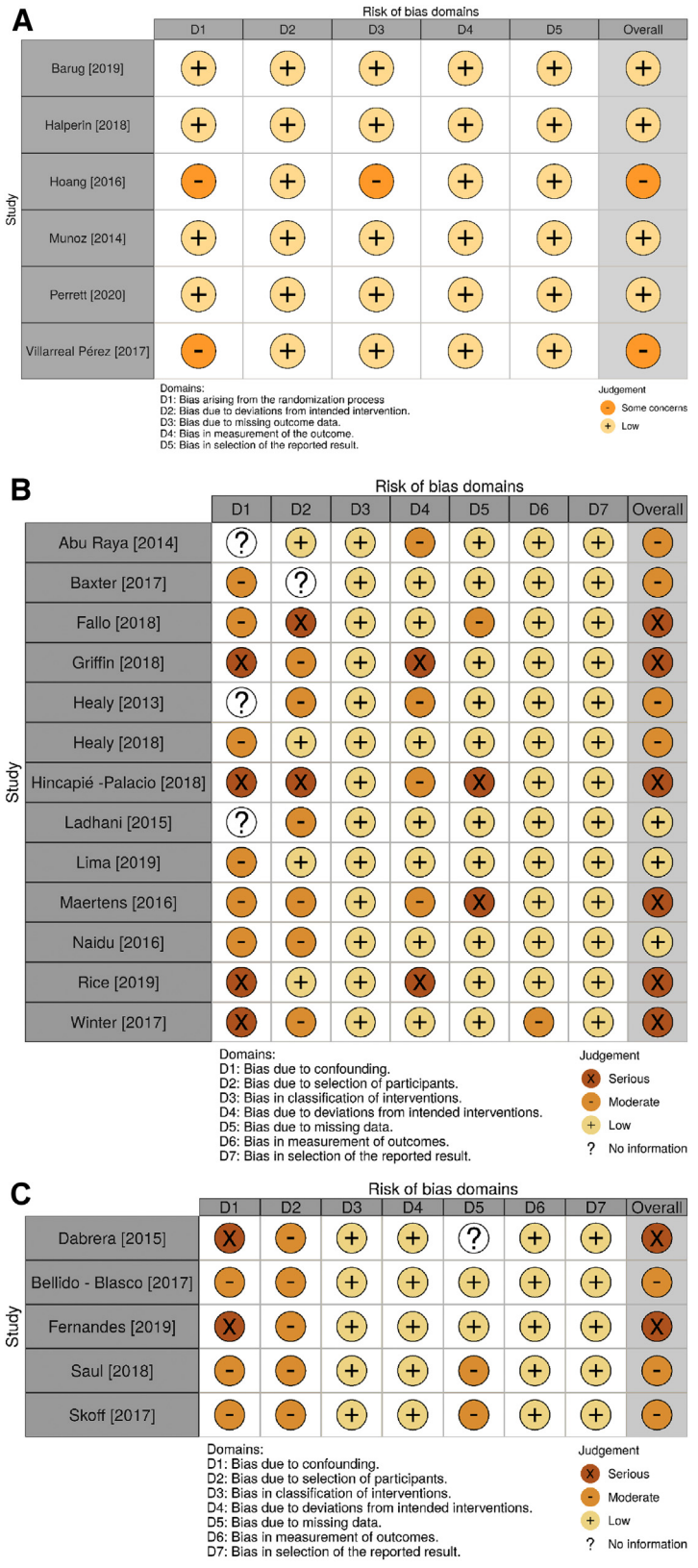
**Supplemental Figure 4.** Anti-PT IgG antibody concentrations in cord blood in the vaccine group at early time (27−30 weeks' gestation) and late time (31−36 weeks' gestation).

**Supplemental Figure 5.** IgG antibody concentrations after the primary schedule vaccination between the vaccine at birth and control groups.

- **Supplemental Figure 5A.** Level of anti-PT IgG.
- **Supplemental Figure 5B.** Level of anti-FHA IgG.
- **Supplemental Figure 5C.** Level of anti-PRN IgG.

**SUPPLEMENTAL FIGURE 1**

**Risk of bias assessment per study and domain**

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**SUPPLEMENTAL FIGURE 1**
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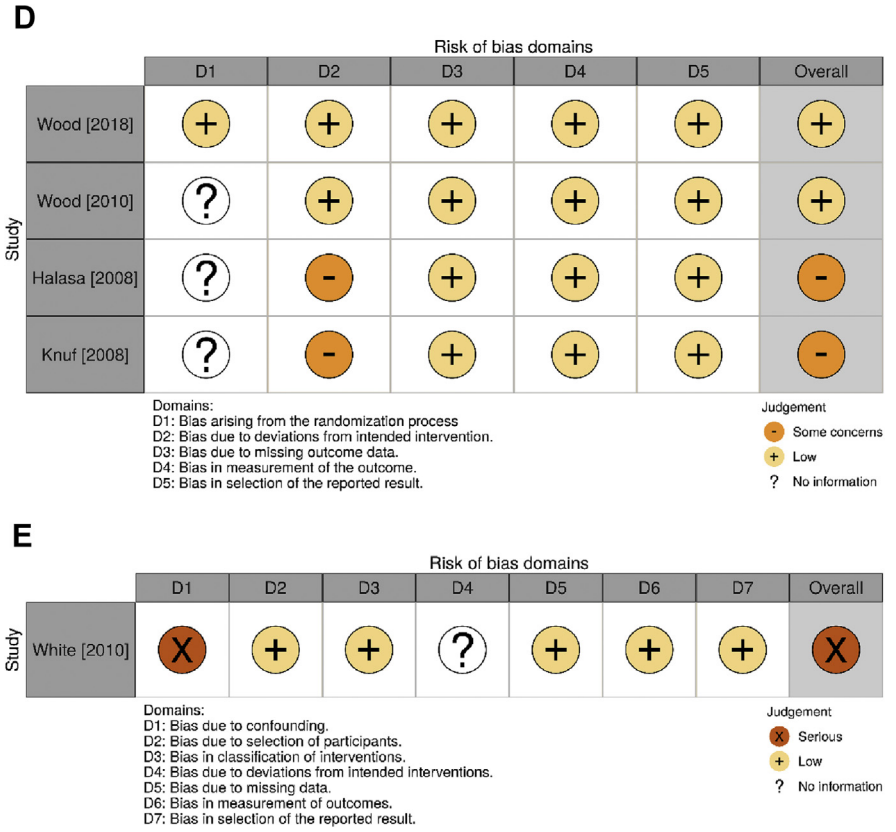


**A,** RCTs regarding the vaccine during pregnancy: 4 studies[1–4] with low risk of bias in bias arising from the randomization process, 5 studies[1–5] with low risk of bias in missing outcome data, and all studies[1–6] with low risk of bias because of deviations from intended interventions in the measurement of the outcome and selection of the reported results (**A**). **B**, Cohort studies regarding the vaccine during pregnancy. **C**, Case-control studies regarding the vaccine during pregnancy. ROBINS-I was used to identify the quality of 13 cohorts (**B**)[7–19] and 5 case-control studies (**C**).[20–24] Notably, 6 studies[10,13,18,19,21,22] were at a serious risk of bias in the confounding domain because of the nonrandomization process. Moreover, 2 studies[9,13] had a serious risk of selection bias. No study presented a serious or critical risk of bias in the misclassified interventions domain. In addition, 2 studies[10,18] had a serious risk of bias because of deviations from intended interventions, and 2 studies[13,16] had a serious risk of bias on the missing data domain. Finally, 1 study[19] had a moderate risk of bias in measure of outcomes, and all studies[23,25–29,31,34–36,38–40,42,44–46,48] had a low risk of bias related to the reported result. **D,** RCTs regarding the vaccine at birth. **E,** Non-RCTs regarding the vaccine at birth. Notably, 3 studies[25–27] had no information in bias arising from the randomization and 2 studies[27,28] had low risk of bias because of deviations from intended interventions. All studies[25–28] had low risk of bias in all the remaining domains (**D**). ROBINS-I was applied to evaluate the quality of 1 cohort study[29] (**E**). This prospective study[29] has a serious risk of confounding bias but low risk of bias in bias because of the selection of participants, classification of interventions, missing data, measure of outcomes, and reported result. No information was reported in bias because of deviations from intended interventions domain.

*RCT*, randomized controlled trial; *ROBINS-I*, Risk Of Bias In Non-randomized Studies of Interventions.

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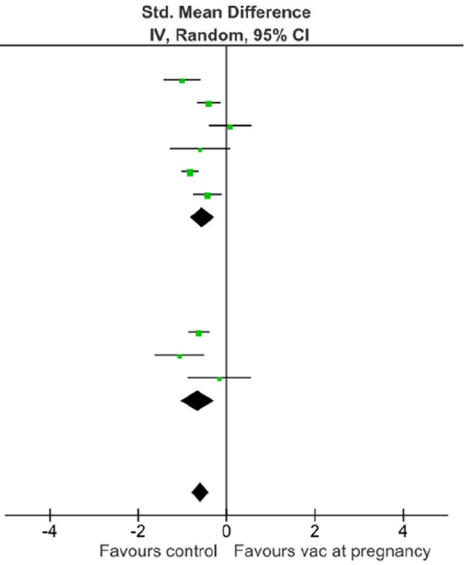
**SUPPLEMENTAL FIGURE 2**

**IgG concentrations after primary schedule vaccination between vaccine during pregnancy and control groups**

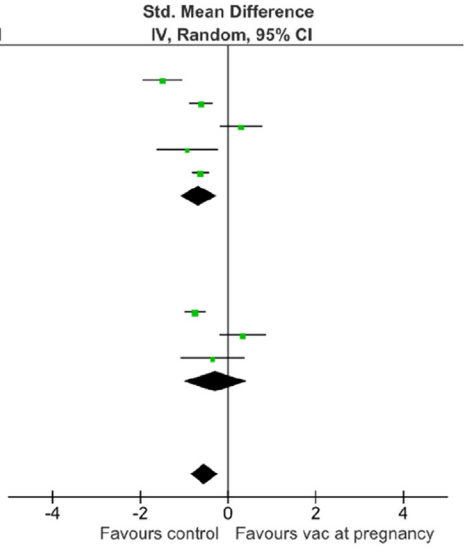
**A**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.1.1 RCT group** | | | | | | | | |
| Baruq 2019 | 3.57 | 0.85 | 53 | 4.42 | 0.83 | 50 | 10.7% | -1.00 [-1.41, -0.59] |
| Halperin 2018 | 4.04 | 0.75 | 118 | 4.35 | 0.79 | 131 | 14.6% | -0.40 [-0.65, -0.15] |
| Hoang 2016 | 4.25 | 0.54 | 35 | 4.2 | 0.67 | 35 | 9.5% | 0.08 [-0.39, 0.55] |
| Munoz 2014 | 4.17 | 0.46 | 26 | 4.57 | 0.92 | 14 | 6.4% | -0.60 [-1.26, 0.07] |
| Perrett 2020 | 3.49 | 0.65 | 266 | 4 | 0.58 | 271 | 16.4% | -0.83 [-1.00, -0.65] |
| Villarreal Pérez 2017 | 3.89 | 0.88 | 90 | 4.24 | 0.71 | 81 | 13.3% | -0.43 [-0.74, -0.13] |
| **Subtotal (95% CI)** | | | **588** | | | **582** | **70.8%** | **-0.55 [-0.82, -0.27]** |
| Heterogeneity: Tau² = 0.08; Chi² = 21.64, df = 5 (P = 0.0006); I² = 77% | | | | | | | | |
| Test for overall effect: Z = 3.84 (P = 0.0001) | | | | | | | | |
| **5.1.2 Cohort group** | | | | | | | | |
| Ladhani 2015 | 3.36 | 0.66 | 129 | 3.77 | 0.65 | 203 | 15.2% | -0.63 [-0.85, -0.40] |
| Maertens 2016 | 3.37 | 0.59 | 49 | 3.99 | 0.55 | 21 | 8.1% | -1.06 [-1.60, -0.52] |
| Rice 2019 | 3.39 | 0.73 | 16 | 3.57 | 1.33 | 15 | 5.9% | -0.16 [-0.87, 0.54] |
| **Subtotal (95% CI)** | | | **194** | | | **239** | **29.2%** | **-0.65 [-1.04, -0.27]** |
| Heterogeneity: Tau² = 0.06; Chi² = 4.05, df = 2 (P = 0.13); I² = 51% | | | | | | | | |
| Test for overall effect: Z = 3.37 (P = 0.0008) | | | | | | | | |
| **Total (95% CI)** | | | **782** | | | **821** | **100.0%** | **-0.58 [-0.79, -0.37]** |
| Heterogeneity: Tau² = 0.06; Chi² = 25.73, df = 8 (P = 0.001); I² = 69% | | | | | | | | |
| Test for overall effect: Z = 5.51 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0% | | | | | | | | |




**B**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.2.1 RCT group** | | | | | | | | |
| Baruq 2019 | 3.44 | 0.69 | 53 | 4.41 | 0.59 | 50 | 12.5% | -1.50 [-1.94, -1.06] |
| Halperin 2018 | 3.93 | 0.83 | 118 | 4.43 | 0.8 | 131 | 14.9% | -0.61 [-0.87, -0.36] |
| Hoang 2016 | 4.34 | 0.45 | 35 | 4.2 | 0.48 | 35 | 12.0% | 0.30 [-0.17, 0.77] |
| Munoz 2014 | 3.7 | 0.7 | 26 | 4.36 | 0.69 | 14 | 9.3% | -0.93 [-1.61, -0.24] |
| Perrett 2020 | 4.23 | 0.63 | 266 | 4.64 | 0.67 | 271 | 15.7% | -0.63 [-0.80, -0.46] |
| **Subtotal (95% CI)** | | | **498** | | | **501** | **64.4%** | **-0.66 [-1.08, -0.24]** |
| Heterogeneity: Tau² = 0.18; Chi² = 30.57, df = 4 (P < 0.00001); I² = 87% | | | | | | | | |
| Test for overall effect: Z = 3.10 (P = 0.002) | | | | | | | | |
| **5.2.2 Cohort group** | | | | | | | | |
| Ladhani 2015 | 3.24 | 0.6 | 131 | 3.72 | 0.66 | 199 | 15.2% | -0.75 [-0.98, -0.52] |
| Maertens 2016 | 4.17 | 0.51 | 49 | 3.99 | 0.59 | 21 | 11.4% | 0.33 [-0.18, 0.85] |
| Rice 2019 | 3.21 | 0.74 | 16 | 3.69 | 1.74 | 15 | 9.0% | -0.35 [-1.06, 0.36] |
| **Subtotal (95% CI)** | | | **196** | | | **235** | **35.6%** | **-0.28 [-1.01, 0.45]** |
| Heterogeneity: Tau² = 0.35; Chi² = 14.62, df = 2 (P = 0.0007); I² = 86% | | | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | | | |
| **Total (95% CI)** | | | **694** | | | **736** | **100.0%** | **-0.53 [-0.85, -0.22]** |
| Heterogeneity: Tau² = 0.16; Chi² = 45.67, df = 7 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 3.34 (P = 0.0008) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0% | | | | | | | | |

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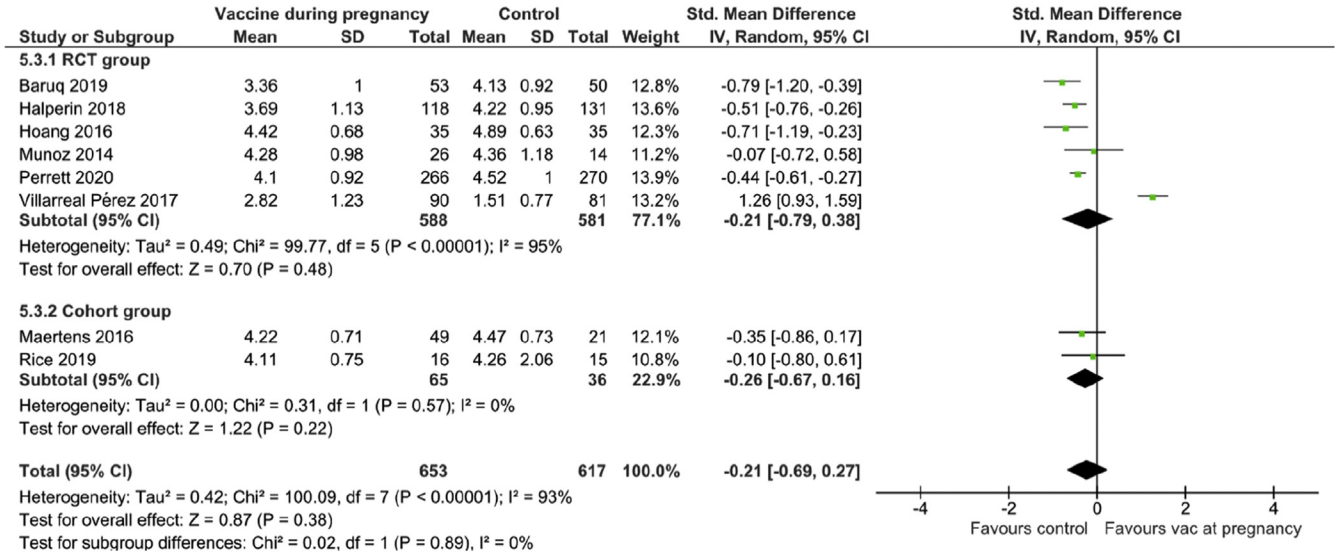
**SUPPLEMENTAL FIGURE 2**
**Continued**

**C**




**A,** Level of antipertussis toxin IgG after the primary schedule vaccination between the vaccine during pregnancy and control groups. **B,** Level of antifilamentous hemagglutinin IgG after the primary schedule vaccination between the vaccine during pregnancy and control groups. **C,** Level of antipertactin IgG after the primary schedule vaccination between the vaccine during pregnancy and control groups.

*CI*, confidence interval; *IgG*, immunoglobulin G; *RCT*, randomized controlled trial; *SD*, standard deviation.

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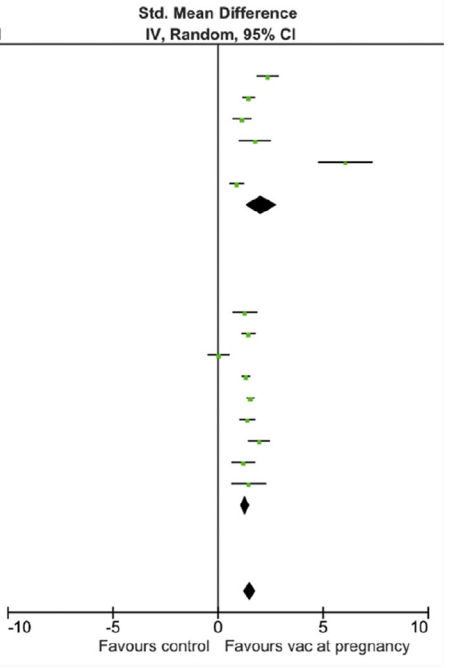
**SUPPLEMENTAL FIGURE 3**

**IgG concentrations at cord blood between vaccine during pregnancy and control groups**

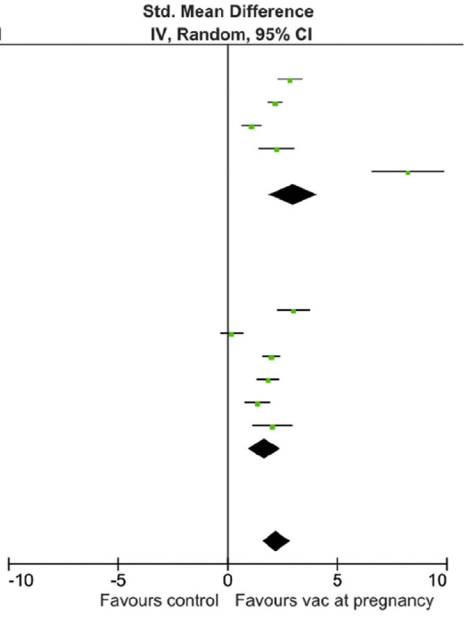
**A**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.1.1 RCT group** | | | | | | | | |
| Baruq 2019 | 4.83 | 1.05 | 54 | 1.72 | 1.53 | 53 | 6.6% | 2.36 [1.86, 2.85] |
| Halperin 2018 | 3.99 | 1.07 | 126 | 2.25 | 1.3 | 132 | 7.8% | 1.45 [1.18, 1.73] |
| Hoang 2016 | 3.04 | 0.98 | 50 | 1.97 | 0.88 | 47 | 7.0% | 1.14 [0.71, 1.57] |
| Munoz 2014 | 4.23 | 0.76 | 31 | 2.64 | 1.13 | 14 | 5.2% | 1.76 [1.02, 2.50] |
| Perrett 2020 | 3.85 | 0.34 | 29 | 1.7 | 0.36 | 29 | 3.0% | 6.06 [4.81, 7.31] |
| Villarreal Pérez 2017 | 3.34 | 1.4 | 90 | 2.08 | 1.43 | 81 | 7.7% | 0.89 [0.57, 1.20] |
| **Subtotal (95% CI)** | | | **380** | | | **356** | **37.4%** | **2.06 [1.33, 2.80]** |
| Heterogeneity: Tau² = 0.75; Chi² = 79.76, df = 5 (P < 0.00001); I² = 94% | | | | | | | | |
| Test for overall effect: Z = 5.48 (P < 0.00001) | | | | | | | | |
| **2.1.2 Cohort group** | | | | | | | | |
| Abu Raya 2014 | 2.85 | 2.14 | 51 | 0.11 | 2.13 | 20 | 6.3% | 1.27 [0.71, 1.83] |
| Fallo 2018 | 3.94 | 1.12 | 105 | 2.45 | 0.92 | 99 | 7.7% | 1.44 [1.14, 1.75] |
| Healy 2013 | 2.85 | 0.91 | 19 | 2.82 | 1.08 | 86 | 6.6% | 0.03 [-0.47, 0.53] |
| Healy 2018 | 3.86 | 1.05 | 312 | 2.56 | 0.9 | 314 | 8.2% | 1.33 [1.15, 1.50] |
| Hincapié-palacio 2018 | 4.06 | 1.02 | 745 | 2.29 | 1.44 | 260 | 8.3% | 1.55 [1.39, 1.70] |
| Lima 2019 | 4 | 1.37 | 66 | 1.82 | 1.67 | 101 | 7.5% | 1.39 [1.05, 1.74] |
| Maertens 2016 | 4.61 | 0.77 | 58 | 2.52 | 1.37 | 41 | 6.7% | 1.96 [1.47, 2.44] |
| Naidu 2016 | 4.18 | 1.1 | 38 | 2.8 | 1.2 | 27 | 6.4% | 1.19 [0.66, 1.73] |
| Rice 2019 | 4.16 | 1.18 | 16 | 2.5 | 1.03 | 15 | 4.9% | 1.46 [0.65, 2.26] |
| **Subtotal (95% CI)** | | | **1410** | | | **963** | **62.6%** | **1.31 [1.06, 1.56]** |
| Heterogeneity: Tau² = 0.10; Chi² = 39.23, df = 8 (P < 0.00001); I² = 80% | | | | | | | | |
| Test for overall effect: Z = 10.30 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1790** | | | **1319** | **100.0%** | **1.51 [1.24, 1.78]** |
| Heterogeneity: Tau² = 0.23; Chi² = 119.23, df = 14 (P < 0.00001); I² = 88% | | | | | | | | |
| Test for overall effect: Z = 10.87 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.60, df = 1 (P = 0.06), I² = 72.2% | | | | | | | | |




**B**

| Study or Subgroup | Vaccine during pregnancy Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.2.1 RCT group** | | | | | | | | |
| Baruq 2019 | 5.8 | 0.87 | 54 | 2.75 | 1.24 | 53 | 9.5% | 2.83 [2.29, 3.37] |
| Halperin 2018 | 5.22 | 0.75 | 126 | 3.06 | 1.19 | 132 | 10.0% | 2.15 [1.85, 2.46] |
| Hoang 2016 | 4.53 | 1.25 | 49 | 3.32 | 0.95 | 46 | 9.8% | 1.08 [0.64, 1.51] |
| Munoz 2014 | 5.46 | 0.67 | 33 | 3.22 | 1.51 | 14 | 8.8% | 2.23 [1.44, 3.01] |
| Perrett 2020 | 5.9 | 0.28 | 29 | 3.12 | 0.38 | 29 | 5.9% | 8.22 [6.58, 9.85] |
| **Subtotal (95% CI)** | | | **291** | | | **274** | **44.0%** | **3.00 [1.88, 4.11]** |
| Heterogeneity: Tau² = 1.45; Chi² = 82.79, df = 4 (P < 0.00001); I² = 95% | | | | | | | | |
| Test for overall effect: Z = 5.26 (P < 0.00001) | | | | | | | | |
| **2.2.2 Cohort group** | | | | | | | | |
| Abu Raya 2014 | 5.28 | 0.66 | 51 | 2.84 | 1.1 | 20 | 9.0% | 3.00 [2.27, 3.72] |
| Healy 2013 | 4.47 | 0.92 | 19 | 4.29 | 1.11 | 86 | 9.6% | 0.17 [-0.33, 0.66] |
| Lima 2019 | 5.8 | 1.11 | 66 | 3.47 | 1.2 | 101 | 9.9% | 1.99 [1.61, 2.37] |
| Maertens 2016 | 4.94 | 0.95 | 58 | 3.31 | 0.77 | 41 | 9.7% | 1.84 [1.36, 2.32] |
| Naidu 2016 | 5.56 | 0.93 | 38 | 4.21 | 1.06 | 27 | 9.5% | 1.35 [0.80, 1.90] |
| Rice 2019 | 5.27 | 0.87 | 16 | 3.02 | 1.26 | 15 | 8.4% | 2.04 [1.15, 2.93] |
| **Subtotal (95% CI)** | | | **248** | | | **290** | **56.0%** | **1.71 [0.98, 2.43]** |
| Heterogeneity: Tau² = 0.72; Chi² = 52.95, df = 5 (P < 0.00001); I² = 91% | | | | | | | | |
| Test for overall effect: Z = 4.63 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **539** | | | **564** | **100.0%** | **2.23 [1.62, 2.84]** |
| Heterogeneity: Tau² = 0.94; Chi² = 145.61, df = 10 (P < 0.00001); I² = 93% | | | | | | | | |
| Test for overall effect: Z = 7.16 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.62, df = 1 (P = 0.06), I² = 72.3% | | | | | | | | |

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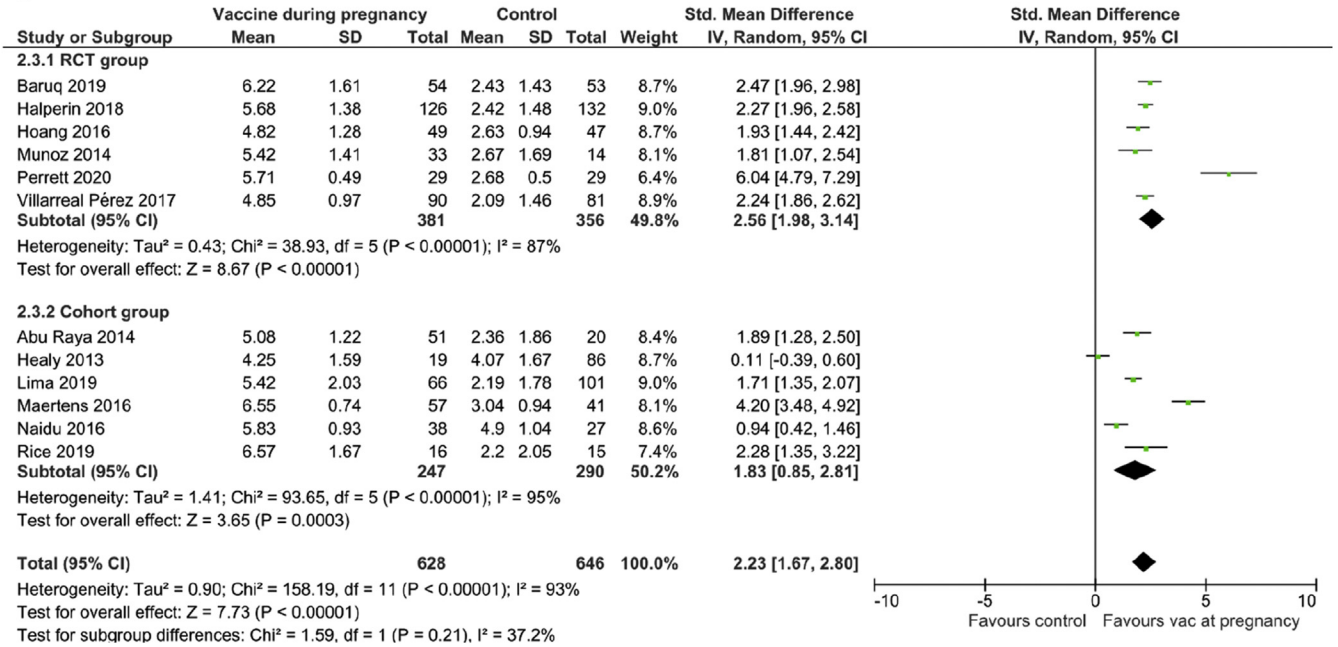
**SUPPLEMENTAL FIGURE 3**
**Continued**

**C**




**A,** Level of antipertussis toxin IgG at cord blood between the vaccine during pregnancy and the control groups. **B,** Level of antifilamentous hemagglutinin IgG at cord blood between the vaccine during pregnancy and control groups. **C,** Level of antipertactin IgG at cord blood between the vaccine during pregnancy and the control groups.

*CI*, confidence interval; *IgG*, immunoglobulin G; *RCT*, randomized controlled trial; *SD*, standard deviation.

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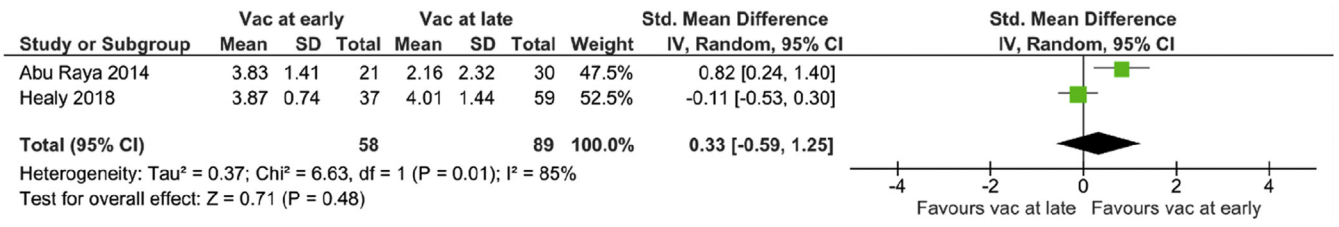
**SUPPLEMENTAL FIGURE 4**
**Anti-PT IgG concentrations at cord blood in vaccine group at early (27–30 weeks' gestation) and late (31–36 weeks' gestation) time**




*anti-PT*, antipertussis toxin; *CI*, confidence interval; *IgG*, immunoglobulin G; *SD*, standard deviation.

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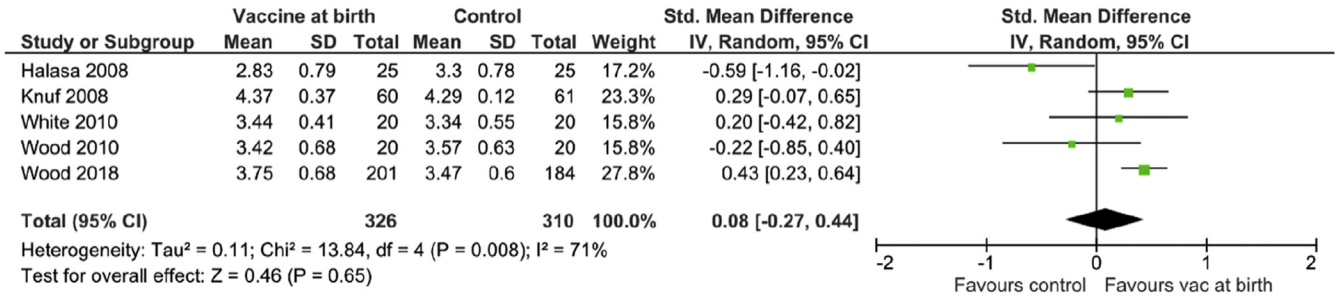
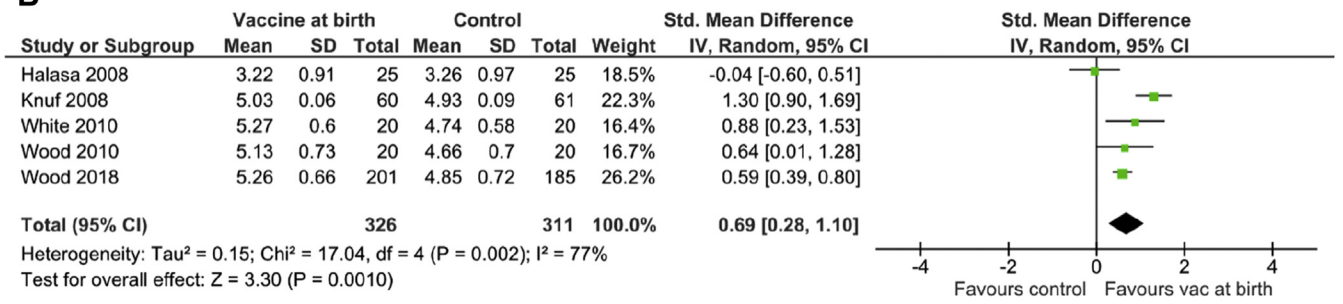
**SUPPLEMENTAL FIGURE 5**

**IgG concentrations after primary schedule vaccination between vaccine at birth and control groups**

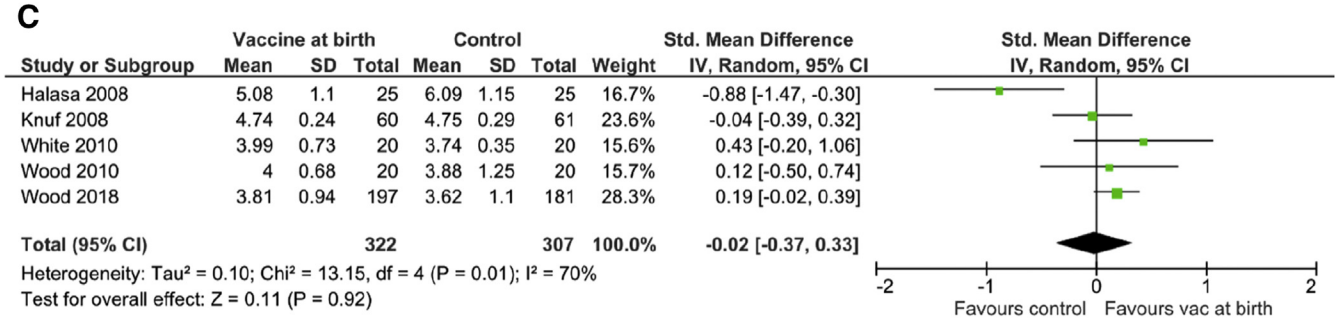
**A**




**B**




**C**




**A,** Level of antipertussis toxin IgG after the primary schedule vaccination between the vaccine at birth and the control groups. **B,** Level of antifilamentous hemagglutinin IgG after the primary schedule vaccination between the vaccine at birth and the control groups. **C,** Level of antipertactin IgG after the primary schedule vaccination between the vaccine at birth and the control groups.

*CI*, confidence interval; *IgG*, immunoglobulin G; *SD*, standard deviation.

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**PRISMA 2009 Checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 4 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 7 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7-8 |

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*(continued)*

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10-11 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10-11 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 12-16 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12-116 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 11 |
| 9Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 12-16 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 20 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 21 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 22 |

For more information, visit: www.prisma-statement.org.

Adapted from Moher et al.[20]

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