Review of vaccination in pregnancy to prevent pertussis in early infancy

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Abstract

Maternal pertussis vaccination has been introduced in several countries to protect infants from birth until routine infant vaccination takes place. This review assesses existing evidence on the effectiveness and safety of immunization in pregnancy. The search was finalized in April 2017 and was based on searches using several databases. The selection criteria included any experimental or observational study reporting on the immunogenicity, effectiveness or safety of vaccination with a pertussis-containing vaccine in pregnant women and their infants. Following de-duplication and exclusions, we identified 8395 studies, which were reduced to 46 for inclusion. The overall risk of bias was low, with the exception of some early studies and pharmacovigilance safety data. The evidence demonstrates efficient transplacental transfer of maternal antibodies in infants whose mothers were vaccinated with Tdap or Tdap/IPV in pregnancy, with good evidence that this protects against disease in young infants. Safety studies covering more than 150,000 women vaccinated mostly in the late second or third trimesters are generally consistent and provide reassurance of no significant increased risk of recognized maternal conditions or of adverse events (including congenital anomalies) in infants born to vaccinated women. The clinical significance of reduced seroconversion to pertussis following routine immunization is not yet clear, but no increased risk of pertussis in infants whose mothers were vaccinated in pregnancy was found following primary immunizations in North American and English studies. Most post-booster studies suggest that any blunting effect is short-lived and that longer-term protection in infants from active immunization is not compromised.

BACKGROUND

Pertussis (whooping cough) is a vaccine-preventable, acute bacterial respiratory infection caused by the organism Bordetella pertussis. It is characterized by a protracted coughing illness and can result in severe complications, including death, particularly in young unimmunized infants who remain at a disproportionate risk of severe or complicated disease, whilst adolescents and adults tend to display milder symptoms [1]. The primary aim of the pertussis immunization programme is therefore to minimize infant morbidity and mortality.

Pertussis whole-cell (wP) vaccines, made from killed whole B. pertussis bacteria, have been available since the 1940s. Despite some heterogeneity amongst combination diphtheria/tetanus/wP (DTwP) vaccines, these vaccines have had a dramatic impact on the global burden of pertussis [2]. In England, for example, the reported disease rates declined from 106 cases per million infants in 1954–57 to 13 cases per million infants in 1970–73, following the introduction of wP vaccination from 1957 [1]. However, protection from natural infection and vaccination is not life-long and the disease continues to peak cyclically every 3 to 4 years in many countries with established vaccine programmes.

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Abbreviations: 3aP, 3 component acellular pertussis; 5aP, 5 component acellular pertussis; AEFI, adverse events following immunization; AEs, adverse events; aP, acellular pertussis; APR, adjusted prevalence ratio; ARR, adjusted risk ratio; CDPH, California Department of Public Health; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DT, diphtheria/tetanus; FHA, filamentous hemagglutinin; FIM, fimbriae proteins; GMC, geometric mean concentrations; IgG, immunoglobulin class G; IPV, inactivated polio virus; KNPC, Kaiser Permanente of Northern California; NICU, neonatal intensive care unit; OR, odds ratio; PHE, Public Health England; PT, pertussis toxoid; RAI, relative avidity index; RCTs, randomized controlled trials; RR, risk ratio; SAEs, serious adverse events; TT, tetanus toxoid; VE, vaccine effectiveness; VSD, Vaccine Safety Datalink; WHO, World Health Organization; wP, whole-cell pertussis.
Pertussis remains an under-recognized disease, especially in teenagers and adults, despite new laboratory methods in some countries, such as serological and other antibody tests, which have contributed to improved ascertainment [3]. However, direct comparison between countries remains difficult due to differences in the sensitivity of surveillance systems, differing schedules and the different pertussis vaccines in use, as well as potential differences in the local disease burden and transmission patterns.

Clinical trials during the 1990s suggested that new aP vaccines were less reactogenic and conferred comparable effectiveness, depending on the wP- and aP-containing vaccine used [4]. As a result, high-income countries started replacing combined DTwP vaccines with combination aP vaccines from the 1990s, primarily due to the reduced reactogenicity of the aP component [5]. More recent studies indicated that aP vaccines may be less effective than the highest efficacy wP vaccines, with more rapid waning of protection following the primary infant series [4, 6], and in primate studies aP vaccine failed to prevent infection and transmission [7]. A number of developed countries with long-standing vaccination programmes also reported a resurgence of pertussis despite sustained high vaccine coverage [8–13]. As a result, the World Health Organization (WHO) recommended that low-income countries using wP-containing vaccines should only consider switching to aP-containing vaccines if additional booster or maternal immunization could be assured and sustained [6]. This also led to a growing international debate on strategies to optimize pertussis control and maximize protection in infants, particularly infants too young to be vaccinated when they are at high risk of severe disease. The WHO considered vaccination of pregnant women to be the most cost-effective additional strategy to protect infants during this susceptible period, and whilst the ‘cocooning’ strategy has been adopted in some countries, it is difficult to achieve high uptake and evidence of its effectiveness is inconsistent [6].

In 2011, following an increase in pertussis, the USA became the first country to advise that pertussis vaccine be administered to pregnant women in the third trimester [14], and in October 2012 this advice was updated to recommend vaccination in every pregnancy [15]. Argentina introduced universal free maternal pertussis vaccination in February 2012 from 20 weeks of pregnancy [16]. In the UK, a temporary maternal vaccination programme was introduced in October 2012 in response to an outbreak [17]. Other countries, including Australia, Belgium and Spain, have since introduced maternal pertussis vaccination programmes. At the time of programme introduction, evidence of effectiveness was largely extrapolated from immunogenicity studies. Antenatal maternal immunization programmes for other vaccine-preventable diseases, such as tetanus, are well established and effective in reducing neonatal mortality [18]. Maternal influenza vaccination protects both infants and pregnant women against severe disease and death, and with pregnant women being identified by the WHO in 2012 as the highest priority group for seasonal influenza vaccination, this programme is now routine in a number of countries [19].

Studies of antibody responses in women of child-bearing age suggest that this is maximal for pertussis-containing vaccines approximately 14 days after immunization [20]. All subclasses of immunoglobulin class G (IgG) are transferred from mother to infant across the placenta, primarily during the third trimester of pregnancy [21]. Transplacental pertussis IgG antibody transfer has been demonstrated, with the concentrations in newborns [22, 23] or cord serum samples [22, 24, 25] being reflective of those in the mother. Maternal antibodies are thought to have a half-life of approximately 6 weeks and so, if boosted to sufficiently high levels, are likely to provide time-limited, passive protection for newborn infants prior to their first childhood immunizations [23, 26], although there is no clear immunological correlate of protection for pertussis.

The early safety data for aP-containing vaccines during pregnancy were largely derived from pregnancy registries; thus population-based safety evaluation has been a priority. Enhanced reactogenicity of aP pertussis vaccines has been described with increasing numbers of doses in infants and young children and is associated with more pronounced local side-effects for the tetanus component [27], but data following maternal antenatal vaccination are required.

There has been concern that maternally derived antibodies could interfere significantly with the infant’s own response to pertussis vaccine antigens and other antigens in the primary infant series. The clinical relevance of any observed inhibitory effect (blunting), if any, was difficult to ascertain, however, prior to the implementation of national programmes due to the lack of an agreed correlate of protection for pertussis. Research suggested that pre-existing maternal pertussis antibodies did not affect the PT antibody response to DTaP in infants, although modest inhibitory effects were seen with other pertussis antibodies [28]. Blunting has, however, been demonstrated for other vaccines, such as measles [29], and with pertussis-containing vaccines administered at birth [28, 30, 31]. Any blunting effect may differ depending on the infant immunization schedule in place and whether infants receive wP or aP vaccines for their primary series, as suggested in the study by Englund et al. [28].

This review aimed to assess existing evidence for the effectiveness and safety of immunization in pregnancy (in any trimester) in preventing pertussis disease in infants too young to be protected by routine primary vaccinations.

**METHODS**

We included any primary experimental or observational study, or secondary study reporting on the effectiveness, immunogenicity or safety of antenatal vaccination with a pertussis-containing vaccine.

We included studies that reported on: pregnant women of all ages and gestations of pregnancy, with any pregnancy
(single, multiple, complicated or uncomplicated) or parity, and their infants. We excluded animal studies.

The review included studies with any pertussis-containing vaccine (aP or wP) administered at any stage of pregnancy, as compared with no vaccination, sham or placebo vaccination. In most countries, the vaccines used in the maternal programmes are licensed Tdap vaccines, e.g. Adacel or Boostrix in the USA (ACIP 2011, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6037a3.htm?s_cid=mm6037a3_w). In the UK dTaP-IPV vaccine (Repevax and Boostrix-IPV) is used as the licensed aP booster vaccine for use in adults and adolescents (PHE 2016, https://www.gov.uk/government/publications/pertussis-the-green-book-chapter-24).

Primary outcome measures were:

1) Evidence of protection against pertussis disease in infants following pertussis immunization in pregnancy, where pertussis was specified as the primary diagnosis or a major contributing factor.
(2) Evidence of the safety of vaccination in pregnancy, as demonstrated by consideration of major adverse events in the mother and/or in the foetus/newborn/infant. We excluded any study that considered only minor (self-limiting) adverse events.

Secondary outcome measures were:

- Antibody response in the mother following pertussis vaccination in pregnancy.
- Transplacental transfer of antibody as evidenced by cord, foetal or infant blood titres of maternally derived antibody to any vaccine component at birth or prior to the first primary vaccination.
(3) The effect of the timing of maternal vaccination on the transplacental transfer of maternal antibodies or on the risk of disease in the infant.

(4) Blunting of the immunological response to primary childhood vaccinations as evidenced by antibody levels to any vaccine component and clinically or laboratory-confirmed pertussis disease.

We initially searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1946 to March 2014), CINAHL (1981 to March 2014), Embase (1974 to March 2014), LILACS (1982 to March 2014) and Web of Science (1985 to March 2014). A further search was undertaken from February 2014 to March 2016 using the same criteria, other than Web of Science, which was replaced with Scopus due to the licensing arrangements of Public Health England (PHE). A final literature search was conducted using the same search criteria as in the latter case for the period 1 March 2016 to 30 April 2017 in order to identify studies published after the comprehensive review had been completed. The search strategies are detailed in the supplementary material. We did not use any language, date or publication restrictions because this has been shown to be a potential source of bias [32].

In addition, snowballing techniques such as reference and citation tracking were carried out for all included papers. We merged the results using reference management software (Mendeley).

**Data collection and analysis**

Pairs of authors were randomly allocated references to review the titles and abstracts of all selected citations and obtain full-text articles when they appeared to meet the eligibility criteria, or when there was insufficient information to assess eligibility. Each author assessed the eligibility of the studies independently and we resolved any discordant assessments by discussion. When full text was obtained reasons for exclusions were assigned as inappropriate study type based on the intervention, population or outcome (see Fig. 1). We used Google Translate to assess the eligibility of papers in languages other than English and did not need to translate any full-length papers.

Three pairs of review authors were then randomly allocated selected references. One of each pair of review authors independently extracted data on study characteristics, participant characteristics and specifics of the intervention from the manuscript using pre-tested data extraction forms. The second author in the pair independently checked this for accuracy.

We assessed the risk of bias based on the seven domains of the adapted Cochrane risk of bias tool [33]. One review author assessed bias, a second author in the pair verified and one author (NA) collated whilst checking for consistency. For each domain we used categories of high risk, intermediate risk, low risk and not applicable. Not applicable was used when a domain was not relevant, which usually applied to random sequence generation, allocation concealment and blinding of participants for observational studies. To make the tool more relevant to the multifactorial outcomes we were assessing, we divided the 'other' category into three and used it to assess the implications of the risk of bias in the other domains, as well as other biases such as confounding of the outcomes relating to safety, immunogenicity and effectiveness/efficacy. The justification for each category was documented. We assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes.

We could not perform a meta-analysis of studies as the intervention, design and end points were dissimilar. We therefore summarized the results of different studies, including the quality of the available evidence for each outcome, but have not produced pooled estimates. Evidence from randomized controlled trials (RCTs) was analysed separately from observational evidence.

**RESULTS**

We identified 7269 records through database searching from the 1940s to end March 2014, which were reduced to 7184 records after de-duplication, while a further 6947 records were excluded on initial review of the titles and abstracts (Fig. 1). Of the 237 publications identified for screening, 7 could not be obtained. Twenty-three additional records were found by snowballing. These 253 full-text articles were reduced to 11 for inclusion in the review. In the later searches covering the period February 2014 to April 2017, 1038 unique new publications were identified. On review of the title and abstract, a further 987 were excluded and 51 full-text articles were assessed for eligibility, of which 35 were included in the final review.

Therefore, of the 304 full articles screened, 46 were included in the review. A summary of the exclusion categories is shown in Fig. 1 and details of the excluded studies are available on request. The 46 included studies were divided into categories according to the specified primary and secondary outcomes and further categorized according to whether wP or aP vaccines were used. Funding sources were not always clear, but in 2 studies the only sources mentioned were pharmaceutical companies, while 6 had partial funding or laboratory support from pharmaceutical companies, 14 had no funding source listed and 24 were funded by non-pharmaceutical sources.

**Risk of bias in included studies**

The risk of bias in the included studies is summarized in Fig. 2 (rationale available in supplementary materials). Most of the studies were non-randomized and so were not assessed for random sequence generation, allocation concealment or for blinding of participants and personnel, but it should be recognized that such studies are at risk of selection bias where women choosing not to be vaccinated are inherently different in a way that may also affect the
<table>
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<tr>
<th>Study ID (Ref)</th>
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<td>[47]</td>
<td>Vaccine effectiveness of maternal vaccination against laboratory-confirmed disease in infants under 2 months and under 3 months of age</td>
<td>Retrospective cohort using the screening method based on national laboratory-confirmed cases between October 2012 and September 2013. Primary VE analysis based on 82 confirmed infant cases</td>
<td>England (1 year post-implementation)</td>
<td>National enhanced surveillance of laboratory-confirmed pertussis in infants. Vaccine coverage data from Sentinel Primary care data source (CPRD). Hospital admissions from Hospital Episode Statistics</td>
<td>Td5aP-IPV from 28 weeks’ gestation</td>
<td>Vaccine effectiveness against laboratory-confirmed pertussis in infants under 2 months of age and under 3 months of age</td>
<td>VE 90 % (95 % CI: 82 to 95) in infants under 2 months of age</td>
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<td>[48]</td>
<td>Vaccine effectiveness of maternal vaccination against infant deaths and laboratory-confirmed disease in infants under 2 months and under 3 months of age. Comparative effectiveness of dT5aP/IPV and dT3aP/IPV on infant disease and of impact blunting on clinical disease</td>
<td>Retrospective cohort study using the screening method using national laboratory-confirmed cases between October 2012 and September 2015 across England. Primary VE analysis based on 243 confirmed infant cases</td>
<td>England (3 years post-implementation)</td>
<td>National enhanced surveillance of laboratory-confirmed pertussis in infants. Vaccine coverage data from Sentinel Primary care data source (CPRD). Pertussis deaths reconciled from: ONS, follow-up of laboratory-confirmed cases, Hospital Episode statistics and HPZone</td>
<td>dT5aP/IPV and dT3aP/IPV from 28 weeks' gestation</td>
<td>Vaccine effectiveness against laboratory-confirmed pertussis in infants under 2 months of age and under 3 months of age</td>
<td>VE 91 % (95 % CI: 88 to 94) when given up to 7 days before delivery. VE against death was 95 % (95 % CI:79 to 100). No significant difference between dT5aP/IPV and dT3aP/IPV. No evidence of increased risk of clinical disease/blunting in infants born to vaccinated mothers after three doses [VE 46 % (95 %CI: −96 to 85)]</td>
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<td>[52]</td>
<td>Vaccine effectiveness of maternal Tdap vaccine against hospital-confirmed pertussis in infants under 2 months and the first 12 months of life accounting for infant vaccination</td>
<td>Retrospective cohort study from 2010 to 2015. n=148 981. Mothers vaccinated during pregnancy=68 168 (45.8%) and not vaccinated=79 292 (53.2%). Vaccinated 1–7 days before birth and excluded from VE analysis=1521. Pertussis cases n=103 included who tested positive for pertussis in the first year of life Vaccine effectiveness of maternal Tdap vaccine against hospital-confirmed pertussis in infants under 2 months and the first 12 months of life</td>
<td>Kaiser Permanente of Northern California (KNPC) Hospitals, California, USA</td>
<td>Infants born full-term (&gt;37 weeks' gestation) in KNPC Hospitals and enrolled in Kaiser health plan by 4 months of age with mothers who were continuously enrolled in Kaiser during pregnancy. Mothers born pre-1996 to ensure they had received wP priming</td>
<td>All maternal Tdap and infant DTaP vaccine doses were counted beginning 8 days after receipt to allow time for the immune response</td>
<td>Vaccine effectiveness against pertussis in infants under 2 months and under 12 months of age</td>
<td>Maternal Tdap VE 91.4 % (95 % CI: 85.9 to 99.1) in infants &lt;2 months of age. No evidence of increased risk of clinical disease/blunting in infants born to vaccinated mothers as VE was 65.9 % (95 %CI: 4.5 to 87.8) after 3 doses. Maternal Tdap after pregnancy did not significantly reduce pertussis risk at &lt;2 months or during the first year of life</td>
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<td>[46]</td>
<td>Vaccine effectiveness, safety and immunogenicity of the pertussis vaccine in pregnant women and their infants</td>
<td>Immunological studies undertaken by the authors and follow-up of babies by unspecified method for symptoms of pertussis</td>
<td>USA</td>
<td>Whole-cell pertussis vaccine developed by Mishulow of New York Lab</td>
<td>Vaccine effectiveness against pertussis in infants between 0–5 months of age and 6–11 months of age</td>
<td>Vaccinated</td>
<td>Aged 0 to 5 months: 0 cases/100 (from 6 exposures); 6–11 months: 2 cases/100 Unvaccinated Aged 0 to 5 months: 3 cases/100 (from 6 exposures); 6–11 months: 2 cases/100</td>
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<td>[49]</td>
<td>Vaccine effectiveness of maternal pertussis vaccination in protecting infants against laboratory-confirmed pertussis infection under 8 weeks of age</td>
<td>with 10 up to 8 1/2 months of age. Control group (n=100). Case-control study from October 2012 through July 2013. Cases: 58. Controls: 55. Twenty-eight cases had no controls, so unmatched analysis was performed</td>
<td>England and Wales after the introduction of maternal pertussis vaccination</td>
<td>Cases: reference laboratory-confirmed pertussis in infants under 8 weeks. Controls: up to 2 infants born consecutively after the pertussis case, from same GP surgery from surgery. Maternal vaccination information, hospitalization date and gestational age at delivery were sought from GP</td>
<td>Acellular pertussis vaccine (Td5aP-IPV) between 28 and 38 weeks' gestation</td>
<td>Vaccine effectiveness against laboratory-confirmed pertussis in infants under &lt;8 weeks of age</td>
<td>VE 93 % (95 % CI: 81 to 97) in infants &lt;8 weeks of age</td>
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<td>[50]</td>
<td>Vaccine effectiveness of maternal Tdap vaccination against severe reported whooping cough cases in infants under 63 days of age</td>
<td>Retrospective cohort study of infants &lt;63 days of age born from January 2011 through December 2015. n=752; known maternal vaccination status=420 [prenatal Tdap vaccination (n=49), no prenatal Tdap (n=371)]</td>
<td>California, USA</td>
<td>CDPH pertussis surveillance reports, CDPH Centre for Health Statistics (birth certificate records) and California Immunization Registry (Tdap immunization records of mothers)</td>
<td>Tdap vaccine during pregnancy</td>
<td>Vaccine effectiveness against hospitalization with pertussis in infants under the age of 63 days</td>
<td>Infected infants with vaccinated mothers were significantly less likely to be hospitalized OR 0.4 (95 % CI: 0.2 to 0.9). VE 58 % (95 % CI: 15 to 80) after adjustment. Hospitalized infants with vaccinated mothers had shorter periods of admission and none required intubation or died</td>
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<td>[51]</td>
<td>Vaccine effectiveness of antenatal vs postpartum Tdap vaccination against reported pertussis cases in infants under 8 weeks of age</td>
<td>Retrospective cohort study from 2013 through 2014. Mother–infant pairs (n=7494)</td>
<td>California, USA</td>
<td>California Department of Public Health (CDPH) pertussis surveillance reports, CDPH Centre for Health Statistics (birth certificate records) and California Immunization Registry (Tdap immunization records of mothers, linked records)</td>
<td>Women aged 14–44 years vaccinated with Tdap vaccine during pregnancy (27–36 weeks) and Tdap vaccine during postpartum (within 14 days of pregnancy). CDPH pertussis surveillance data to identify pertussis cases in infants &lt;12 weeks of age</td>
<td>Vaccine effectiveness against reported pertussis in infants under 8 weeks of age born to vaccinated mothers vs unvaccinated mothers (postpartum)</td>
<td>Tdap vaccination received at 27–36 weeks' gestation was 85 % (95 % CI: 33 to 98 %) more effective than postpartum vaccination at preventing pertussis in infants &lt;8 weeks. Vaccination at 27–36 weeks’ gestation was more effective at preventing pertussis in infants compared to vaccination in the second trimester</td>
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outcomes. This is most likely to impact on safety outcomes, where potential confounding variables could be concomitant drug treatment, medical and obstetric history, smoking and body mass index. It should also be noted that a number of the observational studies had restrictive inclusion criteria, potentially impacting on the external validity of their findings. For the randomized studies, details of how the random sequence was generated and concealed as well as blinding were generally missing. It is recognized that a lack of appropriate randomization might result in selection bias, although little additional risk of bias for immunogenicity/safety outcomes was identified. For non-randomized studies it is clear that study participants and personnel will know the vaccine given/received, but it is not necessary for those assessing the end points to know the vaccination status. Although this was rarely documented, this is unlikely to introduce bias for objective measures such as immunogenicity or adverse events, but may bias more subjective assessments such as clinical assessment or referral for testing. Attrition bias (incomplete outcome data) was unlikely in most studies, but in four instances it was deemed to be high [34–37]. Most studies reported on all of the outcomes described in the methods, making reporting bias unlikely, with one exception [34]. Bias for safety, immunogenicity and effectiveness outcomes are summarized further within each section describing the results.

The risk of bias due to industry funding was judged to be low in the two studies where this was the only source of funding identified; in one the company had no input into the study design, analysis or writing [38], and in the other the grant was unrestricted and the company’s main involvement was blinded laboratory analysis [39]. In five of the the six studies with partial funding this was done indirectly through university-allocated post funding or laboratory support from pharmaceutical companies [40–44], while in the other (a safety study) it was done by funding one of two study locations [45]. In this last study the authors are non-pharmaceutical, but it is not made clear whether the company had any influence on the study analysis and publication, so this is a potential source of bias in this study.

**Protection against pertussis disease in infants**

There were seven studies (one with wP and six using aP) that estimated the effectiveness of maternal pertussis vaccination in protecting young infants against pertussis disease before infant vaccination (Table 1). Cohen and Scadron [46] used a wP vaccine in an intervention study and found no pertussis cases by 5 months of age (0 cases/100, from 8 known exposures) and 2 cases between the ages of 6 and 11 months (2 cases/100, exposures not provided) in children with vaccinated mothers [46]. In children born to unvaccinated mothers, there were 3 cases to 5 months of age (3 cases/100, from 6 known exposures) and 2 cases between 6 and 11 months (2 cases/100, exposures not provided).

Two recent observational studies in England [47, 48] assessed the national maternal aP-vaccination programme, recommended from 28 weeks’ gestation, with vaccine effectiveness being estimated using the screening method. One unmatched case–control study [49] has also been published based on data from England. Three studies in the USA were prospective cohort studies of babies born to women immunized with aP-containing vaccine which was recommended at 27–36 weeks’ gestation [50–52]. There was consistency in the level of VE estimated from all of these studies at 90–93% against disease and 95% against death from pertussis [48, 52] in infants <2 months (or <8 weeks) of age. A comparison of the effectiveness of maternal dT5a-IPV and dT3a-IPV vaccines used in England found no statistically significant difference between the two vaccines [48]. Winter found that vaccination in pregnancy reduced the risk of hospitalization from pertussis and that babies hospitalized with pertussis had a shorter duration of stay if their mother had been vaccinated [50]. Tdap vaccination during 27–36 weeks’ gestation was 85% more effective than postpartum vaccination at preventing pertussis in infants <8 weeks of age [51].

The risk of bias for effectiveness was intermediate in all of the studies except for that by Cohen and Scadron [46], where it was judged to be high due to the lack of clarity concerning the selection of unimmunized mothers (Fig. 2). The studies in England allowed for the most likely confounder of time period, as well as maternal age, whereas the US cohort studies adjusted for additional variables, such as ethnicity and parity, but not all possible confounders. A low risk of bias could not be assigned due to the lack of a randomized study, but the consistency of results across these studies and populations provides fairly robust evidence of protection.

**Pertussis vaccination safety for mothers and infants during pregnancy**

Three studies which used wP vaccine in pregnant women (totalling around 350 women) reported on safety with no detailed methodology and minimal details on participants [34, 46, 53]. These studies reported no premature births or postpartum complications ascribed to vaccination and babies were described as doing equally well in those born to both immunized and unimmunized mothers.

Sixteen studies of aP vaccination in pregnancy [36, 37, 41, 42, 44, 45, 54–63] looked at vaccine safety in a total of nearly 150 000 vaccinated women (Table 2). The sample sizes ranged from 33 to over 53 000 and the studies assessed the safety of different aP-containing combination vaccines used in programmes globally. These included Tdap and Tdap/IPV vaccines with three or five pertussis components, with the timing of vaccination ranging from 19 to 38 weeks where specified. One study also included women immunized in the first and second trimesters, but the analysis could not be broken down by trimester [37] and results were only analysed by 0–14 weeks’ or 27–36 weeks’ gestation in one study (specifically on microencephaly), with no increased risk identified [62].
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<td>[61]</td>
<td>To assess maternal and infant outcomes associated with administration of TdaP</td>
<td>A retrospective cohort with a review of records</td>
<td>Galveston County, University</td>
<td>Electronic medical records of all women who delivered a singleton infant. One thousand</td>
<td>TdaP vaccine for pregnant women</td>
<td>Maternal health outcomes (chorioamnionitis, postpartum endometritis, preterm premature rupture of membranes, preterm delivery and mode of delivery)</td>
<td>No significant differences for combined maternal or infant outcomes except longer length of stay in NICU for infants of non-vaccinated mothers (P&lt;0.001) and vaccinated mothers less likely to deliver by caesarean [OR 0.78 (95% CI: 0.63–0.98)], Chorioamnionitis OR in vaccinated mothers was 1.53 (95%CI: 0.80 to 2.90) Immunization had no effect on the pregnancy or delivery. No premature births or postpartum complications were attributable to vaccination. The babies thrived and did as well as control babies</td>
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<td>[34]</td>
<td>Effect of maternal pertussis vaccination on maternal and infant antibody levels,</td>
<td>Intervention study from March 1941–February 1942</td>
<td>USA</td>
<td>Mothers Treatment (n=167): 29 women selected for immunological test Control: numbers were unclear – data for up to 6 infants were presented together</td>
<td>Pertussis vaccine prepared by Mishulow of New York laboratories given in the fifth or sixth month of pregnancy administered every 2 weeks for six injections at increasing doses</td>
<td>Immunization had no effect – there was no detailed method for ascertainment of adverse events</td>
<td>Immunization had no effect on the pregnancy or delivery. No premature births or postpartum complications were attributable to vaccination. The babies thrived and did as well as control babies</td>
</tr>
<tr>
<td>[46]</td>
<td>Vaccine effectiveness, safety and immunogenicity of the pertussis vaccine in pregnant women and their infants</td>
<td>Intervention study</td>
<td>USA</td>
<td>Mother Treatment (n=170): 100 mothers followed up for pertussis. 30 vaccinated mothers had immunological studies done Control (n=100): 10 vaccinated mothers had immunological studies done up to 10 months after vaccination</td>
<td>Whole-cell pertussis vaccine developed by Mishulow of New York laboratory</td>
<td>Observable maternal and infant deleterious effects</td>
<td>No deleterious effect upon offspring and no ill effect upon pregnancy</td>
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<td>[62]</td>
<td>To assess the association of maternal Tdap vaccination with structural birth defects in infants</td>
<td>Retrospective cohort study from January 2007 through September 2013</td>
<td>Seven sites, USA</td>
<td>Vaccine Safety Datalink (VSD) with 41,654 Tdap exposed and 282,809 unexposed</td>
<td>Tdap with timing of administration specified only as first trimester (0–14 weeks) or recommended period (27–36 weeks’ gestation)</td>
<td>Any structural birth defects, including microcephaly</td>
<td>No increased risk for: any structural birth defects – adjusted prevalence ratio (APR) 0.98 (95 % CI: 0.94 to 1.03)</td>
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<tr>
<td>[54]</td>
<td>To examine the safety of pertussis vaccination in pregnancy</td>
<td>Retrospective observational cohort study from October 2010 to September 2012</td>
<td>United Kingdom</td>
<td>Clinical Practice Research Datalink (CPRD)</td>
<td>Vaccinated: 20,074 pregnant women, of whom 15,560 had &gt;28 days’ follow-up and 6,185 with pregnancy outcome</td>
<td>Still birth, maternal and neonatal death (within 7 days), pre-eclampsia/eclampsia, placenta previa, intrauterine growth retardation, low birth weight, caesarean section, premature labour, postpartum haemorrhage</td>
<td>No increased risk of any serious adverse events (SAEs) related to pregnancy. Primary study outcome of still birth had incidence rate ratio 0.85 (95 % CI: 0.45–1.61)</td>
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<tr>
<td>[41]</td>
<td>The primary aims were to look at immunogenicity through maternal antibody transference, possible interference with the infant response and safety in the mother, together with possible congenital abnormalities in the baby</td>
<td>Randomized controlled study of pregnant women recruited during routine preventive visits who received Tdap or TT vaccine</td>
<td>Three villages of one region in northern Vietnam</td>
<td>Systemic reactions up to 30 min post-vaccination. Collection of other AEs using a 1-month diary and visits to the local health centre with serious AEs (non-specified) recorded throughout pregnancy. Congenital abnormalities were monitored in the babies</td>
<td>Tdap-52 women vaccinated with one lost to follow up. TT – 51 women vaccinated with 3 lost to follow-up and their babies</td>
<td>Systemic reactions, other adverse events with SAEs (non-specified). Congenital abnormalities in the babies</td>
<td>Six women experienced SAEs with one in the TT group resulting in a stillbirth 5 weeks after vaccination. No unexpected AEs were observed in the women, only expected side-effects based on the product characteristics. No serious events or congenital abnormalities in the infants</td>
</tr>
<tr>
<td>[55]</td>
<td>To identify any association between maternal vaccination and adverse obstetric events and adverse birth outcomes</td>
<td>Retrospective cohort study from January 2010 to November 2012</td>
<td>Kaiser Permanente, north and south California, USA</td>
<td>Administrative healthcare databases from Vaccine Safety data link site; 26,229 vaccinated and 97,265 unvaccinated pregnant women</td>
<td>Tdap from 20 weeks’ gestation</td>
<td>Chorioamnionitis and hypertensive disorders of pregnancy, preterm and small for gestational age births</td>
<td>No increased risk of adverse outcomes except a small but statistically significant risk of chorioamnionitis [RR 1.19 (95 % CI: 1.13 to 1.26)]</td>
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<tr>
<td>[56]</td>
<td>To evaluate risks for selected acute adverse events occurring 0–42 days in</td>
<td>Retrospective observational cohort study from January 2007</td>
<td>Administrative and electronic healthcare databases from Vaccine Safety datalink</td>
<td>Tdap at any time in pregnancy as well as in those at 20 weeks’</td>
<td>Neurological events, including seizures, proteinuria, gestational</td>
<td>Neurological events, including seizures, proteinuria, gestational</td>
<td>No statistically increased risk for pre-specified maternal safety outcomes within</td>
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<tr>
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<td>[42]</td>
<td>Effect of vaccination in pregnancy on new-born cord antibody levels (DTP) and any effect on antibody levels (DTP) after primary immunization. Safety in the mother and possible congenital abnormalities in the baby</td>
<td>Prospective controlled cohort study from April 2012 to April 2014.</td>
<td>Five hospitals in one Belgian province</td>
<td>Systemic reactions up to 30 min post-vaccination. Collection of other adverse events for 30 days with serious adverse events (non-specified) recorded throughout. Vaccinated pregnant women (n=57) and their infants (n=55); unvaccinated pregnant women (n=42) and their infants (n=26)</td>
<td>Mothers, Td3aP at 22 to 33 weeks’ gestation</td>
<td>Systemic reactions, other AEs with SAEs (non-specified). Congenital abnormalities in the babies</td>
<td>AEs in 11/57 vaccinated women categorized as serious but not related to vaccination and in line with those expected within the general population. There were serious AEs in 3/41 control women. There was no unexpected risk pattern in infants and no congenital disorders were detected</td>
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<tr>
<td>[44]</td>
<td>Possible remaining interference of maternal antibodies with the infant humoral immune responses after a fourth aP containing vaccine dose at 15 months with safety evaluation in those children</td>
<td>Prospective controlled cohort study of children born from April 2012 to April 2014 (continuation of [42])</td>
<td>Five hospitals in one Belgian province</td>
<td>Vaccine group: children born from vaccinated women (n=55) Control group: children born from women not vaccinated with a pertussis containing vaccine for at least 10 years (n=26)</td>
<td>Maternal Tda3P between 18 and 34 weeks’ gestation. Infants (DTa3P-IPV-Hib-HepB) at 8, 12 and 16 weeks and 15 months</td>
<td>Medical history of diseases in the household, mainly respiratory diseases, was assessed. All SAEs in the infants occurring to 15/16 months. All infants were examined by a medical doctor at 15 or 16 months of age using the Van Wiechen developmental test for neurodevelopment</td>
<td>Infants hospitalized did not differ between maternal vaccine group 10.9% versus control group 12.5% (P=0.838). Toddlers in the vaccine group were significantly better developed for two items in comparison with control group toddlers, but as there is no cutoff or end score to judge the development of the toddlers, the results of the test were not detailed</td>
</tr>
<tr>
<td>[53]</td>
<td>Effect of pertussis vaccination in pregnancy on maternal antibody levels</td>
<td>Intervention study (details not given)</td>
<td>USA</td>
<td>Pregnant mothers (n=29) in third trimester. Three women who were not immunized in pregnancy</td>
<td>Whole-cell Pertussis toxin vaccine (Mishulow vaccine) given at 2 week intervals with an increasing dose Td5aP or Td3aP at or after 32 weeks of gestation</td>
<td>Method of collecting information on AEs not described</td>
<td>Reported no severe reactions or untoward results in any of the patients</td>
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<tr>
<td>[57]</td>
<td>Evaluate pregnancy outcome among women who received Tdap at or after 32 weeks of gestation</td>
<td>Retrospective cohort study from June 2013 to July 2014</td>
<td>Parkland Hospital, Dallas County, Texas, USA</td>
<td>Centralized electronic medical charting system; 7152 vaccinated and 226 unvaccinated pregnant women Women who received Tdap in this and a prior pregnancy in the previous 5 years were compared with</td>
<td>Still birth, congenital anomalies, chorioamnionitis, 5 min APGAR score, cord blood pH, neonatal complications requiring ventilations, intraventricular hemorrhage, neonatal death rates, preterm birth</td>
<td>No increased risk of adverse outcomes. Significantly lower preterm births, shorter neonatal hospital stay and higher birth weight in vaccinated group. No difference in neonatal outcomes between women administered ≥2 Tdap</td>
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Table 2. cont.

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<tr>
<th>Study ID</th>
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<tbody>
<tr>
<td>[36]</td>
<td>To examine the safety of maternal TdaP vaccination in mothers and their infants</td>
<td>Retrospective review of reported AEs in cohort of pregnant women who had received Tdap between January 2011 and June 2015 as compared to the pattern between January 2005 and June 2010</td>
<td>USA</td>
<td>Vaccine Adverse Event Reporting System; 392 vaccinated women</td>
<td>Comparison of routine DTaP to historic unplanned DTaP in pregnancy</td>
<td>All adverse events following immunization (AEFI) were observed according to predefined search criteria (events not described in detail in methodology)</td>
<td>No unusual or unexpected increase in the number of reports or in the pattern of maternal, foetal, or infant AEs.</td>
</tr>
<tr>
<td>[63]</td>
<td>Study of maternal and infant adverse events, pertussis illness, infant growth and development to 13 months. Immunogenicity of maternal Tdap immunization and any blunting effect in infants</td>
<td>Phase 1–2, randomized, double-blind, placebo-controlled clinical trial from October 2008 to May 2012</td>
<td>Three National Institutes of Health Vaccine Treatment Evaluation Unit sites in the USA</td>
<td>Vaccinated antepartum (n=33), vaccinated postpartum (n=15) and non-pregnant women (n=32) and their newborn infants (n=48)</td>
<td>Td5aP vaccine for pregnant and non-pregnant women. Infants received DTaP-IPV-Hib vaccine</td>
<td>Injection site and systematic reactions, delivery outcome, infant growth and development and pertussis illness in mother and infants</td>
<td>No significant differences in delivery outcome, gestational ages, Apgar score, birth weight, neonatal examinations or complications and at 13 months in infant growth and development or pertussis illness in women and infants</td>
</tr>
<tr>
<td>[45]</td>
<td>To examine the safety of pertussis vaccination in pregnancy</td>
<td>Prospective observational study from January 2014 to June 2014</td>
<td>Two different regions of New Zealand</td>
<td>Four weeks’ follow-up with mothers who had received Tdap during pregnancy by diary and telephone or postal survey. n=793 with 28% having influenza vaccine co-administered. Compared to background rates</td>
<td>Td3aP between 28 to 38 weeks’ gestation</td>
<td>SAEs following immunization as per the ICH definition (any untoward medical occurrence that: results in death; is life-threatening; requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or requires intervention to prevent permanent impairment or damage)</td>
<td>None of the SAEs were considered likely to have a causal association with TdaP vaccine administered during pregnancy. On the basis of NZ data, the rates of SAEs in the study were not higher than the expected background rate</td>
</tr>
<tr>
<td>[58]</td>
<td>Assessment of pregnancy and birth outcomes in infants born to vaccinated (Tdap) and unvaccinated mothers</td>
<td>Retrospective cohort study from May 2005 to August 2009, prior to recommendation of Tdap</td>
<td>Intermountain Healthcare facilities, Utah, USA</td>
<td>Intermountain Healthcare Enterprise Data Warehouse; 138 pregnant women vaccinated for wound prophylaxis (cases)</td>
<td>Tdap vaccine within 280 days of pregnancy</td>
<td>Pregnancy outcomes included spontaneous or elective abortions, stillbirths and live births, preterm delivery, birth weight,</td>
<td>No significant increase in serious adverse outcomes or congenital anomalies in cases and their infants compared to controls</td>
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<td>[60]</td>
<td>To evaluate the safety, immunogenicity and blunting of the TdaP vaccine in pregnant women and their children</td>
<td>Randomized, double-blind, parallel group-controlled clinical trial from September 2011 to August 2014</td>
<td>Twelve outpatient health centres, Mexico</td>
<td>Vaccinated pregnant women (n = 90) and unvaccinated pregnant women (n = 81)</td>
<td>TdaP vaccine (experimental) or normal saline (controls) between 30 and 32 weeks’ gestation. Infant received DTaP-IPV-Hib vaccine</td>
<td>All AEFI were observed (not described in detail in methodology)</td>
<td>No increased risk of SAEs at 30 min, 24 h, 48 h and 1 month after vaccination</td>
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<tr>
<td>[59]</td>
<td>Describe any AEFI related to Tdap vaccine administration during pregnancy with a focus on infant outcomes</td>
<td>Prospective cohort study from September 2012 through November 2014 (n = 403). Compared to New Zealand background rates</td>
<td>Canterbury region, New Zealand</td>
<td>The safety monitoring of adverse reactions to Tdap Vaccine in Pregnancy, part of national study on AEFIs associated with TdaP vaccination in pregnancy</td>
<td>Tdap at 28 to 38 weeks’ gestation</td>
<td>Congenital anomalies, preterm, low birth weight, and adverse events during pregnancy or in infants</td>
<td>No increased risk of AEs in mother or infants as compared to baseline rates in New Zealand. Congenital anomalies (27 % vs 4-6 %) and the preterm birth rate (6 % Vs. 8 %) were lower than the baseline rate</td>
</tr>
<tr>
<td>[37]</td>
<td>To assess reporting of adverse events (AEs) after Tdap administered to pregnant women compared to inactivated influenza vaccine</td>
<td>Retrospective review of reported AEs in pregnant women who had received Tdap from 2005 to 2010 when Tdap was not routinely recommended for pregnant women</td>
<td>USA</td>
<td>Vaccine Adverse Event Reporting System on 132 pregnant women who received Tdap</td>
<td>dTa3P or dTa5P during pregnancy with 85/110 (77 %) in the first trimester, 21/110 (19 %) in the second trimester and 4/110 (4 %) in the third trimester and 12 not known</td>
<td>All AEFI were observed according to predefined search criteria (events not described in detail in methodology), proportional reporting ratios for Tdap exposures were calculated compared to inactivated influenza vaccines</td>
<td>No disproportionality was observed in reporting spontaneous abortion, still birth or preterm deliveries among pregnant women who received Tdap</td>
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<td>[73]</td>
<td>Effect of timing of vaccination in pregnancy on newborn cord pertussis antibody levels</td>
<td>Prospective cohort study from November 2013 to May 2014</td>
<td>Israel</td>
<td>Vaccinated pregnant women (n=61), unvaccinated pregnant women (n=20)</td>
<td>Td3aP 23 to 38 weeks’ gestation</td>
<td>GMCs IgG to PT, FHA and pertactin in the cord blood</td>
<td>Women with Tdap in the third trimester had higher GMCs of IgA PT and FHA than unimmunized women (P&lt;0.001 and P&lt;0.001, respectively)</td>
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<td>[70]</td>
<td>Effect on maternal pertussis antibody levels after immunization during pregnancy</td>
<td>Prospective cohort study conducted in January and February 2015 (enrolled November 2013 to May 2014)</td>
<td>Northern Israel</td>
<td>Vaccinated pregnant women (n=38), unvaccinated pregnant women (n=10)</td>
<td>Td3aP</td>
<td>GMCs of maternal IgG to PT, FHA and pertacin and IgA to PT and FHA 9–15 months after delivery</td>
<td>Higher RAI of umbilical cord IgG to PT was found in newborns of Tdap vaccinated women than in newborns of unvaccinated women (P&lt;0.001). RAI of umbilical cord IgG to PT was significantly higher for newborns of women immunized at 27–30+6 weeks’ gestation (n=20) when compared with 31–36 weeks (n=22) and &gt;36 weeks (n=7) (P&lt;0.03). RAI of umbilical cord IgG to PT increased linearly as a function of time between Tdap boosting and delivery (P&lt;0.01)</td>
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<td>[76]</td>
<td>To assess the relative avidity index (RAI) of umbilical cord IgG to PT for newborns of women vaccinated with Tdap during pregnancy and to assess whether the timing of this affects the RAI of umbilical cord IgG to PT</td>
<td>Prospective cohort study with women who were previously enrolled between November 2013 to May 2014 (Abu Raya 2015)</td>
<td>Northern Israel</td>
<td>Final inclusion of: newborns of women vaccinated during late pregnancy (n=52) and newborns of unvaccinated women (n=8)</td>
<td>Td3aP</td>
<td>The umbilical cord IgG to PT levels were measured and the RAI was calculated</td>
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<td>[34]</td>
<td>Effect of maternal pertussis vaccination on maternal and infant antibody levels</td>
<td>Intervention study from March 1941 to February 1942</td>
<td>USA</td>
<td>Mothers Treatment (n=167): 29 women selected for immunological test Infants n= 27 babies (one set of twins) selected for Pertussis vaccine prepared by Mishulow of New York laboratories</td>
<td>Titre of protective pertussis antibody level</td>
<td></td>
<td>Interventions group: 27/29 inoculated mothers and their babies showed very high titres in protective antibodies using the mouse protection test Control group: two or three of nine babies of un inoculated mothers showed some degree of titres in protective antibodies using the mouse protection test</td>
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<td>[46]</td>
<td>Vaccine effectiveness, safety and immunogenicity of the pertussis vaccine in pregnant women and their infants</td>
<td>Intervention study</td>
<td>USA</td>
<td>Immunological test; control (n=6+3) <strong>Mother</strong> Treatment (n=170): 100 mothers followed up for pertussis, 30 vaccinated mothers had immunological studies; control (n=100); 10 vaccinated mothers had immunological studies <strong>Infants</strong> Treatment (n=100): 30 babies had immunological studies; control (n=100) 10 babies had immunological studies</td>
<td>Whole cell pertussis vaccine developed by Mishulow of New York laboratories</td>
<td>Pertussis antibody level in mother and infants</td>
<td>Maternal protective antibodies</td>
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<tr>
<td>[75]</td>
<td>Effect of timing of vaccination in pregnancy on newborn cord pertussis antibody levels</td>
<td>Prospective observational non-inferiority study</td>
<td>University Hospital of Geneva, Switzerland</td>
<td>Pregnant women who had been routinely vaccinated during the third trimester (≥26 gestational weeks) n=213 during the second trimester (13–25 g) n=122</td>
<td>Td3aP</td>
<td>GMCs of cord blood IgG to PT and FHA</td>
<td>Cord blood GMCs to PT (P&lt;0.001) and FHA (P&lt;0.001) in cord blood were significantly higher following second trimester immunization compared to immunization in the third trimester</td>
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<tr>
<td>[77]</td>
<td>Effect of timing of vaccination in pregnancy on preterm cord pertussis antibody levels</td>
<td>Prospective observational study</td>
<td>University Hospitals of Geneva, Switzerland</td>
<td>Pregnant women who had been routinely vaccinated in second trimester (n=37) and third trimester (n=48). Overall n=85 immunized mother and preterm infant pairs (n=85)</td>
<td>Td3aP any time after gestational week 13</td>
<td>Cord blood GMCs of IgG to PT and FHA in preterm infants</td>
<td>Cord blood Cord blood GMCs of IgG to PT (P=0.024) and FHA (P=0.04) were significantly higher after second trimester vaccination. The ratio of anti-PT IgG in second compared to third trimester vaccination remained significantly higher after adjustment. None of 37 infants born after second trimester vaccination were seronegative compared with 11 of 48 in the third-trimester group Maternal and cord blood The GMCs of IgG to PT in vaccinated mothers at delivery and cord blood were significantly higher (P&lt;0.001) Infants GMCs of IgG to PT in infants showed decline by 63.4% at 1 month and 76% at 2 months of age in comparison to cord blood level</td>
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<tr>
<td>[67]</td>
<td>Effect of vaccination in pregnancy on maternal and newborn cord pertussis antibody levels</td>
<td>A prospective observational study in two consecutive periods: from 2011 to 2012 and from 2013 to 2014</td>
<td>Buenos Aires, Argentina</td>
<td>Pregnant nonimmunized women (2011–2012) (n=99), nonpregnant nonimmunized female controls (2011–2012) (n=69), and pregnant immunized women (n=105) and their infants (2013–2014)</td>
<td>Td5aP at 13.2 to 36.6 weeks' gestation</td>
<td>Maternal GMCs IgG to PT Cord blood and infants’ blood (at 1 and 2 months; GMCs IgG to PT)</td>
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<tr>
<td>[66]</td>
<td>Effect of vaccination in pregnancy on maternal and newborn cord pertussis antibody levels</td>
<td>Non-randomized trial (prospective cohort) from October 2008 through December 2009, before Tdap vaccination in pregnancy was recommended</td>
<td>University of Louisville Obstetrical Clinic, Kentucky, USA</td>
<td>Vaccinated pregnant women (n=52), unvaccinated pregnant women (n=52) and respective newborns based on review of vaccine history after collection of paired samples at birth</td>
<td>Tdap administered. Timing of vaccination could not be determined and some received vaccine prior to pregnancy</td>
<td>GMCs of paired maternal and cord blood IgG to DT, TT, pertactin, PT, FHA and FIM 2/3</td>
<td>Infants significantly higher levels of DT (P&lt;0.001), TT (P=0.009), pertactin (P=0.0001), PT (P=0.0001) were observed in infants born to vaccinated mothers in the maternally vaccinated infants</td>
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<tr>
<td>[40]</td>
<td>Effect of vaccination in pregnancy on maternal and newborn cord pertussis antibody levels</td>
<td>Prospective cohort study from June 2009 to May 2011</td>
<td>Ben Taub General Hospital, Houston, Texas, USA</td>
<td>Mother–newborn cord pairs of 105 women who had documented Tdap vaccination within the previous 2 years with delivery at &gt;37 weeks’ gestation: Tdap before pregnancy (n=86); Tdap during pregnancy (n=19), of whom 14 were vaccinated in the first trimester (11 before the sixth week)</td>
<td>Tdap GMCs of residual paired maternal delivery plasma and cord blood IgG to PT, FHA, FIM and pertactin</td>
<td>Maternal</td>
<td>No difference in GMCs for pertussis-specific antibodies in maternal or cord blood for women immunized before or during pregnancy</td>
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<tr>
<td>[69]</td>
<td>Effect of maternal pertussis vaccination in pregnancy on maternal antibody levels and cellular immune response compared to vaccination in age-matched non-pregnant women</td>
<td>Intervention study, Women were recruited and vaccinated between October 2012 and April 2013. Method of recruitment unclear. These women were also in [62]</td>
<td>Belgium</td>
<td>Belgium</td>
<td>Tdap administered.</td>
<td>Vaccine-specific IgG responses were similar in both groups of women. Vaccine-specific Th1 type cellular responses to DT, PT, FHA and TT were increased in non-pregnant women but only TT in pregnant women. Vaccine specific IFN-γ response to FHA and TT were increased in both groups and IFN-γ responses to DT were increased during pregnancy and transient in both groups.</td>
<td>Immune responses were measured by measuring polyclonal cytokine release in response to PT, FHA and TT.</td>
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</table>

Note: GMC = geometric mean concentration; D = diphtheria; T = tetanus; P = pertussis; A = acellular pertussis vaccine; FIM = filamentous hemagglutinin; FHA = filamentous hemagglutinin A and B; TdaP = tetanus–diphtheria–acellular pertussis; Tda5P = tetanus–diphtheria–acellular pertussis/subunit pertussis.
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| [35]     | Effect of maternal pertussis vaccination in pregnancy in newborns | Non-randomized trial from 1936 to 1937 | Obstetric outpatient departments of two hospitals, USA | Treatment (n=42 pregnant women, 28 with complete results) immunized x 3 (where possible) in the last 6 weeks of pregnancy; control [n=22 with results (original recruited NK)] | Commercial vaccine prepared from *H. pertussis* organisms in phase I, according to the method of Sauer [86] | The opsono-cytophagic reaction of the blood for *H. pertussis* in both mother (pre and post-delivery) and newborn | Infants

Babies of vaccinated mothers had around three times the opsonic activity of babies in the non-immunized group

Babies of immunized mothers had higher titres than those born to unimmunized mothers but overall titres in babies were lower than their mothers. The average titre of babies was 48 and that of mothers 105, a ratio of 1:2.2

Maternal

The mean 'index' of the immunized mothers did not increase as a result of immunization

Babies

Newborns born to immunized mothers had significantly higher opsonocytaphagic 'indices' means than babies born to unimmunized women. Babies born to women with a history of pertussis had significantly higher opsonocytaphagic indices mean than babies born to women who had not had pertussis

There was a correlation between the phagocytic capacity of mother and her infant's blood

Maternal

Antibodies were present in 100 % post-vaccination (93.1 % had agglutinins, 75.8 % complement-fixing antibodies)

[53] Effect of pertussis vaccination in pregnancy on maternal antibody levels

Non-randomized intervention study from prior to 1942 (details not given; n=29)

Pregnant mothers (n=29). Three non-immunized pregnant women were added at delivery

Whole-cell pertussis toxin vaccine developed by Mishulow with 'several doses' administered at 2-week intervals during pregnancy

Pertussis agglutinating and complement-fixing antibodies were looked for in blood samples pre-and post-vaccination, although proportion with 'protective antibodies' was not defined

[65] Effect of timing of vaccination in pregnancy on newborn cord pertussis antibody levels

Prospective cohort study, pregnant women were recruited from April through September 2014

Tertiary obstetric hospital, Australia

Early third trimester (28–32 weeks) vaccinated pregnant women (n=53). Late third trimester (33–36 wks) vaccinated pregnant women (n=62). Unvaccinated pregnant women

Maternal and cord blood antibody levels to PT, pertactin and FHA

Maternal

PT level was significantly higher (P=0.05) in early vaccinated group. No significant difference between maternal FHA and pertactin level among three groups

Cord blood

Cord blood IgG level to PT (P<0.001), FHA (P<0.001) and pertactin (P=0.001) statistically significantly higher in infants born to
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<th>Study ID</th>
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<tbody>
<tr>
<td>[68]</td>
<td>Effect of vaccination in pregnancy on maternal and newborn cord pertussis antibody levels</td>
<td>Prospective observational study between May 2012 and August 2013</td>
<td>Maternal–Foetal Unit of the Hospital Clinic of Barcelona (HCB), Spain</td>
<td>Mothers and their infants (n=132)</td>
<td>TdaP vaccine between 20 and 36 weeks of gestation</td>
<td>Maternal and infant GMT of IgG to PT</td>
<td>Cord blood PT (P=0.06) and pertactin (P=0.003) statistically significantly higher in early vaccinated group in comparison to late vaccinated group. No significant difference for FHA (P=0.16)</td>
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<tr>
<td>[72]</td>
<td>Assessment of the persistence of anti-PT antibody levels between delivery and administration of primary vaccination in babies whose mothers had Tdap vaccination in pregnancy</td>
<td>Prospective observational study of infants born in November 2014</td>
<td>Hospital Clinic of Barcelona, Spain</td>
<td>Infants of mothers who received Tdap vaccination during pregnancy, and who delivered at Hospital Clinic of Barcelona in November 2014 (n=37)</td>
<td>Td5aP (Triaxis) from 21 to 38 weeks of gestation</td>
<td>Cord blood and infant blood measured by ELISA between the first and second month of life (GMT of IgG to PT) and estimated at 2 months. Timing of maternal vaccination was stratified with GMC in the infant at delivery and pre-immunization</td>
<td>Estimated that 66% of infants will have anti-PT GMT levels of &gt;10 IU ml⁻¹ at administration of the first dose of vaccine if vaccinated aged 2 months</td>
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(n=39)

Maternal GMT of IgG to PT was 7.9 IU ml⁻¹ in maternal pre-vaccination sera, 31.1 IU ml⁻¹ in maternal post-vaccination sera and 37.8 IU ml⁻¹ in newborns (P=0.001). Anti-PT (≥10 IU ml⁻¹) levels were found in 37.1% of maternal pre-vaccination and 90.2% of post-vaccination samples

Cord or heel blood

Anti-PT (≥10 IU ml⁻¹) levels were found in 94.7% of newborns

Infant GMT of IgG to PT declined significantly between birth and pre-immunization. The median half-life of maternal antibodies was 47 days, with 51.4% infants having detectable anti-PT IgG before infant vaccination

Numbers were too small to identify a significant difference in infant antibody levels by timing of maternal vaccination
These largely retrospective observational studies from Europe, New Zealand, North America, Mexico and Vietnam investigated a range of maternal, foetal and neonatal outcomes. Despite the large variation in size, the study findings are generally consistent and provide reassuring evidence of no significant increased risk of recognized maternal conditions (including pre-eclampsia, preterm delivery and still birth) or of congenital anomalies in their babies. One large observational study of over 26,000 vaccinated women [55] demonstrated a small but statistically significant increased risk of chorioamnionitis (RR 1.19; 95% CI: 1.13 to 1.26), although the authors found no evidence of increased risk of preterm birth, which would be expected in association with chorioamnionitis. No significant risk for either chorioamnionitis or preterm birth was identified in the other studies covered by the period of this review: in a study of over 1000 vaccinated women, Berenson et al. found an adjusted relative risk of 1.53 (95% CI: 0.80 to 2.9) [61], while Morgan et al.’s study of over 7000 vaccinated women reported chorioamnionitis in 6% of vaccinated and 4% of unvaccinated pregnancies (P=0.31) [57].

Four studies undertook infant follow-up beyond the neonatal period. Munoz et al undertook a small case–control study that reported no differences in infant growth or development at 13 months [63]. Shakib et al. retrospectively compared recorded health encounters and diagnoses by 12 months of age in infants born to vaccinated and unvaccinated mothers [58]. They had similar rates of healthcare utilization (62% with vaccinated mothers vs 61% with unvaccinated mothers) and no significant difference in the proportion of these infants diagnosed with complex chronic health conditions (3.6 vs 10.4% with unvaccinated mothers, P=0.54). A prospective observational study in New Zealand undertook follow-up of infants born to immunized mothers with infant outcomes collected from maternal reporting and routine health records to 12 months of age [59]. Analysis was undertaken on 408 infants followed to at least 6 months of age: no increased risk of congenital anomaly was found compared to background rates in New Zealand and infant weights were normally distributed at the 5-month check. In a prospective controlled cohort study followed up infants to 15–16 months of age; this reported no statistically significant difference in the proportion of infants hospitalized during the study period between maternally vaccinated and unvaccinated study groups (10.9 vs 12.5% hospitalized, respectively) [44]. A neurological development test undertaken as part of this study found that the infants in the vaccine group were significantly better developed for 2 of 11 items in comparison with infants from the control group; as these skills were not expected to be present among all infants of that age, the results were not presented by the authors.

The risk of bias for safety was judged to be low in 3 studies, intermediate in 11 studies and high in 5 studies (Fig. 2). The high risk was found in the older studies, such as Cohen and Scadron [34, 46] and Mishulow et al. [53], where details were limited, and in the pharmacovigilance studies of Moro et al. [36] and Zheteyeva et al. [37]. The low risk applied to two clinical trials [60, 63] and Walls et al. [59], where there was good follow-up. It is, however, acknowledged that the details of randomization were often lacking, perhaps resulting in selection bias.

**Secondary outcome: maternal antibody response following pertussis vaccination during pregnancy**

Five older studies used different whole-cell pertussis vaccines in pregnant women and applied different tests to study their response. Four of these studies demonstrated higher responses in vaccinated compared to unvaccinated women [34, 46, 53, 64] (Table 3), and whilst Lichty et al. did not find a significant increase in phagocytic activity in women following immunization [35], they did observe that this was higher in babies born to immunized women and to women with a history of pertussis. Eleven studies using different aP-containing vaccines consistently showed that IgG antibodies against the pertussis antigens considered were significantly higher at delivery in vaccinated women when compared to unvaccinated pregnant women, women immunized with a vaccine that did not contain aP or women immunized postpartum [39–41, 60, 63, 65–70]. Pertussis-specific IgG levels decreased significantly 9 to 15 months after delivery in two studies [69, 70], but were still higher than those of unimmunized women. Vaccine specific CMI responses were boosted to a lesser extent in pregnant than in non-pregnant women, but this stimulation was transient and only observed at 1 month and not at 1 year after vaccination [69].

**Secondary outcome: transplacental transfer of antibodies**

Five studies of wP vaccine administration in pregnant women found evidence of pertussis responses in their infants that were greater than those in infants born to women who had not been vaccinated [34, 35, 46, 64], although Greenberg et al. suggested that the difference they detected was too low to make any inferences and that their vaccine schedule required adjustments [71].

We have taken studies using cord blood samples to be indicative of antibody levels in the newborn. Statistically higher levels of aP-vaccine antibodies have consistently been found in 14 studies of babies born to vaccinated pregnant women compared to those born to women who were not vaccinated in pregnancy [39, 41, 42, 60, 63, 65–67, 72–74], to be in line with suggested levels of protection [68, 75] or to induce higher antibody avidity [76]. In addition, Eberhardt et al. [77] and Kent et al. [38] specifically studied preterm infants and found antibody levels consistent with putative levels of protection and higher antibody levels, respectively, at 2 months in infants following maternal vaccination, but these were lower in the maternally vaccinated cohort after primary vaccination [38].

Whilst the difference did not reach statistical significance, Healy et al. identified that placental transport of pertussis
antibodies was better in women immunized during pregnancy than women immunized a short time before, and that pertussis-specific IgG concentrations waned rapidly [40]. Despite the waning of maternal pertussis antibodies in infants during the first 2 months of life, the levels remained elevated in babies born to mothers vaccinated in pregnancy until the age that routine infant vaccination began, resulting in a closure of the susceptibility gap for the youngest infants [39, 41, 42, 60, 67, 68, 72, 74], including those born prematurely [38]; this is consistent with evidence of the effectiveness of maternal pertussis vaccination in protecting young infants.

Secondary outcome: the effect of the timing of maternal vaccination on the transplacental transfer of maternal antibodies or on the risk of disease in the infant

We found seven studies reporting on the timing of maternal aP vaccination responses and infant antibody levels, but in one the numbers were too small to identify a significant difference [72]. Healy et al.’s findings suggested that whilst there was highly efficient placental transport of maternal antibodies in women immunized up to 2 years prior to delivery, pertussis antigen-specific IgG concentrations in their newborns were unlikely to be high enough to passively protect them through 2 or 3 months of age. More infants whose mothers were immunized in pregnancy had nominally adequate PT levels at birth, but only three women in their study were immunized after 20 weeks’ gestation [40]. Abu Raya et al. [73] reported higher anti-PT and FHA antibody concentrations following immunization at 27–30 weeks compared to beyond 31 weeks, with similarly significantly higher antibody avidity in cord sera of newborns with mothers vaccinated at 27–30 weeks’ gestation compared to those with mothers vaccinated after 30 weeks [76]. Ladhani et al. [74] found that the timing of antenatal pertussis immunization in the third trimester did not affect infant antibody concentrations at 2 months in the infant. Naidu et al. [78] found that the cord blood levels of anti-pertussis antibodies were higher in babies whose mothers had been vaccinated at 28–32 weeks as compared to those whose mothers were vaccinated at 33–36 weeks.

Only Eberhardt et al. [75] reported on earlier vaccination and found higher infant anti-PT and -FHA antibody concentrations following immunization at 13–25 weeks rather than from 26 weeks, and they later published a prospective observational study that found higher PT and FHA antibodies in preterm babies born to women vaccinated in the second compared to the third trimester [77]. Eberhardt et al.’s overall findings were not consistent with those in Winter et al.’s study, which reported that infants whose mothers were vaccinated during the second trimester were significantly more likely to have pertussis by age <8 weeks or ≤12 weeks than those whose mothers were vaccinated at 27–36 weeks’ gestation, when controlling for the age of the mother, number of prior births and preterm birth [51]. There were, however, some limitations to Winter et al.’s observational study, as only 14% of women received Tdap vaccine before 27 weeks’ gestation; this was outside the routine recommendations and therefore these women may have differed from women who were vaccinated within the recommendations. The distribution of the timing of vaccination was not presented and it is not clear how many women received vaccine in the second trimester but close to the national recommendation of 27 weeks.

Secondary outcome: blunting

Concern over maternally derived antibodies interfering with the infant response resulted in several studies evaluating this blunting effect. Our review identified 10 studies (Table 4) that had assessed laboratory markers of pertussis responses following primary schedule in infants following maternal vaccination with different Tdap or Tdap/ IPV vaccines (three- and five-component pertussis vaccines) conducted in a number of settings using different infant schedules [38, 39, 41–44, 60, 63, 74, 79]. In most of the studies, evidence of lower responses to one or more pertussis antigen were observed amongst infants born to vaccinated mothers following the completion of their primary schedule when compared to infants whose mothers had not been vaccinated. However, the antibody responses to specific pertussis antigens differed between studies, with some increases reported inconsistently. In one study, differences based on antibody avidity were reported to be non-significant after the primary course [79]. Premature infants had significantly higher GMCs of IgG to pertussis antigens, tetanus and diphtheria toxoid (DT) before primary vaccination if their mother had been vaccinated, although FHA and DT were significantly lower after completion of the primary course [38]. Importantly, no evidence of a clinically significant blunting effect was found in England and the USA based on studies of infant disease in the first year of life after maternal vaccination and primary infant doses [48, 52].

In four studies, lowered response to pertussis components in maternally vaccinated infants was no longer significant following the booster dose in the second year of life [39, 43, 44, 63], suggesting that any blunting effect may be short-lived and that longer-term protection conferred to infants from active immunization is not compromised. Cabore et al. [79] found that only avidity to PT was significantly lower in the maternally vaccinated group after booster vaccination at 15 months [79].

In five studies other routine antigens were assessed [41–43, 63, 74], with some evidence indicating an enhancement of the response to tetanus and tetanus-conjugated vaccines and a decline in diphtheria and CRM-conjugated vaccine responses. However, similar proportions of infants attained levels consistent with protection for diphtheria and group C meningococcus [74]. Maertens also reported significantly lower anti-TT antibody titres in infants whose mothers were Tdap-vaccinated, rather than TT-vaccinated, following the booster dose [43]. Whilst an effect of maternal Tdap on
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<tr>
<td>[79]</td>
<td>Effect of vaccination in pregnancy on antibody avidity in infant blood following fourth dose of vaccine</td>
<td>Prospective controlled cohort of infants born between April 2012 and April 2014</td>
<td>Five hospitals in one Belgian province</td>
<td>Infants born to vaccinated pregnant women (n=46; 45 after D; infants born to unvaccinated pregnant women (n=24;23 after D)</td>
<td>Mothers: Td3aP at 22-33 weeks gestation. Infants: DTaP-HBV-IPV/Hib (Infanrix) at 8, 12 and 16 weeks and 15 months</td>
<td>Antibody avidity of IgG to DT, TT, PT, FHA and pertactin before and after the fourth dose (given at 15 months)</td>
<td>Prior to fourth dose (both groups) At baseline, there were non-significant differences in antibody avidity for all antibodies in both sets of infants. Antibody avidity was moderate (RAI: 40 to 60 %) for TT, PT, FHA and pertactin but low (RAI&lt;40 %) for DT After fourth dose (both groups) There was a significant increase in avidity for all vaccine antigens in the control groups and a non-significant increase for DT and FHA in the maternally vaccinated group, whilst TT, PT and Prn significantly increased Between 2 groups after boosting Avidity to PT was significantly lower in the vaccine than in the control group (P=0.003). There were no significant differences in antibody avidity to TT, DT, FHA and pertactin. Avidity to TT, PT and pertactin was high in both groups, while FHA was moderate and DT was low Infants Average titre of 93 at birth and 22 at 3 months in babies with immunized mothers. This was considered inadequate for protection and to require changes to the schedule After primary vaccination In general, the children...</td>
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<td>[71]</td>
<td>The value of prenatal immunization and interference of inherited antibodies with the response to the pertussis component of primary vaccination</td>
<td>Prospective intervention study with women allocated to vaccinated or unvaccinated groups</td>
<td>Prenatal clinic in Montreal and the well-baby clinic at the same health centre</td>
<td>Unclear. Results presented for 28 babies of immunized mothers at birth and 35 at 3 months. Then for 23 infants with inherited antibody and 20 infants without inherited antibody 1 month post-immunization</td>
<td>Alum-precipitated whole-cell pertussis vaccine with alum phosphate. Controls given alum phosphate. Two doses given 1 month apart from sixth or seventh month of pregnancy. Infants had an alum-precipitated DTwP</td>
<td>Agglutination titre was used as the measure of immune response.</td>
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<td>[39]</td>
<td>Effect of maternal Tdap vaccination on infant immunological responses to routine paediatric vaccines</td>
<td>Prospective cohort study (March 2008 and February 2009) with historic vaccinated comparator (2006)</td>
<td>Serology laboratory at Sanofi Pasteur</td>
<td>Vaccinated (TdaP) group - Pregnant women (n=16) vaccinated in 2006 control group - women who delivered between March 2008 to February 2009 (n=54)</td>
<td>Td5aP in pregnant women</td>
<td>Maternal, cord and infants’ antibody concentrations against PT, FHA, pertactin and FIM 2/3</td>
<td>without inherited antibody showed higher titres than those with inherited antibody, but the authors state the differences are so low that they should not be given undue significance</td>
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**Mothers and cord blood**
Maternal and cord antibody concentrations to PT, FHA, pertactin and FIM were higher in the Tdap group

**Infants**
These were similarly higher before primary immunization

**Post-primary vaccination**
GMCs of IgG to PT, FHA, pertactin were lower in vaccinated group, while FIM 2/3 remained higher

**Post-booster**
Post-DTaP booster antibody levels against PT, FHA, pertactin and FIM 2/3 were similar in maternally vaccinated and unvaccinated groups

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| [41]     | To assess the effect of vaccination in pregnancy on newborn cord pertussis antibody levels and possible interference of Tdap vaccination in pregnancy with humoral immune responses to primary vaccination in infants | Controlled, prospective, randomized clinical trial of mothers recruited during routine preventive visits whose infants were born between February 2013 and October 2013 | Three villages of Ha Nam province, northern Vietnam | Tdap-vaccinated pregnant women (n=52; 51 with follow-up), TT-vaccinated pregnant women (n=51; 48 with follow-up) | Td5aP or TT (IVAC, Vietnam) vaccine between 19 and 35 weeks’ gestation; infants received DtaP-IPV-HepB/Hib | GMCs IgG to PT, FHA, pertactin, TT and DT in mothers at baseline, 1 month post-vaccination and at delivery. The same IgGs were measured in infants in cord blood, before and after a 2, 3 and 4 month primary series (with a mean age of 3 months for first dose in practice) | Mothers
GMGs of PT, FHA, pertactin, DT (P<0.001) and TT (P=0.001) were significantly higher at delivery in Tdap group compared to TT group

**Cord blood and infants**
GMGs of PT, FHA, pertactin, DT (P<0.001) and TT (P<0.05) were significantly higher in cord blood of infants born to Tdap group and at 2 months of age for all antigens other than TT (45 babies in Tdap group and 48 in TT group)

**Post-primary vaccination**
One month after primary infant vaccination, there was
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<tr>
<td>[38]</td>
<td>Effect of maternal TdaP vaccination on immunological response in premature infants following primary vaccination</td>
<td>Prospective observational cohort sub-study of a larger multicentre, randomized controlled vaccination trial in premature infants</td>
<td>Eight neonatal units in England between May 2012 and May 2014</td>
<td>Vaccine group: premature infants born to mothers receiving TdaP in pregnancy (n=30) Control group: premature infants born to Mothers not receiving TdaP in pregnancy (n=121)</td>
<td>Maternal: Td5aP/IPV Infants: DT5aP/IPV-Hib, meningococcal C-CRM vaccine, pneumococcal 13-valent conjugate vaccine</td>
<td>GMCs IgG to PT, FHA, FIM 2/3, TT and DT of infants measured before primary vaccination at age of 2 months, 1 month after completion of primary vaccination at 5 months and at 12 months of age</td>
<td>no significant difference between groups of infants in PT and FHA IgG. Anti-pertactin and -diphtheria toxoid IgG GMCs were significantly higher in the control group (n=35). Tetanus antibody titres were significantly higher (P=0.006) in the TdaP group (n=35). Infants At 2 months of age GMCs of IgG to PT, FHA, FIM 2/3, TT and DT were significantly higher (P&lt;0.001) in the vaccinated group Post-primary vaccination At 5 months of age FHA and DT were significantly lower (P=0.003) in the vaccinated group. No significant variation in GMCs of all other antigens</td>
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<td>[74]</td>
<td>Effect of vaccination in pregnancy on newborn cord antibody levels (DTP) and any subsequent effect on antibody levels (DTP) after primary immunization</td>
<td>Prospective observational cohort (December 2012 to July 2014) with historical cohort (February 2011 to December 2012)</td>
<td>Hertfordshire, Gloucestershire, and South London, UK</td>
<td>Cases Children born to vaccinated mothers n=141 historical controls Children born to unvaccinated mothers n=246</td>
<td>Td5aP-IPV (Repevax) during pregnancy</td>
<td>GMCs IgG to PT, FHA, FIM, TT, DT, Hib, MenC SBA and serotype-specific pneumococcal antibodies before and 1 month after primary immunization (at 2, 3 and 4 months) Vaccinated cohort (before and after primary immunization) PT increased (P&lt;0.001), FHA decreased (P&lt;0.001) and FIM had no change (P=0.22) Vaccinated vs historical cohort post-immunization PT, FHA and FIM were all lower in the vaccinated group (P&lt;0.001). DT was lower (P&lt;0.001), but TT high (P=0.11) and Hib higher (P&lt;0.001). For PCV13 serotypes, GMC of 7 (1, 3, 4, 5, 6A, 7F and 9V) were significantly lower (P&lt;0.001 for all except 7F P=0.005 and 9V P=0.014)</td>
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<td>[42]</td>
<td>Effect of vaccination in pregnancy on newborn cord antibody levels (DTP) and any</td>
<td>Prospective controlled cohort with infants born from April 2012 to April 2014</td>
<td>Five hospitals in one Belgian province</td>
<td>Vaccinated pregnant women (n=57) and their infants (n=55) Unvaccinated pregnant</td>
<td>Mothers Td3aP at 22 to 33 weeks’ gestation Infants (DT3aP-IPV-Hib-HepB) at</td>
<td>GMCs IgG to PT, FHA and pertactin, DT and TT from blood samples taken before and after Maternal Vaccinated women had significantly higher GMCs to all antigens at delivery</td>
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<td>[43]</td>
<td>Possible blunting effect of maternal immunization with the infant humoral immune responses after booster immunization</td>
<td>Randomized controlled trial</td>
<td>Commune health centre, Vietnam</td>
<td>Cases: children born to mothers vaccinated with TdaP (n=30) Controls: children born to mothers vaccinated with TT (n=37)</td>
<td>Td5aP in mothers during GW 18–36 weeks Booster aP vaccine given as Infanrix Hexa to children at 18 months of age</td>
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<td>[44]</td>
<td>Effect of vaccination in pregnancy on newborn cord antibody levels (DTP) and any subsequent effect on antibody levels (DTP) after booster</td>
<td>Prospective controlled cohort from April 2012 to April 2014, Continuation of Maertens [42]</td>
<td>Five hospitals in one Belgian province</td>
<td>Vaccine group: children born from vaccinated women (n=55) Control group: children born from women not vaccinated with a pertussis containing</td>
<td>Mother DT3aP between 18 and 34 weeks’ gestation. Infants (Infanrix hexa) at 8, 12, 16 weeks and 15 months</td>
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**Table 4. cont.**

Study ID: sub subsequent effect on antibody levels (DTP) after primary immunization  
Participants: women (n=42) and their infants (n=26)  
Intervention: maternal vaccination, in cord blood and in infants before and 1 month after completion of the primary course at 8, 12 and 16 weeks  
Findings: compared with women from the control group, except for tetanus (P=0.064)  

**Cord blood**  
Significantly higher antibody concentrations in the cord blood of the vaccine group compared with the control group for all antigens, except tetanus  

**Infants**  
Antibody titres significantly decreased between birth and 8 weeks, however the GMCs to all antigens were still significantly higher in infants from vaccinated mothers compared with infants from unvaccinated mothers  

**After primary vaccination**  
One month after the third primary dose, GMCs to PT (P<0.001) and DT (P=0.002) were significantly lower in the vaccine group compared with the control group; but antibody GMCs for both antigens were higher than at 8 weeks. For Prn, TT and FHA differences in GMCs were not significant  

**Post-booster vaccination**  
After booster dose, anti-PT IgG, anti-PRN IgG and anti-FHA IgG tireds were comparable in both groups. Only GMC of IgG to TT was significantly lower (P<0.001) in TdaP group  

**Pre-booster vaccination**  
Before administration of booster dose GMCs of IgG to TT (P=0.07), pertactin (P=0.003) and DT (P=0.023) were significantly lower in immunized group
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| [80]     | Effect of maternal Tdap vaccination on infant immunological responses to infant pneumococcal vaccines | Prospective controlled cohort study from 2011 to 2015 | Belgium         | Vaccine group: mother (Tdap in pregnancy) and infant pairs (n=52)                                      | Tdap to mothers                                                                                                         | GMCs of serotype 1, 3, 4, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F at post-primary (5 months) and post-booster (15 months)       | Post-booster vaccination  
One month after fourth dose antibody titres had risen against all antigens; IgG to PT was significantly lower (P=0.006) in maternally vaccinated group  
Infants pre-booster  
At the age of 5 months GMCs of IgG serotypes 1, 3, 4, 6A, 6B, 7F, 9V, 14 and 19A were significantly lower (P<0.05) in vaccine group. No differences in other serotypes  
Infants post booster  
At the age of 15 months GMCs of IgG serotypes 1 and 4 were significantly different. No differences in other serotypes, but proportions of infants achieving protective concentrations of serotype-specific IgG were similar irrespective of maternal vaccination status  
Maternal and cord blood  
Significantly higher (P<0.001) level of DT, TT, FHA, pertactin and FIM 2/3 in antepartum vaccinated women at delivery and cord blood  
Infants  
Two months  
Significantly higher (P<0.001) level of GMCs of IgG to DT and TT, PT, FHA, pertactin and FIM 2/3 in infants born to antepartum group. There was no significant difference in GMCs at the age of 7 and 13 months except for FHA at 7 months (higher concentration in postpartum group (P<0.001)) and TT |
Table 4. cont.

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<td>[60]</td>
<td>To evaluate the safety, immunogenicity and blunting of the Tdap vaccine in pregnant women and their children</td>
<td>Randomized, double-blind, parallel group-controlled clinical trial from September 2011 to August 2014</td>
<td>12 outpatient health centres of the Nuevo Leon Health Services, Mexico</td>
<td>Participants (n=171) Vaccinated pregnant women (n=90) and unvaccinated pregnant women (n=81)</td>
<td>Tdap vaccine (experimental group, n=90) or normal saline (control group, n=81) between 30 and 32 weeks' gestation. Infants vaccinated at 2, 4 and 6 months, in line with routine vaccination in Mexico with pentavalent DTaP/IPV-Hib</td>
<td>Maternal GMCs IgG to pertactin and PT pre- and post-immunization</td>
<td>Maternal significantly higher (P&lt;0.001) maternal GMCs of IgG to PT and pertactin after vaccination in vaccinated group</td>
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<td>Cord blood and infants’ blood (at 2, 4 and 6 months) GMCs IgG to pertactin and PT</td>
<td>Cord significantly higher (P=0.001) cord blood GMCs of IgG to PT and pertactin in vaccinated group</td>
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<td>Infants Two months of age</td>
<td>Infants significantly higher (P=0.001) GMCs of IgG to PT and pertactin in those with vaccinated mothers</td>
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<td>Four and six months of age</td>
<td>Pertactin level remains significantly higher at 4 and 6 months (P=0.001), while PT was significantly lower (P&lt;0.01) in the maternally vaccinated infants at both time points</td>
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a lowered infant response to primary pneumococcal conjugate vaccination [74, 80] has been reported, this effect disappeared after a booster dose at the age of 12 months, except for serotypes 1 and 4 [80], and the proportion of children reaching the protective threshold for all pneumococcal serotypes was the same in both the exposed and unexposed cohorts.

The risk of bias for the various immunogenicity outcomes was deemed to be low for 18 studies, intermediate for 10 studies and only high for [34] due to selective reporting and outcome data (Fig. 2). This generally lower risk of bias was because of the more objective nature of immunogenicity assessment, but it was still deemed to be intermediate in studies where the groups differed (e.g. according to the time in pregnancy of the blood test, the period of study, or the time when laboratory analysis performed).

**DISCUSSION AND CONCLUSIONS**

Whilst the safety and efficacy of pertussis vaccines in pregnancy were first assessed using wP vaccines in the 1940s, it was not until 2011 that aP pertussis-containing vaccines were first recommended in pregnancy. Universal maternal vaccination programmes have been introduced in a number of countries following reported disease incidence increases and relatively high morbidity and mortality in young unimmunized infants, and a lack of convincing evidence on the effectiveness of cocooning strategies. These recommendations were informed by national epidemiology and available immunogenicity and safety data. There was also evidence of very low levels of pertussis antibodies as a baseline even in young women from countries with an adolescent programme [40]. However, the lack of an established correlate of protection for pertussis meant that the efficacy of this strategy in preventing infant disease could not be extrapolated directly from these data. The implementation of maternal pertussis vaccination programs in some middle- and high-income countries has provided opportunities to further assess the safety of the programme at a population level and provide the first evidence of its effectiveness in preventing infant disease.

In this review, a total of 46 relevant studies with around 345,000 participants in total were included. These studies considered women who received either acellular or whole-cell pertussis vaccine during pregnancy. These comprised 4 RCTs [41, 43, 60, 63], 7 quasi-experimental studies [34, 35, 46, 53, 64, 69, 71], 1 case–control study [49], 14 prospective cohort studies [38–40, 42, 44, 59, 65, 66, 70, 73, 74, 76, 79, 80], 13 retrospective cohort studies [36, 47, 48, 50–52, 54–58, 61, 62], 6 other prospective observational studies [45, 67, 68, 72, 75, 77] and 1 case series [37]. These evaluated the following relevant outcomes: vaccine effectiveness (7 studies), vaccine safety (19 studies), immunogenicity (15 studies) and blunting (12 studies, with some also covering maternal and/or infant immunogenicity). A number of studies reported on more than one of these outcomes [34, 41, 42, 44, 46, 53, 60, 63].

Limited evidence for wP administered in pregnancy from early studies has shown transplacental transfer of maternal antibodies [34, 66]. Studies of women vaccinated during pregnancy with aP vaccines have found consistent evidence of high levels of maternal pertussis antibody transfer following vaccination in the second and third trimesters of pregnancy [39, 41, 42, 60, 63, 65, 68–70, 74, 75, 77]. Raised antibody levels have now been demonstrated in infants whose mothers were vaccinated with different aP vaccines under different schedules [39–42, 57, 60, 63, 67, 69, 73, 74, 76]. England was the first country to demonstrate high effectiveness (~90%) of maternal immunization with a five-component DTaP-IPV vaccine in preventing disease in young infants, using both the screening and case-control methods [47, 49]. Similar overall vaccine effectiveness was found 3 years post-implementation in England, with a lower point estimate of VE in infants with mothers vaccinated with a three-component compared to a five-component vaccine that did not reach statistical significance [48]. One study in the USA found remarkably similar VE [52] and others concluded that Tdap vaccination in pregnancy was more effective than postpartum vaccination at preventing pertussis in young infants [51], lowered the risk of hospitalization and intensive care unit admission and was associated with shorter hospital stays [50].

It would clearly be desirable to demonstrate effectiveness against infant disease under more maternal programmes using different schedules and wP in the infant schedule and/or establish a correlate of protection. The rapid waning of antibody levels in women who were vaccinated in pregnancy and the greater efficiency of transplacental antibody transfer after around 34 weeks’ gestation informed the decision in most countries to offer maternal vaccination from 28 weeks [40]. More recent studies found optimal neonatal pertussis antibody concentrations were elicited following maternal vaccination between 13 and 33 weeks’ gestation [75, 77], although the data on vaccination in the second trimester are currently limited and inconsistent, with Winter et al. finding a higher risk of pertussis in infants whose mothers were vaccinated in the second compared to the third trimester [51]. However, studies in the third trimester found higher maternal and infant pertussis antibody levels (consistently pertussis toxin) and avidity in infants when vaccination was earlier rather than later in the third trimester [73, 76, 78], or that there was no significant difference [74]. There is currently a paucity of data on cell-mediated immunity following maternal immunization and such data could further our understanding of the significance of waning antibody levels. The recommendation in the UK (currently from week 16 of pregnancy) changed following evidence of a potential improvement in neonatal antibody levels [75] and in recognition that earlier vaccination in pregnancy would provide more opportunities for women to be vaccinated and offer protection to infants born at earlier gestation [77, 81]. Vaccine uptake in the UK has since improved [82] and estimates of the effectiveness of earlier
vaccination in pregnancy against infant disease are underway.

Despite the success of maternal immunization programmes in countries such as the UK, there are still some gaps in our understanding of this strategy. In particular, current evidence has shown lower pertussis responses to primary infant vaccination, with a lack of consistency in the response to specific antigens (notably PT and FHA) in infants born to vaccinated mothers. This could be due to other factors affecting the likelihood of pertussis exposure or simply reflect the difficulty of interpreting pertussis Ig responses, as these may not directly correlate with levels of protection. Further, there is currently no evidence of increased risk of pertussis disease in infants with vaccinated mothers following primary vaccinations in the first year of life.

For many countries with a pertussis booster scheduled in the second year of life, any clinically significant blunting will likely be mitigated through the booster dose. For countries only offering boosting at pre-school, the relevance of blunting is particularly pertinent and requires close monitoring. Determination of a laboratory correlate of protection has been an ongoing priority, but we now have the opportunity to make progress in this area by assessing the levels of antibodies in cord blood and the risk of infant disease. Longer-term follow-up is required to assess whether maternal vaccination leads to more rapid waning after the completion of primary and early booster schedules and any effect from different maternal and primary schedules and repeated maternal vaccination. Evidence of interference with Tdap and PCV vaccines using the diphtheria-derived CRM carrier protein and the enhancement of the response to tetanus vaccine and vaccines using tetanus toxoid carrier protein are important findings that are likely to help inform future vaccine development and potential changes to the vaccine programme to minimize any blunting effect. It is also important to generate robust data on any lasting blunting effect post-booster.

Safety studies covering more than 150,000 women vaccinated mostly in the late second or third trimesters are generally consistent and provide reassuring evidence of no significant increased risk of recognized maternal conditions, including pregnancy outcome, or of adverse events (including congenital anomalies) in infants born to vaccinated women. The identification of a small but statistically significant risk of chorioamnionitis from one published safety study may benefit from further specific study as current evidence is not convincing and there is no clear biological plausibility for such an association or identified increased risk for associated outcomes. Other safety studies published at the time of the review did not replicate this finding. Two further studies that found a small increased relative risk of chorioamnionitis: one was conducted by Layton et al. [83] [RR=1.11, (95% CI: 1.07–1.15), overall risk=2.8 %] and the other was conducted by DeSilva et al. [84] [ARR=1.23, (95% CI: 1.17–1.28)] who also reported no clinically significant infant outcomes associated with maternal chorioamnionitis. Layton et al. also described an increased risk of postpartum haemorrhage [RR=1.23 (95% CI: 1.18–1.28), overall risk=2.4 %] but found no increased risk of any adverse newborn outcome in babies born to vaccinated women [82]. Another consideration is that the existing safety data, with limited exceptions [44, 58, 59], are largely based on assessment covering the period during pregnancy and up to delivery. Further studies with longer follow-up periods would provide additional reassurance.

Biases in the review process may have occurred in the selection of included studies and by the review not being blinded to the study authors. The included studies only included those that adhered to our search criteria. The review authors were not blinded to study authorship or journal of publication, allowing the potential for bias during study selection and data extraction. The use of predefined criteria for study inclusion and rules for data extraction helped to minimize this potential [85]. When the authors of this review were co-authors in an included study, the potential for bias was minimized by ensuring that the criteria for study inclusion were checked by a different review author.

Current evidence supports the effectiveness of maternal pertussis immunization to protect from birth in those settings where there is a significant burden of pertussis disease in young infants despite high coverage of the routine vaccination programme. Good epidemiological data are therefore also key prior to the introduction of such programmes. Reassuring data on the safety of vaccination in pregnancy for mother and infant at birth are available in a range of settings. Current recommendations around maternal vaccination indicate that vaccination should be offered to women in every pregnancy. However, there remains a need for more data on the need to repeat vaccination in every pregnancy to ensure effectiveness, optimal timing for vaccination in pregnancy and further assurance on safety with longer-term follow-up of infants and larger studies that include pregnancy outcomes not restricted to those with live birth. In addition, there is an absence of data for maternal vaccination in settings where wP is used in the primary infant schedule.

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Conflicts of interest
GA received expenses reimbursement to present on maternal pertussis immunization programme at ESPID 2016, Brighton by Medscape Education (through an unrestricted grant from Glaxo SmithKline). GA and HC received an educational grant from Sanofi Pasteur for peer review publication of “Historical review of pertussis control” September 2013.

The Immunisation, Hepatitis and Blood Safety Department has provided vaccine manufacturers with post-marketing surveillance reports (not pertussis-containing vaccines to date) which the companies are
required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. In accordance with PHE policy a cost recovery charge is made for these reports.
GD received payment for the completion of a systematic review ‘Vaccination of Health Care Workers to Protect Patients at Increased Risk for Acute Respiratory Disease’, commissioned from the University of Nottingham, by the WHO. Work commissioned and funded by the WHO Global Influenza Programme.

No other conflicts of interest exist.

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