Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Complementary literature review of vaccination in pregnancy to prevent pertussis in early infancy.

Background. Partial protection against pertussis at birth is provided by maternal antibodies transported via the placenta during pregnancy and via lactation afterwards. These maternal antibodies wane during the first months of life with a half-life of approximately 36–40 days. The interval between the loss of maternal protection and the onset of infant vaccine-induced protection should be as short as possible (Leuridan 2010, Leuridan 2011).

A rise of pertussis morbidity and mortality among infants in several countries over the past few years has led to recommendations for maternal vaccination against pertussis in many countries, including Australia, Israel, the US, New Zealand, Denmark, Belgium, Switzerland, the UK, the Czech Republic, Ireland, Italy, Portugal, and Spain (Forsyth 2015, Immunise Health Australia 2017, CDC 2018, Mazzilli, review 2018, ECDC 2019, Sundhedsstyrelsen 2019)

The Public Health Agency of Sweden published a systematic literature review in 2015 with the aim of evaluating the evidence for different prevention strategies to reduce pertussis among infants. Vaccination during pregnancy was evaluated in this report that was based on literature published from 1970 until the 2nd of March 2015 and concluded that the body of evidence for maternal vaccination against pertussis was limited with regard to safety and effectiveness (Folkhälsomyndigheten 2015, Folkhälsomyndigheten 2016).

The aim of the current literature review is to update previous reviews on this topic and based on articles published from February 2015 to December 2018.

Methods. The current update is a rapid, systematic literature review of studies published from February 2015 until December 2018.
The PICO model was used to define clinical questions about studied population, intervention, controls, and outcomes (Table 1).

Table 1. Current PICO (Population, Intervention, Control, Outcome)

Population	Pregnant women
Intervention	Acellular Pertussis (aP)-containing vaccine given during pregnancy
Control	No vaccination/other vaccine/historical controls
Outcome	Modified after Campbell et al. (Campbell, review 2018) (Table 2)

In a recent high-quality review of pertussis vaccination during pregnancy based on literature published from 1946 until April 2017, 46 relevant studies with around 345,000 participants in total were included in order to obtain a comprehensive evaluation of vaccine effectiveness, vaccine safety, immunogenicity, and interference after acellular pertussis (aP) or whole-cell pertussis vaccines given during pregnancy.

Outcome measures in this complementary literature review were modified after Campbell et al. (Campbell, review 2018) (Table 2).

Table 2. Primary and secondary outcome measures

Primary outcome measures	
1	Evidence for protection against pertussis infection and disease in infants.
2	Evidence for the safety of vaccination in pregnancy, as demonstrated by the consideration of adverse events post vaccination in the mother and/or in the foetus/infant.
Secondary outcome measures	
1	Antibody response in the mother following maternal pertussis vaccination.
2	Transplacental transfer of antibody as evidenced by cord, foetal, or infant blood titres of maternally derived antibodies to any vaccine antigens at birth or prior to the first primary vaccination in infancy.
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 antigens and clinically or laboratory-confirmed pertussis disease.

We included experimental and observational studies with data on effectiveness, immunogenicity, or safety of vaccination during pregnancy with aP-containing vaccine. We included studies with data from 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, *in vitro* studies, studies on cell-mediated immunity, and health economic and/or modelling studies. In most countries, the vaccines used in the maternal programmes were licensed tetanus, diphtheria, acellular pertussis (Tdap) vaccines, e.g. Adacel® or Boostrix® in the US (ACIP 2011, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6037a3.htm?s_cid=mm6037a3_w) or dTaP-Inactivated Polio (IPV) vaccine, e.g. Repevax® and Boostrix-IPV® in the UK (PHE 2016, https://www.gov.uk/government/publications/pertussis-the-green-bookchapter-24).

Results. From the literature search, articles were retrieved after exclusion of duplicates. Following screening of titles and abstracts, 97 articles remained. After further screening for full text and excluding those not fulfilling the selection criteria, or those with serious methodological issues, 45 articles were included, 9 of which assessed vaccine effectiveness and 16 assessed primary outcome measures on safety.
In total, 21 articles were included to address secondary outcome measures. Also, 7 review articles and 5 articles evaluating the impact on the population level were included (Table 3).
During the selection process, reference lists of included articles were scrutinized for possible additional articles and grey literature. All articles were read by two researchers.

Table 3. Selection of articles according to primary and secondary outcome measures

Primary outcome measures
1. Evidence for protection against pertussis infection and disease in infants.
Dabrera 2015, Amirthalingam 2016, Vizzotti 2016, Baxter 2017, Bellido-Blasco 2017, Skoff 2017, Winter 2017 (a), Winter 2017 (b), Saul 2018
2. Evidence for the safety of vaccination in pregnancy, as demonstrated by the consideration of adverse events post vaccination in the mother and/or in the foetus/infant.
Morgan 2015, Berenson 2016, Desilva 2016, Kharbanda 2016, Maertens 2016 (a), Maertens 2016 (b), Moro 2016, Petousis-Harris 2016, Regan 2016, Walls 2016, Layton 2017, Villareal Perez 2017, Griffin 2018, Halperin 2018, Sukumaran 2018, Wanlapakorn 2018
Secondary outcome measures
1. Antibody response in the mother following maternal pertussis vaccination.
Abu Raya 2015 (a), Huygen 2015, Vilajeliu 2015, Villareal Perez 2017, Fallo 2018
2. Transplacental transfer of antibodies as evidenced by cord, foetal, or infant blood titres of maternally derived antibodies to any vaccine antigens at birth or prior to the first primary vaccination in infancy.
Abu Raya 2015 (b), Vilajeliu 2015, Hoang 2016, Kent 2016, Maertens 2016 (a), Vilajeliu 2016, Villareal Perez 2017, Fallo 2018, Halperin 2018, Wanlapakorn 2018
3. The effect of the timing of maternal pertussis vaccination on the transplacental transfer of maternal antibodies or on the risk of disease in the infant.
Abu Raya 2015 (b), Amirthalingam 2016, Eberhardt 2016, Naidu 2016, Eberhardt 2017, Winter 2017 (b), Becker-Dreps 2018, Fallo 2018, Healy 2018, Wanlapakorn 2018
4. Blunting of the immunological response to primary childhood vaccinations as evidenced by antibody levels to any vaccine antigens and clinically or laboratory-confirmed pertussis disease.
Ladhani 2015, Maertens 2016 (a), (b) and (c), Hoang 2016, Baxter 2017, Cabore 2017, Maertens 2017, Halperin 2018
Review articles
Augustynowicz 2017, Calvert 2017, Leuridan 2017, Lumbreras Areta 2017, McMillian 2017, Perrett 2017, Campbell 2018, Mazzilli 2018
Impact on the population level
Amirthalingam 2016, Vizzotti 2016, Becker-Dreps 2018, Byrne 2018, Gentile 2018

Primary outcome measures

1. **Evidence for protection against pertussis infection and disease in infants.**
   There were nine studies that estimated the effectiveness of maternal pertussis vaccination in protecting young infants against pertussis disease (Table 3). Maternal aP vaccine impact on reducing infant disease burden was estimated based on data from the Argentinean Health Surveillance System (Vizzotti 2016). One observational study in England (Amirthalingam 2016) 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 was also based on data from the UK (Dabrera 2015). Three studies in the US were retrospective cohort studies of babies born to women immunized with aP-containing vaccine, which was recommended at 27–36 weeks' gestation (Winter 2017 (a), Winter 2017 (b), Baxter 2017). A matched case-control study was also based on US data evaluating aP-containing vaccine administered during the third trimester (Skoff 2017), and another case-control study performed in Spain evaluated aP-containing vaccine administered according to national recommendations (Bellido-Blasco 2017). One matched case-control study was conducted in Australia assessing the national maternal aP-vaccination programme recommended at 28–38 gestational weeks (Saul 2018).

   The level of vaccine effectiveness estimated from all of these studies was 90–93% against disease and more than 95% against death from pertussis in infants <2 months of age (Amirthalingam 2016, Baxter 2017). For infants below 3 months of age, vaccine effectiveness against infection, including mild pertussis, was estimated to be 69% and against hospitalisation was estimated to be 94% (Saul 2018).
   Winter found that vaccination in pregnancy reduced the risk of hospitalisation from pertussis and that babies hospitalised with pertussis had a shorter duration of stay if their mother had been vaccinated (Winter 2017 (b)).

   In summary: Maternal pertussis vaccination is highly effective in preventing severe disease and pertussis-related deaths in the youngest infants, but is somewhat less effective at preventing milder disease that does not require hospitalisation.

2. **Evidence for the safety of vaccination in pregnancy, as demonstrated by the consideration of adverse events post vaccination in the mother and/or in the foetus/infant.**
   In the review by Campbell et al., 16 different studies were listed with information on the safety of aP-containing vaccines during pregnancy (Campbell, review 2018). Overall, the studies did not disclose any negative results. Vaccination in those 16 studies was performed between gestational weeks 19 and 38, and the study findings were generally consistent and provide reassuring evidence of no significant increased risk of recognised maternal conditions, including pre-eclampsia, preterm delivery, stillbirth, or congenital anomalies in their babies.
   In this complementary literature review, safety data from an additional five studies are included (Layton 2017, Griffin 2018, Halperin 2018, Sukumaran 2018, Wanlapakorn 2018).

   In Griffin, et al. the use of Tdap in pregnancy was not associated with an increase in the rate of primary outcomes, including preterm labour, pre-eclampsia, pre-eclampsia with severe features, eclampsia, gestational hypertension, foetal growth restriction, or post-partum haemorrhage. Vaccination with Tdap also did not increase the risk of gestational diabetes mellitus, antenatal bleeding, placental abruption, premature rupture of membranes, preterm delivery, foetal distress, chorioamnionitis, or maternal fever during or after labour (Griffin 2018). Sukumaran et al. demonstrated that there was no association between vaccination during pregnancy and risk of infant hospitalisation or death in the first six months of life (Sukumaran 2018).
   Additionally, an observer-blind, multicentre, clinical, randomized controlled trial regarding the safety of the aP vaccine component showed that rates of adverse events were similar in both groups of women who received either Tdap or tetanus, diphtheria (Td)-containing vaccine in the third trimester (Halperin

2018). Furthermore, the reactogenicity of Tdap vaccine administered during pregnancy was not affected by prior tetanus immunization (Wanlapakorn 2018).
In a previous retrospective cohort study in California using data from Kaiser Permanente, a small but statistically significant risk was found for a diagnosis of chorioamnionitis (ICD-9 code 658.41) among vaccinated women (relative risk = 1.19) compared to unvaccinated women (Kharbanda 2014). Adjustment for risk factors of chorioamnionitis could not be done in the original data set, but it was stated that there was no evidence of increased risk of preterm birth, and among 220 cases randomly selected for case note review chorioamnionitis was confirmed histologically in only 19.6 % of the cases (McMillan, review 2017), indicating possible residual confounding and diagnostic imprecision (Layton 2017).
Chorioamnionitis data from the US were further investigated in the Vaccine Adverse Event Reporting System, and the signal of a possible relationship with Tdap administration could not be confirmed in subsequent studies (Leuridan, review 2017).

In summary: Reassuring data on the safety of maternal vaccination against pertussis for mother and infant at birth are available from many countries. There is still a need for more safety data with longer-term follow-up of children (at present there are follow-up data covering the first 6 years of life).

Secondary outcome measures

1) **Antibody response in the mother following maternal pertussis vaccination.**
Five studies using different aP-containing vaccines consistently showed that IgG antibodies against pertussis antigens were significantly higher at delivery in vaccinated women compared to unvaccinated pregnant women (Vilajeliu 2015, Abu Raya 2015 (a), Huygen 2015, Villareal Perez 2017, Fallo 2018). Pertussis-specific IgG levels decreased significantly 9 to 15 months after delivery in two studies (Abu Raya 2015 (a), Huygen 2015), but were still higher than those of unimmunised women. One study on specific cell-mediated immune responses showed impaired and transient responses in pregnant women compared to non-pregnant women (Huygen 2015).

In summary: Maternal pertussis vaccination was found to elicit evident antipertussis immune responses in pregnant women. There is no known serological correlate of protection against pertussis, but antibody levels were generally as high as those obtained in the clinical vaccine studies in children and adults that demonstrated that aP vaccines are efficacious.

2) **Transplacental transfer of antibodies as evidenced by cord, foetal, or infant blood titres of maternally derived antibodies to any vaccine antigens at birth or prior to the first primary vaccination.**
Statistically higher levels of antipertussis antibodies were consistently found in eight studies of babies born to vaccinated pregnant women compared to those born to women who were not vaccinated during pregnancy (Abu Raya 2015 (b), Hoang 2016, Maertens 2016 (a), Villareal Perez 2017, Fallo 2018, Vilajeliu 2015, Halperin 2018, Wanlapakorn 2018), which is in line with putative levels of protection (Vilajeliu 2016). In addition, Kent et al. specifically studied preterm infants and found antibody levels consistent with putative levels of protection in infants at two months of age (Kent 2016).

In summary: Statistically higher levels of antipertussis antibodies have consistently been found in studies of full-term babies born to vaccinated pregnant women compared to babies born to unvaccinated women.

3) **The effect of the timing of maternal pertussis vaccination on the transplacental transfer of maternal antibodies or on the risk of disease in the infant.**
There were seven studies reporting on the timing of maternal vaccination responses and infant antipertussis antibody levels. In addition, three studies reported on the timing of maternal vaccination responses and subsequent protection against pertussis disease during infancy (Table 3).

Abu Raya et al. reported higher levels of antipertussis antibody concentrations following vaccination at 27–30 gestational weeks compared to vaccination later during pregnancy (Abu Raya 2015 (b)).

Naidu et al. found that the cord blood levels of antipertussis antibodies were higher in babies whose mothers had been vaccinated early in the third trimester (28–32 weeks' gestation) compared to later in pregnancy (33–36 weeks' gestation) (Naidu 2016).

In a recent study, levels of antipertussis antibodies were highest when vaccination was administered during weeks 27 through 30 and declined thereafter, reaching a peak at week 30 (Healy 2018). Pregnant women who were vaccinated at 26–36 gestational weeks, had high titres to all antipertussis antibodies studied (Wanlapakorn 2018).

Eberhardt et al. reported on earlier vaccination during the first and second trimester and found higher infant antipertussis antibody concentrations following vaccination at 13–25 gestational weeks compared to 26 gestational weeks onwards (Eberhardt 2016). In addition, a prospective observational study in preterm babies found higher antipertussis antibodies in preterm babies born to women vaccinated in the second compared to the third trimester (Eberhardt 2017). However, a registry-based cohort study could not demonstrate that infants whose mothers were vaccinated earlier than 27 weeks of gestation had reductions in pertussis rates (Becker-Dreps 2018). In Fallo et al. (2018), mothers were immunized at a mean of 24.7 ± 4.8 weeks' gestation, but vaccination timing did not affect the levels of antipertussis antibodies in infants' serum at birth.

In Amirthalingam et al. (2016), vaccine effectiveness was calculated in relation to the timing of vaccination. Vaccine effectiveness was 91% for infants whose mothers received the vaccine at least 4 weeks and 1–3 weeks prior to delivery. For the small number of infants whose mothers received vaccine up to 1 week before delivery and within 1–2 weeks following delivery, vaccine effectiveness declined to 43% (Amirthalingam 2016). Winter et al.'s study reported that infants whose mothers were vaccinated during the second trimester were significantly more likely to be diagnosed with pertussis by age <8 weeks or ≤12 weeks than those whose mothers were vaccinated at 27–36 weeks' gestation (Winter 2017 (b)).

In summary: Maternal pertussis vaccination during the third trimester was found to be effective in causing higher levels of antipertussis antibody levels in new-born infants compared to no vaccination. Vaccination during gestational week 27–32 appears more effective than later in pregnancy.

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

A recent review has shown that the blunting phenomenon is a general effect seen for almost all vaccines in global general vaccination programmes, and it is known that both maternal antibody concentration and infant age at first vaccination influence infant vaccine responses (Voysey 2017).

A number of studies indicate that even though infants whose mothers were vaccinated during pregnancy may have a small reduction in antibody responses after vaccination with various childhood vaccines (diphtheria, pertussis, pneumococci), the blunting effects seen during the first year of life tend to disappear with time and usually are no longer evident after a booster dose in the second year of life (Ladhani 2015, Baxter 2017, Cabore 2017). However, two different studies indicated blunting effects with somewhat longer duration (Maertens 2016 (a, c), Halperin 2018), where antipertussis toxin responses were still somewhat lower after the booster dose (dose 4) given at 12–15 months of age. The clinical relevance of these findings is still unclear.

Epidemiological follow-up studies have not shown any increased risk of pertussis infection among maternally vaccinated children in any country that has introduced a maternal vaccination programme with aP-containing vaccines (Amirthalingam 2016, Winter 2017 (b), Saul 2018).

In summary: There are moderate blunting effects after maternal pertussis vaccination not only for antipertussis antibodies, but also for antibodies against pneumococci and diphtheria. There is currently no evidence of increased risk of pertussis or other infectious diseases in children following maternal vaccinations with aP-containing vaccines (at present there are follow-up data covering the first 6 years of life).

Conclusions. Since 2011 universal mass vaccination against pertussis during pregnancy has been introduced in some countries, first and foremost in the UK and USA, and a series of studies have been conducted on important issues such as safety, effectiveness, and various immunological outcomes in mothers and children.
This current review is an update of a previous Swedish literature review published in 2015. At that time we concluded that the body of evidence was limited with regard to both safety and effectiveness, and maternal vaccination was not recommended in Sweden.
This current review leans heavily on a comprehensive 2018 review by Campbell et al., with the addition of some publications from 2015 to December 2018.

The current collected body of evidence allows for more precise public health advice as follows:

- Primary outcome 1: Maternal pertussis vaccination is highly effective in preventing severe pertussis disease, hospitalisations, and death in small infants (vaccine effectiveness = 90–93%).
- Primary outcome 2: Follow-up of mothers and children has not disclosed any consistent significant adverse events or other medical problems caused by the vaccination.
- Secondary outcome 1: Maternal pertussis vaccination elicits antipertussis immune responses in mothers of the same order of magnitude that has previously been found to be correlated with efficacy against disease in clinical trials.
- Secondary outcome 2: Children born after maternal pertussis vaccination have higher levels of protective antipertussis antibodies compared to controls.
- Secondary outcome 3: The bulk of the current evidence indicates that vaccination during gestational weeks 27–32 appears to be optimal in a national vaccination programme.
- Secondary outcome 4: Maternal vaccination is linked to moderate blunting of the immune response to many childhood vaccines, including pertussis vaccine. The clinical significance of this blunting effect is not known, or if there is any significance at all. Clinical and epidemiological studies in countries with maternal pertussis vaccination programmes have so far not demonstrated any adverse effects, neither at the individual level or the population level (at present there are follow-up data covering the first 6 years of life).

Concluding remarks. The pertussis incidence in Sweden in infants is still low compared to countries that have already decided to recommend maternal pertussis vaccination. In total, four pertussis-related deaths in infants were reported in Sweden between the years 2008 and 2018 (Folkhälsomyndigheten 2019, 21st annual report, pertussis surveillance in Sweden). Reassuring data on the safety of maternal vaccination against pertussis for mothers and infants at birth are available from many countries. There is still a need for more data on long-term immunological and clinical effects.
At present the pertussis situation is relatively well controlled in Sweden using other control measures than maternal pertussis vaccinations. However, many countries have experienced a sudden and unexpected resurgence of pertussis with increased morbidity and mortality.
If a similar situation should also occur in Sweden, there is now further support for the use of maternal pertussis vaccination during outbreaks as an effective and safe control measure that could be implemented at short notice.

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