The Immunisation Advisory Centre

# Review of evidence to inform the New Zealand National Immunisation Schedule, 2018: Pertussis

Prepared as part of a Ministry of Health contract for services by
Dr Mary Nowlan at the Immunisation Advisory Centre

This review is part of a series of literature reviews commissioned by the Ministry of Health to help inform the National Immunisation Programme.

October 2018 [edited February 2019]

# Contents

# Figures and tables



# Acknowledgements

I would like to thank Professor Peter McIntyre, Senior Professorial Fellow at the National Centre of Immunisation Research and Surveillance for Vaccine Preventable Diseases and Professor of Paediatrics and Child Health at the School of Public Health, University of Sydney, Australia, for providing his expertise and feedback for this review.

# Abbreviations

| | |
|---|---|
| aP | Acellular pertussis |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence interval |
| CRM | Diphtheria-derived cross-reactive material-197 |
| DT | Diphtheria toxin / toxoid |
| DTaP-IPV-HepB/Hib | Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines. |
| ESR | Institute for Environmental and Scientific Research |
| EU/ml | ELISA units per millilitre |
| FHA | Filamentous haemagglutinin |
| FIM2/3 | Fimbriae 2 and 3 |
| GSK | GlaxoSmithKline Ltd |
| GMC | Geometric mean concentration |
| Hib | *Haemophilus influenzae* type b |
| HR | Hazard ratio |
| IgG | Immunoglobulin G |
| NZ | New Zealand |
| OR | Odds ratio |
| PCV (-10, -13) | Pneumococcal conjugate vaccine (10 and 13 valent) |
| PT | Pertussis toxin |
| PRN | Pertactin |
| RCT | Randomised controlled trial |
| RR | Relative risk |
| SD | Standard deviation of mean |
| Tdap | Tetanus, diphtheria and acellular pertussis vaccine (reduced antigen doses) |
| Tdap-IPV | Combined diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccines |
| TT | Tetanus toxin / toxoid |
| UK | United Kingdom |
| US | United States of America |
| VE | Vaccine effectiveness |
| WHO | World Health Organization |
| wP | Whole cell pertussis |

# Executive summary

Even with immunisation programmes, pertussis remains a significant cause of morbidity and mortality worldwide. Infants are especially vulnerable to this highly contagious bacterial infection due to the immaturity of their immune and respiratory systems.

Pertussis epidemics occur every 3 to 5 years in most high income countries, including New Zealand (NZ). During the previous epidemic in NZ from 2011-2013, six infants under the age of 2 months died and hundreds were hospitalised. A national pertussis outbreak is ongoing as of October 2018. From the official start of the outbreak period on the 16 October 2017 to the end of December 2018, 3,944 pertussis cases were notified, 308 were aged less than 1 year and approximately half of these infants were hospitalised (section 2.1).[1, 2]

In this review, the most recent literature published during January 2016 to September 2018 is presented to answer key questions relevant to better pertussis control and the best options for the National Immunisation Schedule (the Schedule). This is not a systematic review, not all aspects of pertussis immunisation have been reviewed, and cost-benefit is not considered.

## Vaccines available in New Zealand

The Schedule in NZ includes combined tetanus-diphtheria three-component acellular pertussis (aP) vaccines for infants and children younger than 7 years (combinations including DTaP, Infanrix®Hexa and Infanrix®-IPV [GlaxoSmithKline/GSK]) and older children and adults (Tdap; Boostrix® [GSK]). A combined five-component Tdap vaccine is also available on the private market (Adacel®, Sanofi Pasteur)(section 1.1).

The antigens included in three-component vaccines are pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN), with the addition of fimbriae 2 and 3 (FIM2/3) in the five-component aP vaccines. Each of these components have been identified as significant virulence factors of *Bordetella pertussis* bacterium that facilitate adhesion of the bacterium and alter the inflammatory response within the respiratory epithelium. Pertussis toxin is the single most significant determinant of severe symptomatic disease and death in unimmunised infants and children. Antibodies against pertussis toxin help to provide considerable, but not complete, protection.

### Comparison between types of vaccines

Comparing the effectiveness between these vaccine formulations is made challenging by differences in, (1) the method by which the pertussis toxin in detoxified, and (2) the quantity of each antigen in the vaccines. This is further complicated by different timing of immunisation schedules in different countries and clinical trials. Although systematic reviews have been conducted, the quality of evidence is low due to the variability between studies. All currently licensed pertussis vaccines are combined with tetanus and diphtheria vaccines. Adult formulations (from 10 years of age) have lower quantities of diphtheria toxoid, and some, as in NZ, have less pertussis toxin (Tdap) than those given in childhood (DTaP).

To add to the difficulty, when evaluating the effectiveness of pertussis immunisation, no definitive antibody correlate of protection for pertussis antigens has been established. Variability between assays means that assay cut-off levels, as used in some studies, cannot be used to compare between studies. There is no defined antibody level for serological protection.

# Pertussis vaccination in pregnancy

Vaccination of mothers during pregnancy provides passive immunity to infants from birth for the first few months of life through IgG transferred across the placenta.

The current recommendations in NZ are for pregnant women to received Tdap vaccination between 28-38 weeks of pregnancy to provide this passive immunity. The timing of the vaccination event in pregnancy to provide the optimum protection for NZ infants is reviewed.

Most pregnant women have no serological evidence of recent pertussis infection or vaccination, and half do not have detectable anti-pertussis toxin antibodies. Without antenatal vaccination, few infants would be born with any passive protection against pertussis.[3]

Routine surveillance data from 1997 – 2014 in Queensland, Australia, showed that the highest disease burden for pertussis was in early infancy before 4 months of age and in women of child-bearing ages of 15-45 years.[4]

Mothers are likely to be a significant source of infection to their infants. Therefore, vaccination in pregnancy provides dual benefits to both age groups by reducing infection in mothers and providing passive protection to newborn infants.[5, 6]

In NZ, the uptake of vaccination in pregnancy has been slow since its introduction to the Schedule in 2013 (estimated to be somewhere from 13% - 44%). Awareness and acceptance have been gradually improving.[7-9]

### Safety of pertussis vaccination in pregnancy (section 3.2)

No safety concerns have been identified for pregnant women or their infants following vaccination during pregnancy with Tdap. Pregnant women reported more severe injection site pain than non-pregnant women, but medical attention was not required.[10]

In NZ, Tdap exposure in pregnancy was associated with some protection against low birth weight, small-for-gestational age, moderate to later preterm birth, and was associated with a higher mean birth weight. A greater likelihood of health-seeking behaviour by vaccinated mothers compared with unvaccinated mothers may result in residual confounding to explain these improved infant outcomes.[8, 11]

### QUESTION: At what time in gestation is the optimal age for maternal vaccination?

Pregnant women respond robustly to Tdap given during pregnancy, although less than for non-pregnant women.[10] However, levels of anti-pertussis antibodies decline rapidly within one year of vaccination. Therefore, to provide adequate passive protection to infants against pertussis toxin, booster doses are required in each pregnancy. No literature was identified that considered the effects of frequent boosters and maternal antibodies for infants later in the birth order from multi-parous mothers (section 3.3).

The presence of maternal antibodies in the infant is protective against pertussis and severe pertussis at least until 2 months of age. Infants born to vaccinated mothers were significantly less likely to be hospitalised with pertussis, were at lower risk of intensive care admission and had shorter hospital stays than infants not vaccinated in pregnancy (section 3.4).[12-15]

### Effect of timing of maternal immunisation on infant pertussis antibody levels and vaccine effectiveness (sections 3.3.3 and 3.4.1)

Several studies have investigated anti-pertussis antibody titres in pregnant women, umbilical cord blood and infants during their primary series. Although these immunogenicity studies can provide an indication of the antibody levels, there is no established correlate of protection for pertussis; caution is needed when using antibody titres to predict clinical effectiveness against disease.

To establish the optimal timing for the maternal vaccination, a balance needs to be achieved between greater accumulation of protective antibody and the waning of antibody in both the mother and the infant. If maternal pertussis IgG levels are too low at birth, seroprotection is unlikely to be maintained until the infant is fully immunised and able to generate sufficient antibodies of their own. If Tdap is given too early in pregnancy, there is a risk that maternal antibody levels wane before birth; if given too late, there is insufficient time for adequate antibody to transfer, particularly for infants born prematurely less than two weeks after vaccination.

Maternally-derived pertussis antibody declines rapidly after birth and by 2 months of age (median half-life of <50 days when given 21-38 weeks gestation) and is significantly influenced by the concentration of antibodies at birth.[16] Anti-pertussis toxin antibodies, which wane more rapidly than anti-FHA antibodies, provide the greatest protection to infants against the systemic effects of pertussis infection.[17]

Maternal pertussis vaccination from 28 weeks to at least 7 days before birth has been shown to be significantly protective (VE 91% against pertussis and 95% against pertussis-related deaths) up to 2 months of age in the UK.[12]

According to US studies, the optimum timing for maternal vaccination is between 27-31 weeks gestation, and up to 36 weeks gestation. Tdap vaccination given between 27-36 weeks gestation was 85% more effective than vaccination given post-partum to mothers in preventing pertussis in infants aged less than 8 weeks of age in the US.[18]

The higher cord blood anti-PT antibody concentrations were achieved when mothers were vaccinated early rather than later in the third trimester (27-31 weeks versus 32-36 weeks, peaking at 30 weeks),[19] although in another study, no significant difference between two similar time periods (27-30 versus 31-36 weeks) were found.[20]

However, a Swiss study found that maternal vaccination in the second trimester (13-25 weeks gestation) resulted in significantly higher anti-PT and FHA IgG in neonates born full-term than when given after 26 weeks. Infant seropositive rates were also higher in those vaccinated in the second trimester than the third (80% vs 55%; odds ratio 3.7, $p<0.001$).[21] Based on these findings, since 2016 in the UK, maternal vaccination has been recommended from 16 weeks gestation, ideally at 20 weeks, on the basis that a longer time between vaccination and delivery increases the antibody levels at birth.[22, 23]

Maternal Tdap received after 20 weeks gestation was shown to be 69% protective against pertussis during the first year of life after three primary doses of DTaP in the US.[13]

### Timing of maternal vaccination to protect infants born prematurely (sections 3.3.3 and 3.4.2)

Infants born prematurely, before 37 weeks gestation, are at greater risk of being hospitalised with pertussis and have longer hospital stays than infants born full-term.[24]

Following the implementation of the maternal vaccination programme in the UK, fewer infants born full-term were hospitalised with pertussis, which meant that a larger proportion

of the infants with pertussis were born preterm (proportion of pertussis cases born preterm rose from 9.8% to 12.1%). Of the full-term cases, 14.3% had received a maternal vaccination after 35 weeks gestation and the latest gestational age for vaccination of any preterm mother was 33 weeks (the programme commenced at 28 weeks gestation).[24] As also observed in Northern Territory, Australia, preterm infants were twice as likely to have been born before their mothers could receive maternal Tdap, when recommended from 28 weeks gestation, than those born full-term, and were less likely to have passive protection.[25]

Most infants born prematurely benefit from maternal vaccination given before 26 weeks gestation or early in the third trimester, and have significantly higher anti-pertussis, tetanus and diphtheria antibody levels up to 2 months of age, as compared with premature infants of unvaccinated mothers. It has therefore been recommended that the maternal immunisation programmes commence at 20 weeks to improve the chances of infants born prematurely to have received a maternal vaccination.[22]

IgG concentrations in umbilical cord-blood were significantly correlated with the number of days between maternal vaccination and delivery in infants born prematurely (at 28-35 weeks gestation) to mothers vaccinated in the third trimester according to the former UK schedule (28-34 weeks). Antibodies to PT and FHA increased 4% and 7% per day, respectively, from maternal vaccination to birth. All the premature infants of vaccinated mothers had significantly higher anti-pertussis, tetanus and diphtheria antibodies at 2 months of age (prior to start of primary series) than those born to unvaccinated mothers.[23]

As part of the Swiss study mentioned above, none of the infants born preterm to mothers who were vaccinated in the second trimester (13-25 weeks) were seronegative, whereas almost one quarter of preterm infants born in the third trimester were seronegative following third trimester vaccination (from 26 weeks; $p=0.002$). To maximise maternal-fetal antibody transfer, a 15-days interval was sufficient to observe significantly higher cord-blood antibody titres in the preterm population.[26]

**Conclusions - At what time in gestation is the optimal age for maternal vaccination?**

- Offering vaccination earlier than 28 weeks gestation would provide protection for more infants born preterm.
- For optimal balance between antibody accumulation and waning too soon, the best timing appears to be around 20-33 weeks gestation.
- Although maternal vaccination has been shown to be effective against pertussis when given at least 7 days before delivery, an interval of at least 15 days between vaccination and delivery is preferred to maximise antibody transfer.
- To improve the current recommendations, pregnant women should be encouraged to be vaccinated as soon as possible within the recommended window.

**QUESTION: Do maternal antibodies interfere with infant primary immunisations?**

The presence of maternal antibodies can affect the immunogenicity of infant primary series vaccinations. Passive protection from maternal antibodies needs to be balanced with the potential for clinically relevant interference of the infants' immunisations. Although maternal pertussis antibodies protect the youngest infants from pertussis prior to commencing the primary series immunisations, it is unclear what clinical effect these may have on pertussis immunity in older infants upon completion of the priming doses.

In the majority of studies reviewed, the primary series immunisations were initiated at 2 months of age. In the NZ context, it is important to consider the influence of maternal antibodies where the primary infant series commences at 6 weeks of age.[27]

If clinically relevant interference is shown as the uptake of maternal vaccination improves, the timing of the start of the infant primary series may need to be delayed to allow more time for maternal antibody levels to wane to minimise this risk, or specifically delayed for infants of vaccinated mothers.

### Effect of interference of maternal antibodies with pertussis immunity and vaccine effectiveness (sections 3.3.4 and 3.3.5)

There is evidence that infants born to mothers vaccinated with Tdap in pregnancy have lower antibody responses to one or more pertussis antigens following the primary schedule. However, no evidence of clinically significant blunting in protection was found during the first year of life after maternal vaccination and primary infant doses for those immunised from 2 months of age in the US or England.[28-30]

Preliminary NZ data have shown maternal Tdap to be 71% effective against pertussis up to 6 weeks of age, with a small additional protective effect among infants who received at least two doses of routine DTaP up to 6 months of age (section 3.4).[14] However, these NZ data suggest that interference of the infant primary immune response against pertussis due to the presence of maternal antibodies when commencing the primary series at the earlier age of 6 weeks (rather than 8 week or 2 months as in other countries) could be clinically relevant (unpublished data).

A meta-analysis of immunogenicity data from several clinical trials (collected prior to routine maternal immunisation programmes) found that pre-existing maternal antibodies inhibited infant responses to 20 out of 21 primary series vaccine antigens. For pertussis antigens, two-fold higher pre-existing antibodies were associated with 11% lower antibody post vaccination against PT and FHA and 22% lower anti-PRN antibody. Mathematical models showed that this effect may be offset by a delay in primary vaccination of between 2.2 to 5 weeks.[31]

Interference appears to be long lasting. Antibody responses to pertussis booster doses given at 12-24 months were also affected, indicating that the quality of the immune response to the first dose of an antigen is important for subsequent exposures.[31] In Canada, lower responses to PT were shown to persist from 6 months to prior to, and one month after, a 12-month booster dose.[29]

Significantly lower anti-PT IgG were also observed at 15 months of age in Belgian infants born to mothers vaccinated in pregnancy ($p=0.006$), whereas anti-tetanus and PRN antibodies were non-significantly higher in the vaccinated group and anti-PRN antibodies were significantly higher 1 month post booster.[32] In a further study, the avidity (indicative of memory and antibody maturation) of anti-PT antibodies were shown to be significantly lower after booster doses at 15 months of age among maternally-vaccinated infants.[33]

In animals, it was observed that infant vaccinations appear to interfere with the protective function of the maternal antibodies. When mother and infant mice were immunised with two different pertussis vaccine formulations (from GSK and Sanofi Pasteur), no interference was observed.[34] The authors suggested that use of different vaccine formulations for the maternal and infant doses might overcome reduction in antibody function seen when the same vaccine was used, but no human data are available to confirm or refute these murine data.

The clinical relevance of this interference remains unclear. It is important to consider how maternal vaccination alters clinical effectiveness of the primary series and to consider whether delaying the start of the primary series for infants vaccinated in pregnancy may be necessary. Further insight is anticipated in a NZ context from an ongoing HRC/PHARMAC funded study (PIPIO2).[27]

### Effect of interference of maternal antibodies on other antigens in primary series immunisation and the timing of the infant immunisation schedule (section 3.3.5 and 4.2)

As mentioned above, the meta-analysis of clinical trial immunogenicity data from clinical trials found that pre-existing maternal antibodies inhibited infant responses to primary vaccines for 20 out of 21 primary series antigens, and that this effect was still evident following booster doses at 12-24 months of age for inactivated polio and diphtheria vaccines. Inhibition was reversed when children were first vaccinated at an older age. For the antigens with known correlates of protection, “blunting” did not appear to reduce antibody protection to below threshold levels in most infants.[31]

The magnitude of any blunting is likely to depend on the timing of the antenatal and primary series vaccinations, but data are too limited to identify optimal maternal or infant vaccination timing, particularly in relation to vaccination programmes in pregnancy.

Following the introduction of the maternal vaccination programme in England, significantly lower immune responses to diphtheria and diphtheria-derived CRM-conjugated antigens (some PCV-13 serotypes and MenC-CRM) were seen in infants of TdaP-IPV vaccinated mothers compared with infants not vaccinated in pregnancy. Antibodies against tetanus and *Haemophilus influenzae* type B (Hib) were significantly higher in maternally-vaccinated infants. The findings favoured either the use of TT-conjugated rather than CRM-conjugated vaccines in infants, and tetanus-pertussis or aP-only vaccines in pregnancy, especially following any prior Tdap booster during a previous pregnancy.[30]

In infants of mothers vaccinated in pregnancy, blunting of the antibody responses was observed against some pneumococcal serotypes after two doses of PCV-13 (at 8 and 16 weeks of age) until 12 months of age in Belgium. Despite the lower antibody responses, the proportion of infants achieving antibody thresholds for presumptive seroprotection was not significantly affected after primary or booster vaccinations.[35]

DTaP is recommended to be administered at the same time as conjugate vaccines, such as meningococcal C or ACWY, pneumococcal or Hib, as part of the primary series to avoid any potentially immunosuppressive effects of epitope competition (for diphtheria proteins, in particular).[36, 37]

The magnitude of any effect of maternal antibodies on primary series and booster vaccinations is likely to depend on the timing of antenatal vaccinations and starting age of the primary series. Current data are too limited to identify an optimal schedule, particularly when commencing the Schedule at 6 weeks of age, as in NZ.

**Conclusions – Do the presence of maternal antibodies interfere with infant primary immunisations?**

- Antibody interference is observed for some primary series vaccines containing diphtheria and pertussis antigens (and polio where TdaP-IPV is given in pregnancy). There is insufficient data, as yet, to confirm or exclude a clinically meaningful interference.
- Any clinical significance of interference is likely to be amplified when starting the schedule at 6 weeks rather than 8 weeks, as in NZ. We are awaiting findings of an ongoing NZ study.
- Less pertussis is observed in the youngest infants when the primary immunisations start at 6 weeks of age rather than at 2 months. However, maternal antibody interference with the primary series could lead to a fairly equivalent increase in disease in the older infants.
- With the aim of reducing interference with diphtheria and tetanus-containing vaccines, an aP-only vaccine (containing PT, FHA and PRN antigens) has been proposed for use in pregnancy. A pertussis toxin-only vaccine has also been suggested to possibly provide passive protection to the infant through neutralising anti-PT antibodies. Where available, data is limited around the use of such vaccines.
- Delaying the infant schedule would only be appropriate if almost all mothers received vaccine in pregnancy, or if it was judged feasible to implement different schedules for infants of mothers either vaccinated or unvaccinated in pregnancy. Data is limited to judge the best age to commence the primary series for maternally-vaccinated infants.

## Addressing the gap between birth and primary vaccinations

**QUESTION: How can we protect infants of mothers who are not vaccinated during pregnancy? (Section 4)**

Beginning the primary series at 6 weeks rather than 2 months of age, accelerates protection against severe pertussis for the youngest infants, but protection remains incomplete until at least two weeks after receipt of the second dose.

Options to protect infants born to mothers who did not received Tdap in pregnancy were reviewed, including administering a pertussis-only vaccine at birth, cocooning by vaccinating close family members, or adjusting the timing of the infant schedule.

### Birth doses

A birth dose of aP-only vaccine, if licensed, has the potential to enhance protection prior to 12 weeks of age to infants born preterm or to mothers who did not receive Tdap in pregnancy (section 4.1). In an Australian clinical trial of infants whose mothers were not vaccinated in pregnancy, significantly more infants who received a dose of aP-only vaccine (unlicensed) at birth had detectable anti-PT and PRN antibodies at 10 weeks of age, after the first scheduled primary dose, than infants who were not vaccinated at birth (93.2% vs 50.8%; $p<0.001$) and four-fold higher anti-PT titres. Some interference in primary series responses (Hib, hepatitis B and diphtheria, not pneumococcal) were observed, but clinical significance was not established.[38]

### Timing of the infant schedule (section 4.2)

Delays in the timeliness of primary immunisations potentially risk reduced disease control in young infants, especially for those born to mothers who were not vaccinated in pregnancy.[37, 39]

Pertussis incidence was predicted by mathematical modelling for four infant immunisation schedules using immunisation data from Argentina (DTwP) and Belgium (DTaP). The highest reduction in pertussis incidence was achieved with a 6-10-14 weeks schedule (36% in infants up to 1 year of age) and a 2-3-4 months schedule (26%), compared with a 2-4-6 months schedule. A delay in the first dose to 3 months (3-4-5 months schedule) increased the risk of severe pertussis by 9%, but reduced total pertussis incidence by 10% up to 1 year of age. Although the model did not consider maternal vaccination or blunting effects of antibodies, it included a protective effect of maternal antibodies up to 6 weeks of age for a fraction of infants.[40]

Data is limited around the effectiveness in terms of pertussis control of a 2+1 immunisation schedule in association with maternal vaccination.

**Conclusions - How can we protect infants of mothers who are not vaccinated against pertussis during pregnancy?**

For infants of unvaccinated mothers, alternative options could be considered, including:

- A birth dose of aP-only vaccine – no licenced vaccine is currently available, but this supports the general notion that in the absence of maternal vaccination, an earlier first dose given before 6 weeks of age, is beneficial.
- Delaying the start of primary series vaccinations for all infants increases the risk of pertussis in those born to mothers not vaccinated in pregnancy.
- Two primary schedules starting at different ages for maternally-vaccinated and maternally-unvaccinated infants could reduce maternal antibody interference, but may cause programmatic challenges.

**QUESTION: Does vaccination of healthcare workers protect infants?**

Tdap vaccination of healthcare workers (HCWs) may provide limited protection to infants in their care. A systematic review found that there is moderate evidence that booster Tdap doses are protective against nosocomial transmission by HCW to all age groups, specifically infants (section 4.4).[41]

Pertussis toxin antibodies wane rapidly, but antibodies against adhesion factors (FHA and pertactin) are longer lived. However, there is insufficient evidence to determine the optimum frequency of booster doses required to maintain protection in adults (section 5.1.2).[42]

**Conclusions - Does vaccination of healthcare workers protect infants?**

- Many people do not know they are infected or show minimal symptoms of pertussis. There is moderate evidence that booster Tdap doses are protective against nosocomial transmission in HCW.
- Due to a lack of correlate of protection for pertussis, data around the requirements and timing for repeat boosters are limited.

**QUESTION: Does vaccination of close contacts protect infants?**

Many adults are unaware that they are infected and potentially transmitting pertussis. At least one positive pertussis case was found to be a possible source of infection to a hospitalised infant aged less than 3 months in 86% of UK households. Out of all the contacts tested from these families, 29% of non-coughers tested positive for pertussis infection and in 38% of the cases, mothers were the probable source of infection, followed by siblings (31%) and fathers (10%).[6]

Vaccinating both parents post-partum provides protection for infants whose mothers did not received Tdap in pregnancy. This 'cocooning' was shown to be somewhat beneficial, although statistical significance was not reached, and may be considered when no antenatal vaccination occurred (section 4.4).[43]

The possibility that inactivated trivalent influenza vaccination in pregnancy might reduce pertussis in mothers and transmission to their infants was raised by retrospective analysis of a RCT from South Africa.[44] The notion that vaccinating parents and other family members against influenza may reduce the risk of symptomatic *B. pertussis* and influenza in the newborn could help promote the importance of maternal influenza immunisation, which lags pertussis (section 3.4.4).

**Conclusions - Does vaccination of close contacts protect infants?**

- Although the current vaccines do not effectively prevent transmission of pertussis, vaccinating those in close contact with infants does help to prevent disease in infants. The incremental benefit when the mother has been immunised is unclear.
- Further protection of infants against pertussis and other respiratory infections may be gained by promoting influenza vaccination of close contacts as well as mothers.

## Duration of protection

**QUESTION: Does waning immunity affect pertussis protection in childhood?**

A positive impact of pertussis vaccination has been demonstrated across all age-groups. Age-appropriate pertussis vaccination was shown to reduce the severity of symptoms and complications of the disease, with a 60% reduction in the odds of severe disease (seizure, encephalopathy, pneumonia and/or hospitalisation) in children aged 7 months to 6 years, and a 30% reduction in post-tussive vomiting in those aged 19 months to 64 years in the US (section 5.2.1).[45]

A major issue with the pertussis vaccination is that it has a limited duration of protection. More rapid waning of immunological memory following booster doses and a resurgence in disease incidence has been particularly associated with the switch from whole cell to acellular pertussis vaccines in most developed countries.[46]

Mathematical modelling based on Australian epidemiological data found that the protection afforded by natural infection was likely to be decades longer than vaccine immunity for either wP or aP vaccines, but especially for aP vaccines (section 5.1).[47]

The more rapid waning in protection from aP vaccines was shown in Canada, where individuals who had been primed with aP vaccines were more than twice as likely to have pertussis than those who had been primed with the previously used wP vaccine. Even after five doses of an aP-containing vaccine, pertussis immunity waned in children at a rate of around 27% per year in those children younger than 12 years. The more remote from the last vaccination, the greater the risk of pertussis.[48]

In children who were solely primed and boosted with aP-containing vaccines from mid-2013 onwards, the incidence rate of laboratory-confirmed pertussis in the UK was 7.7 times higher than during 2009-2011. However, this increase also coincided with commencement of oral fluid pertussis testing of children, so some observed increase may be attributable to greater testing.[12]

Pertussis protection provided by the primary series (commencing at 6 weeks of age) was sustained through to 4 years of age in NZ with VE of at least 91% against pertussis hospitalisation and 84% against notified non-hospitalised pertussis. During the period included in the study (2006-2013), no evidence was found that removal of the toddler booster dose in 2006 had resulted in waning protection.[49] This finding was opposite to a similar Australian study.[50] Both studies were conducted prior to the introduction of maternal vaccination. The potential of reduced antibody responses in infants born to immunised mothers heightens the need to keep the case for a toddler dose under review, especially for children at increased risk of severe pertussis beyond the age of 6 months, such as those born prematurely or with significant cardio-respiratory disease.

Spacing of the primary series of DTaP with the first two doses given at 6 weeks and 3 months and then a third dose in the second year of life (2+1 schedule) may offer immunologically better spacing between the second and third doses and enhance protection against pertussis in the second year of life. Implementation of this schedule would depend upon the influence maternal antibodies has on infant immunity following the first two doses, particularly in infants aged between 6 and 12 months.

**Conclusions - Does waning immunity affect pertussis protection in childhood?**

- Children primed solely with aP vaccines experience shorter duration of protection and increased disease incidence the more remote from the last vaccine dose compared to those initially primed with wP.
- No waning of vaccine effectiveness was observed in NZ before the age of 4 years following the removal of the toddler booster dose and prior to the introduction of the maternal vaccination programme. This contrasted with similar data from Australia.
- Although evidence of reduced antibody responses is relatively well established, it is not known whether maternal vaccination interferes with the clinical effectiveness of the pertussis programme in infants up to the age of 2 years. Such evidence would strengthen the case for a booster dose in the second year of life.
- The case for a booster dose is stronger among children with comorbidities predisposing them to severe pertussis despite full immunisation.
- Immunologically, wider spacing between the second and third doses (i.e. 2+1 schedule) may enhance protection in the second year of life, but risks reduced protection between 6-12 months of age.

**QUESTION: What is the role of the Tdap booster given in adolescence against pertussis? (section 5.4.2)**

It has been estimated that only 10% of those fully immunised with DTaP up to 4 years of age continue to have substantial levels of pertussis antibodies 8.5 years after their last DTaP dose.[37, 51]

A direct benefit of Tdap boosters in adolescents was shown by a systematic review and modelling study, which found that children who completed their full immunisation series by the age of 11 years received considerable added protection against pertussis after a Tdap booster, such that, the relative risk of pertussis was significantly reduced (relative risk 0.3)

and protection remained for at least four years compared to children who only received the primary series (relative risk 0.8).[52]

However, booster doses given after the age of 10-12 years were to shown provide only short-lived direct protection against pertussis, especially when all previous doses were aP vaccines.[47] Immunity typically waned within two to four years, increasing the risk of pertussis by around one-third per year since the Tdap booster and appeared to decline more rapidly in those who were fully primed with aP vaccines in infancy.[53]

Pertussis immunisation is only effective for the recipient groups and does not provide indirect protection. There is no good evidence that adolescent doses prevent disease transmission, and although their contact with infants is typically limited, indirect herd immunity benefits are unlikely to protect infants.

Although protection against disease is short-lived, the clinical severity of pertussis is reduced by boosting the immunity in adolescence, and hence minimising time absent from school at a time of considerable academic pressure (section 5.2.1).[45]

The timing of pertussis boosters is likely to become more relevant as Tdap is given to women in pregnancy who were primed soley with aP vaccines. As protective levels of antibodies wane rapidly, the adolescent booster may influence the response to pertussis vaccination in pregnancy by either improving the antibody response or resulting in more rapid waning.[54]

**Conclusions - What is the role of the Tdap booster given in adolescence against pertussis?**

- The benefits of a booster dose of Tdap given in adolescence is unclear. Currently, as part of the NZ Schedule, adolescents are given Tdap at the age of 11-12 years.
- The protection is likely to be short-lived, particularly in those primed with aP as infants (born since 2000).
- The adolescent booster dose does not appear to provide herd immunity to younger age groups.
- However, the adolescent booster is likely to reduce disease severity, which is most important in adolescents with respiratory co-morbidities.
- Anti-pertussis toxin immunity wanes more rapidly following each booster dose in those primed with aP vaccines.
- It is unclear whether omitting the adolescent Tdap dose in will have an effect on the response to any booster doses given in adulthood, particularly to those given in pregnancy.

**QUESTION: Can we overcome the skewing of the immune response with acellular pertussis vaccine regimens and is it important for the future? (section 5.1)**

### Options for acellular versus whole cell vaccines – if we were to go there?

Immunity declines more rapidly in those who were fully primed with aP vaccines rather than wP in infancy. As the age-cohorts who were solely vaccinated with aP vaccines reach adulthood, it is unclear how effective or long-lasting maternal boosters will be when given to women who were primed only with aP vaccines, rather than those who were immunised with whole-cell pertussis (wP) or mixed wP/aP schedules in childhood.[47]

The first dose of aP vaccine has been purported to determine the characteristics of the T cell response following re-exposure, and this has been associated with lower effectiveness, more

rapid waning and limited ability to prevent transmission compared with wP or wild-type primed immunity.[55, 56]

One hypothesis for the more rapid waning and increased disease incidence seen in aP primed individuals, is that the aP vaccines induce a more T-helper 2 type immune response as compared with a T-helper-1/T-helper-17 type response induced by wP vaccines. Although this aP response generates a good antibody response to reduce virulence of the disease by neutralising pertussis toxin and to prevent adhesion of the bacteria to the cells of respiratory tract by antibodies (generating neutralising immunity), it is less able to kill *B. pertussis* to prevent colonisation and clear infection (sterilising immunity), resulting in more carriage and transmission (section 5.1.1).[55]

There is a risk that as fully-aP primed individuals reach adolescence and adulthood (i.e. those born since 2000), more booster doses will be needed to control pertussis. In that generation, the immunity to pertussis has been permanently altered. For the future, new vaccines are required that perhaps contain adjuvants to prime with a Th1/Th17 bias and/or less altered pertussis toxin.

Although wP pertussis vaccines are associated with less waning of immunity than aP vaccines, they are one of the most reactogenic vaccines and are associated with high fevers, prolonged crying and injection site reactions in infants and young children.[57] In developing countries, as part of the Expanded Programme on Immunisation, DTwP is given within a short time-frame (6-10-14 weeks of age) based on the rationale that reactogenicity is reduced.[58] However, a return to these vaccines is unlikely to be considered a viable option in NZ for the full schedule.

An option proposed in the literature is to give DTwP as the first dose at a young age (6 weeks to 2 months) when the risk of adverse events is less, and for subsequent priming doses to be aP-containing vaccines.[55, 56] However, there is no empirical data and the strength of evidence required to justify a mixed schedule and associated service delivery issues is not yet available. An immunogenicity study has recently been funded in Australia to explore this option.

### Strategies to reduce waning immunity

Some studies suggest that the waning immunogenicity and effectiveness of the current aP vaccines result from the process used to detoxify pertussis toxin. Conformational changes to the pertussis toxin may alter the epitopes presented to the immune system. Priming of the immune response is not affected, but repeat booster doses with the same denatured toxin result in the immune dominance against non-protective rather than protective antigens (section 5.1.3).[54, 59]

Unlike neighbouring countries in 2013 Denmark had not had a pertussis epidemic since 2002. At the time, Denmark used mono-component aP vaccines containing high doses of hydrogen peroxide-detoxified pertussis toxin with high VE in children (93% and 73% against severe and mild pertussis, respectively). In a clinical trial, response rates in adults to the TdaP booster were significantly higher than two multicomponent Tdap vaccines containing lower doses of glutaraldehyde/formaldehyde deactivated PT (92% versus 47.1% and 77.2%).[60]

### Or do we wait for newer vaccines?

The use of alternative methods to detoxify PT, such by hydrogen peroxide treatment or genetic modification, which better maintain the conformational structure of PT, may overcome waning protection and induce more effective antibodies. These vaccines are currently unavailable or continue to be in development (section 5.1.1).

Using recombinant DNA technology, genetically-inactivated PT has been investigated in aP vaccine formulations in clinical trials and was found to show significantly greater immunogenicity and antibody duration than chemically detoxified PT.[61-63]

New vaccine formulations using adjuvants are also being evaluated to induce a more sterilising immunity.

It is important to consider new options to reduce problems in the future with fully aP-primed individuals. However, pertussis is a severe disease, particularly for infants. Maternal vaccination and DTaP priming are helping to protect the youngest infants and should therefore be continued, but the longer term impact of these vaccines in the general population is uncertain.

**Conclusions - How do we overcome the skewing of the immune response using aP regimens and is it important for the future?**

- It is very important to continue to consider the effect the aP vaccines have on the long-term immune response against pertussis. Anyone born since 2000 in NZ will have been primed with aP vaccines.
- This is expected to have consequences for booster doses in pre-schoolers, adolescents and mothers-to-be.
- Repeat boosters with the same vaccine formulation appears to result in dominant immunity against non-protective epitopes and more rapid waning of protection.
- **Options for acellular vaccines vs whole cell – if we were to go there?**
    - Giving wP as a first priming dose may reduce skewing of T cells immunity to Th2, but the overall risk benefit is not well established.
    - Reactogenicity of wP vaccines increases with the number of doses received. Careful consideration is required in relation to vaccine confidence – it has been shown that adverse experiences during the first vaccinations can result in maternal hesitancy for subsequent vaccinations, especially if four-component meningococcal B vaccine (Bexsero®) was to be added to the infant schedule.
    - An alternative means suggested to reduce waning is to use pertussis toxin which has been genetically detoxified rather than chemically detoxified (hydrogen peroxide or formaldehyde) in vaccines. Recent trials of such vaccines have shown superior immunogenicity, but are not yet registered outside of Thailand.
- **Or do we wait for newer vaccines?**
    - New vaccines, using recombinant technology or adjuvants to reduce skewing of the immune response, are in development, but may take several years to be licenced.
    - Pertussis is a severe illness that most seriously affects our youngest infants – the immunisation programme must look to the best use of currently available vaccines with the primary aim of protecting infants against severe pertussis.
    - Maximising maternal vaccination is the single most effective way to protect young infants. High coverage and timeliness of the primary series will maintain this initial protection.

## International schedules

Most high income countries, including Canada, most European countries, the US and the UK start the infant immunisation schedule from 8 weeks or 2 months of age (section 6). Australian recommendations state that the first dose may be given as early as 6 weeks and this has become more common than 8 weeks.

The spacing of the primary series varies between countries – with either two primary doses and a booster in the second year of life (2+1), three primary doses and a toddler booster (3+1), or just three doses and no toddler booster (3+0). Most countries administer a booster before school commences and some provide or recommend a booster in early adolescence and for adults who have not previously received at Tdap booster in adulthood.

Not all countries have a recommendation for vaccination in pregnancy. Since 2016, the UK has recommended routine commencement of maternal vaccination in the second trimester, currently from 16 weeks, ideally from 20 weeks. Switzerland also recommends vaccination from the second trimester (preferably weeks 13-26). Other countries recommend vaccination during the third trimester, commencing from week 27 or 28 to ideally 32 weeks (section 6).

The choice of schedule is determined by the local disease incidence and timing of other vaccines on the schedule.

## Updates suggested for Immunisation Handbook 2017

**14.3.2 NZ epidemiology -** Update required in light of recent epidemic (currently 2015 data are presented).

**14.4.2 Efficacy and effectiveness** – For the childhood schedule (Infanrix-hexa), these were not specifically reviewed for this document, since the focus was on different questions. The data presented in the Handbook were pivotal clinical trial data. Influences of maternal antibodies are not fully defined and therefore may not be appropriate to add to the Handbook at this stage.

**To add** – Pertussis immunisation has a positive impact on disease severity. A positive impact of pertussis vaccination has been demonstrated and age-appropriate pertussis vaccination has been shown to reduce the severity of symptoms and complications of the disease. Age-appropriate vaccination in the US was associated with a 60% reduction in the odds of severe disease (seizure, encephalopathy, pneumonia and/or hospitalisation) in children aged 7 months to 6 years, and a 30% reduction in post-tussive vomiting in those aged 19 months to 64 years (section 5.2.1).

**Duration of protection** - Waning of immunity against pertussis is seen in children, even after five doses of an acellular pertussis-containing (aP) vaccine, at a rate of around 27% per year (section 5.2.3). It has been estimated that only 10% of children vaccinated with DTaP would be immune to pertussis 8.5 years after their last dose. In adolescents, following the adolescent booster, waning is more rapid at around 35% per year, such that VE declines to less than 10% after four or more years (section 5.2.4). Antibodies to FHA and PRN are longer lived than those against pertussis toxin (section 5.1.2).

**4.1.2 During pregnancy**

Include published NZ data demonstrating safety (PIPS study) (section 3.2.1).

Effectiveness of the UK programme – use more up-to-date references for three years of programme and systematic reviews from other countries (section 3.4).

## Outstanding questions and challenges

Several questions remain around pertussis immunisation, globally. The main aim of the immunisation programme is to protect those most vulnerable from severe disease. Morbidity and mortality is highest in infants under 1 year of age. However, it can be a severe disease in all age groups. The current aP vaccines have been shown to be less able to prevent disease transmission and symptoms than the formerly used wP vaccines, but are much less reactogenic and better accepted by parents and health professionals. Key questions for which more data and/or newer vaccines are required include:

- How do we reduce transmission of pertussis to gain herd immunity?
- What effect do maternal antibodies have on clinical effectiveness of primary series vaccines? How can we avoid blunting of protection in infants?
- Should we continue priming with aP vaccines? What is the long-term effect on population immunity?
- What is the best timing to give pertussis vaccine in pregnancy to balance antibody transfer with waning antibody levels post-partum?
- Can we improve pertussis immunity with the existing licensed vaccines? Do we need to consider different formulations or wait for better designed vaccines to be developed?

# Literature Review

## 1 Background – pertussis infection and vaccination

Pertussis, commonly known as whooping cough, can be a life-threatening illness in young children, particular infants under the age of 1 year. As a result, pertussis prevention is a key driver in the design of the National Immunisation Schedule. The primary aim of a pertussis immunisation programme is to reduce the risk of severe pertussis, particularly in infants in whom pertussis-associated morbidity and mortality is the greatest.

There are several challenges around pertussis vaccination, since neither the currently available pertussis vaccines nor infection with wild-type *Bordetella pertussis* seem to induce long-lasting protection.[64]

As stated 30 years ago by the former director of the Pertussis Reference Laboratory in the UK - *'[There] must be few medical subjects that have generated so much controversy and even outright contradiction, as pertussis.'*[65] This comment stills holds true, and even more so, because it was made before development of acellular vaccines.

In 2000 in New Zealand, as in most high-income countries, whole-cell pertussis (wP) vaccines containing killed *B. pertussis* were replaced with acellular pertussis (aP) vaccines, which contain up to five antigenic virulence proteins. These aP vaccines are considerably less reactogenic than the wP vaccines, but appear to have lower effectiveness, are less able to prevent transmission, and induce shorter-lived immunity.[64] Prior to the switch to DTaP, DTwP vaccine had been used routinely in New Zealand since 1960.

This is a review of scientific literature published from 2016-2018, additional to literature around pertussis vaccinations already presented in a previous review of literature examining childhood immunisation scheduling in 2017,[37] and expanding on topics discussed in 2015 at workshop hosted by the Immunisation Advisory Centre and the Ministry of Health that discussed pertussis control strategies in NZ.[9, 66]

The aim of this review is to answer key questions relevant to better pertussis control and the best options for the Schedule in NZ. It is not a systematic review, not all the aspects of pertussis immunisation have been reviewed, and cost-benefit analyses are not considered. Since wP vaccines are not part of the NZ Schedule, this review will focus on aP vaccines only. Conclusions given represent the author and reviewer's interpretation and comprehension of the literature.

### 1.1 Pertussis-containing vaccines licensed in New Zealand

There are two main types of acellular pertussis-containing vaccines available – those containing full antigen doses of diphtheria toxoid, tetanus toxoid and acellular pertussis antigens (DTaP) and those with reduced antigen doses (Tdap). The number of *Bordetella pertussis* antigens can vary between vaccine brands. In New Zealand, a three-antigen pertussis vaccine is available as part of the Schedule containing detoxified pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). These vaccines are used in children under the age of 7 years as part of the primary series or as early boosters, and are given in combination with other vaccines to reduce the numbers of injections required at any

one time, including inactivated poliovirus (IPV), hepatitis B (HepB) and conjugated *Haemophilus influenzae* type B (Hib) vaccines.

Reduced antigen formulations are available as booster doses from 7 years of age. These contain tetanus toxoid and reduced doses of diphtheria toxoid and pertussis antigens (Tdap). They are also used as part of a catch-up primary series for unimmunised individuals from 10 years of age. Three-antigen and five-antigen (with additional FIM2/3 antigens) acellular pertussis vaccines are available. Also available in some countries are TdaP vaccines that contain higher pertussis antigen content than the Tdap vaccine in New Zealand.

The pertussis vaccines licensed for use in New Zealand are listed below and described in Table 1. [67-70]

| **DTaP combinations** | |
|---|---|
| **Infanrix-hexa®, GSK**<br>DTaP-IPV-HepB-Hib | **Three pertussis antigens**<br>Combined diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type B vaccine (DTaP-IPV-HepB/Hib), containing ≥30IU DT, ≥40IU TT, 25µg PT, 25µg FHA, 8µg PRN, as well as HepB surface antigen, IPV types 1, 2 and 3, Hib-PRP conjugated to TT. |
| **Infanrix-IPV®, GSK**<br>DTaP-IPV | Combined diphtheria-tetanus-acellular pertussis and inactivated poliovirus vaccine (DTaP-IPV), containing ≥30IU DT, ≥40IU TT, 25µg PT, 25µg FHA, 8µg PRN and IPV types 1, 2 and 3 |
| **Tdap combinations** | |
| **Boostrix®, GSK**<br>**Boostrix®-IPV** | **Three pertussis antigens**<br>Combined tetanus, reduced antigen dose of diphtheria and three-component acellular pertussis vaccine (Tdap) containing ≥2IU DT, ≥20IU TT, 8µg PT, 8µg FHA and 2.5µg PRN adsorbed 0.5mg aluminium and suspended in isotonic sodium chloride. A formulation combined with IPV is also available for catch-up. |
| **Adacel®, Sanofi-Pasteur**<br>**Adacel®-Polio** | **Five pertussis antigens, private market only**<br>Combined five-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids (Tdap) containing ≥20IU TT, ≥2IU DT, 2.5µg PT, 5µg FHA, 3µg PRN and 5µg FIM2/3 adsorbed with 0.5mg aluminium. Also available is a formulation combined with IPV types 1, 2 and 3. |
| Abbreviations: DT – diphtheria toxoid; FHA – filamentous haemagglutinin; FIM2/3 -fimbriae types 2 and 3; GSK – GlaxoSmithKline; IU – international units; HepB – hepatitis B, Hib – *Haemophilus influenzae* type B; IPV - inactivated poliovirus; PRN – pertactin, PRP - polysaccharide polyribosylribitol phosphate; PT – pertussis toxin; SSI - Statens Serum Institut | |

***Table 1: Pertussis-containing vaccines available in New Zealand, October 2018. (Source: Medsafe)***

# 2 Epidemiology

## 2.1 New Zealand epidemiology

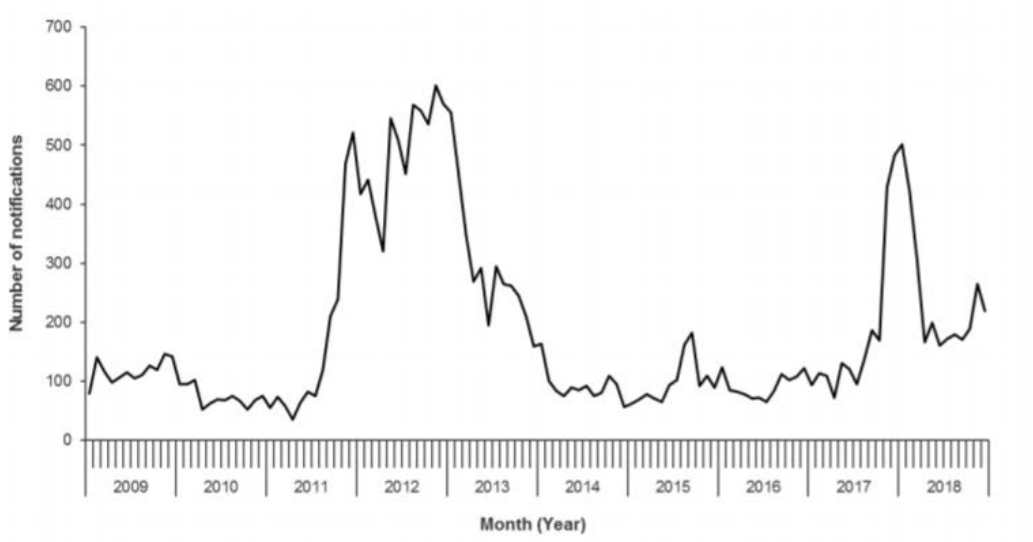
Epidemics of pertussis occur every 3-5 years in New Zealand and elsewhere. During the more recent epidemic from 2011-2014, several hundred infants were hospitalised and three infants aged under 6 weeks died. In response, in 2013, pregnant women were encouraged to be vaccinated in the third trimester (weeks 28-38 of gestation). However, uptake of this vaccine has been slow and the data around maternal vaccinations is limited.

he focus of the current National Immunisation Schedule is to protect infants too young to be immunised and to protect immunised infants when they are most vulnerable, particularly those of Māori and Pacific ethnicity, who continue to be at high risk of severe disease. The most recent epidemic was declared as of 16 October 2017. Pertussis notifications since 2009 are shown in Figure 1. From October to December 2017, 967 cases of pertussis were notified (576 confirmed, 367 probable and 24 suspect). During 2017, there were a total of 2,101 cases; 127 were in infants younger than 1 year, of which 66 (52%) were hospitalised. The highest rates were reported in infants (214.4/100,000) and children aged 5-9 years (90.3/100,000).[2] Although it is a notifiable disease, many more less severe cases in older children and adults are likely to be circulating disease within the community.

From 1 January 2018 to 31 December 2018, a further 2,943 cases were notified (56.5 cases per 100,000 population) and in total, 222 cases (7.5%) were hospitalised. Of the notified cases, 181 (6.2%) were infants younger than 1 year of which 93 cases (51.4%) were hospitalised, as presented in Table 2. The highest rates were seen in infant cases <1 year of Māori and Pacific ethnicities (515.8 and 525.8 per 100,000, respectively), while the highest rates in children aged 1-4 years were European and Other (194.5/100,000) and Māori (135.1/100,000).[1]

It has not been determined yet what effect the introduction of antenatal vaccination has on the incidence and severity of pertussis in infants in New Zealand.

***Figure 1: Number of pertussis notifications by month and year, January 2009 - December 2018. (Source: ESR)***




Note: Includes confirmed, probable, and suspect cases only. Cases still under investigation are excluded.

| Age group (years) | Total | | | Hospitalised | | |
|---|---|---|---|---|---|---|
| | December | 2018[1] | Rate[2] | December | 2018[1] | Percent[3] |
| <1 | 13 | 181 | 298.8 | 11 | 93 | 51.4 |
| 1-4 | 27 | 368 | 150.0 | 0 | 27 | 7.3 |
| 5-9 | 35 | 408 | 125.0 | 1 | 6 | 1.5 |
| 10-14 | 28 | 307 | 101.9 | 1 | 3 | 1.0 |
| 15-19 | 14 | 191 | 60.3 | 0 | 4 | 2.1 |
| 20+ | 102 | 1488 | 42.0 | 11 | 89 | 6.0 |
| **All ages** | **167** | **2275** | **61.4** | **24** | **222** | **7.5** |

[1] Cumulative total Jan – Dec 2018

[2] Rate per 100,000 population calculated using 2017 mid-year population estimates

[3] Percentage of notified cases for January to December that were hospitalised

***Table 2: Number of (confirmed, probable and suspect) pertussis notifications, rates and hospitalisations by age group, January-December 2018 (Source: ESR)***

# 3 Maternal vaccination

## 3.1 Background

In recent years, the main focus for pertussis prevention in infants too young to be immunised has been through passive immunity by giving maternal booster doses of tetanus-diphtheria and acellular pertussis (Tdap) vaccines during pregnancy. In this way, the infant is provided temporary protection until fully immunised through their own vaccinations. By vaccinating during pregnancy, infants are protected by both passive antibody transfer from the mother and also by reducing the risk of the mother acquiring the infection and passing it to her baby. Mothers have been shown to be a significant source of pertussis infection to their infants.(6)

A study that analysed routine surveillance data from 1997 to 2014 in Queensland, Australia, found that the highest pertussis disease burden, prior to the introduction of the maternal vaccination programme, was in early infancy (younger than 4 months of age) and women of child-bearing ages (15-45 years). Therefore, maternal vaccination is likely to provide dual benefit to both of these groups.(4)

Considerable research has been conducted both internationally and in New Zealand to assess the immunity, safety and effectiveness of giving pertussis booster vaccinations to pregnant women to protect their infants. This section will review some of this work.

Maternal pertussis vaccinations (with Tdap) from 28 to 38 weeks gestation have been funded as part of the National Immunisation Schedule since 2013 in NZ. The uptake has been slow and difficult to monitor due to the way claims for funded vaccine were made in primary care. Maternal vaccination is now recorded on the National Immunisation Register, but the accuracy of the data entry for pregnancy vaccination is currently unclear. In NZ, maternity care is predominantly midwife-led, often with independent midwives rather than midwives associated with a general practice, whereas the delivery of the vaccine is predominantly through general practice. As a result, mothers are less likely to access vaccination services provided by their general practice during their pregnancy. Estimates

suggest that uptake ranges from 13% - 44%.[7-9] However, awareness and acceptance of vaccinations during pregnancy have been gradually increasing.

In the light of the current pertussis outbreak, it is especially important to consider the influence maternal pertussis vaccination will have on the incidence and severity of pertussis in infants, particularly those under 6 months of age.

The role of maternal immunisation in protecting infants against disease prior to the commencement of their primary immunisation is being recognised internationally. A 2017 systematic review of the literature published during 2011-2016 demonstrated an increasing body of evidence to support pertussis vaccination in pregnancy to reduce pertussis morbidity and mortality in young infants in terms of safety (based on 10 papers), immunogenicity (14 papers) and effectiveness (two papers).[5] Some of the most recent literature is presented here.

## 3.2 Safety of maternal vaccination

A major consideration of vaccinating in pregnancy is the safety of the fetus and birth outcomes. There is no plausible biological reason for aP vaccines or Tdap vaccines to be unsafe when given in pregnancy, because only the IgG antibodies induced by the vaccine, and not the vaccine components, are passed across the placenta to the fetus. However, it is important to assess this fully.

### 3.2.1 Pregnancy outcomes

In studies conducted by the University of Auckland and collaborators, the safety of pertussis immunisation in pregnancy and pregnancy outcomes have been assessed in New Zealand following immunisation with Tdap (Boostrix) during weeks 28-38 of gestation.

No biologically plausible adverse maternal outcomes were detected following Tdap immunisation in pregnancy in New Zealand. A national retrospective observation study, the Pertussis Immunisation in Pregnancy Study (PIPS), was conducted using linked administrative datasets for a cohort of 68,550 vaccine-eligible women during 2013, of which 8,178 (11%) were vaccinated. The study found no unexpected safety risks associated with Tdap vaccination. A protective effect was observed for pre-eclampsia with severe features, preterm labour, preterm delivery and antenatal bleeding.[8]

PIPS found no association between receipt of Tdap and gestational diabetes mellitus, fetal growth restriction, placental abruption, chorioamnionitis, labour dysfunction, fetal distress, post-partum haemorrhage, maternal fever during or after labour, C-section delivery, maternal sepsis, anaemia or neurologic disorders. An increased risk of lactation disorders and perineal tears were observed and considered likely to be attributed to residual confounding, such as differential healthcare among vaccinated and non-vaccinated women. Vaccinated women were disproportionately European, had higher incomes, obstetrician antenatal care, and were more likely to have differential health-seeking behaviours or the likelihood of receiving interventions than unvaccinated women.[11]

### 3.2.2 Infant outcomes

When the infant outcomes were considered as part of PIPS, no safety concerns were identified in infants of women who were vaccinated in pregnancy.[8] There was a protective effect of Tdap exposure against low birth weight, small-for-gestational age, and moderate to later preterm birth, and it was associated with a higher mean birth weight. Maternal Tdap exposure in pregnancy did not affect sepsis or infection in the newborn, asphyxia, microcephaly, deformities of the feet or infant Apgar score. Infant exposure to Tdap during

pregnancy was associated with a higher risk for ankyloglossia ('tongue-tie'), which may be associated with the observed increase in diagnoses related to concerns over lactation disorders. These are likely also to be attributed to residual confounding and differential health-seeking behaviours of vaccinated women with a greater likelihood of receiving interventions than unvaccinated women.[11]

During 2012-2014, a small prospective observational study (Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy [SMART-VIP]) was conducted in the Canterbury region of NZ. Infants were followed for between 6-12 months after birth. When compared with the baseline population, no significant differences in birth weight, gestational age at birth, congenital abnormalities or infant groups were detected in infants of mothers who received Tdap in pregnancy. No cases of pertussis occurred in this cohort despite high rates of disease in the community at that time.[71]

### 3.2.3 Vaccination response in pregnancy

Tdap was concluded to be equally well-tolerated in pregnant and non-pregnant women. An observational study was conducted in the US to compare injection-site and systemic reactions following receipt of Tdap in 374 pregnant (gestational age 20-34 weeks, median age 28.9 years) and 225 non-pregnant women (median age 28.3 years). Fewer than 3% reported severe local or systemic reactions or any fever. Significantly more pregnant women reported moderate to severe injection site pain compared with non-pregnant, but did not seek medical attention (17.9% vs 11.1%). No other moderate or severe systemic or local reactions differed significantly between the women who were pregnant or not. Prior Tdap receipt did not increase moderate to severe local or systemic reactions in pregnant women.[10]

### 3.2.4 Summary of vaccine safety in pregnancy

No safety concerns have been identified for pregnant women, their fetuses or their infants following vaccination during pregnancy with Tdap. The severity of injection site pain was increased in pregnant compared with non-pregnant women, but medical attention was not required.

Tdap exposure was associated with some protection against low birth weight, small-for-gestational age, moderate to later preterm birth and was associated with a higher mean birth weight. Residual confounding related to health-seeking behaviour of vaccinated mothers is also likely to be associated with improved infant outcomes.

Although, documented lactation disorders and ankyloglossia were increased in infants of vaccinated mothers, this was not thought to be as a direct result of vaccination; rather, the health-seeking and socioeconomic status of the mothers who chose to be vaccinated.

## 3.3 Immunogenicity of vaccination in pregnancy

### 3.3.1 Maternal antibody levels

A study in Canada found that most infants born to mothers not vaccinated in pregnancy would receive little or no passive protection from maternal antibodies. Although there is no established antibody correlate of protection for pertussis, based on the WHO Standard Pertussis Antiserum (National Institute for Biological Standards and Control) code: 06/140, a cut-off of anti-PT IgG ≤35 IU/ml was considered negative for pertussis protection and >45 IU/ml considered to be positive and consistent with exposure through infection or vaccination. When anti-PT IgG titres were measured in plasma samples from 1,752 women in the second trimester of pregnancy (gestation weeks not defined), almost all (97.5%) had

no serological evidence of recent pertussis infection or vaccination, and nearly half (43.6%) had antibody titres below the assay limit (geometric mean titre 5.5 IU/ml, range 0-154 IU/ml). Only 31 women (2%) had anti-PT levels ≥45 IU/ml suggestive of a recent infection or re-immunisation. The women were recruited as part of a larger study between 2008 and 2011 from ten Canadian cities.[3]

When the immunogenicity of Tdap vaccination was compared between pregnant (at 20-34 GW) and non-pregnant women in the US, the serological response to all vaccine antigens were robust and rose significantly above baseline for all antigens in both groups. However, post vaccination titres against PT, FHA, tetanus and diphtheria were significantly higher in non-pregnant women as compared with pregnant women ($p<0.01$), but not for FIM or PRN GMTs. Both pre- and post-vaccination antibody levels were lower among pregnant than non-pregnant women.[10]

Post-partum antibody levels were measured in women vaccinated with either Tdap or Td as part of a RCT in Canada. Mean gestation when vaccinated was 34.5 weeks with a mean interval of 5.2 (SD 1.3) weeks before delivery.[29] Antibody levels against all pertussis antigens peaked at delivery to 2 months post-partum, then decreased by just over 50% over the year post-partum. All remained significantly higher than pre-immunisation levels.

**Conclusions**

Pregnant women have a robust immunological response to Tdap during pregnancy. Since the levels of pertussis antibodies are below protective levels in most women, without vaccination few infants would receive sufficient passive immunity to protect against pertussis.

Anti-pertussis antibody levels wane rapidly within a year post-partum but remain higher than pre-vaccination levels.

### 3.3.2 Waning of post-partum antibody levels in infants born to mothers vaccinated in pregnancy

A study in Spain found that, due to the rapid decline in maternal antibodies after birth, it was important to start infant vaccination on time at 2 months of age. The study, which included 37 infants born in Spain to mothers who were vaccinated with Tdap between 21 and 38 weeks of gestation, found that anti-PT IgG geometric mean concentrations (GMCs) declined significantly from 52.7 IU/ml (95% CI 34.7-80.2) in cord blood to an estimated 7.5 IU/ml (4.2-13.3; $p<0.001$) at 2 months of age. The median half-life of maternal antibodies was 47 days and it was estimated that 51.4% of infants would have detectable anti-PT IgG before the start of their primary vaccinations at 2 months of age – the presence of antibody at 2 months was significantly influenced by higher cord-blood concentrations ($p<0.001$).[16]

In Mexico, a double-blind parallel group RCT evaluated the safety and immunogenicity of Tdap in 171 pregnant women and their children (90 received Tdap and 81 controls received saline placebo). Six blood samples were collected immediately prior to and 4 weeks after Tdap vaccination or placebo given at 30 to 32 weeks gestation, from umbilical cord blood and from infants of the participants at 2, 4 and 6 months of age prior to administration of routine pentavalent DTaP-IPV/Hib vaccine.[17] Except for samples taken prior to vaccination, anti-pertussis levels were significantly higher in vaccinated mothers and their infants up to 2 months of age than in the control group mothers and infants. Figure 2 and Figure 3 (see section 3.3.4) show a decline in antibody levels was observed from birth (cord blood) to 2 months of age with a ratio of 1.78 for anti-PRN IgG and 2.5 for anti-PT IgG. Since the antibody titres required for protection against pertussis is undefined, it is unclear whether the levels of remaining antibody in these infants are sufficiently protective. There was a sharp decline in anti-PRN IgG up to 6 months of age. There was no PRN response in either

group following infant vaccination - DTaP vaccine used in Mexico appears to only contain pertussis toxin, not PRN antigens.[72]

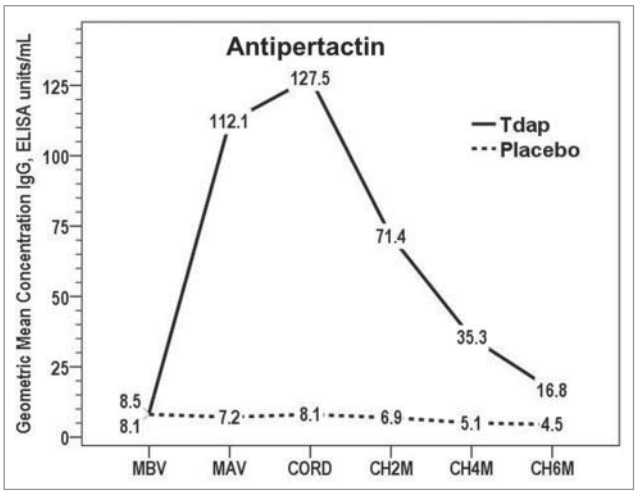



***Figure 2: Anti-pertactin IgG antibodies in maternal and infant serum. (Reproduced with permission, Villarreal Perez, 2017)***
***MBV – mother before Tdap or placebo vaccination; MAV – mother after vaccination; COR – umbilical cord; CH2M, CH4M, CH6M – child at 2, 4, 6 months of age prior to routine immunisations***

**Conclusions**

Maternally-derived antibody levels in the newborn decline rapidly after birth and particularly after 2 months of age. Depending on the concentration of antibodies at birth, infants may have insufficient levels of pertussis antibodies to provide protection against the disease after 2 months of age.

### 3.3.3 Effect of timing of maternal immunisation on infant pertussis antibody levels

The timing of maternal immunisation is important to consider - to balance the waning of anti-PT antibody in the mother with the accumulation of sufficient antibody to protect the newborn for the first few months of life. Preterm infants may not acquire sufficient antibody or may be born before the mother has been vaccinated, whereas vaccination too early in pregnancy may result in insufficient antibody levels at birth in full-term infants.

When vaccination is considered within the third trimester, as recommended in many countries, the optimum timing is unclear. One study in the US did not find that antibody concentrations in cord blood varied significantly by gestational age at vaccination, when given between 27-36 weeks. Cord blood anti-PT IgG (at ≥10 EU/ml) were achieved in 87% and 97% of those vaccinated at 27-30 weeks and 31-36 weeks of gestation (p=0.13), respectively. The study enrolled 88 pregnant women in New York who were vaccinated with Tdap (Adacel).[19]

However, another US study based in Texas found that immunisation early in the third trimester was associated with the highest antibody concentrations. This prospective observational cohort study investigated the cord blood anti-PT antibody levels from mothers vaccinated with Tdap (vaccine brand not disclosed) during pregnancy weeks 27 to 36. The peak in cord blood GMC was seen when vaccination was given at week 30. GMC of anti-PT antibodies slightly increased from 27 to 30 weeks (slope estimate 0.04; p=0.58), were highest when Tdap was administered during weeks 27-30, and thereafter declined significantly (slope -0.05, p=0.01). In a post hoc analysis, comparing those mothers vaccinated in 27–31 weeks gestation to those vaccinated in 32-36 weeks, the adjusted GMC ratio (adjusted for maternal age, ethnicity and gestation at delivery) was 1.4 (1.1-1.8; p=0.007).[20]

A comparison between vaccination in the second and third trimester was made as part of a prospective observational study conducted in Switzerland between July 2014 and February 2016. Cord blood samples were collected from term and preterm neonates of mothers who had received Tdap during the second trimester (weeks 13 – 25 of gestation) or according to Swiss recommendations in the third trimester from 26 weeks gestation.[21, 26]

The study found that earlier, second trimester maternal Tdap immunisation (from 13 to 25 weeks gestation) significantly increased anti-PT and anti-FHA IgG antibodies in neonates born at full term ($p<0.001$ for both antigens), as compared with vaccination after 26 weeks gestation: anti-PT 57.1 EU/ml (95% CI 47.8-68.2) versus 31.1 EU/ml (25.7-37.7); anti-FHA 284.4 EU/ml (241.3-335.2) vs 140.2 EU/ml (115.3-170.3). The expected infant seropositivity rates (defined as anti-PT IgG at birth of >30 EU/ml, with antibody persistence >5 EU/ml at 3 months) were significantly higher following second trimester (80%) compared with third trimester (55%) vaccination, and with an adjusted odds ratio of 3.7 (95% CI 2.1-6.5; $p<0.001$). The full-term infant part of the study included 122 mother-infant pairs immunised in the second trimester and 213 pairs immunised in the third trimester.[21]

Based on this study, the Joint Committee on Vaccination and Immunisation in the UK advised that maternal pertussis vaccination be offered between 16 and 32 weeks of gestation from 1 April 2016.[22] This timing coincides with the routine 20-week ultrasound scan.

#### *3.3.3.1 Premature infants – timing of maternal vaccination*

As part of the Swiss study described above, birth antibody levels in the preterm infants were also significantly higher for both anti-PT and anti-FHA antibodies following vaccination in the second trimester (at 13-25 weeks gestation) compared with vaccination in the third trimester (after 26 weeks): anti-PT IgG 41.3 (95% CI 29.6-57.5) vs 22.1 EU/ml (14.3-34.2), $p=0.024$; anti-FHA IgG 201.1 (149.7-270.1) vs 120.2 (80.6-179.2) EU/ml, $p=0.040$. None of the 37 preterm infants born to mothers immunised in the second trimester were seronegative. Eleven out of 48 infants born following third trimester immunisation were seronegative, 38% of these infants were born at between weeks 30-33 of gestation and 20% were born at 34-36 weeks. The study concluded that, although placental antibody transfer has been established as being most efficient during the third trimester, a longer transfer time appears to result in a greater accumulation of antibody in the fetus. To maximise maternal-fetal antibody transfer, a 15-day interval was sufficient to observe significantly higher cord antibody titres in the preterm population.[26]

In a UK-based study, IgG concentrations in infants at 2 months of age were positively correlated with the number of days between maternal vaccination and delivery. Anti-PT IgG increased 4% per day (95% CI 1-6%; $p=0.011$) and anti-FHA increased 7% per day (95% CI 3-10%; $p=0.001$) in infants born prematurely at 28-35 weeks gestation to mothers who were vaccinated during the third trimester (Tdap-IPV was routinely offered from 28-34 weeks gestation; median interval between vaccination at delivery was 24 days [interquartile range 9-35 days]).[23] Compared with premature infants of unvaccinated mothers, infants of vaccinated mothers had significantly higher pertussis, diphtheria and tetanus antibody levels at 2 months of age, prior to their first vaccinations ($p<0.001$). In this UK-based study, 31 out of 160 premature infants were born to mothers who received Tdap-IPV in pregnancy.[23]

**Conclusions**

Particularly to extend protection to infants born prematurely, maternal vaccination in the second trimester is suggested. Antibody is transferred and accumulates from at least 13 weeks gestation.

Infants born prematurely benefit from maternal vaccination when given early in the third trimester and have significantly higher anti-pertussis, tetanus and diphtheria antibody levels to at least 2 months of age as compared with premature infants of unvaccinated mothers. The longer the time between vaccination and delivery the greater the protection achieved. One study found that more infants are seropositive for up to 3 months after birth if their mothers were vaccinated before 26 weeks gestation than those vaccinated after (80% vs 55%).

However, the longevity of the maternal antibodies in the mother and the infant is unclear. If the antibody response is induced as early as 16 weeks, it is unknown whether there are sufficient levels to continue to protect full-term infants in the first months of life, as compared with when vaccination occurs later in the pregnancy.

Vaccination late in the third trimester (after 34 weeks) results in less antibody transfer than when given earlier. Despite this, it is likely better to vaccinate the mother at least 2 weeks before delivery than to risk her infant being born with no passive pertussis protection.

Due to waning maternal pertussis antibody levels in the infant - even in infants of vaccinated mothers - it appears necessary to commence the primary series by 2 months of age.

### 3.3.4 Interference of infant pertussis immune response to primary series

A review of ten studies that assessed laboratory markers of pertussis responses following primary vaccination schedule of infants showed evidence of lower response to one or more pertussis antigen in infants of vaccinated mothers.[28]

In one reviewed study of premature infants born to mothers who had been vaccinated with Tdap (from 28 weeks gestation), IgG GMCs were significantly higher at age 2 months against pertussis antigens, tetanus and diphtheria prior to primary vaccination (DTaP-IPV-Hib [Pediacel®] at 2, 3 and 4 months), although after completion of the primary course, antibodies to FHA and diphtheria were significantly lower at age 5 months. As part of the UK immunisation schedule, these infants also received MenC-CRM and PCV-13 vaccines concurrently.[23]

However, no evidence of clinically significant blunting was found in the US and England in the first year of life after maternal vaccination and primary infant doses (starting at age 2 months).[13, 28]

A, RCT in Canada (as described in section 3.3.1) found that infants of mothers who received Tdap in pregnancy had significantly higher PT antibody levels at birth and at 2 months of age, and significantly higher FHA, PRN and FIM antibody levels at birth, age 2 and 4 months, but significantly lower pertussis antibody levels at age 6 and 7 months, than infants whose mothers had received Td in pregnancy ($p<0.001$, for each).[29] These differences persisted for PT, FHA and FIM antibodies until 12 months of age and 1 month after a 12-month booster. Infants of Tdap vaccinated mothers had higher diphtheria antibody levels at 6 months and tetanus antibody at 12 months ($p=0.043$ and 0.039, respectively). The clinical relevance of these blunted responses to primary immunisations is not clear, but could lead to increased risk of pertussis from the second half of the first year of life or later. A total of 272 infants were born to mothers who received either Tdap or Td at an average of 34.5 weeks gestation (on average 5.2 weeks prior to delivery). The infants were vaccinated according to the Canadian immunisation schedule 2-4-6 months of age and a booster was given early at 12 months instead of 18 months.[29]

A blunting effect against pertussis was observed in a study in England, in which the immune responses to primary series vaccines were investigated in infants of TdaP-IPV-vaccinated mothers (Repevax®, 5-component aP). Infants ($n=141$) were vaccinated with $DTaP_5$-IPV-

Hib-TT (Pediacel®) vaccine at 2, 3 and 4 months. Immune responses were compared with a historical cohort of infants born to mothers not vaccinated in pregnancy. Infants of vaccinated mothers had high pertussis antibody levels pre-immunisation, but only PT antibodies increased post-immunisation and FHA antibodies fell. Antenatal pertussis vaccination blunted subsequent responses in infants to pertussis vaccine, but at levels not considered to affect disease control.[30]

In the Mexican RCT (mentioned above in section 3.3.2), apparent interference was observed between maternal antibodies and the production of anti-PT antibodies in response to DTaP in the infants of Tdap-vaccinated mothers when compared with mothers given placebo controls. A lower, or possibly delayed anti-PT response to DTaP was observed at 4 and 6 months of age than was seen in controls (Figure 3).[17]

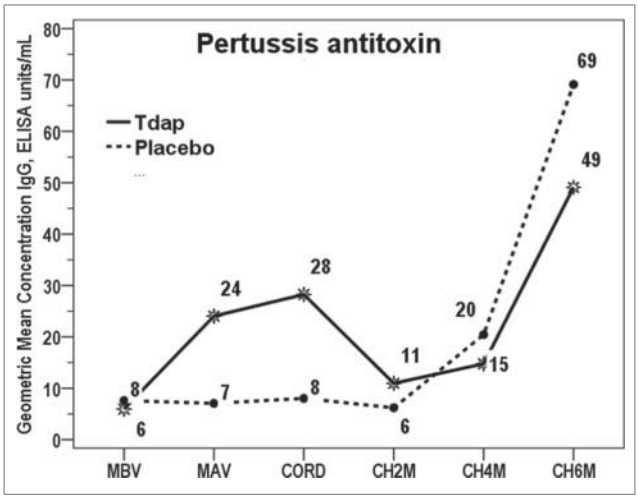



***Figure 3: Anti-pertussis toxin IgG in maternal and infants pairs. (Reproduced with permission, Villarreal Perez, 2017)***
***MBV – mother before vaccination; MAV – mother after vaccination; COR – umbilical cord; CH2M, CH4M, CH6M – child at 2, 4, 6 months of age prior to routine immunisations***

Based on animal studies, further evaluations of the effect of maternal antibodies may consider using different vaccine formulations for the maternal and infant doses to overcome the apparent loss of antibody function seen when the same vaccine is used. When mother and infant mice were immunised with two different vaccines, infant vaccination was not found to interfere with the protective effects of maternal antibodies. This interference did not affect antibody titres, rather infant vaccination reduced the protective functions of the maternally–derived antibodies in vitro and in vivo.[34]

A recent publication (published 2019) investigated the antibody responses to primary vaccinations in infants born to mothers who were vaccinated in pregnancy compared with those unvaccinated in pregnancy (31 mother-infant pairs in total). The results from the prospective cohort study in the UK supported maternal immunisation as a method of protecting infants for their first few weeks of life. Infants from Tdap vaccinated mothers had significantly elevated antibodies to all Tdap antigens at birth and at 7 weeks of age (prior to primary series at 8 weeks) compared with infants of mothers unvaccinated in pregnancy. Following primary pertussis immunisations (at 8, 12 and 16 weeks of age), the antibody levels in infants were also comparable between groups. Vaccination in pregnancy did not effect the half-life of Tdap antibodies in the infant compared with those that were present from previous vaccinations or exposure.[73]

#### *3.3.4.1 Response after toddler dose*

At one month after administration of DTaP at 15 months of age (following Belgian primary schedule at 8, 12, and 16 weeks), the GMC of anti-PT Ig G was significantly lower in infants of vaccinated mother (Tdap [Boostrix] in weeks 18-34 gestation) compared with control

groups (not vaccinated against pertussis for at least 10 years; p=0.006) and non-significantly lower for diphtheria and FHA antibodies, whereas, tetanus and PRN antibodies were non-significantly higher in the vaccinated group. Following the booster dose, the only significant difference in antibodies observed after one month were significantly higher titres of anti-PRN IgG (p= 0.001) in the vaccinated group.[32]

As part of a spin-off study of above, the influence of maternal vaccination on the avidity (strength of binding to antigen) of pertussis antibodies in infants following their primary series was analysed. Avidity is used to assess priming of immunological memory and antibody maturation. The avidity of IgG against diphtheria toxin (DT), tetanus toxin (TT), pertussis toxin, FHA and pertactin was measured one month before and one month after dose four of DTaP vaccination at age 15 months. The study included 55 infants born to mothers vaccinated in pregnancy with Tdap and 26 infants born to mothers not vaccinated. Prior to the fourth dose, there was no significant difference in the avidity of any of the vaccine-specific IgG between the groups (relative avidity index between 40-60% for TT, PT, FHA and PRN, less than 40% for DT). Although it increased in both groups, the avidity of PT-specific IgG was significantly lower after the fourth dose in infants born to vaccinated mothers (68.1% vs 78.7%; p<0.003). Since there is no defined levels of protection for pertussis or data around the functional properties of these antibodies, the clinical relevance is unknown.[33]

In a review described previously, four studies found that lowered pertussis components in maternally vaccinated infants were no longer significant following a booster dose in the second year of life, suggesting that long-term protection was not compromised.[28]

**Conclusions**

The presence of maternal antibodies may affect the immunogenicity of infant pertussis vaccinations. However, it is unclear whether there is any clinical relevance in terms of pertussis protection for infants born to mothers vaccinated in pregnancy.

The studies to date have predominantly investigated antibody responses when the first primary dose is given at 2 months of age. Some literature suggests that this blunting continues in to the second year of life. It is especially relevant to consider the role of the presence of maternal antibodies in blunting the infant primary immune response in relation to pertussis control in infants in the NZ context, where the primary infant series commences before 2 months at 6 weeks of age and no toddler booster is given.

### 3.3.5 Interference with the immune response of other schedule vaccines

Maternal antibody concentrations in infants and the timing of infant immunisations can influence infant vaccine responses. In a meta-analysis, de-identified immunogenicity data were obtained from serum collected during 32 GSK-sponsored clinical trials of licensed and unlicensed vaccines that were administered to more than 7,600 infants in 17 countries across Africa, Australia, East Asia, Europe, Latin America and Russia. Antigen-specific antibody concentrations were compared prior to priming vaccinations (given according to four schedules at 6-10-14 weeks, 2-3-4 months, 2-4-6 months or 3-4-5 months), one month after priming, and before and after booster vaccinations. Pre-existing maternal antibodies inhibited infant antibody responses to priming doses for 20 out of 21 primary series antigens. Children who were vaccinated at an older age had higher antibody responses to priming doses for 18 to 21 antigens after adjusting for maternal antibody concentrations (ranging from 10-71% higher per month older; 15% per month for ant-PT antibodies). The largest effect was seen for IPV with two-fold higher pre-existing antibody resulting in 20-28% lower post-vaccination geometric mean ratios. For pertussis antigens, two-fold higher pre-existing antibody was associated with 11% lower post vaccination

antibody against PT and FHA and 22% lower anti-PRN antibody. Models showed that an inhibitory effect in infants of two- to five-fold increase in maternal antibodies due to prenatal immunisation can be offset by a delay in primary vaccination of between 2.2 and 5 weeks (pertussis 2.2 to 5.04 weeks, diphtheria 2.6 to 5.9 weeks and tetanus 1.7 to 3.9 weeks). It was noted that the clinical relevance was not known and these data were obtained prior to the introduction of routine maternal immunisation programmes. None-the-less, this meta-analysis study found that the effects of maternal antibodies and the infants' age at the start of the primary series are not only observed in response to the pertussis priming series, but for many antigens, continue to affect antibody responses to booster vaccinations given at 12-24 months. Hence, the quality of the immune response to the first dose of antigen is suggested to be of importance.[31]

As well as an observed blunting effect against pertussis, a study in England also observed blunting in the immune response to primary series vaccines against diphtheria and diphtheria-derived CRM-conjugated antigens in infants of TdaP-IPV-vaccinated mothers (from 28 weeks gestation) compared with a historical cohort of infants born to mothers not vaccinated in pregnancy. Infants (n=141) were vaccinated according to the immunisation schedule with DTaP-IPV-Hib-TT vaccine at 2, 3 and 4 months, PCV-13 at 2-4 months and one or two doses of MenC-CRM or MenC-TT at 3-4 months of age. Following antenatal Tdap vaccination, infant antibody levels to diphtheria and some CRM-conjugated antigens (pneumococcal serotypes 3, 5, 9V and MenC-CRM given at 3 months) were significantly lower ($p<0.001$) than those of unvaccinated mothers, but in most infants antibodies achieved protective threshold levels and were not considered to adversely affect disease control. Antibodies against tetanus and Hib were higher in infants whose mothers had been vaccinated antenatally ($p<0.001$). This study favoured the use of TT-conjugated rather than CRM-conjugated vaccines in the infant programme or a tetanus-pertussis only vaccine for mothers.[30]

As part of a prospective controlled trial of Tdap vaccination in pregnancy conducted in Belgium, a blunting effect was observed after primary vaccination for some pneumococcal serotypes in infants of mothers who were vaccinated in pregnancy compared with controls. The GMC of antibodies against serotypes 1 3, 4, 5, 6A, 7F, 9V, 14 and 19A were significantly lower after two doses of PCV-13 given 8 and 16 weeks of age until 12 months of age in infants of mothers who received Tdap (mean gestation 28.8 weeks). Despite this blunting effect on antibody levels, there was no significant difference in the seroprotection rates between the vaccine and control group after primary or booster vaccination (except for serotype 3). The study concluded that in a Belgian setting, the clinical effect was likely to be low since protective antibody levels were achieved for almost all the serotypes and circulation of vaccine serotypes was almost non-existent.[35]

**Conclusions**

Infants born to mothers who were vaccinated in pregnancy have blunted antibody responses to primary vaccinations commenced after 8 weeks of age. The clinical relevance of this interference is not yet determined, and for most antigens with known levels of protection, antibody levels remain above seroprotective thresholds. Responses to poliovirus (when given Tdap-IPV in pregnancy), pertussis antigens and diphtheria or diphtheria-derived protein conjugates are most affected.

### 3.3.6 Potential role for an anti-pertussis toxin only vaccine in pregnancy

To overcome the risk that antibodies to the tetanus and diphtheria antigens in Tdap boosters might interfere with the infant primary series vaccinations, including the polysaccharide conjugated vaccines such as pneumococcal, Hib and meningococcal vaccines, a study in baboons used a monocomponent aP vaccine (containing pertussis toxin inactivated with hydrogen peroxide) in eight pregnant baboons and found it to be sufficient to protect young baboons against clinical pertussis disease when challenged at 5 weeks of age. It was found that the challenged infants were heavily colonised with *B. pertussis*, confirming that the presence of neutralising anti-PT antibodies can prevent the most severe symptoms associated with pertussis. The authors anticipate that human mothers with prior experience of pertussis vaccination or infection are likely to produce a stronger antibody response to the vaccine.[74]

### 3.3.7 Summary - immunogenicity of maternal vaccination and effect on infant immunity

Without antenatal vaccination, few infants would be born with any passive protection against pertussis. Since there is no defined correlate of protection for pertussis antibodies, immunogenicity studies do not inform clinical protection.

Pregnant women respond robustly to Tdap given during pregnancy. However, maternally-derived antibody declines rapidly in both the mother and the infant after birth. By four months, the levels in infants of vaccinated mothers are similar to infants of mothers not vaccinated antenatally. Depending on the concentration of antibodies at birth, infants may have insufficient levels of pertussis antibodies to provide protection against the disease until fully immunised.

Infants born prematurely can benefit from maternal vaccination given earlier than 26 weeks gestation or early in the third trimester, and have significantly higher anti-pertussis, tetanus and diphtheria antibody levels up to 2 months of age as compared with premature infants of unvaccinated mothers. Sufficient time between vaccination and delivery helps to increase the protection from passive transfer of antibody.

No recent literature was found that described the pattern of waning more than a few months after delivery in the mother. However, since maternal antibodies wane within a couple of months of birth, it is likely that levels in the mother during a subsequent pregnancy would not be sufficient to provide protection to another fetus and therefore, booster doses each pregnancy would be necessary. It may be beneficial to give pregnant women aP only vaccines, especially following a previous Tdap booster.

Passive protection from maternal antibodies needs to be balanced with interference with the infants' immunisations. The presence of maternal antibodies can affect the immunogenicity of infant primary series vaccinations, as has been shown for pertussis and diphtheria antibodies. However, the clinical relevance is unclear and it is unknown to what extent infants born to mothers vaccinated in pregnancy may have reduced disease control.

For the antigens with known correlates of protection, this blunting does not appear to reduce protection below protective threshold levels in most infants. The magnitude of this effect is likely to depend on the timing of the primary series and antenatal vaccinations. Data is limited to identify an optimum schedule.

A delay in the timing of the first dose of the primary series may overcome this effect somewhat, but may also put the youngest infants at higher risk of some other vaccine-preventable disease in their first 6 months.

## 3.4 Effectiveness of maternal vaccination in disease control

Maternal vaccination aims to control pertussis and reduce disease severity in infants prior to being fully immunised with their primary series vaccinations. The clinical relevance of the effect the presence of maternal antibodies may have on the infant immunisation is important to consider in terms of pertussis control. Recent data published in the last two years on the effectiveness of maternal pertussis vaccination are reviewed in this section.

Three years following the introduction of maternal pertussis vaccinations in the UK with TdaP-IPV vaccine, given after 28 weeks gestation and at least seven days before delivery, vaccine effectiveness (VE) against laboratory-confirmed pertussis has been sustained at 91% (95% CI 88-94%) in infants <3 months of age and 90% (86-93%) for infants aged <2 months. Maternal vaccination, given more than seven days before delivery, was shown to be 95% effective against infant deaths due to pertussis. There was no evidence of increased risk of disease after primary immunisation (at 2-3-4 months) for infants who received maternal vaccination. Maternal vaccination coverage was around 70%, with more than two-thirds receiving vaccine more than eight weeks prior to delivery. Additional protection was retained after the first infant dose at 2 months of age (VE 82%), VE declined to 69% after the second primary dose (at 3 months), but there was no evidence of additional protection after the third infant dose (at 4 months), although the numbers are small.[12]

Infants with pertussis aged less than 63 days had significantly lower risk of hospitalisation if their mothers had received Tdap during pregnancy (at 27-36 weeks gestation) compared with infants of mothers who were not vaccinated in pregnancy (unadjusted VE 72% [95% CI 49-85%] according to a retrospective cohort study conducted in California, US. When adjusted for chronological and gestational age and DTaP receipt ≥14 days prior to disease onset), VE was 58%. Hospitalised infants of vaccinated mothers were at a lower risk of intensive care unit admission and had shorter hospital stays (relative risk 0.5 [0.4-0.6] and 0.8 [0.7-0.9], respectively). The age cut-off for pertussis onset was set at 63 days as the first dose of DTaP was scheduled at 2 months of age. No infants of vaccinated mothers with pertussis died or required intubation.[15]

Another study conducted by the same research groups found that Tdap vaccination in pregnancy was 85% (33-98%) more effective than post-partum Tdap vaccination in preventing pertussis in infants less than 8 weeks of age. The cohort consisted of 74,504 mother-infant pairs, of which, 42,941 (58%) were vaccinated in pregnancy and 31,563 (42%) were vaccinated post-partum (representing 7.5% of the California birth cohort).[18]

A US-based retrospective cohort study, using healthcare service data from Kaiser Permanente North California, found that maternal Tdap was 91.4% (95% CI 19.5-99.1%) effective against pertussis in infants during the first 2 months of life and 69.0% (43.6-82.9%) effective during the first year of life. VE was 87.9% (41.4 to 97.5%) before any DTaP doses, 81.4% (42.5-94.0%) between doses one and two, and 6.4% (-165.1 to 66.9 [wide 95% CI due to low numbers]) between doses two and three, and 65.6% (4.5 – 87.8) after three primary doses. The data time period from 2010-2015 encompassed two pertussis epidemics. The study population included 148,981 infants born from 2010, and of these, 68,168 (45.8%) of the infants' mothers had received Tdap after 20 weeks of pregnancy. There were 110 laboratory-confirmed pertussis cases aged ≤1 year, including 17 cases aged ≤2 months.[13]

Most recent data in NZ comes from the Pertussis in Pregnancy Infant Outcomes (PIPIO) study (HRC grant reference 14/682), conducted at the University of Auckland, in which data from combined from several national health administrative databases in NZ were used to investigate the relationship between fetal exposure to maternal pertussis vaccination (given

during 28-38 weeks gestation) and pertussis disease in infants first 6 weeks and first 6 months of life (unpublished, presented in project report).[14] The large population-based retrospective cohort study found that the adjusted point estimate VE for protection from maternal vaccination against pertussis in the first 6 weeks of life was 71% (95% CI -115 to 96), and was consistent with other studies. Unfortunately this study was underpowered to achieve statistical significance for pertussis diagnosis at under 6 weeks of age. A repeat study is underway. A small additional protective effect of maternal vaccination was observed among infants who received ≥2 doses of routine vaccination up to 6 months of age.[14]

**Conclusions**

Tdap vaccination during the third trimester of pregnancy protects young infants under 8 weeks of age against pertussis as compared with infants born to mothers who were not vaccinated or those vaccinated post-partum. The effect declined with time until completion of the infants' primary series immunisation.

### 3.4.1 Timing of the maternal dose - effectiveness

A Californian study found that infants of mothers who received Tdap vaccination at 27-36 weeks gestation (in particular, from 27-31 weeks) were significantly less likely to have pertussis under the age of 12 weeks than infants whose mothers received Tdap during pregnancy, but outside of the 27-36 weeks window (OR 0.22 [95% CI 0.8-0.63]). The overall VE of Tdap at 27-36 weeks gestation was 85% (33-89%) for preventing pertussis in infants less than 8 weeks of age, and VE was 64% (11-85%) when vaccinated at any point in pregnancy, as compared with post-partum vaccination of the mother (adjusted VE 72% vs 53% against pertussis <12 weeks of age, respectively). The timing of Tdap in the second trimester (14-26 weeks) increased the odds of pertussis by 12 weeks of age compared with during the 26-36 weeks window (OR 4.60 [1.39-15.25] – based on 11 cases and 35,959 controls).[18]

A national cohort study in the US found that infants whose mothers received antenatal Tdap (up to 2 weeks prior to delivery) had a 43% lower rate of pertussis (HR =0.57 [0.35-0.92] and 68% lower risk of hospitalised pertussis (HR 0.32 [0.11-0.91]) than those whose mothers were not vaccinated or received Tdap postpartum. The cohort included 675,167 mother-infant pairs born during 2010-2014 (insured population). Pertussis rates were lowest for infants of mothers who received Tdap in the third trimester (from 27 weeks to at least 2 weeks prior to delivery; HR = 0.42 [0.23-0.78]. In comparison, in those whose mothers receive Tdap earlier than 27 weeks gestation, the rates of pertussis hospitalisations tended to be less, but the rates for any pertussis were not reduced (HR 1.10 [0.54-2.25]). However, it was noted that the number of cases born to mothers who received Tdap prior to 27 weeks was very small (ten cases [0.06%] hospitalised).[75]

In the UK, the VE of maternal vaccination on infant pertussis was shown to be 91% when given at least 28 days and 7-28 days before delivery, but for a small number of cases, VE declined to 43% (based on only three cases) when given 0-6 days before or 1-13 days after delivery.[12]

### 3.4.2 Preterm infants

It was found that preterm infants (born at before 37 weeks gestation in the UK) were at increased risk of being hospitalised with pertussis and benefited less than full-term infants (born after 36 weeks gestation) from maternal vaccination programmes starting at 28 weeks gestation. The effect of the introduction of maternal pertussis vaccination on pertussis infection and disease severity in preterm infants was considered in a UK based study. Hospitalised pertussis cases of infants aged <60 days, before they were eligible for primary vaccinations and admitted between April 2009 to March 2016, were compared pre and post-implementation of the maternal vaccination programme (which began in 2012 from 28 weeks gestation). During this time there were 13 infant deaths associated with pertussis, of which, five (38.5%) were born prematurely. A higher proportion of preterm infants were hospitalised with pertussis (138/1309, 10.6%) than the population estimate of 7.4% live births being born preterm, and this proportion increased from 9.8% (83/847) to 12.1% (56/462) following the programme implementation. Hospital stays of a longer duration were associated with prematurity, younger age, additional respiratory illness and mothers unvaccinated in pregnancy: mothers were vaccinated in 26.1% full-term vs 14.3% preterm cases [p=0.092]; in 14.3% of full-term cases the mothers were vaccinated after 35 weeks. The study concluded that mothers of preterm infants had reduced opportunity to be vaccinated (available from 28 weeks gestation at the time of the study), since the latest gestational age for vaccination of any preterm mother was 33 weeks.[24]

A cross-sectional population study in Australia's Northern Territory found that a significant proportion of preterm infants (66.5%) did not benefit from maternal vaccination starting at 28 weeks gestation (maternal coverage in 2016 was 48.9%). The mothers of infants born at term were twice more likely to have received antenatal Tdap than preterm births (aOR =1.97 [95% CI 1.53-2.50], p<0.0001). To maximise protection for all infants, the authors recommended the implementation of pertussis vaccination from 20 weeks gestation.[25]

Since 1 April 2016, the UK has recommended Tdap vaccination from 20 weeks of gestation and funded vaccine is available from 16 weeks gestation.[22]

### 3.4.3 Maternal antibody interference

There is evidence that the presence of maternal antibodies in infants of mothers who were vaccinated in pregnancy interferes with the immune response in infants to primary series immunisations and may lead to reduced effectiveness of the infant immunisation programme. Clinical data is limited.

Preliminary data from the PIPIO study in NZ suggest that the presence of maternal antibodies could interfere with infant immunity to pertussis following completion of the primary series when vaccinations are begun at an early age (scheduled to commence at 6 weeks in NZ rather than from 8 weeks as in the UK), potentially resulting in an increased risk of pertussis in infants after maternal antibodies have waned below protective levels. Funded by a PHARMAC-HRC partnership (HRC reference 18/773), an extension study designated PIPIO2 is underway to address this concern further within the NZ context.[27]

### 3.4.4 Protective role for maternal influenza vaccination

A potential role for inactivated trivalent influenza vaccination in pregnancy was identified to protect against pertussis by retrospective testing of pharyngeal specimens collected during 2011-2012 as part of an RCT conducted in South Africa. Enrolled participants were monitored for respiratory illness during pregnancy and for 24 weeks post-partum. A total of 3,125 specimens were tested for *B. pertussis*. Eleven vaccine recipients and 26 placebo recipients tested positive for pertussis (risk ratio 0.4 [95% CI 0.2-0.8]; p=0.012); the

overall risk ratio including indeterminate pertussis episodes was 0.5 (0.2-0.7; p=0.007). This post-hoc observation suggested that influenza vaccination may have a protective effect on the rates of pertussis infection in adult women and a possible synergy between the two pathogens.[44]

It is plausible that vaccinating both parents and other family members against influenza may also help to reduce the risk of the infant's exposure to *B. pertussis*.

## 3.5 Summary – maternal vaccination

Most women have no serological evidence of recent pertussis infection or vaccination, and around half do not have detectable anti-PT antibodies. Without antenatal vaccination, few infants would be born with any passive protection against pertussis toxin, the major virulence factor in pertussis disease.

The immune response in pregnant women to Tdap boosters is robust and generate good antibody responses. Vaccination of mothers during pregnancy provides passive immunity to infants for the first few months of life through IgG transferred across the placenta.

There are no safety concerns for the mother or her fetus following vaccination with Tdap in pregnancy.

The presence of maternal antibodies in the infant is protective against pertussis and severe pertussis at least until 2 months of age (VE >90%).

The optimal timing for the maternal vaccination has not yet been established. Too early risks maternal antibody levels waning, and too late gives insufficient time for antibody to be generated and transferred, particularly for infants born before 36 weeks gestation. A balance needs to be achieved between greater accumulation of antibody and the waning of antibody in the mother and the infant.

Based on the studies reviewed, the timing likely to provide the best protection for most preterm and full-term infants appears to be from 20 weeks to around 33 weeks of gestation (latter half of trimester two and first half of trimester three). Currently in New Zealand, the recommendations are for vaccination during weeks 28-38. However, the UK recently updated recommendations for vaccination from ideally 20 weeks, and as early as 16 weeks gestation, on the basis that a longer time between vaccination and delivery increases the antibody protection. Elsewhere, studies have found that the optimal time is from 27-31 weeks (early in trimester three). Although, this timing is preferred, infants of mothers vaccinated more than 7 days prior to delivery received sufficient antibody protection until 8 weeks of age (VE 91% against pertussis and 95% against pertussis death), therefore the current recommendation of up to 38 weeks is valid for most full-term deliveries.

There is limited literature around the protectiveness of maternal antibodies beyond the start of the primary series. However, these antibodies appear to create some interference with the infant immune response to their primary series vaccinations. This interference may be off-set by a delay in the commencement of the primary series. The clinical relevance has not yet been determined, particularly in the NZ context.

In the majority of studies presented, the primary series immunisations were initiated at 8 weeks or 2 months of age. It is especially relevant to consider the influence of maternal antibodies in the NZ context where the primary infant series currently commences earlier at 6 weeks of age. Although maternal vaccination has been shown to be protective against pertussis in infants under 6 weeks of age in NZ, unconfirmed data indicate that starting the immunisation schedule at this earlier age could result in greater, more clinically relevant

interference of the vaccine responses to the primary series. Timing at the start of the infant series for those who have received maternal vaccination may need to be delayed to at least 8 weeks reduce this risk and to allow more time for maternal antibody levels to wane.

For immunity against other vaccine-preventable diseases, this blunting of the immune response does not appear to reduce seroprotection below threshold levels in most infants for non-pertussis antigens with known correlates of protection. The magnitude of the blunting effect is likely to depend upon timing of the primary and antenatal vaccinations. Data is limited to identify an optimum schedule for pertussis or other vaccine antigens in light of maternal vaccination.

# 4 Approaches to address the gap between birth and primary immunisations

This section considers other options to improve the protection against pertussis, especially for the youngest infants before they are fully immunised with their primary series vaccinations in the absence of maternally transferred antibody protection.

## 4.1 Birth doses of pertussis vaccine

In the 1940s, whole cell pertussis vaccines given at birth were shown to interfere with vaccination responses to the primary course. When DTaP was given at birth in 2008, immune interference to subsequent vaccines was observed due to the diphtheria and tetanus antigens.[76]

More recently, a RCT in Australia used an investigational aP-only vaccine at birth and demonstrated good immunogenicity and higher antibody titres against PT and PRN at 10 weeks of age than those who had not received a birth dose.[38] The trial was conducted at four sites in Australia and involved 440 healthy full-term infants to compare the IgG antibody responses to vaccines at 6, 10, 24 and 32 weeks of age following vaccination at birth (up to 5 days of age) with three-component aP vaccine and HepB vaccine, or HepB alone. After stratification by maternal Tdap receipt during or prior to pregnancy, the infants were randomised to receive aP-only vaccine or not. The infants were also vaccinated according to the Australian Immunisation Schedule at 6, 16 and 24 weeks.[38]

Birth doses induced higher levels of anti-PT, PRN and FHA antibodies at 6 weeks of age in infants whose mothers had been vaccinated within 5 years of delivery. At 10 weeks of age, 192/206 (93.2%) of infants vaccinated at birth had detectable anti-PT and anti-PRN antibodies, as compared with 98/193 (50.8%) infants in the HepB only control group ($p<0.001$). Those vaccinated at birth had four-fold higher anti-PT IgG GMC than the control group.[38]

At 32 weeks of age, all the infants who received aP vaccine at birth had detectable anti-PT IgG. Those that received a birth aP dose had significantly lower GMC for Hib, HepB, diphtheria and tetanus antibodies than the control group, but the proportion of infants with antibody levels above protective thresholds were the same in both groups and no differences were detected for any pneumococcal serotypes. The highest anti-pertussis antibody levels at 32 weeks were among infants born to mothers who had not been vaccinated within 5 years in those given aP at birth, followed by the control group.[38]

The study concluded that a birth dose of aP-only vaccine has the potential to provide protection against severe pertussis among infants whose mothers were not vaccinated

during pregnancy with Tdap. The availability of monovalent pertussis vaccine may also be beneficial for the maternal vaccination programme where additional boosting against tetanus and diphtheria is not necessary.[38]

## 4.2 Timing of infant schedule

The WHO recommends that the first three doses of DTaP or DTwP be given before 6 months of age. Many developed countries follow a 3+1 or 2+1 primary series. It is recommended that the first dose be given from 6 weeks of age, ideally between age 6-8 weeks and the subsequent doses 4-8 weeks apart. As reviewed by Martinón-Torres et al (2018), in 2015 around 86% of infants globally received three doses of combined DTaP or DTwP vaccine with 130 countries achieving at least 90% coverage. However, a proportion of these infants did not receive the first dose within this time window.[77]

Since our previous literature review on the childhood schedule assessed the effect of delays in primary doses from older publications (pre-2016),[37] this section reviews only the most recently published data (from 2016-2018).

In summary, although there is no consensus as to what spacing is optimum for the infant schedule, timeliness is potentially important for disease control. Recommendations to start at 6 weeks of age may help enable earlier infant protection and to reduce any delay in the delivery of the first dose, which is offered at 8 weeks, 2 or 3 months of age in most high income countries.[37] In Australia, changing from age 8 weeks to 6 weeks was estimated to reduce annual pertussis notifications by 8% and hospitalisations by 9%.[39]

A mathematical model was used to compute pertussis transmission incidence for four infant immunisation schedules based on immunisation data from Argentina and Belgium (using DTwP and DTaP vaccines). The model did include a protective effect of maternal antibodies up to 6 weeks of age for a fraction of infants, but did not consider vaccination during pregnancy or blunting effects of the antibodies. The model also assumed protection from wP and aP vaccines was similar during the primary series. It found the highest reduction in incidence was achieved through a 6-10-14 week schedule, in which a 36% reduction pertussis incidence was reached in 0-1 year-olds when compared with a 2-4-6 month schedule. A significant decrease in severe pertussis incidence was shown when the first dose of the 2-4-6 months schedule was accelerated to 6 weeks of age. Lower incidences were also obtained by using a 2-3-4 months schedule in which 26% reduction in total incidence was predicted. A delay in the first dose to 3 months (3-4-5 months) increased the risk of severe pertussis by 9%, but reduced total pertussis by 10% up to 1 year of age.[40]

These findings were based on high coverage (85-99%) and vaccine effectiveness (from 0.5 after dose one to 0.9 after doses two and three). These results did not consider differences in VE in the youngest age group (as may be observed with higher levels of maternal antibodies), but the authors commented that if VE of the first dose was 20% lower when given at 6 weeks rather than 2 months, the incidence of severe disease for the 0-2 months age group would be reduced by 6%. However, for greater reductions in VE, there was no noticeable benefit for the 0-2-months age group and incidence of severe cases increased by over 5% in the 0-1-year age group, overall.[40]

**Conclusion**

The timing of the infant doses can have a significant effect on disease incidence in the very young and up to 1 year of age. Delays in infant doses increase the risk of pertussis disease in the youngest infants, but not the older infants. Depending on the VE, starting the schedule at 6 weeks is more protective than at 2 months. However, this does not take into

consideration the affect higher levels of maternal antibodies have on vaccine effectiveness when vaccinated at 6 weeks.

## 4.3 To avoid interference with co-administered vaccines

Consideration of the primary schedule needs to ensure that disease control is maintained for other diseases as well as pertussis. DTaP-containing vaccines are recommended to be given at the same time as conjugate vaccines, such as meningococcal C or ACWY, PCV and Hib vaccines, to avoid potentially immunosuppressive effects of epitope competition.[36] Further details were presented in our previous literature review.[37] Briefly, pre-existing dominant immune responses to conjugate proteins can either inhibit or enhance the immune response to the polysaccharide that is conjugated.

## 4.4 Cocooning protection for close contacts

### 4.4.1 Vaccination of family members

A study in the UK found that in 54 out of 63 households (86%) at least one positive pertussis case was found to be a possible source of infection to a hospitalised infant aged under 3 months. Out of all the contacts tested from these families, 97/220 (44%) tested positive and 31/108 (29%) who were non-coughers tested positive for pertussis infection. In 38% of the cases, mothers were the probable source of infection, followed by siblings (31%) and fathers (10%).[6]

Vaccination of both parents after delivery and at least 28 days prior to illness onset was had a VE of 77% (95% CI 18-93%) in reducing pertussis infection in Australian infants who did not have maternal vaccination protection. Adjusted VE was 64% (-58 to 92%) after adjusting for maternal education, presence of a sibling within the household and the infant's primary course status. The study conducted in Victoria, Australia used a matched case-control design for cases notified between January 2010 and December 2011 in infants aged <1 year and born during a state-led cocooning programme (prior to maternal vaccination programmes). It was concluded that, although statistical significance was not reached, some protection may be provided to infants by cocoon immunisations of both parents post-partum, particularly in circumstances where maternal antenatal vaccination did not occur.[43]

According to the Victoria Immunisation Schedule, as of July 2018, Victoria funds Tdap boosters for pregnant women from 28 weeks gestation for every pregnancy, and for partners of women who are at least 28 weeks pregnant and parents/guardians of infants under 6 months of age who have not received a Tdap booster in the last 10 years.

As mentioned in section 3.4.4, influenza vaccination of mothers can help to protect infants against pertussis infection.[44] Therefore, it is plausible that vaccinating both parents and other family members against influenza may also help to reduce the risk of the infant's exposure to *B. pertussis*.

### 4.4.2 Vaccination of healthcare workers

A systematic review found moderate evidence that Tdap vaccinations in healthcare workers were effective in preventing pertussis in all age groups and specifically in infants. The review investigated the effectiveness of Tdap against nosocomial pertussis outbreaks or infections among unprotected infants, and focussed on eight studies involving healthy adolescents and adults, and simulated populations. The duration of protection and rate of waning was unclear.[41]

## 4.5 Summary – schedule options to protect infants

Beginning the primary series at 6 weeks rather than 2 months of age provides protection from pertussis for the younger infants, but those who are not fully immunised remain at risk, particularly infants too young to have received their first dose.

Options to protect infants born to mothers who did not received Tdap in pregnancy include administering a pertussis-only vaccine at birth, cocooning by vaccinating close family members or adjusting the timing of the infant schedule.

Infants who received a dose of aP-only vaccine at birth had significantly more anti-pertussis antibodies at 10 weeks of age, after the first scheduled dose, than infants who were not vaccinated at birth (in the absence of maternal vaccination). Some interference in primary series responses was observed, but the clinical significance of this was not established. This option may provide protection for the first few months of life to infants born preterm or to mothers who did not receive Tdap in pregnancy.

Vaccinating both parents may provide some indirect protection to infants whose mothers did not received Tdap in pregnancy, although statistical significance was not reached. Influenza vaccine given during pregnancy may also provide additional protection to the mother against acquiring pertussis and thereby reduce the risk of passing it to her infant.

There is some evidence that vaccination of healthcare workers caring for neonates and infants provides protection to infants against pertussis, but the duration of protection and optimum timing of booster doses is unknown.

# 5 Duration of protection of pertussis immunisation

A major issue with pertussis vaccination is that a limited duration of protection has been observed, especially for acellular vaccines. More rapid waning of immunological memory following booster doses and a resurgence in disease incidence has been particularly associated with the switch from whole cell to acellular pertussis vaccines in most developed countries. Another factor in the apparent resurgence has been the use of polymerase chain reaction (PCR) assays to diagnose more pertussis cases, particularly in adolescents and adults, which are more sensitive and rapid than cultures.[78]

This section will describe recent studies investigating this phenomenon and the effect waning immunity has had on pertussis immunisation programmes, focussing on acellular pertussis vaccinations.

## 5.1 Immunological memory

Immunological memory is the cornerstone for immunisation. Protection against circulating disease, such as pertussis, relies on establishing and maintaining memory against the disease. Factors that influence immunological memory associated with acellular pertussis vaccines are considered.

Although pertussis immunity is not reported as being long-lived, a modelling study in Australia found that, based on observed epidemiology, the protection afforded by natural infection was likely to be decades longer than vaccine immunity (for wP and aP vaccines),

and that median duration of protection from wP was longer than from aP vaccines, but the difference was not statistically significant.[47]

### 5.1.1 Immune response to acellular pertussis vaccines

There are two key functions for the immune response against pertussis:

1. To reduce virulence of the disease by neutralising pertussis toxin and to prevent adhesion of the bacteria to the cells of respiratory tract by antibodies.
2. To kill the organism to prevent colonisation and transmission from the respiratory tract, known as sterilising immunity.

As described in more detail in a previous literature review, acellular pertussis vaccines have been shown to induce permanent mixed T cell response with a T helper-2 (Th2)/T helper-17 bias of cellular response to pertussis antigens.[37] This bias appears to be fixed for life after the first dose of aP vaccine and is not altered by subsequent exposure to aP boosters, wild type infection or wP antigens.[55] Although this aP response generates a good antibody response to reduce virulence of the disease by neutralising pertussis toxin and to prevent adhesion of the bacteria to the cells of respiratory tract by antibodies (generating neutralising immunity), it is less able to kill *B. pertussis* to prevent colonisation and clear infection, resulting in more carriage and transmission (sterilising immunity).[55]

In lieu of improved pertussis vaccines being developed, first dose priming with wP-containing vaccine (DTwP) may induce longer-lived T helper-1 (Th1)-dominant immunity, and help to more rapidly clear infection and thereby reduce transmission.[55, 56] Subsequent primary series doses, booster doses and pregnancy doses could continue with aP-containing vaccines. However, this strategy would need to be balanced against the concerns for the higher reactogenicity profile of wP-containing vaccines, which was the reason most developed countries moved away from these vaccines.

The adverse reactions associated with wP vaccines included injection site reactions and mild fevers in about a half of DTwP recipients. Some infants are reported to have prolonged, high pitch crying beginning within 12 hours of vaccination. However, in the UK a change of schedule from 3-5-10 months to 2-3-4 months substantially reduced post-vaccination fever and injection site redness and reaction rates of wP did not differ from aP vaccines. Successive vaccinations were associated with increased incidence of injection site reactions and fever (up to 18 month booster). Hypotonic-hyporesponsive episodes and febrile seizures were uncommon (both at a rate of 0.06% compared with DT only). These reactions are disturbing to parents.[57]

For the Expanded Programme on Immunisation the diphtheria-tetanus-pertussis schedule is given at 6-10-14 weeks (i.e. 4 weeks apart) in developing countries. The rationale is that the reactogenicity of wP vaccines is significantly reduced when given in early short timeframe schedules.[58]

### 5.1.2 Antibody persistence in adults

As reported in section 3.3.1, the serum of most pregnant women contains almost no detectable pertussis antibody, prior to vaccination. However, booster doses of Tdap given to adults can provide seroprotection for a few years. A phase II RCT extension study in the US followed adults aged 19-64 years for five and nine years after vaccination with three- or five-pertussis component Tdap vaccines, and were compared with newly recruited controls (age 28-73 years) in year nine. At nine years, both participants in the vaccinated and control groups received a booster dose. Seroprotection rates at years five and nine were ≥98% for diphtheria and tetanus. The proportion of participants with antibody concentrations above assay cut-off (seropositive) was similar between the two vaccine

groups: year five ≥76.6% PT, ≥99.2% for FHA and ≥96.5% for PRN, and year nine ≥84.9% PT, ≥99.2% FHA and ≥98.5% for PRN. The anti-pertussis antibody GMCs were higher than pre-vaccination levels at year nine, but tended to decrease between years five and nine (for example, anti-PT GMC in Tdap3 group was 14.6 EU/ml in year five and 8.2 EU/ml in year nine) At one month post booster, the percentage of participants with anti-pertussis antibodies above assay cut-off was ≥98.8% for PT and 100% each for FHA and PRN in all three groups, and GMCs increased around seven to eight times higher for each pertussis antigen. It was concluded that this study supported decennial booster doses of Tdap to adults.[42]

To evaluate decennial booster responses, an observer-blind RCT was conducted in the US. It showed robust antibody responses to booster doses of Tdap (Adacel®) in 1,002 adults (aged 18-64 years, mean 29 years) compared with Td given 8-12 years after a dose of Tdap was previously administered. Geometric mean titre ratios post to pre-vaccination were: 8:1 for PT, 5.9 for FHA, 6.4 for PRN and 5.2 for FIM2/3 antibodies. Responses to tetanus and diphtheria were non-inferior between the groups and seroprotective in more than 99% of recipients. The booster doses were well tolerated, with no significant differences in injection site or systemic reactions.[79]

### 5.1.3 Epitope alteration of pertussis toxin by detoxification.

One hypothesis for waning effectiveness reported following booster doses is that priming with aP vaccines risks inducing immune memory towards non-protective neo-epitopes created as a result of chemically detoxifying the pertussis toxin used in these vaccines. Although the antibodies induced by primary vaccination are effective in disease prevention, booster doses or exposure to the natural infection are likely to stimulate memory B cells against non-effective PT epitopes to produce ineffective, and therefore, less protective antibodies (described as ‘antigenic sin’). Additional booster doses are likely to exacerbate this by activating more dominant memory T and B cells specific for the non-protective epitopes, leading to reduced vaccine effectiveness and less durable protection.[54]

It has been known for over 20 years that epitope changes could to interfere with mouse monoclonal antibody binding to pertussis toxoids. As published in 1996, genetic, hydrogen peroxide or formaldehyde detoxification of PT reduced epitope binding in solid-phase assay by 2.9%, 31.4% and 78.1%, respectively, and 9.1%, 50.0% and 71.4% in solution when compared with native pertussis toxin. It was concluded that these effects are likely to have implications for the quality assessment of detoxified PT in aP vaccines.[59]

The T cell responses induced by two different aP-containing vaccines were compared in 97 children aged 6-7 years in Italy. Positive T cell responses to PT were detected in 36% of children five years after primary vaccination (at 3, 5 and 11 months of age). Positive PT-specific T-cell proliferation and CD4 IL-2+ cells were significantly higher in the children primed with Hexavac® (Sanofi Pasteur) than in those who received Infanrix-hexa® (GSK) vaccine. These differences were maintained at a lower level in the children who had received the preschool booster (Boostrix®, GSK). The reasons for these differences were unclear. One hypothesis was that the method of detoxification of PT alters expression of protective or non-protective epitopes, since in Hexavac the PT is detoxified with glutaraldehyde only, compared with glutaraldehyde and formaldehyde as used in Infanrix.[80]

To overcome this ‘antigenic sin’ phenomenon, high dose (40µg vs 20µg) hydrogen peroxide detoxified PT vaccines could be used in the childhood schedule, which have less epitope disruption.[54] For example, unlike in neighbouring countries, in Denmark no pertussis epidemics were seen from 2002 to 2014 and deaths are rare (one every 2 -3 years, none between 2010 and 2014).[81] This has been attributed to the use of mono-component aP

combination vaccines, which contain high doses of less denatured hydrogen peroxide-detoxified PT (40µg PT priming DTaP and 20µg PT in TdaP booster; Staten Serum Institut).[60] The primary series is given at 3, 5 and 12 months and a preschool booster at 5 years (to extend immunity and provide indirect protection to infants).[81] VE of 93% was shown against severe and 73% against mild pertussis in 500,000 Danish children during a double-blind RCT. Response rates to the TdaP booster were significantly higher (92%) in adults than to the two multicomponent aP vaccines that contain lower doses of glutaraldehyde/formaldehyde deactivated PT (47.1% and 77.2%).[60]

Note that, according to the Staten Serum Institut (SSI), a short—lived pertussis epidemic was reported in the summer and autumn of 2016 (53% of cases under 2 years of age were unvaccinated).[82] Denmark routinely used DTaP-IPV-Hib vaccine, DiTeKiPol/Hib® (AJ Vaccines) until March 2019.

Genetically-inactivated pertussis toxin has been investigated in aP vaccine formulations, as reviewed by McIntyre and Edwards (2018), and were found to show significantly greater immunogenicity and antibody duration than chemically detoxified PT in clinical trials. Through the use of recombinant DNA technology, the native structure of immunogenic PT epitopes is maintained.[61, 62] Recombinant aP and Tdap vaccines demonstrated significantly higher immune responses to PT and FHA in health adults as compared with a conventional Tdap vaccine (Adacel) in a phase I/II RCT in Thailand.[63]

**Conclusions**

The chemical methods used to detoxify pertussis toxin cause conformational changes to the antigen, exposing different epitopes, which may result in dominant immunity against non-protective epitopes rather than protective immunity. Booster doses with the same vaccines are likely to enhance this altered immune specificity, resulting in fewer protective antibodies being produced. Since there are fewer protective antibodies, they wane below seroprotective levels in a short time period. Priming with vaccines containing hydrogen peroxide or genetically detoxified PT may help to overcome the rapid waning in protection seen following booster doses, particularly in adolescents.

High doses of less denatured, detoxified PT may further enhance the immune response and booster responses against protective epitopes.

### 5.1.4 Summary – immunological memory

The first dose of aP vaccine determines the characteristics of the T cell response following re-exposure, and this has been associated with lower effectiveness, more rapid waning and limited ability to prevent transmission compared with wP or wild-type immunity.

Furthermore, there are concerns that the methods for detoxifying pertussis toxin in the aP vaccines may result in more dominant immunity against non-protective epitopes, resulting in less protective immunity later in life following booster doses, particularly for those primed with aP vaccines.

To reduce this effect, more consideration of the formulation of vaccines used for priming and boosting is required.

Pertussis vaccination provides immunological memory against vaccine antigens. Antibodies, particularly against FHA and PRN persist for at least nine years, however, pertussis toxin antibodies wane more rapidly.

## 5.2 Duration of effectiveness and impact

In association with waning in immune memory and antibody levels, the effectiveness of pertussis vaccination has also been reported to decline rapidly. This decline appears to be particularly pronounced in individuals primed with acellular rather than whole cell vaccines.

This section considers recently published literature on the impact pertussis vaccination has on pertussis disease control and the effect of waning protection. Since the focus of this review is on aP vaccines, comparisons between wP and aP vaccines are not presented unless applicable to aP vaccinations.

### 5.2.1 Impact of pertussis vaccination

A positive impact of pertussis vaccination has been demonstrated, showing that age-appropriate pertussis vaccination reduces the severity of symptoms and complications of the disease.[45]

Based on 9,801 pertussis cases aged at least 3 months and reported through the Enhance Pertussis Surveillance programme in the US, age-appropriate vaccination was associated with a 60% reduction in the odds of severe disease (seizure, encephalopathy, pneumonia and/or hospitalisation) in children aged 7 months to 6 years, and a 30% reduction in post-tussive vomiting in those aged 19 months to 64 years. Of these cases, 77.6% were appropriately vaccinated, 78.9% were aged under 20 years and 55.8% were aged 7-19 years. In those aged 13-19 years, there was a marginally significant association with increased odds of severe disease for each additional year following Tdap vaccination (1.33-fold increase; 95% CI 1.00-1.76; p=0.049). No association was observed between time since Tdap receipt and severe disease or post-tussive vomiting in any other age group. Health-seeking behaviour to receive early treatment of symptoms, such as post-tussive vomiting, is also more likely in those who had been vaccinated and to contribute to this protective effect. Age-appropriate vaccination was defined as DTaP by age 3-4 months, 5-6 months, and 7-18 months for doses one to three of primary series; four doses by 19 months to 6 years; five doses (or four if given after fourth birthday) at 7-12 years, and six doses (or five if dose four given after fourth birthday or Tdap received) at 13-19 years; and for ages ≥20 years Tdap received regardless of other vaccination history. It is important to note that the majority of those aged older than 16 years would have received at least one dose of wP vaccine.[45]

### 5.2.2 Duration of protection in toddlers

A case-control study conducted in NZ did not show waning VE in young children, in contrast to what was observed in a similar Australia study.[49] In Australia, in the absence of a toddler dose, waning VE was reported in children aged less than 4 years.[50] The NZ study found that pertussis protection provided by the primary series (commencing at 6 weeks of age) was sustained through to 4 years of age, with VE of at least 91% against pertussis hospitalisation. The VE against non-hospitalised, notified pertussis was sustained after three DTaP doses from 86% in the 5-11 months age group to 84% among 3 year-olds. VE following the first booster at 4 years of age continued to 7 years of age (VE 93% to ≥91%). At the time (2006-2013), the NZ study did not find that removal of the toddler dose in 2006 disproportionately affected disease incidence among toddlers and supported the current schedule starting at 6 weeks of age with a booster at age 4 years.[49]

It should be noted the data used in this study was prior to the commencement of the maternal vaccination programme. A booster dose in the second year of life may become increasingly necessary in NZ. As maternal Tdap vaccination uptake increases, interference of

maternal antibodies with the infant response to primary series could be observed in more infants, and which may lead to increased incidence of pertussis in toddlers.

A 2+1 series, with the third dose given around 12 months of age, potentially offers immunologically better spacing between second to third doses and enhances protection in the second year of life. However, any interference from maternal antibodies during the priming doses could result in infants aged 6-12 months being less well protected against pertussis.[37]

The use of 2+1 schedules is increasing in developed countries in line with co-administration with pneumococcal conjugate and rotavirus vaccines. A $DTaP_5$-IPV-Hib vaccine (Pediacel®) is licensed in a 2+1 schedule in Europe. An investigative $DTaP_5$-IPV-HepB-Hib vaccine was compared with Pediacel when administered as a 2+1 schedule (2, 4 and 11-12 months of age) and found to have comparable immunogenicity, and to have comparable immunogenicity to a 2+1 schedule with $DTaP_3$-IPV-HepB/Hib vaccine (Infanrix-hexa) used as part of the primary series in NZ.[83]

### 5.2.3 Duration of protection in children

Children (aged <12 years, prior to Tdap) who were more remote from their fifth dose of DTaP were less well protected against pertussis than those who had more recently received dose-5 of DTaP (recommended at ages 2, 4, 6, 15-18 months and 4-6 years). The adjusted OR of pertussis increased by 1.30 per year (1.15-1.46) after five doses of DTaP compared with PCR-negative controls in a case-control study conducted in California using Kaiser Permanente Northern California health system data. Protection waned at an average rate of 27% per year.[46]

A test-negative case-control study conducted in Ontario, Canada found that VE was 80% (95% CI 71-86%) against pertussis from two weeks to a year following vaccination, after one to three years VE was 84% (77-89%), declining to 62% (42-75%) after four to seven years and to 41% (0-66%) at eight or more years after vaccination. The schedule in Ontario recommends DTaP to be given at age 2, 4, 6, 18 months and 4-6 years, Tdap at 14-16 years and a single adult dose. Adjusted OR for waning effectiveness of the aP vaccine was 1.27 (1.20-1.34) per year since vaccination among those up-to-date for age. Individuals who were primed with aP had 2.2 times increased odds of pertussis than those who had been primed with the previously used wP vaccine. The study linked 5,867 individuals born after 1 April 1992 and tested for pertussis during December 2009 to March 2013: 486 pertussis-positive (mean age ± SD = 7.7 ± 5.7 years) and 5,381 pertussis-negative (mean age 5.0 ± 5.0); excluding infants younger than 3 months and those registered with the Ontario health insurance after the age of 6 months.[48]

In the UK from mid-2013 onwards, the greatest increase in incidence of laboratory-confirmed pertussis disease was noted in children aged 5-9 years who were solely primed and boosted with aP-containing vaccines. In this age group, the rate during 2013-2015 was 7.7 times higher in than during 2009-2011 (from 0.6 to 4.6/100,000). The average rate of incidence was 4.1/100,000 during 2009-2011 and 7.5/100,000 from 2013-2015 (1.8 times higher) across the population. Oral fluid testing enhanced case ascertainment in ages 5-16 years from 2013.[12]

*Conclusions*

Waning of immunity against pertussis is seen in children, even after five doses of a pertussis-containing vaccine, at an average rate of 27% per year. The more remote from the last vaccination, the greater the risk of pertussis. Note that these studies only consider laboratory-tested pertussis and not milder cases that may further reduce disease control.

Protection of children immunised solely with aP vaccinations may decline more rapidly than those who have had mixed schedules and been primed with wP vaccines.

### 5.2.4 Duration of protection in adolescents

A meta-analysis, described in more detail in the previous schedule review, estimated that only 10% of those vaccinated with DTaP would be immune to pertussis 8.5 years after their last DTaP dose. It reported that where a preschool booster was offered at 4-6 years, a booster is likely to be required for adolescents from the age of 10 years, in line with the current Tdap booster at 11 years of age in New Zealand.[37, 51]

However, little protection remains two to three years after vaccination with a Tdap booster in adolescents previously immunised with only DTaP. The effectiveness and waning immunity of Tdap was investigated among adolescents vaccinated exclusively with DTaP using Kaiser Permanente Northern California data. Based on 1,207 pertussis cases aged 10-19 years, the VE of Tdap during the first year after vaccination was 68.8% (59.7-75.9%) and decreased to 8.9% (-30.6 to 36.4%) after four or more years post vaccination - equivalent to an average waning of protection of 35% per year. Adolescents with a longer post-vaccination period from their last Tdap were more likely to test positive for pertussis (hazard ratio per year 1.35 [1.22-1.50]). In California, 96.5% received Tdap by their 14$^{th}$ birthday.[84]

A retrospective cohort analysis found that protection against pertussis declines significantly within two years in adolescents following Tdap booster regardless of the type of primary vaccine given in childhood. Data from two integrated healthcare systems, Kaiser Permanente Washington and Northwest, were used to identify those aged 11-18 years following the introduction of the 11 year-old Tdap booster (n=165,541, May 2005 – December 2012). A total of 187 pertussis cases were confirmed; of these 114 (61%) had completed the five-dose primary series. Within two years of vaccination with Tdap, VE was 69% (54-79%) and significantly decreased after two or more years among the entire study population to 34% (1-55%; p<0.01).[85]

#### *5.2.4.1 Effectiveness of booster doses in adolescents*

A systematic review and modelling study was conducted by Chit et al (2018), which investigated the effectiveness of pertussis vaccination over time. It estimated that the absolute VE of the full aP series (five DTaP doses and one Tdap dose) to be 85% (95% CI 84-86%) against pertussis and declined by 11.7% (11.1-12.3%) per year. The relative VE of boosting with Tdap compared with only five-dose primary series was estimated to be 91% (87-95%) which declined by 9.6% per year. At 3, 5 and 7 years after the full aP series, the absolute protection against pertussis was expected to be 49%, 37% and 28%, respectively.[52] At one year after Tdap booster, children who completed their full series by the age of 11 years received considerable added protection against pertussis from their Tdap booster, such that, as compared to children who only received the primary series, the RR of pertussis was 0.3 (0.25 to 0.36) and was retained for at least four years (RR 0.8 [ 0.69-0.94]).[52] (Details of timing of primary series not given. As all studies reviewed were US-based, it was likely to commence at 2 months of age)

The effectiveness of the Tdap vaccination programme against pertussis in adolescents aged 11-18 years was evaluated in the US and included consideration of the transition between wP and aP vaccines between 1990 to 2014. The incidence of pertussis increased from 1.7 to 2.0 per 100,000 between 1990 and 2003 and was highest in infants aged less than 1 year. Among all other age groups, pertussis rates were comparable until the late 2000s. By 2014, the second highest incidence was seen in 11-18 year olds. A positive impact of Tdap was seen immediately following its introduction to adolescents (slope -0.50, p<0.001), but the

trend reversed in 2010 and disease rates increased at a faster rate than all other age groups combined (slope 0.57, p <0.01). This change corresponded to the ageing of the cohorts fully primed with aP vaccines in infancy.[53]

Following an increase in pertussis cases in Israel, booster doses of Tdap were added to the routine immunisation schedule for 7 year-olds in 2005. During 2008-2010, catch-up booster were also given to 13 year-olds who had not received the previous booster. Since 2011, all children are offered a second booster dose of Tdap in eighth grade (13 year-olds) to replace Td boosters. Immunisation coverage averaged 90% and 93% for the first and second boosters, respectively. The effectiveness of the booster programmes was assessed using age-group incidence from 1999 to 2016, before and after the programme.[86]

Significant differences were seen in disease incidence between the three cohorts (no booster, one booster at 13 years or both boosters at 7 and 13 years). When adjusted for cyclical incidence variations (as approximated by incidence in those aged older than 65 years), VE following one booster was 80.9% and two boosters was 94.6% at age 14 years. In the following year (at age 15), adjusted VE declined to 74.5% and 91.8%, respectively. The programme did not appear to prevent transmission of disease, VE declined one year after the adolescent booster, crude morbidity rates were not reduced and the programme was only effective among the recipient groups. The gains in VE of the second booster were much smaller than the gains from no booster to one dose at age 13 for two years (VE increased by 14-17% after second booster, compared with VE of 75-81% for one dose).[86]

#### *5.2.4.2 Modelling the role of booster doses for vaccine-acquired immunity.*

Based on Australian sero-epidemiological data, predictive models were used to compare alternative vaccination schedules and booster doses to mitigate pertussis infection.[47] It was shown that replacement of the 18 months dose with an adolescent dose in 2003 resulted in a 40% increase in pertussis infections by 2013 in the 18-37 months age groups. The model compared three dosing schedules:

- Six-doses: 2-4-6, 18 months, 4 years and 15 years (reinstate toddler dose to schedule)
- Five doses: 2-4-6, 18 months, and 4 years (replace adolescent dose with toddler dose)
- Five doses: 2, 4, 12 months, 4 years, 15 years (delay 6-month dose to 12 months)

Based on observed epidemiology, the protection afforded by natural infection was found to be decades longer than vaccine immunity (for wP and aP vaccines), and that median duration of protection from wP was longer, but not significantly different, from aP vaccines.[47]

When future scenarios were considered, the addition of the 18 month-dose to the current schedule produced the greatest reduction in infant incidence. A 43% reduction in incidence over 2014-2020 was predicted in the 18 months – 4 years age-group and an 8% reduction was predicted in infants. Replacing the adolescent dose with an 18-month dose benefited pre-schoolers (35% reduction), but resulted in resurgence in the 15-30 years age group (by 23%). In the third scenario, replacing the 6-month with a 12-month dose, had some benefit to the 18 month to <4 year range (25% reduction) but increased infections during the first year of life by 6%. To maximise reduction in infections, it was concluded that multiple booster doses over the first two decades of life were needed to provide comparatively short-lived vaccine-acquired immunity.[47]

There were limitations for data used in this model, including that it did not consider the role of maternal vaccination in pertussis incidence in women and their infants, since the data

were collected prior to the introduction of the maternal vaccination programme.[47] It was also based on primary series commencing at 2 months not 6 weeks as in NZ and now in Australia. Additionally, the details of prior vaccinations were not obtained for the individual pertussis cases and the model was only as good as the notification data – milder cases may not have been notified.

**Conclusions**

Booster doses in adolescents provide short-lived direct protection against pertussis, but do not appear to prevent disease transmission to other age groups.

Protection against pertussis wanes rapidly, within 2-3 years after booster doses of Tdap in adolescence (35% per year), and declines more rapidly in those who were fully primed with aP vaccines in infancy than those primed solely with wP or both.

According to a mathematical model, to maximise protection against pertussis infection multiple booster doses are required, including a toddler and adolescent dose. Delaying the third primary dose from 6 months to 12 months could help to improve infection rates in toddlers but likely to result in increased disease in the first year of life, when the consequence of infection are most serious.

### 5.2.5 Duration of protection in adults

To date in developed countries, a high proportion of mothers-to-be were primed with wP vaccines in childhood. However, the generation (born since 2000 in New Zealand) who have been solely primed with aP vaccines are beginning to approach parenthood. In a commentary, van den Biggelaar discussed the implications for 'all-aP'-primed adolescents and adults. Booster doses given in early adolescence do not appear to provide adequate protection for older adolescents or young adults. Waning in protection and the risk of mild pertussis infection in aP-vaccinated adults is likely to put infants at increased risk of infection transmitted from their parents. The author argues that although maternal vaccination appears very effective in preventing infant pertussis in the current cohorts of pregnant women who were primed with wP or mixed wP/aP schedules, the effectiveness of repeat Tdap boosters in 'all-aP'-primed mothers is unclear and may lead to inadequate protection of infants.[54]

## 5.3 Summary – duration of protection

A positive impact of pertussis vaccination has been demonstrated and age-appropriate pertussis vaccination reduces the severity of symptoms and complications of the disease. However, waning of immunity against pertussis is seen in children, even after five doses of a pertussis-containing vaccine, at a rate of around 27% per year. The more remote from the last vaccination, the greater the risk of pertussis.

Pertussis vaccination provides immunological memory against vaccine antigens. Antibodies, particularly against FHA and PRN persist for at least 9 years, however, pertussis toxin antibodies wane more rapidly. Conformational changes to the pertussis toxin are likely to occur during chemical detoxification and repeat boosters with the same denatured toxin risk the development of dominant immune responses to non-protective epitopes.

Booster doses in adolescence provide short-lived direct protection against pertussis, but do not prevent disease transmission to other age groups. Within two to three years after booster doses of Tdap in adolescence, protection against pertussis wanes rapidly at a rate of around 35% per year and most rapidly in those who were fully primed with aP vaccines in infancy. The waning of immunity appears be more rapid following repeat booster doses into

adulthood. The effectiveness or duration of immunity of maternal boosters is uncertain when given to women who were primed only with aP vaccines in childhood.

The addition of a toddler dose is likely to improve protection against pertussis for children prior to the start of school, but an adolescent dose is likely to continue to be required to boost immunity in teenagers and young adults. However, a high uptake of parental vaccination may negate the need for this dose, since the protective antibodies induced are not long-lasting, do not provide indirect protection to other age groups and disease is less severe than in young children.

# 6 International policy and practice

This section provides a review of the immunisation practices and recommendations for acellular pertussis vaccines, internationally. This review has been restricted to immunisation schedules and policies in Australia, Canada, selected European countries, the UK and the US. Regional variations between provinces, states and territories have not been individually reviewed. Refer to Table 3 for a summary.

## 6.1 Australia

The Australian schedule provides DTaP-IPV-HepB/Hib at starting from 6 weeks-2 months and 4 and 6 months of age, with DTaP-containing vaccine at 18 months, and DTaP-IPV at 4 years of age. Tdap boosters are given at age 10-15 years through state-led school-based programmes and in the third trimester of each pregnancy (optimally between 28-32 weeks gestation).[87]

## 6.2 Canada

In Canada, the primary series is given at 2, 4 and 6 months of age with DTaP-IPV-HepB/Hib and a booster at 18 months with DTaP-IPV-Hib or DTaP-IPV-HepB/Hib. Booster doses are given preschool at age 4-6 years with either Tdap-IPV or DTaP-IPV; Tdap is also recommended at age 13-16 years (school grade 7-9), as one booster per adult life-time, and in each pregnancy after 26 weeks (in some provinces only).[88, 89]

The National Advisory committee on Immunisation (NACI) recommended immunisation with Tdap in each pregnancy from February 2018. The ideal timing was given to be 27 to 32 week gestation, but evidence was also found to support a wider range from 13 week to delivery.[90]

## 6.3 Europe

The pertussis immunisation schedules vary widely across Europe: some recommend vaccination at 2, 3, 4 months, 2, 4, 6 months or 3, 5 and 11 months of age. In some European countries, the first two primary doses are close together at 2 and 4 or 3 and 5 months with a gap to 11 or 12 months of age for the third dose (2+1). Several countries have mandatory vaccination. Most countries have boosters in the second year of life (from 11-18 months of age), except the UK and Ireland.  Poland is the only European country to continue using whole-cell pertussis vaccination (unless contraindicated) with an acellular pertussis booster at 6 years of age.[91]

Recommendations for vaccination in pregnancy from the second semester have been in place in Switzerland since 2013 (when no pertussis vaccine had been given in more than 5 years). However, the most recent recommendations are for vaccination during weeks 13-26 gestation in each pregnancy independent of previous vaccinations.[92, 93]

## 6.4 United Kingdom

As of September 2018, the national immunisations schedule in the UK provides DTaP-IPV-HepB/Hib at 8, 12 and 16 weeks of age, with a DTaP-IPV booster at 3 years 4 months of age and a Td-IPV booster at 14 years. Tdap-IPV is provided in pregnancy from 16 weeks gestation (ideally at 20 weeks).[94]

## 6.5 United States

As part of the US immunisation schedule, DTaP-containing vaccines are given at 2, 4, 6 months of age and boosters at 15-18 months and 4-6 years (under 7 years) of age. Tdap-containing boosters are recommended at age 11-12 years; in pregnancy at between 27-36 weeks gestation; and for adults, one dose with Tdap is recommended then Td every 10 years.[95]

## 6.6 Summary

International recommendations are summarised in Table 3.

***Table 3: Summary of international immunisation recommendations for pertussis vaccines, as of October 2018***

| Country | Age of pertussis vaccination | Primary Schedule | Special recommendations |
|---|---|---|---|
| USA | 2, 4, 6, 15-18m<br>4-6y, 11-12y | 3+1 | Pregnancy 27-36gw |
| Canada | 2, 4, 6m, 18m<br>4-6y, 13-16y | 3+1 | One aP dose per adult life-time<br>Pregnancy from prior to 36gw (ideally 27-32 weeks) |
| Australia | 6w/2, 4, 6m, 18m<br>4y, 10-15y | 3+1 | Pregnancy third trimester (28-32gw ideal) |
| NZ | 6w, 3, 5m<br>4y, 11y | 3+0 | Pregnancy 28-38gw |
| Austria | 2, 4, 11m<br>6y | 2+1 | Tdap-IPV every 10 years from age 18-60y, unfunded Tdap 12y, if received Td-IPV at 7-9y |
| Denmark | 3, 5, 12m<br>5y | 2+1 | Mono-component aP vaccine. |
| France | 8w or 2, 4, 11m<br>6y, 11-13y | 2+1 | Mandatory primary series<br>Tdap-IPV booster at 25y if no pertussis containing booster given in previous 5 years (until 39y) |
| Germany | 2, 3, 4, 11-13m<br>5-6y, 9-17y | 3+1 | From 18y, first booster as Tdap, then Td 10 yearly |
| Ireland | 2, 4, 6<br>4-6y, 12-13y | 3+0 | Pregnancy 27-36 gw (only funded with medical card) |
| Sweden | 3, 5, 11m<br>5y, 13-15y | 2+1 | |
| UK | 2, 3, 4m<br>3y and 4m | 3+0 | In pregnancy from 16 gw (ideally from 20gw) |
| Abbrev: w - weeks, gw – gestational weeks, m – months, y –years; Td – tetanus-diphtheria; Tdap – tetanus-diphtheria-acellular pertussis; IPV –inactivated polio vaccine. | | | |

# 7 Updates suggested for Immunisation Handbook 2017

**14.4.2 Efficacy and effectiveness** – for the childhood schedule (Infanrix-hexa), these were not specifically reviewed for this document, since the focus was on other specific questions. The data presented in the Handbook were pivotal clinical trial data. Influences of maternal antibodies are not fully defined and therefore may not be appropriate to add to the Handbook at this stage.

**To add** – Pertussis immunisation has a positive impact on disease severity. A positive impact of pertussis vaccination has been demonstrated and age-appropriate pertussis vaccination has been shown to reduce the severity of symptoms and complications of the disease. In the US, age-appropriate vaccination was associated with a 60% reduction in the odds of severe disease (seizure, encephalopathy, pneumonia and/or hospitalisation) in children aged 7 months to 6 years, and a 30% reduction in post-tussive vomiting in those aged 19 months to 64 years (section 5.2.1).

**Duration of protection** - Waning of immunity against pertussis is seen in children, even after five doses of an acellular pertussis-containing (aP) vaccine at a rate of around 27% per year (section 5.2.3). It has been estimated that only 10% of children vaccinated with DTaP would be immune to pertussis 8.5 years after their last dose. In adolescents, following the adolescent booster, waning is more rapid at around 35% per year, such that VE declines to less than 10% after four or more years (section 5.2.4). Antibodies to FHA and PRN are longer lived than those against pertussis toxin (section 5.1.2).

**4.1.2 During pregnancy**

Include NZ data demonstrating safety from PIPS study (section 3.2.1).

No safety concerns have been identified for pregnant women or their infants following vaccination during pregnancy with Tdap. In a NZ-based study, Tdap exposure was associated with some protection against low birth weight, small-for-gestational age, moderate to later preterm birth, and with a higher mean birth weight. Residual confounding for improved infant outcomes may be influenced by greater likelihood of health-seeking behaviour by vaccinated mothers compared with unvaccinated mothers.

Effectiveness of the UK programme – use more up-to-date references for three years of programme. Three years following the introduction of maternal pertussis vaccinations in the UK with TdaP-IPV vaccine, given after 28 weeks gestation and at least seven days before delivery, vaccine effectiveness (VE) against laboratory-confirmed pertussis has been sustained at 91% (95% CI 88-94%) in infants <3 months of age and 90% (86-93%) for infants aged <2 months. Maternal vaccination, given more than seven days before delivery, was shown to be 95% effective against infant deaths due to pertussis (section 3.4).

# 8 Methodology for review

## 8.1 Objectives

## 8.2 Literature search strategy

### Medline search terms and strategy

1. Pertussis vaccine – Keyword MeSH map, all subheadings = 4958
2. Limit English, Human, 2016 – current [27/8/18] 249 – selected 103
3. Pertussis vaccine [kw] NOT whole-cell [title] 241
4. Limit #3 to English, human, 2015-current [27/8/18] 27

### Pubmed searches

1. Search Pertussis vaccine effectiveness, limit 2017-2018 selected 18 out of 81
2. Pertussis [MeSH] Whooping cough focus, epi immunology prevention & control transmission = 3599

   Limit English, humans 2016-current [4/9/18] – 249, selected 111, removed duplicates = 64

3. ("adolescent"[MeSH Terms] OR "adolescent"[All Fields]) AND ("whooping cough"[MeSH Terms] OR ("whooping"[All Fields] AND "cough"[All Fields]) OR "whooping cough"[All Fields] OR "pertussis"[All Fields]) AND ("immunity, herd"[MeSH Terms] OR ("immunity"[All Fields] AND "herd"[All Fields]) OR "herd immunity"[All Fields] OR ("herd"[All Fields] AND "immunity"[All Fields])) = 49
   Limit 2015-2018 – 6 out of 7 selected

### Grey literature

Grey literature consisted of unpublished study reports or reports of studies from which data has been presented at international conferences. Use of data given by permission from the principal investigator.

### Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. All duplicates were removed from the final library.

#### 8.2.1 Final Endnote Library 289, including articles and reports

Where systematic reviews and/or meta-analyses were available the preceding literature has been excluded from the review, unless further details were required from the original papers.

## 8.3 Participants/populations

This study primarily reviewed the use of pertussis vaccines in pregnant women, newborn infants, infants, children and adolescents. The role and timing of these vaccines were considered in terms of pertussis disease control.

## 8.4 Study designs

The studies included in this update are meta-analyses, systematic reviews, reviews, randomised controlled trials, case-control studies, case reports and observational studies using database matching.

# 9 References


1. ESR. Pertussis report December 2018 Wellington, New Zealand: Institute of Environmental Surveillance and Research; 2018 [updated 10 January 2019; cited 2018 20 February]. Available from: https://surv.esr.cri.nz/PDF_surveillance/PertussisRpt/2018/PertussisReportDecember2018.pdf

2. ESR. Pertussis Report 16 December 2017 - 12 January 2018: Institute of Environmental Surveillance and Research; 2018 [updated 23 January 2018; cited 2018 9 October]. Available from: https://surv.esr.cri.nz/PDF_surveillance/PertussisRpt/2018/PertussisReport12January20182.pdf

3. Brooks JI, Bell CA, Rotondo J, Gilbert NL, Tunis M, Ward BJ, et al. Low levels of detectable pertussis antibody among a large cohort of pregnant women in Canada. Vaccine. 2018;36(41):6138-43.

4. McHugh L, Viney KA, Andrews RM, Lambert SB. Pertussis epidemiology prior to the introduction of a maternal vaccination program, Queensland Australia. Epidemiol Infect. 2018;146(2):207-17.

5. Gkentzi D, Katsakiori P, Marangos M, Hsia Y, Amirthalingam G, Heath PT, et al. Maternal vaccination against pertussis: a systematic review of the recent literature. Archives of disease in childhood Fetal and neonatal edition. 2017;102(5):F456-F63.

6. Kara EO, Campbell H, Ribeiro S, Fry NK, Litt D, Eletu S, et al. Survey of Household Contacts of Infants With Laboratory-confirmed Pertussis Infection During a National Pertussis Outbreak in England and Wales. The Pediatric infectious disease journal. 2017;36(2):140-5.

7. Deverall EJ, Gilmore B, Illing S, Peiris-John R. Pertussis vaccination uptake in pregnancy: lessons to be learned from an integrated healthcare approach. The New Zealand medical journal. 2018;131(1473):42-7.

8. Griffin JB, Yu L, Watson D, Turner N, Walls T, Howe AS, et al. Pertussis Immunisation in Pregnancy Safety (PIPS) Study: A retrospective cohort study of safety outcomes in pregnant women vaccinated with Tdap vaccine. Vaccine. 2018;36(34):5173-9.

9. Ministry of Health. Pertussis Control Strategies 2015: A consistent approach for New Zealand. Wellington: Ministry of Health; 2015.

10. Fortner KB, Swamy GK, Broder KR, Jimenez-Truque N, Zhu Y, Moro PL, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. Vaccine. 2018;36(42):6354-60.

11. PIPS1 study team. Study 1 Retrospective cohort study of safety outcomes in pregnant women vaccinated with Tdap vaccine, and for their infants

With Supplementary Study 2—Infant Outcomes Report. . Auckland, New Zealand: Auckland Uniservices Ltd 2017 2 October 2017.

12. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(suppl 4):S236-S43.

13. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics. 2017;139(5).

14. Petousis-Harris H, Goodyear-Smith F, Jiang Y, Lu L, Watson D. Report: Effectiveness of maternal pertussis booster in pregnancy – outcomes in infants. Auckland, New Zealand: Auckland Uniservices Ltd; 2017 26 July 2017.

15. Winter K, Cherry JD, Harriman K. Effectiveness of Prenatal Tetanus, Diphtheria, and Acellular Pertussis Vaccination on Pertussis Severity in Infants. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;64(1):9-14.

16. Vilajeliu A, Ferrer L, Munros J, Gonce A, Lopez M, Costa J, et al. Pertussis vaccination during pregnancy: Antibody persistence in infants. Vaccine. 2016;34(33):3719-22.

17. Villarreal Perez JZ, Ramirez Aranda JM, de la OCM, Zamudio Osuna MJ, Perales Davila J, Ballesteros Elizondo MR, et al. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. Hum Vaccin Immunother. 2017;13(1):128-35.

18. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;64(1):3-8.

19. Abraham C, Pichichero M, Eisenberg J, Singh S. Third-Trimester Maternal Vaccination Against Pertussis and Pertussis Antibody Concentrations. Obstet Gynecol. 2018;131(2):364-9.

20. Healy CM, Rench MA, Swaim LS, Smith EO, Sangi-Haghpeykar H, Mathis MH, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. JAMA. 2018;320(14):1464-70.

21. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, Boukrid M, Combescure C, Othenin-Girard V, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;62(7):829-36.

22. Joint Committee on Vaccination and Immunisation. Minute of meeting on 3 February 2016 Oxford, UK. Available from: http://www.nitag-resource.org/uploads/media/default/0001/03/5c7ce952ec60f9f20ae4d307822b1de6d9ae3d57.pdf

23. Kent A, Ladhani SN, Andrews NJ, Matheson M, England A, Miller E, et al. Pertussis Antibody Concentrations in Infants Born Prematurely to Mothers Vaccinated in Pregnancy. Pediatrics. 2016;138(1):07.

24. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. Arch Dis Child. 2018;103(3):224-9.

25. Janagaraj PD, Gurusamy PSR, Webby R. Current antenatal pertussis vaccination guidelines miss preterm infants: An epidemiological study from the Northern Territory. The Australian & New Zealand journal of obstetrics & gynaecology. 2018.

26. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, Combescure C, Othenin-Girard V, Chilin A, et al. Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;64(8):1129-32.

27. Research aims to find 'sweet spot' for pertussis vaccination in babies. [press release]. Health Research Council of New Zealand2018.

28. Campbell H, Gupta S, Dolan GP, Kapadia SJ, Kumar Singh A, Andrews N, et al. Review of vaccination in pregnancy to prevent pertussis in early infancy. J Med Microbiol. 2018;67(10):1426-56.

29. Halperin SA, Langley JM, Ye L, MacKinnon-Cameron D, Elsherif M, Allen VM, et al. A Randomized Controlled Trial of the Safety and Immunogenicity of Tetanus, Diphtheria, and Acellular Pertussis Vaccine Immunization During Pregnancy and Subsequent Infant Immune Response. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018;67(7):1063-71.

30. Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(11):1637-44.

31. Voysey M, Kelly DF, Fanshawe TR, Sadarangani M, O'Brien KL, Perera R, et al. The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses : An Individual Participant Meta-analysis. JAMA Pediatr. 2017;171(7):637-46.

32. Maertens K, Cabore RN, Huygen K, Vermeiren S, Hens N, Van Damme P, et al. Pertussis vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. Vaccine. 2016;34(31):3613-9.

33. Cabore RN, Maertens K, Dobly A, Leuridan E, Van Damme P, Huygen K. Influence of maternal vaccination against diphtheria, tetanus, and pertussis on the avidity of infant antibody responses to a pertussis containing vaccine in Belgium. Virulence. 2017;8(7):1245-54.

34. Feunou PF, Mielcarek N, Locht C. Reciprocal interference of maternal and infant immunization in protection against pertussis. Vaccine. 2016;34(8):1062-9.

35. Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E. Pneumococcal Immune Response in Infants Whose Mothers Received Tetanus, Diphtheria and Acellular Pertussis Vaccination During Pregnancy. The Pediatric infectious disease journal. 2017;36(12):1186-92.

36. Findlow H, Borrow R. Interactions of conjugate vaccines and co-administered vaccines. Hum Vaccin Immunother. 2016;12(1):226-30.

37. The Immunisation Advisory Centre. Antigen Literature Review for the New Zealand National Immunisation Schedule, 2017: Childhood schedule. The University of Auckland.; 2017.

38. Wood N, Nolan T, Marshall H, Richmond P, Gibbs E, Perrett K, et al. Immunogenicity and Safety of Monovalent Acellular Pertussis Vaccine at Birth: A Randomized Clinical Trial. JAMA Pediatr. 2018.

39. Foxwell AR, McIntyre P, Quinn H, Roper K, Clements MS. Severe pertussis in infants: estimated impact of first vaccine dose at 6 versus 8 weeks in australia. The Pediatric infectious disease journal. 2011;30(2):161-3.

40. Bergero PE, Fabricius G, Hozbor DF, Theeten H, Hens N. Potential Impact of Changes in the Schedule for Primary Diphtheria-Tetanus Toxoids-Pertussis Immunization as Control Strategy for Pertussis. The Pediatric infectious disease journal. 2018;37(2):e36-e42.

41. van den Hoogen A, Duijn JM, Bode LGM, Vijlbrief DC, de Hooge L, Ockhuijsen HDL. Systematic review found that there was moderate evidence that vaccinating healthcare workers prevented pertussis in infants. Acta paediatrica (Oslo, Norway : 1992). 2018;107(2):210-8.

42. Brandon D, Kimmel M, Kuriyakose SO, Kostanyan L, Mesaros N. Antibody persistence and safety and immunogenicity of a second booster dose nine years after a first booster vaccination with a reduced antigen diphtheria-tetanus-acellular pertussis vaccine (Tdap) in adults. Vaccine. 2018;36(42):6325-33.

43. Rowe SL, Tay EL, Franklin LJ, Stephens N, Ware RS, Kaczmarek MC, et al. Effectiveness of parental cocooning as a vaccination strategy to prevent pertussis infection in infants: A case-control study. Vaccine. 2018;36(15):2012-9.

44. Nunes MC, Cutland CL, Madhi SA. Influenza Vaccination during Pregnancy and Protection against Pertussis. N Engl J Med. 2018;378(13):1257-8.

45. McNamara LA, Skoff T, Faulkner A, Miller L, Kudish K, Kenyon C, et al. Reduced Severity of Pertussis in Persons With Age-Appropriate Pertussis Vaccination-United States, 2010-2012. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(5):811-8.

46. Klein NP, Bartlett J, Fireman B, Aukes L, Buck PO, Krishnarajah G, et al. Waning protection following 5 doses of a 3-component diphtheria, tetanus, and acellular pertussis vaccine. Vaccine. 2017;35(26):3395-400.

47. Campbell PT, McCaw JM, McIntyre P, McVernon J. Defining long-term drivers of pertussis resurgence, and optimal vaccine control strategies. Vaccine. 2015;33(43):5794-800.

48. Schwartz KL, Kwong JC, Deeks SL, Campitelli MA, Jamieson FB, Marchand-Austin A, et al. Effectiveness of pertussis vaccination and duration of immunity. CMAJ. 2016;188(16):E399-E406.

49. Radke S, Petousis-Harris H, Watson D, Gentles D, Turner N. Age-specific effectiveness following each dose of acellular pertussis vaccine among infants and children in New Zealand. Vaccine. 2017;35(1):177-83.

50. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics. 2014;133(3):e513-9.

51. McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics. 2015;135(2):331-43.

52. Chit A, Zivaripiran H, Shin T, Lee JKH, Tomovici A, Macina D, et al. Acellular pertussis vaccines effectiveness over time: A systematic review, meta-analysis and modeling study. PloS one. 2018;13(6):e0197970.

53. Skoff TH, Martin SW. Impact of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccinations on Reported Pertussis Cases Among Those 11 to 18 Years of Age in an Era of Waning Pertussis Immunity: A Follow-up Analysis. JAMA Pediatr. 2016;170(5):453-8.

54. van den Biggelaar AH, Poolman JT. Predicting future trends in the burden of pertussis in the 21st century: implications for infant pertussis and the success of maternal immunization. Expert Rev Vaccines. 2016;15(1):69-80.

55. Bancroft T, Dillon MB, da Silva Antunes R, Paul S, Peters B, Crotty S, et al. Th1 versus Th2 T cell polarization by whole-cell and acellular childhood pertussis vaccines persists upon re-immunization in adolescence and adulthood. Cellular immunology. 2016;304-305:35-43.

56. Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. JAMA. 2012;308(5):454-6.

57. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines 7th Edition. Elsevier 2018.

58. World Health Organization. Pertussis vaccines: WHO position paper - September 2015. Releve epidemiologique hebdomadaire. 2015;90(35):433-58.

59. Ibsen PH. The effect of formaldehyde, hydrogen peroxide and genetic detoxification of pertussis toxin on epitope recognition by murine monoclonal antibodies. Vaccine. 1996;14(5):359-68.

60. Thierry-Carstensen B, Dalby T, Stevner MA, Robbins JB, Schneerson R, Trollfors B. Experience with monocomponent acellular pertussis combination vaccines for infants, children, adolescents and adults--a review of safety, immunogenicity, efficacy and effectiveness studies and 15 years of field experience. Vaccine. 2013;31(45):5178-91.

61. McIntyre PB, Edwards KM. Genetically modified pertussis toxin: a quantum leap? The Lancet Infectious diseases. 2018.

62. Pitisuttithum P, Chokephaibulkit K, Sirivichayakul C, Sricharoenchai S, Dhitavat J, Pitisuthitham A, et al. Antibody persistence after vaccination of adolescents with monovalent and combined acellular pertussis vaccines containing genetically inactivated pertussis toxin: a phase 2/3 randomised, controlled, non-inferiority trial. The Lancet Infectious diseases. 2018.

63. Sirivichayakul C, Chanthavanich P, Limkittikul K, Siegrist CA, Wijagkanalan W, Chinwangso P, et al. Safety and immunogenicity of a combined Tetanus, Diphtheria, recombinant acellular Pertussis vaccine (TdaP) in healthy Thai adults. Hum Vaccin Immunother. 2017;13(1):136-43.

64. WHO. Pertussis vaccines: WHO position paper, August 2015--Recommendations. Vaccine. 2016;34(12):1423-5.

65. Preston N. Pertussis today. In: Wardlaw AC, Parton R, editors. Pathogenesis and immunity in pertussis. Chichester, UK:: John Wiley & Son Limited; 1988. p. 1–19.

66. Nowlan M, Turner N, Kiedrzynski T, Murfitt D, Sawicki N. Pertussis control strategies: A consistent approach for New Zealand. Synopsis of Ministry of Health Workshop, April 2015. The New Zealand medical journal. 2016;129(1433):78-85.

67. GlaxoSmithKline Ltd. NZ Datasheet: Infanrix-hexa. Medsafe; 2015.

68. GlaxoSmithKline Ltd. NZ Datasheet: Infanrix-IPV. Medsafe; 2015.

69. GlaxoSmithKline Ltd. NZ datasheet: Boostrix. Medsafe; 2016.

70. Sanofi New Zealand. NZ Datasheet: Adacel. Medsafe; 2017.

71. Walls T, Graham P, Petousis-Harris H, Hill L, Austin N. Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study. BMJ Open. 2016;6(1):e009536.

72. Centro Nacional para la Salud de la Infancia y Adolescencia. Vacuna Pentevalente Acelular Mexico: gob.mx; 2015 [cited 2018 18 October]. Available from: https://www.gob.mx/salud/censia/articulos/vacuna-pentavalente-acelular-131142?state=published

73. Rice TF, Diavatopoulos DA, Smits GP, van Gageldonk P, Berbers G, van der Klis F, et al. Antibody responses to Bordetella pertussis and other childhood vaccines in infants born to mothers who received pertussis vaccine in pregnancy- a prospective, observational cohort study from the UK. Clinical and experimental immunology. 2019.

74. Kapil P, Papin JF, Wolf RF, Zimmerman LI, Wagner LD, Merkel TJ. Maternal Vaccination With a Monocomponent Pertussis Toxoid Vaccine Is Sufficient to Protect Infants in a Baboon Model of Whooping Cough. J Infect Dis. 2018;217(8):1231-6.

75. Becker-Dreps S, Butler AM, McGrath LJ, Boggess KA, Weber DJ, Li D, et al. Effectiveness of Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination in the Prevention of Infant Pertussis in the U.S. American journal of preventive medicine. 2018;55(2):159-66.

76. Edwards KM. Protecting Infants From Pertussis Disease. JAMA Pediatr. 2018.

77. Martinón-Torres F, Heininger U, Thomson A, Wirsing von Konig CH. Controlling pertussis: how can we do it? A focus on immunization. Expert Rev Vaccines. 2018;17(4):289-97.

78. Chiappini E, Stival A, Galli L, de Martino M. Pertussis re-emergence in the post-vaccination era. BMC Infect Dis. 2013;13:151.

79. Halperin SA, Donovan C, Marshall GS, Pool V, Decker MD, Johnson DR, et al. Randomized Controlled Trial of the Safety and Immunogenicity of Revaccination With Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) in Adults 10 Years After a Previous Dose. J Pediatric Infect Dis Soc. 2018.

80. Palazzo R, Carollo M, Bianco M, Fedele G, Schiavoni I, Pandolfi E, et al. Persistence of T-cell immune response induced by two acellular pertussis vaccines in children five years after primary vaccination. New Microbiol. 2016;39(1):35-47.

81. SAGE. WHO SAGE pertussis working group Background paper SAGE April 2014. World Health Organization; 2014 14 March 2014.

82. Staten Serum Institut. Laboratory-confirmed whooping cough 2017 Arillerivej, Denmark: Staten Serum Institut; 2018 [updated 25 April 2018]. Available from: https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-denmark/annual-reports-on-disease-incidence/laboratory-confirmed-whooping-cough-2017

83. Silfverdal SA, Icardi G, Vesikari T, Flores SA, Pagnoni MF, Xu J, et al. A Phase III randomized, double-blind, clinical trial of an investigational hexavalent vaccine given at 2, 4, and 11-12 months. Vaccine. 2016;34(33):3810-6.

84. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in Adolescents. Pediatrics. 2016;137(3):e20153326.

85. Briere EC, Pondo T, Schmidt M, Skoff T, Shang N, Naleway A, et al. Assessment of Tdap Vaccination Effectiveness in Adolescents in Integrated Health-Care Systems. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2018;62(6):661-6.

86. Anis E, Moerman L, Ginsberg G, Karakis I, Slater PE, Warshavsky B, et al. Did two booster doses for schoolchildren change the epidemiology of pertussis in Israel? Journal of public health policy. 2018;39(3):304-17.

87. Australian Government Department of Health. National Immunisation Program Schedule: Commonwealth of Australia; 2018 [updated 3 September 2018; cited 2018 9 October]. Available from: https://beta.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule

88. Government of Canada. Canada's Provincial and Territorial Routine (and Catch-up) Vaccination Routine Schedule Programs for Infants and Children 2018 [updated August 2018; cited 2018 9 October ]. Available from: https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/provincial-territorial-routine-vaccination-programs-infants-children.html

89. Government of Canada. Provincial and Territorial Routine Vaccination Programs for Healthy, Previously Immunized Adults: Canada.ca; 2018 [updated 10 September 2018; cited 2018 9 October]. Available from: https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/routine-vaccination-healthy-previously-immunized-adult.html

90. Brophy J, Baclic O, Tunis MC, on behalf of the National Advisory Committee on Immunization (NACI). Summary of the NACI Update on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine. . Can Commun Dis Rep. 2018;44(3/4):91-4.

91. ECDC. Vaccine Schedular. Pertussis: Recommended vaccinations: European Centre for Disease Prevention and Control (ECDC); 2018 [cited 2018 9 October]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=3&SelectedCountryIdByDisease=-1

92. Commission fédérale pour les vaccinations. Plan de vaccination suisse 2018. Directives et recommandations. [Internet]. Berne: Office fédéral de la santé publique,; 2018 [cited 4 February 2019]. Available from: www.bag.admin.ch/plandevaccination

93. Blanchard-Rohner G, Eberhardt C. Review of maternal immunisation during pregnancy: focus on pertussis and influenza. Swiss Med Wkly. 2017;147:w14526.

94. Public Health England. Complete routine immunisation schedule: Crown copyright; 2018 [updated 17 September 2018; cited 2018 9 October]. Available from: https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule

95. Centers for Disease Control and Prevention. Immunization Schedules: US Department of Health and Human Services; 2018 [updated 6 February 2018; cited 2018 9 October]. Available from: https://www.cdc.gov/vaccines/schedules/index.html