Review of evidence to inform the New Zealand National Immunisation Programme, 2024: Pertussis

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Immunisation Advisory Centre

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Executive Summary

Purpose of the review of evidence on pertussis, 2024

The aim of this document is to review key questions relevant to improving pertussis control by immunisation in Aotearoa New Zealand (NZ), focussing on protecting infants. It will consider scientific evidence published from 2019 – 2024, and since our previous reviews in 2018 and 2019.[1, 2] It is not a systematic review. Not all the aspects of pertussis immunisation have been reviewed (e.g. pertussis infection in adults and cost-benefit analyses are not considered). Conclusions given represent the author and reviewer's interpretation of the literature.

Key questions

1. Immunisation schedule
    a. What implications are there for commencing the infant schedule at age 6 weeks in the context of antenatal vaccination?
    b. What is the optimal timing and frequency of vaccinations in pregnancy?
    c. As a follow-up from a previous review, should the NZ National Immunisation Schedule (Schedule) include an additional pertussis vaccination with a DTaP vaccine in the second year of life (toddler booster)?
    d. Is there a role for the adolescent booster in pertussis control?
2. Occupational vaccinations and cocooning
    a. Does occupational vaccination and caregiver/household cocooning provide additional protection to vulnerable groups?
    b. How frequently are doses needed and for whom? Are there safety concerns around repeated dosing?
    c. What vaccine options are there?
3. Vaccine choice
    a. What are the benefits and risks of a whole cell / acellular mixed schedule?
    b. Can monovalent recombinant acellular pertussis vaccine be used effectively to reduce tetanus and diphtheria toxoid exposures?
    c. What other vaccine options are in development? (eg live attenuate nasal vaccines and other technologies)

Burden of pertussis

Infants too young to commence the primary immunisation course are at greatest risk of severe pertussis, hospitalisation, ICU admission and death,[3] but the risk of ICU admission and death is reduced by more than 90% by appropriately timed antenatal vaccination. Preterm birth before 37 weeks gestation is further associated with the most severe pertussis and longer hospital stays.[4, 5] Other risk factors for high disease severity include the presence of certain comorbidities, such as respiratory, heart or kidney disease, HIV infection and being under nourished.[6, 7] Virtually all pertussis-associated deaths are in unimmunised infants,

usually younger than 3 months of age. Nasopharyngeal carriage of *Bordetella pertussis* in caregivers is a significant risk factor for infection of infants (at around 14 times the risk).[7]

The introduction of acellular pertussis (aP) vaccines shifted the burden of pertussis in young children to older children, adolescents and young adults.[8] A booster dose given in early adolescence helped to reduce this burden in that age group. Although pertussis is not life-threatening in most young people, it can have high levels of morbidity and risks transmission to peers and infants, particularly if those infected are parents.

Pertussis following the COVID-19 pandemic

The public health measures and the impact of COVID-19 on healthcare systems has altered the usual three-to-five yearly pattern of pertussis outbreaks.[9, 10] A resurgence in pertussis infections is being observed globally.[11] This is associated with reduced population immunity due to a lack of exposure to *B. pertussis* and a decline in immunisation coverage.[12] Declines in coverage for childhood vaccinations and poor uptake of antenatal pertussis vaccinations have resulted in a high rate of infant hospitalisations. This gap in immunity was associated with infant deaths in NZ in 2023 and the UK in 2024.[13, 14] On 22 November 2024, a pertussis epidemic was officially declared in NZ. At that time, with a total of 1,009 confirmed, probably and suspected pertussis cases, 46 out of 63 (73%) of pertussis cases aged under 1 year and 13 out of 113 (9.8%) cases aged 1-4 years were hospitalised. No deaths had been reported in 2024 by 22 November. At the time of writing, case numbers continue to climb rapidly.

Vaccine effectiveness in infants and young children

This review considers the most recent literature on the effectiveness of pertussis vaccination in infants with combined diphtheria, tetanus and acellular pertussis vaccines (DTaP). Infants require a three-dose primary course of a pertussis-containing vaccine to be optimally protected against pertussis in the first year of life. Vaccine effectiveness significantly increases with each dose given in infancy.[5, 15, 16] A fourth dose in the second year of life provides a very high level of protection to young children.[16] Compared with fully vaccinated children, unvaccinated children were shown to be 13 times more likely to have pertussis infection and twice as likely as partially vaccinated children.[17] However, unvaccinated and partially vaccinated children are only a small proportion of the total pertussis cases. Having at least one dose of pertussis vaccine halves the risk of pertussis hospitalisation in those aged 2 – 11 months, two doses are around 75% and three doses 98% effective against pertussis hospitalisation.[15, 16]

Children with comorbidities

Comorbidities increase the risk of severe pertussis in children. On-time vaccination and antenatal vaccination improves the outcomes for all infants up to the age of 6 months. But hospitalisation risk is six times higher for children with comorbidities from age 6 months (ie after dose three) than for healthy children.[6] To improve pertussis outcomes in infants with complex health conditions, particularly during the months between completion of the primary course and the toddler booster, further measures such as additional doses or improved vaccines are likely to be needed in addition to the routine schedule.[6] Children in NZ do not currently receive a booster dose in the second year of life, including those with comorbidities – this is likely to increase the risk of severe pertussis in high-risk toddlers.

Duration of protection

Protection provided by pertussis vaccines lasts for a few years, but the risk of infection increases with time since the last dose.[17] In young children, who have received fewer doses than older children, protection

wanes within three to five years.[18, 19] Additional doses after the primary course help reduce the risk of pertussis in children.

Conclusions

The three-dose primary course is highly protective for infants. Children more distant from their vaccinations are at a higher risk of pertussis, which can be temporarily reduced by additional doses after the primary course. The need for a booster dose is especially important for young children with comorbidities or other factors, such as under nourishment, that increase their risk of requiring hospital care for pertussis.

Pertussis vaccination given in pregnancy - infant's 'dose zero'

Vaccinating during pregnancy with Tdap (combined tetanus, diphtheria and acellular pertussis vaccine), to provide passive antibody protection against pertussis to young infants, was first introduced in 2011 in the United States of America (US), in 2012 in the United Kingdom (UK) and in Aotearoa New Zealand in 2013. More than 40 countries have implemented maternal Tdap vaccination, although uptake is suboptimal in many of these countries including New Zealand. Recommendations around the timing of pertussis vaccination in pregnancy varies widely around the world.[20] This review assesses the recent evidence on the safety, effectiveness and the optimal timing for maternal vaccination.

Safety of pertussis vaccination in pregnancy

Safety data on pertussis vaccination support the recommendations to be vaccinated in pregnancy.[20, 21] Pregnancy is associated with complications unrelated to vaccination, making it more challenging to decipher any adverse events that are temporally and not causally associated with vaccination. An example investigated was chorioamnionitis, which occurs in almost 3% of unvaccinated pregnancies.[22] Despite a systematic review predicting three additional cases per 1,000 vaccinated women, no association between pertussis vaccination and clinical consequences of chorioamnionitis (ie. preterm birth and sepsis) were shown.[22]

Reassuringly, in relation to the recommendation to repeat Tdap vaccination in each pregnancy, the systemic and local reactions were not increased with repeat vaccinations given one to five years apart in subsequent pregnancies.[23] Unfortunately, monitoring of vaccine safety in pregnancy suffers from a lack of standardisation because, despite established definitions for adverse events (GAIA) recognised by the Brighton Collaboration, these are rarely used in studies.[24] However, robust data have demonstrated that there are no concerns for biologically plausible adverse events associated with Tdap in pregnancy.

Immunogenicity of antenatal vaccination and passive antibody transfer

Timing of vaccination in pregnancy

Data is limited around differences in timing in pregnancy of Tdap vaccination, particularly when given earlier than the late second trimester. Although antibody levels at birth in infants born at term appear to be lower if the vaccine is given earlier, without a defined correlate of protection, the clinical relevance cannot be extrapolated.[20, 25]

Preterm infants

Infants born prematurely benefit the most from earlier vaccine administration in pregnancy.[25] These infants are at highest risk of severe pertussis[26] and would not receive sufficient maternal antibody if vaccine were

given later in pregnancy. Early vaccination recommendations would apply to all pregnancies since timing of birth is not predictable.

Subsequent pregnancy

Although antibody transfer during a subsequent pregnancy after prior vaccination seems to be slightly diminished, its clinical significance remains unclear.[27] Nonetheless, vaccination is significantly more beneficial than not vaccinating, particularly since infants are at risk of pertussis exposure from older siblings.

Coadministration

Coadministration with influenza and COVID-19 vaccines in pregnancy did not significantly affect maternal pertussis antibody titres against Tdap antigens.[28, 29]

Effectiveness of antenatal vaccination in protecting infants

Antenatal vaccination against pertussis has been shown to be around 90% effective overall in preventing pertussis of young infants.[30] The greatest effectiveness is observed in infants under 2 months old (over 90%) against pertussis hospitalisation, with substantial protection maintained for up to 8 months.[31] Infants born to vaccinated mothers tend to develop pertussis at a later age than those who are unvaccinated in pregnancy. This allows more time for infants to become fully vaccinated, for their body and airway size to increase, and their immune system to develop, thereby likely reduce disease severity.[31]

Timing of vaccination in pregnancy

Data is limited around differences in effectiveness in relation to timing in pregnancy of Tdap vaccination, particularly when given in the second trimester. The timing of antenatal vaccination does not seem to significantly affect vaccine effectiveness in infants up to 6 months, if administered more than seven days before delivery.[32] A longer interval before delivery may enhance effectiveness slightly. Offering pertussis vaccination earlier in pregnancy has been shown to increase vaccine uptake.[32] Early vaccination also provides protection against pertussis for infants born prematurely.

Maternal antibody interference of the infant immune response

There is good evidence that the presence of maternal antibody results in some interference with the antibody response to the infant primary course, whether vaccinated in pregnancy or not.[33] The implications of this interference are uncertain in the absence of a defined correlate of protection for pertussis. It does not appear to increase the risk for more severe disease. Maternal antibodies diminish quickly after birth, making it crucial to time the completion of infant's primary vaccinations before this protection wanes completely.

Evidence strongly suggests that infants born to vaccinated mothers continue to be protected even with reduced antibody titres and that maternal vaccination provides passive antibody protection beyond the completion of the primary course.[31] For New Zealand, it is unclear whether moving the start of the immunisation schedule from 6 weeks to 2 or 3 months would make a difference to pertussis control in infants born to mothers who are vaccinated in pregnancy.[34]

Effectiveness of infants' primary course following antenatal vaccination

The long-term impact of maternal vaccination causing potential blunting of the infant antibody responses to primary vaccinations is poorly understood. The limited evidence shows little impactful effect on vaccine effectiveness.[31, 35] Findings support the role of maternal vaccination in protecting infants, even in the

presence of blunted primary course responses. Continual monitoring, particularly now that pertussis cases are on the increase, is required to further determine whether the antibody interference is clinically meaningful.

Immunogenicity following booster doses following antenatal vaccination

In infants who received a three-dose primary course and booster at age 18 months, maternal antibody did not significantly impact infant pertussis antibody titres post booster.[36] In the absence of a toddler booster dose, lower antibody levels against pertussis toxin continue to be observed in preschool-aged children who were born to mothers vaccinated against pertussis in pregnancy.[37] A preschool booster can help to remedy this. Furthermore, it is unclear whether the blunting from antenatal vaccination is clinically relevant since, although antibody levels tend to be lower in toddlers (even after a booster dose)[38] or preschool children (in the absence of toddler booster)[37] who were vaccinated antenatally, the absolute differences between titres were small.

Conclusions of pertussis vaccination given pregnancy

Maternal vaccination is highly effective at protecting infants against pertussis prior to completing their primary course. This age group are at the highest risk of severe pertussis and death due to pertussis.

The limited evidence shows little impact of antenatal vaccination on the vaccine effectiveness of the infant primary course and early childhood booster doses against pertussis. Despite lower antibody responses in infants and toddlers born to mothers who were vaccinated in pregnancy, it is unclear whether this is clinically relevant. Although antibody levels trended lower in toddlers (even after a booster dose) or preschool children (in the absence of toddler booster) who were vaccinated antenatally, the absolute differences between titres were small.

In the current NZ context, without a booster dose in the second year of life and starting the primary course at 6 weeks of age, this interference could be more impactful for infants and young children aged from 6 months to 4 years.

Immunisation schedules and booster doses

To achieve optimal control of pertussis with the current vaccines could mean adjusting the immunisation schedule. This review considered the evidence for the infant primary course and for booster doses in toddlers, children and adolescents.

Infant primary course and toddler booster doses

New Zealand has a three-dose primary (3+0) pertussis immunisation schedule starting at age of 6 weeks. The studies reviewed suggest that a booster dose given in the second year of life improves protection against pertussis in toddlers. Timing of the primary course appears to be less important than completing the primary course, but timing differs with each country.[39] Three-dose schedules, whether given as two primary plus booster (2+1) or three primary (3+0) doses, appear to be less protective than four dose schedules (3+1).[36, 40] Most countries found a 2+1 schedule (2-3-11/12 months) to be less protective under the age of 2 years than a 3+1 course (2-3-4 and 16/18 m), particularly for those born to mothers who were vaccinated in pregnancy.[36, 41]

Adolescent boosters

A booster dose given to adolescents can provide direct protection to the individual, and possibly indirect protection to their age cohort, but limited indirect protection to younger age groups.[42, 43] In our previous review[2], it was noted that disease severity is reduced in vaccinated adolescents, and this would be particularly beneficial to those with respiratory comorbidities.

Conclusion

A three-dose primary course plus a booster in the second year of life is the most effective strategy to provide active protection to infants, particularly for infants born to mothers vaccinated in pregnancy. Adolescent boosters provide direct protection against pertussis and indirect protection to their peer group, but are less able to prevent transmission and provide indirect protection to younger age groups.

Booster doses in non-pregnant adults

Although the current vaccines do not effectively prevent carriage of *B. pertussis*, vaccinating those in close contact with infants, such those working in birthing and neonatal care, can help to prevent disease in infants. The incremental benefit of vaccinating close contacts (cocooning) when an infant has passive immunity through vaccination in pregnancy is unclear.

Over recent years, as a consequence of COVID-19 control measures, natural boosting of pertussis immunity has been reduced due to low exposure to circulating *B. pertussis*.[10, 12] Therefore, the use of booster doses could be more important in occupational and household settings than pre-2020.

Recent data on the safety and effectiveness of repeated occupational vaccinations is limited. Given the waning immunity seen following aP vaccination, it seems logical to maintain recommendations for repeat Tdap booster doses every five to 10 years in those working closely with young infants and other high-risk groups. This is becoming increasingly important for younger staff who were born since 2000 and primed solely with aP vaccines. Pertussis vaccination is also encouraged in settings beyond health care, such as early childhood education and daycare centres.[44]

One concern for health care workers receiving repeated Tdap doses is around safety and the potential for an increased risk for adverse events. The risk for solicited local and systemic adverse events in adults was slightly higher (94% vs 88%) when given five years[45] apart compared with 10 years[46] apart, but both were generally well tolerated. Modest protection (52% effectiveness) against PCR-confirmed pertussis has been demonstrated for up to six years after a Tdap booster dose in older adults (aged 46 – 81 years) in Australia.[47] This review did not identify any recent papers investigating transmission of *B. pertussis* from health care workers to patients with time since vaccination. In the US, due to its limited ability to interrupt transmission, Tdap revaccination of healthcare workers is not generally used.

For cocooning of young infants to be an effective strategy, vaccination of all caregivers needs to be conducted preferably prior to the birth of an infant. Antenatal vaccination of the pregnant person is the most effective way to protect to the youngest infants.[32] Other caregivers also should not wait until the birth to be immunised to provide an additional layer of protection. In many cases though, where maternal vaccination does not happen the other caregivers are also unvaccinated, particularly for those visiting from overseas.[48]

Conclusion

Passive immunity provided by antenatal vaccination provides the greatest protection for infants too young to be fully immunised. Evidence for effectiveness of household cocooning is weak and not sufficient to be a reliable way to protect the youngest infants. For any incremental benefit, ideally, household members of newborn infants need to be vaccinated prior to the infant's birth and in conjunction with antenatal vaccination. An important question to be considered is, 'what would be the most effective strategy if maternal vaccination is missed?' In all cases, emphasis needs to be direct protection of the infant, at least by vaccinating the infant on time.

Although aP vaccines are less able to prevent nasopharyngeal carriage of *B. pertussis*, they can reduce disease spread by reducing the risk of active infection and symptoms, like coughing. Occupational vaccination and household cocooning has modest effectiveness in preventing pertussis, but it is a valid strategy alongside direct vaccination of pregnant women, infants and young children. Five yearly Tdap vaccination is likely to be most effective to prevent symptomatic transmission to patients. This is particularly relevant for those who were born since 2000 and those working with the most high-risk individuals (such as in neonatal units, birthing units, and with severely immunocompromised individuals). However, vaccination is unlikely to prevent transmission from those who are not symptomatic or acquisition of *B. pertussis* in the nasopharynx.

Comparison of whole-cell and acellular pertussis vaccines

A major focus of research around pertussis vaccination is the long-lasting differences in immune response between whole-cell pertussis (wP) and acellular pertussis (aP) vaccines. The resurgence in pertussis in the last few decades is potentially associated with the change from wP vaccines following the introduction of aP vaccines in the late 1990s and early 2000s. A range of factors have been attributed to this resurgence. These include those related to the switch to aP vaccines resulting in more rapid waning immunity and transmission from asymptomatic carriers, but also from evolutionary selective pressure on *B. pertussis* due to vaccine antigens, and improvements in pertussis detection and surveillance identifying more cases.[49]

Immunogenicity

In recent years, emerging evidence suggests a difference in how the immune system is primed with acellular or whole-cell pertussis vaccines. Differences in the antibody[50] and T cell[51] profile are shown between those primed with aP or wP vaccines. This difference in priming polarises the subsequent responses to vaccination or wild-type infection towards either a T helper-1 (Th1) type profile for wP or a T helper-2 type response (Th2/Th17) for aP.[52] Further studies have shown that this difference affects the immune memory within mucosal tissue into adulthood.[51, 53] Those primed with whole-cell pertussis vaccines appear to have longer lasting immunity.

Effectiveness

Children vaccinated solely with three-component aP vaccines appear to have less protection against pertussis than those who were fully vaccinated with wP vaccines or primed with wP in mixed wP/aP schedules.[54]

Mixed whole cell and acellular pertussis vaccine primary course

There may be a role for giving infants a wP-containing vaccine as the first infant dose to improve pertussis control for the long term. Waning antibody levels and a lack of sterilising immunity is associated with the aP programme introduction. Priming with the first dose of wP and then following up with less reactogenic aP vaccinations could prevent the skewing of the T cell response towards the Th2 profile, thereby, improving the duration of protection and sterilising immunity of pertussis vaccinations. However, there is limited data to date to determine whether this is a valid strategy. Noting also that no wP-containing vaccines are available nor approved for use in NZ.

Mixed schedules have been proposed since reactogenicity and adverse reactions increase with subsequent doses of wP. There appears to be no additional safety concerns when wP is given as a single first dose instead of aP.[55] Furthermore, a study of administrative data appeared to show a reduced risk of food allergies in children given wP as a first dose.[56] An ongoing study in Australia is investigating this further.[57]

A Thai study found that the presence of maternal antibody following antenatal vaccination had a greater impact on the pertussis-specific antibody response to wP vaccination than aP. Despite this, at all stages of the schedule, the antibody functionality was greater for the infants vaccinated with wP vaccine.[58]

But this strategy would add a layer of complexity to an already busy immunisation schedule, and any signs of increased reactogenicity could be barriers for uptake. Careful consideration is required in relation to vaccine confidence – it is known that adverse experiences during the first vaccination event can result in parental hesitancy to return for subsequent vaccinations.[59] However, despite higher rates of self-limiting injection-site pain and irritability in infants who received wP first dose, the Australian study found that parental acceptance of wP was high and they would consider the schedule again for subsequent children.[57] During this study, no cases of hypotonic hyporesponsive episodes were reported. [57] New Zealand has introduced meningococcal B vaccination for infants, and due to an increased risk of fever, recommends anti-pyrectics (paracetamol or ibuprofen) prior to and soon after vaccination. Evidence suggests that this approach could also reduce the reactogenicity of wP vaccines without impacting on immunogenicity.[57]

Conclusion

Theoretically, the evidence suggests that a mixed wP/aP schedule could overcome the limitations of aP vaccines. In practice, several challenges remain.

- No wP-containing pertussis vaccines are approved for use in New Zealand.
- It remains uncertain as to whether this approach could reduce the reactogenicity of wP vaccines without reducing immunogenicity.
- The potential for greater reactogenicity with wP vaccines could reduce parental confidence after dose one, and result in delayed uptake of aP doses. It may be better accepted if given alongside the meningococcal B vaccine with paracetamol. But it is unknown whether the risk of adverse events would increase if wP and meningococcal B vaccines were given concurrently.
- By having a different vaccine for the first primary dose from subsequent primary doses, is likely to cause confusion and errors in service delivery.

Recombinant and other vaccines

Due to the limitations of the whole-cell and acellular vaccines, other vaccine technologies are being evaluated. This includes a recombinant genetically detoxified pertussis toxin vaccine, live attenuate whole-cell pertussis and novel adjuvant technologies.

Recombinant acellular pertussis vaccines

Pertussis-only or combined recombinant aP vaccines contain genetically detoxified pertussis toxin (PT_{gen}). They have been found to be a safe and immunogenic option for pertussis booster vaccination in adolescents and adults, including in pregnancy. [60-62] A pertussis-only (aP_{gen}) vaccine, (Pertagen® manufactured by BioNet), is used routinely in Asia, including in pregnancy in Thailand, and is undergoing regulatory review in Australia and Europe.

The advantage of a pertussis-only vaccine is that repeat doses, in subsequent pregnancies or for occupational vaccination, can be given without the reactogenicity concerns of giving more tetanus and diphtheria toxoid vaccinations than necessary. The safety and immunogenicity of PT_{gen}-containing monovalent aP and Tdap vaccines were favourable. There were no safety concerns in pregnant and non-pregnant recipients. Like standard Tdap vaccines, mild to moderate localised injection-site pain and muscle pain were the most reported reactions. The immunogenicity of genetically detoxified PT appeared to be superior to chemically detoxified PT, with longer lasting and higher levels of pertussis neutralising antibodies.[61] The use of the pertussis-only aP_{gen} vaccine in infants also looks promising as a birth dose for those not vaccinated in pregnancy, but data is limited to date.[63]

Other vaccine candidates and technologies

Improvements to pertussis vaccination strategies, to prevent transmission (sterilising immunity) and to produce longer lasting immunity without increasing reactogenicity, require alternative approaches to vaccine design and reverse vaccinology. A range of avenues are being explored.

Clinical development of an intranasal live-attenuated whole cell vaccine (designated BPZE1) is investigating induction of a sterilising mucosal response.[64-66] Tissue-residence memory cells in mucosal tissue have been shown to be important for pertussis immune memory and IgA production.[51] Other avenues include the use of recombinant DNA technology to identify different pertussis epitope targets. Also, following the success of meningococcal B vaccines, a role for B. pertussis outer membrane vesicles is being evaluated. Other approaches include the development of adjuvants to overcome the skewing of the T cell response by the current alum-adjuvanted aP vaccines.[67]

Overall conclusions of this review

Topic	Questions	Findings
Immunisation schedule	Does passively transferred antibody interfere with the primary course of childhood vaccinations?	• Pregnancy dose needs to be considered as infant's dose zero and a full primary course is required thereafter. • Passive immunity lasts for around 6 months, but it remains important for infants to be vaccinated on time by 6 months of age according to the schedule to maintain full protection. • Immunologically, there is evidence for interference of maternal antibodies with the primary course. The clinical relevance is unclear, particularly between age of 8 months to first booster dose.
	Timing and frequency antenatal/maternal doses.	• Data is limited for vaccination given before the late 2nd trimester. Vaccination is effective from the 2nd trimester up to 7 days before birth. Earlier vaccination provides protection for preterm infants. No safety concerns around giving vaccination in each pregnancy. • Possible slight reduction in antibody transfer in a second pregnancy, but the clinical relevance is unclear. Being vaccinated in pregnancy is better than not.
	Booster in second year of life	• With low immunity boosting with reduced circulation of *B. pertussis* during the COVID-19 pandemic and potential interference from maternal vaccination, evidence suggests that toddlers benefit from a booster dose given around a year after their last primary dose. • Young children with comorbidities would be better protected with at least one additional dose.
	Booster in adolescence	• Adolescent boosters can provide indirect protection within their peer groups but no evidence of this to younger children. The pertussis can be severe in this age group. When primed with aP vaccines, protection is unlikely to last into adulthood / parenthood.
Occupational vaccinations and household cocooning	What is the evidence of protection to vulnerable groups?	• Those primed with aP vaccines are more likely to require 5-yearly doses than those primed with wP. Boosters prevent symptomatic infection but not carriage of *B. pertussis.* • Data is limited the risk of transmission with time since last booster. But it is expected to be less in asymptomatic people than in those with active disease. • The incidence of AE is slightly higher with closer doses, but these are generally well tolerated. • More frequent doses are recommended for those in close contact to young infants, unvaccinated pregnant people, and individuals with comorbidities that increase from pertussis. • Maternal immunisation is the most effective strategy. There is limited evidence that cocooning of household members, especially postpartum, is beneficial.
Vaccine choice	Whole cell / acellular mixed schedule	• Giving wP as a first dose in infancy then subsequent doses with aP induces a more protective T cell profile. • Reactogenicity increases with each wP dose given, therefore, acceptability of a single first dose with wP is higher. Particularly where meningococcal B vaccine is given with paracetamol. • Sterilising immunity provided by wP priming improves the ability of pertussis vaccines to prevent *B. pertussis* carriage and thereby transmission from asymptomatic carriers.
	Monovalent recombinant acellular pertussis vaccine	• A recombinant aP vaccine appears to have a longer duration of immunity (10-yearly vaccination) than current aP vaccines. A pertussis-only vaccine formulation could be used where Td vaccination is not required. This vaccine is not approved for use or available in NZ. • Offering aP-only vaccine would be beneficial and probably more acceptable to women who have multiple pregnancies. Also, to other people requiring multiple doses in their working lifetime. • Data is limited to date on the immunogenicity and effectiveness of birth dose of monovalent aP, for those not vaccinated antenatally.
	Other vaccine options	• The live attenuate intranasal pertussis vaccine induces a mucosal response and has a better accepted route of delivery. • Other technologies in development could improve the duration of protection of pertussis vaccinations and a broader, more protective response.

Recommendations and challenges for NZ

The following summarises the findings of this review in terms of the New Zealand National Immunisation Programme.

- Maximising antenatal vaccination is the single most effective way to protect young infants. High coverage and timeliness of the primary series will maintain this initial protection.
- Maternal pertussis vaccine uptake is an essential component of pertussis control to prevent severe consequences of pertussis in the youngest infants.
    - Uptake remains suboptimal, particularly in Māori and Pacific women, despite the vaccine being available and funded in pregnancy for over a decade.
- Addition of booster dose is recommended in the second year of life.
    - This is due to potentially reduced immunogenicity following the primary course and low population immunity post-COVID-19.
    - Older infants and toddlers with comorbidities are particularly at risk of severe pertussis as protective antibody levels wane.
    - This will be especially important once high maternal pertussis vaccine uptake is achieved.
- Despite the potential for blunting of the immune response, from the current evidence, we cannot confirm whether changing the start of the immunisation schedule (ie from 6 weeks to 2 or 3 months) for infants born to mothers vaccinated in pregnancy will significantly reduce interference of maternal antibodies on the infant antibody levels or improve protection.
- Were there two schedules, one for those vaccinated in pregnancy and one for those not, it would make service delivery more complex.
    - A later first dose for those who were vaccinated in pregnancy risks those who were not also to receive delayed vaccination, thereby defeating the purpose of starting the schedule at 6 weeks.
    - Currently, the AIR does not record when a vaccination is given in pregnancy and is unable to link infants' immunisation record to the maternal record. Therefore, providers are unable to identify if a newborn was vaccinated in pregnancy or not.
- There remains a role for preschool and adolescent booster doses, particularly for those primed with aP vaccines.
    - To reduce the risk of adverse reactions, Tdap is recommended at age 4 years if DTaP is given in the second year of life.
- Although a mixed wP/aP schedule may improve the immunogenicity and duration of protection of pertussis vaccinations, parental acceptance and concerns about reactogenicity, and the risk for administration of the wrong vaccine are significant constraining factors for implementation. Furthermore, wP-containing vaccines are not approved for use in New Zealand.
- Funding a vaccine for close household members and caregivers of newborn infants, for those born to mothers who missed maternal vaccination or were born too soon after maternal vaccination (ie within 14 days), may be beneficial. But in practice, be challenging to implement to ensure vaccination of caregivers was received soon enough after birth to be effective.

- Consider introducing a recombinant monovalent aP vaccine for occupational vaccinations and maternal vaccinations where Td is not required. (dependent on Medsafe approval, manufacturing capacity and cost). Applications for regulatory approval have been submitted in Europe and Australia.
- Evaluate future vaccine products as they become available – the first likely to be the intranasally administered live attenuated pertussis vaccine. It will be quite some time before this can be considered (as in bullet point above).

Outstanding questions and challenges

In 2015, the Ministry of Health and IMAC held a workshop to discuss strategies of pertussis control. It covered aspects of immunisation schedule timing, antenatal immunisation and communication, improving immunisation coverage and service delivery, and data collection and surveillance.[68] Perhaps it is time to revisit this in 2025? Progress has been made in the last decade, particularly around maternal vaccinations, but questions and barriers remain.

The biggest question in New Zealand is whether higher uptake of maternal vaccination will affect the epidemiology of pertussis in toddlers, in the absence of a booster dose. Evidence suggests that this is very unlikely to affect protection against severe disease but may result in milder infections.[31] Currently, maternal uptake is suboptimal and timeliness of infant vaccinations is poor. As well as improving maternal and infant vaccine coverage, the work to answer this question would require improved data collection and data linking between maternal vaccinations, aligning infant vaccination records with maternal records, and identification and notification of all suspected pertussis cases. But the limited testing capacity of NZ laboratories would not enable suspected cases to be confirmed.

The evidence does not suggest any additional benefit in vaccinating of household contacts through cocooning after the infant is born, when the mother was not vaccinated in pregnancy. In these cases, is there any advantage of vaccinating infants before 6 weeks of age? Australia considers a first dose of DTaP-IPV-HepB/Hib given from 4 weeks of age as a valid dose (note that this in conjunction with a booster dose given in the second year of life).[69] However, unless there were extenuating circumstances as to why the mother was unable to be vaccinated in pregnancy, this concept raises the question as to whether people who have not been vaccinated in pregnancy would be agreeable to or could access vaccination of their infant earlier than 6 weeks. Generally, parents who choose to be vaccinated in pregnancy are more likely to vaccinate their infants and on time.[31, 70]

In addition to infants, older adults may also be at increased risk of pertussis hospitalisation. This group was not covered in this review of evidence. A further review of the literature is required to quantify this risk and identify which adult groups are at the highest risk from severe disease or adverse outcomes.

Updates suggested for the Immunisation Handbook 2024

- Effectiveness data for maternal vaccination.
- Additional vaccine safety data for maternal vaccination.
- Emphasise that maternal vaccination is a priority. In addition to vaccination as soon as possible during pregnancy, vaccination of close household members of a newborn is best conducted prior to birth or two weeks prior to seeing the infant.

Abbreviations

AEFI	adverse events following immunisation
AESI	adverse events of special interest
aP	acellular pertussis vaccine
aP_{gen}	recombinant acellular pertussis vaccine with genetically detoxified pertussis toxin
BC	British Colombia
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DT	diphtheria toxoid
DTaP-IPV-HepB/Hib	combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines.
ECE	early childhood education
EPI	Expanded programme for immunisation
ESR	Institute for Environmental and Scientific Research
EU/ml	ELISA units per millilitre
FHA	filamentous haemagglutinin
FIM2/3	fimbriae 2 and 3
GAIA	Global Alignment on Immunisation Safety Assessment in Pregnancy
GMC	geometric mean concentration
GMR	geometric mean ratio
Hib	*Haemophilus influenzae* type b
HHE	hypotonic hyporesponsive episode
HR or aHR	hazard ratio or adjusted hazard ratio
IgA	immunoglobulin A
IgG	immunoglobulin G
IU/ml	International units per millilitre
NSW	New South Wales, Australia
NZ	Aotearoa New Zealand
OMV	outer membrane vesicles
OR or aOR	odds ratio or adjusted odds ratio
PBMC	peripheral blood monocytes
PCV13 or PCV10	pneumococcal conjugate vaccine (13 valent or 10-valent)
PT	pertussis toxin
PRN	pertactin
RCT	randomised controlled trial
RR or aRR	risk ratio or adjusted risk ratio
RT-PCR or PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse events
SD	standard deviation of mean
SR/MA	systematic review and meta-analysis
Tdap	tetanus, diphtheria and acellular pertussis vaccine (reduced antigen doses)
$TdaP_{chem}$	tetanus, diphtheria and acellular pertussis vaccine with chemically detoxified pertussis toxin
$TdaP_{gen}$	combined tetanus, diphtheria and recombinant acellular pertussis vaccine

Tdap-IPV	combined tetanus, diphtheria, acellular pertussis and inactivated poliovirus vaccines
TMC	tonsil monocyte cells
T_{RM} cells	tissue resident memory cells
TT	tetanus toxoid
UK	United Kingdom
US	United States of America
VAERS	vaccine adverse events reporting system
VE	vaccine effectiveness
WA	Western Australia
WHO	World Health Organization
wP	whole cell pertussis vaccine

Introduction

Purpose of the review of evidence on pertussis, 2024

The aim of this review is to answer key questions relevant to improving pertussis control in New Zealand (see the table below). It will consider scientific evidence published from 2019 – 2024 since our previous reviews in 2018 and 2019.[1, 2] It is not a systematic review. Not all aspects of pertussis immunisation have been reviewed. Cost-benefit analyses are outside of the scope of this review. Conclusions given represent the author and reviewer's interpretation and comprehension of the literature.

Note, in relation to vaccination in pregnancy and birthing parents, the words maternal and women are used. IMAC acknowledges that people who do not identify as female can become pregnant and are to be included where these terms are used.

Key questions for this review

Topic	Questions	
Immunisation Schedule	Does passively transferred antibody interfere with a child's primary course?	• What are the implications of commencing the infant schedule at age 6 weeks in the context of antenatal vaccination?
	Timing and frequency maternal doses.	• What is the optimal timing and frequency of vaccinations in pregnancy? • For how long do maternal antibodies provide protection? • Does infant birth order affect the effectiveness? • Is there an increasing risk for adverse reactions when giving vaccination in each pregnancy?
	Booster in second year of life (toddler booster)	• Should NZ include an additional dose in the second year of life to the Schedule? • Is there a benefit for high-risk infants?
	Booster in adolescence	• Is there a role for the adolescent booster in pertussis control?
Occupational vaccinations and household cocooning	What is the evidence of protection to vulnerable groups?	• How frequently are doses needed? • Who should be recommended frequent vaccinations? • Are there safety concerns around repeated dosing? • What vaccine options are there?
Vaccine choice	Whole cell / acellular mixed schedule	• Can we overcome the rapid waning in immunity seen with acellular pertussis vaccines? • Is the reactogenicity better than whole cell alone? • Can it reduce pertussis transmission?
	Monovalent recombinant acellular pertussis vaccine	• Does it improve immunogenicity of acellular pertussis vaccines? • Could it have a role in pregnancy? • Can it be given before age 6 weeks in those not vaccinated in pregnancy? • Will it be a better option for repeated doses in occupational pertussis immunisation?
	Other vaccine options	• live attenuate intranasal pertussis vaccine • What other technologies are in development?

Background

Pertussis epidemics usually occur every three to five years, but changes in behaviour and respiratory infection transmission during the COVID-19 pandemic have delayed this cycle. Aotearoa New Zealand (NZ) has now declared pertussis epidemic, as of 22 November 2024, with lowest population immunity than ever before due to a lack of exposure to wild-type infection and several years of declining immunisation coverage. Almost one quarter of young children aged under 2 years are recorded as not fully immunised (coverage of 77%, 30 June 2024) on the Aotearoa Immunisation Register (AIR). Infants bear the greatest burden of pertussis. Their small body size and immature immune system mean that the virulent effects of pertussis toxin are amplified. Medical interventions are unable to reduce disease severity, they can only support breathing and reduce the adverse effects of metabolic changes.

Pertussis is a complex extracellular and intracellular infection. How *B. pertussis* evades body defences and how the immune response works to prevent disease is poorly understood.[71] The bacterium can adhere to and be internalised by the ciliated epithelial cells of the respiratory tract, cause signalling changes within those cells, and to locally and systemically modulate the innate and cellular immune system. Not only does the infection manifest as respiratory disease, but it is also able to cause metabolic disturbance, hypoglycaemia and toxicity in the brain, particularly in young infants.

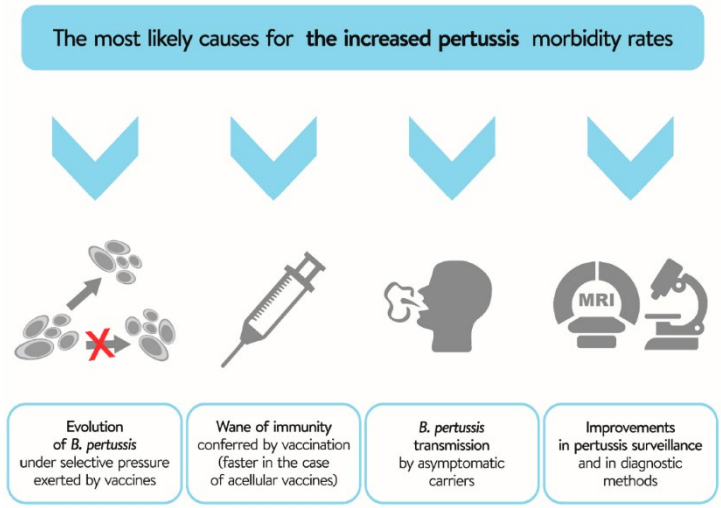
To help to protect the youngest infants before they can be fully immunised, vaccination in pregnancy with tetanus-diphtheria-acellular pertussis vaccine (Tdap, funded in NZ from 13 weeks gestation) provides passive immunity. In this way, maternal antibodies transferred across the placenta to the infant's blood can rapidly neutralise the highly virulent pertussis antigens, in particular pertussis toxin.

Over the last two decades, since acellular pertussis (aP) vaccines replaced whole cell (wP) vaccines in the late 1990s (2000 in NZ), a resurgence in pertussis has been observed in many developed countries using aP vaccines. Two factors related directly to the vaccines have been attributed to this increase.

1. Firstly, immunity following vaccination with aP vaccination wanes faster than wP vaccines.
2. Secondly, aP vaccines are unable to prevent nasopharyngeal carriage of *Bordetella pertussis* and enable transmission from asymptomatic and mildly symptomatic carriers.

Other factors associated in with an increase in cases include improved pertussis surveillance and diagnostic testing, and selective evolutionary pressures on *B. pertussis* exerted by vaccination (Figure 1).[49]

Figure 1: Plausible factors contributing to the increased incidence of whooping cough in recent decades (Szwejser-Zawislak, 2023, open access)



Along with low population immunity, due to an apparent lack of natural boosting and low immunisation coverage, pertussis cases are surging worldwide. The fear in NZ is that with low maternal vaccination uptake and delays in vaccination of infants, infants will be significantly impacted by pertussis. This gap in immunity has been associated with infant deaths in NZ in 2023 and the UK in 2024.[13, 14] The poor immunisation coverage in under 5-year-olds risks there being higher rates of spread and for more severe disease to emerge in age groups that were previously well protected by vaccination.

Findings of previous reviews of evidence, in 2018 and 2019

Previous reviews of evidence conducted in 2018 and 2019 by the Immunisation Advisory Centre at The University of Auckland have investigated similar questions to the ones being asked for this latest review.[1, 2]

Data clearly show that protection of our youngest infants against pertussis can be achieved by vaccinating in pregnancy. There are no safety concerns around vaccinating during pregnancy and it improves infant outcomes. There is good evidence that infants born to mothers who were vaccinated during pregnancy are likely to also be vaccinated on time according to the Schedule. Maximising antenatal vaccination is the single most effective way to protect young infants. High coverage and timeliness of the primary series will maintain this initial protection.

The immunisation programme must look for the best use of currently available vaccines with the primary aim of protecting infants against severe pertussis and consideration of the timing of protection required from other vaccines in the schedule.

However, questions remain around the timing of the start of the schedule in the presence of maternal antibody and how to best protect infants born to mothers who did not receive antenatal vaccinations. Generally, in the absence of a defined correlate of protection for pertussis antibodies, there is insufficient data to confirm or exclude any clinically meaningful interference or duration of protection.

New Zealand Immunisation Schedule

The pertussis vaccines approved for use in New Zealand are listed below and described in Table 1. In 2000, NZ switched from whole cell pertussis (wP) to acellular pertussis (aP) vaccines. 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 of diphtheria toxoid and pertussis antigens (Tdap, as indicated by the lower-case letters). The number of *Bordetella pertussis* antigens can vary between vaccine brands (see Table 1).

Table 1: Pertussis-containing vaccines available in New Zealand, December 2024. (Source: Medsafe data sheets)

DTaP combinations	
Infanrix-hexa® (GSK) DTaP-IPV-HepB/Hib	Three pertussis antigens 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) 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) Tdap	Three pertussis antigens 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.
Adacel® (Sanofi-Pasteur) Adacel®-Polio	Five pertussis antigens, private market only 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; IU – international units; HepB – hepatitis B, Hib – *Haemophilus influenzae* type B; IPV - inactivated poliovirus; PRN – pertactin, PRP - polysaccharide polyribosylribitol phosphate; PT – pertussis toxin	

In NZ, three-antigen pertussis vaccines are available as part of the National Immunisation Schedule (the Schedule, see Table 2) containing chemically detoxified pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). Children aged under 7 years receive DTaP-containing vaccines as part of the primary series or as a preschool booster (scheduled at age 4 years).

Table 2: New Zealand immunisation schedule for pertussis containing vaccines, July 2024

Age / Antigen(s)	DTaP-IPV-HepB/Hib	DTaP-IPV	Tdap
Pregnancy			✓
6 weeks	✓		
3 months	✓		
5 months	✓		
12 months			
15 months			
4 years		✓	
11 or 12 years			✓
45 years§			✓
65 years†			✓
§ if have received fewer than four lifetime tetanus doses. † given ≥10 years after previous tetanus dose			

Reduced antigen vaccine (Tdap) is usually given after the age of 10 years but is available for use from age 4 years and funded as booster doses from age 7 years, for catch-up vaccinations. Tdap is also used as part of a catch-up primary course for unimmunised individuals from 10 years of age. Three-antigen and five-antigen (with two additional fimbriae antigens, FIM2/3) Tdap vaccines are available. Also available in some countries are TdaP vaccines that contain higher pertussis antigen content than the Tdap vaccine in New Zealand (ie 25µg vs 8µg of inactivated pertussis toxin).

The Schedule in New Zealand differs from many other countries (for details see Table 6) by commencing the primary course at age 6 weeks, rather than 8 weeks or 2 months. It also does not include a DTaP booster dose in the second year of life. Although Tdap is offered at age 65 years, this is primarily for tetanus and diphtheria protection.

Review of recent literature

The following will present the findings of the latest published evidence (from January 2019 – October 2024) and consider any new questions that have arisen since 2019. For details of the studies presented see the Summary of evidence tables.

Epidemiology and burden of pertussis

Globally, pertussis is a significant cause of infant mortality and hospitalisation. In older children and adults, it can range from a mild respiratory disease to violent episodes (paroxysmal) of coughing lasting several months, that can cause rib fractures, haemorrhages, incontinence and vomiting.

Burden of pertussis in infants

Recent evidence

A pharma-sponsored systematic review of 67 articles, published between 2005 and 2018, was conducted by Kandeil et al (2020). They reported that, prior to the introduction of maternal vaccination, the incidence rates of pertussis in infants aged under 2 or 3 months exceeded 1,000 cases per 100,000 population during outbreaks in some countries. Virtually all pertussis-associated deaths occurred in this age group. Most of the available data was from Europe or the Americas, but based on limited data, a higher or similar burden was seen in Africa, Eastern Mediterranean and Asia. For countries where pertussis was not notifiable only hospital data was available.[3] As a comparison, during the previous pertussis epidemic New Zealand in 2018, ESR reported the highest rate of cases was in aged under 1 year at 274 per 100,000 and more than 50% were hospitalised; by ethnicity, the highest rate was for Pacific infants at 553 cases per 100,000.[72]

A Dutch study found that infants born at or prior to 37 weeks gestation were at a greater risk of pertussis hospitalisation than infants born at term (12% premature vs 8% birth cohort).[4] Compared with term infants, the median age of hospital admission for preterm infants was significantly higher (age 3 months vs 2 months, p<0.001). Although ICU admission rates were similar between groups, preterm infants required longer stays (15 days versus 6 days). When adjusted for age and presence of coinfections, preterm infants had an almost three-times greater risk of needing artificial respiration (adjusted odds ratio [aOR] 2.8; 95% CI 1.3-6.0) and almost double the odds of apnoea (aOR 1.8; 1.0-3.3).[4]

Infants aged under 2 months were also at greatest risk of pertussis hospitalisation (116 cases per 100,000), ICU admission (33.5 per 100,000) and death in Canada.[5] Independent risk factors for ICU admission were age under 16 weeks, prematurity, encephalopathy and confirmed pertussis diagnosis. There were 21 deaths, and the risk factors for death included age under 4 weeks, prematurity and female sex. The study included children aged up to 16 years admitted to paediatric hospitals with confirmed or suspected pertussis case during 1999–2015, following the introduction of aP vaccine. It showed that vaccination was effective against pertussis hospitalisation, with a large reduction in incidence in those aged 4–5 months and 6–11 months (from 28 cases to five cases per 100,000) and protection was maintained in those aged 1–4 years (0.8 cases per 100,000). But the youngest, unvaccinated infants remained at very high risk from severe pertussis.[5]

Aboriginal children or children with at least one comorbidity, including respiratory, heart or kidney disease or prematurity prior to 32 weeks gestation were identified to be at highest risk of pertussis and severe pertussis by a data-linking study in Australia.[6] During 2001-2012, over 1.3 million infants

were followed for 18 months. Amongst these infants, 3,771 were under 18 months of age when they had their first episode of pertussis and 32% of these were hospitalised. Of the 101 children admitted to ICU, 86 (85%) were aged under 4 months and 68 (67.3%) were under 2 months. Three infants died.[6]

Children in South Africa were shown to be at significantly increased risk of severe pertussis if they were aged younger than two months (adjusted risk ratio [aRR] 2.37, 95% CI 1.03–5.42); infected with (aRR 4.35, 1.24–15.29) or exposed to HIV (aRR risk 4.35, 1.04–12.01); or with mild or moderate under-nourished (mild 2.27, 1.01–5.09; moderate 2.70, 1.13–6.45).[7]

The nasopharyngeal carriage of *B. pertussis* in caregivers was the greatest risk factor associated with infection in infants (aRR 13.82, 7.76–24.62).[7] Vaccination with three or more primary doses significantly reduced the risk (aRR 0.28; 0.10-0.75) in these children.[7]

Key points

- Unvaccinated infants aged under 2 months, too young to receive the first dose of primary course in many countries, are at very high risk of severe pertussis, hospitalisation, ICU admission and death.
- Preterm birth before 37 weeks gestation is further increases the risk of the most severe pertussis and longer hospital stays.
- Other risk factors for high disease severity include certain comorbidities, such as respiratory heart or kidney disease, HIV infection and being under nourished.
- Virtually all pertussis-associated deaths are seen young infants, before their immunisations are commenced.
- Nasopharyngeal carriage of *B. pertussis* in caregivers is also a significant risk factor for infection of infants (increasing the risk by around 14 times).

Pertussis during and after the COVID-19 pandemic

Recent evidence

Over the last four years, the COVID-19 pandemic and non-pharmaceutical infection control measures have had an impact on the circulation of many respiratory infections, including pertussis. Concerns around immunity to respiratory infections are being reported (see Table 7 for details of studies presented below). These effects result from a combination of causes. Firstly, a lack of natural immunity boosting because lockdowns, social distancing and mask wearing reduced the circulation of a range of common respiratory infections. Secondly, with disruptions to overburdened health services and the reaction to mandated vaccination, declines in vaccination coverage have accelerated.

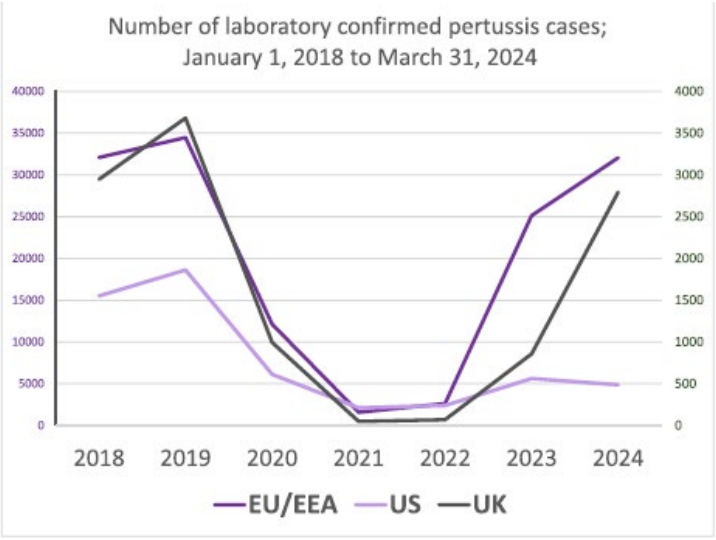
Low immunity is seen in both children and adults, and worryingly, in unvaccinated infants who have missed both maternal doses and primary Schedule immunisations.[13]

Impact of COVID-19 pandemic on pertussis incidence

Pertussis cases have surged in 2024 and severe cases in infants are rising globally.[11] The World Health Organization (WHO) reported that in 2019, prior to the COVID-19-pandemic, the global pertussis incidence rate was 29.8 cases per million. The incidence rate dropped to 9.2 and 4.6 per million in 2020 and 2021, respectively (noting that notification rates and testing were also likely affected by the pandemic, see Figure 3). Incidence began to rise again in 2022 and 2023. In Europe, from January to March 2024, there were already 32,000 cases, compared to a total of approximately 25,000 cases in 2023 (see Figure 4).[11] A 15-fold increase in cases was also reported in China over the same period. From January 2023 to April 2024, 19 deaths due to pertussis have been reported in the European Union (EU/EEA): 11 infants and eight older adults.[11]

Figure 2: Reported pertussis cases 2000-2023. (A) Western Pacific Region (B) global (WHO Dashboard)

Figure 3: Laboratory-confirmed pertussis cases in England, US and Europe, Jan 2018-Mar 2024 (2023 and 2024, provisional data) (Khalil, 2024, open access)



Sources: Pertussis epidemiology England 2024 (www.gov.uk), ECDC Surveillance Atlas of infectious diseases EU/EEA (https://atlas.ecdc.europa.eu/public/index.aspx and US CDC surveillance (https://www.cdc.gov/pertussis/php/surveillance/pertussis-cases-by-year.html)

In England, following a total lockdown and then social distancing and mask wearing measures, the incidence of pertussis dropped from April 2020 despite anticipating a peak year.[9] The total pertussis incidence rate ratio was 0.02 (95% CI 0.01 – 0.02) between July 2020 to June 2021 and July 2014 to June 2019. Prior to the COVID-19 pandemic, from 2014 to 2019, the total incidence rate was 7.60 cases per 100,000 population. This fell in 2020 / 2021 to 0.13 cases per 100,000. In infants aged under 1 year, pertussis incidence declined from 24.5 to 0.5 cases per 100,000. It is however unlikely that pertussis went away – cases were probably under diagnosed as the symptoms and cough were similar to those seen with COVID-19.[9]

Pertussis immunity

Ten infants died during a surge in pertussis cases in early 2024 in England.[14, 73] Between January and August 2024, the majority of the 13,248 laboratory-confirmed cases were aged over 15 years (57%) and aged 10 – 14 years (19%) and aged 5 – 9 years (12%); 3% (407 cases) were in infants aged under 3 months.[73] As with many countries, the UK has seen a decline in routine vaccination. Coverage in England at age 12 months was 91% for DTaP-IPV-HepB/Hib (6-in-1) in 2023/24,[74] but maternal vaccine uptake had decreased from 74.7% in 2017 to 58.9% in March 2024.[73]

A study in the Zhejiang Province in China collected blood samples in 2020 from 4,459 participants aged 0 – 59 years.[10] It found that, although the prevalence of pertussis decreased during the COVID-19 pandemic, a proportion of children, adolescents and adults had serological evidence of a recent infection not identified by diagnosis or routine surveillance (at a lower rate than in a 2014 study). Despite this, a high proportion of the population were susceptible to pertussis infection: around half of those aged 7 – 39 years had undetectable anti-PT IgG.[10]

In Canada, the incidence of pertussis during 2020 (three cases per 100,000) and 2021 (less than one case per 100,000) was the lowest since 1990.[12] When anti-pertussis antibody levels were compared in paired blood samples from 18 healthcare workers of childbearing age, there was a significant decline during 2021 compared 2020 due to low exposure to pertussis and the absence of recent boosting.[12]

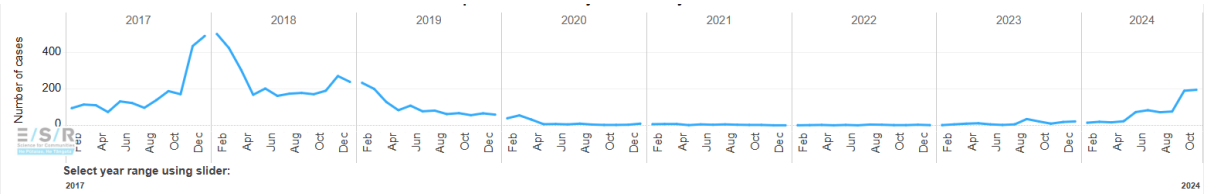
Key points

- The public health measures and the impact of COVID-19 on health care systems has altered the usual pattern of pertussis outbreaks.
- A resurgence in infections is being observed globally, with lower immunity through reduced exposure to wild-type infections and a decline in immunisation coverage.
- Declines in coverage for both maternal and childhood vaccinations have resulted in high rates of infant hospitalisation and led to infant deaths.

New Zealand pertussis epidemiology, 2024

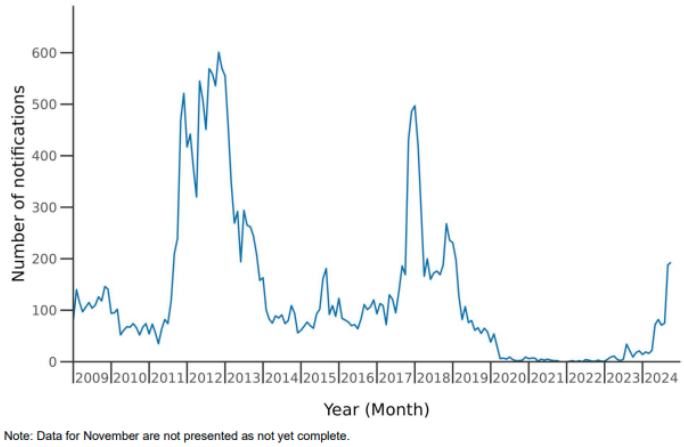
From the end of New Zealand's last pertussis epidemic in May 2019 to early 2024, very few pertussis cases have been reported; ranging from 0 – 11 cases per month from May 2020 – July 2023 (see Figure 4).

Figure 4: Number of pertussis cases by month and year in New Zealand (Source: ESR pertussis dashboard, 22 Nov 2024)



During 2023, a few cases of pertussis were notified in New Zealand without widespread community transmission. Tragically, three geographically unrelated infant deaths (at ages 4, 5 and 8 weeks) occurred during February and March 2023.[13] Since July 2023, the number of confirmed, probably and suspected pertussis cases reported has grown, with a marked increase from May 2024 (see Figure 5). Only 21 pertussis cases were reported in 2023, but from 1 January 2024 to 22 November 2024, 1009 confirmed, probably and suspected cases had been reported, 99 (9.8 %) of the cases were hospitalised (ESR Digital Library). At which point, an epidemic was officially declared.

Figure 5: Pertussis cases by month, January 2009 - October 2024 (ESR Pertussis surveillance report, 26 October – 22 November 2024)



From 1 January to 22 November 2024, 46 out of 63 (73.0%) of pertussis cases aged under 1 year and 13 out of 133 (9.8%) cases aged 1-4 years were hospitalised. Fortunately, there have been no deaths, to date. See Table 3 for breakdown by age for those aged under 1 year.

Table 3: Number of pertussis cases and hospitalisation aged less than 1 year (ESR pertussis report, 26 Oct – 22 Nov 2024)

Age Group	26 October–22 November		01 January–22 November 2024	
	Cases	Hospitalised	Cases	Hospitalised
<2 months	4	4 (100.0%)	13	12 (92.3%)
2–5 months	5	5 (100.0%)	25	22 (88.0%)
6–11 months	5	1 (20.0%)	25	12 (48.0%)

As well as young children, adults aged over 65 years are at increased risk of being hospitalised due to pertussis, with around 30% of cases hospitalised (11 hospitalised out of 38 cases), but this age group makes up a small proportion (4%) of the total cases notified. By ethnicity, the highest proportions hospitalised during 2024 were Pacific (27%), Asian (18%), Māori (16%) and Middle Eastern/Latin/American/African (15%) compared with European and Other (5%). For the latest data, see Pertussis dashboard (esr.cri.nz)

Pertussis vaccine effectiveness in infants

The effectiveness of aP vaccines is not as robust as it was for the wP vaccines. As the duration of protection appears to be shorter, cases have shifted from infants and young children to adolescents and adults. However, infants aged less than 12 months remain at highest risk from severe disease, particularly those too young to be fully vaccinated. For further details of the evidence presented below, see Table 8.

Effectiveness of the childhood programme

Effectiveness of one or two doses in infants aged under 1 year

Having at least one dose of aP vaccine was almost 60% effective against pertussis in infants aged 2 – 11 months (59%; 95% CI 36 – 73%) in Europe.[15] A large test-negative design study used surveillance data collected by the Pertussis in Infants European Network (PERTINENT) between December 2015 to December 2019 to examine vaccine effectiveness. Vaccination with one dose halved the risk of being hospitalised with pertussis: VE at ages 2 – 5 months was 48% (5 – 72%), and at ages 2 – 11 months was 56% (28 – 73%). Two doses between ages 2 – 11 months, increased vaccine effectiveness to 73% (50 – 86%).[15]

A Swiss study demonstrated dose-dependent increases in effectiveness of a three-component aP vaccine against hospitalisation with pertussis in infants aged 2.5 months to 2 years. At the time of the study, pertussis vaccinations were scheduled at ages 2, 4, 6 and 15 – 24 months. After one dose, vaccine effectiveness was 42% (95% CI 11.3 – 62.6), this increased to 84% (70% – 92%) after dose two, and after dose three to 98% (96 – 99%). No cases were reported after dose four (VE 100%, 96 – 100%).[16] There were 327 pertussis cases in infants between 2006 and 2010, and 196 during 2013 to 2017; these were compared with 20,633 randomly selected controls.[16]

Effectiveness of complete course

A systematic review conducted by Wilkinson et al (2021) found that the studies investigating effectiveness of pertussis vaccination against disease to be highly heterogenous, with difference in timing, magnitude of pertussis activity, vaccination schedules and products used.[19] It gave a pooled estimate for VE of 91% (95% CI 87 – 94%, I^2 = 67%, six studies) against severe pertussis (hospitalisation or death) in children.[19]

A cohort study in the US concluded that, although un- or under-vaccinated children were at high risk of pertussis, they represented small proportion of the cases (4% of person-years of follow-up and 20% of total cases, combined).[17] The study followed 469,982 children from age 3 months until they tested positive for pertussis, received Tdap or turned 11 years (average 4.6 years follow-up per child). The children were born between 1999 and 2016 at Kaiser Permanente Northern California.[17] Of the 738 pertussis cases identified, 99 were unvaccinated, 36 were under-vaccinated, 515 were fully vaccinated for age with DTaP, and 88 were fully vaccinated plus one dose (ie received five doses, given at ages 2, 4, 6, 12–18 months and 4 – 6 years). Pertussis risk for the unvaccinated children was 13 times higher than fully vaccinated children (adjusted hazard ratio [aHR] 13.5, 95% CI 10.6 – 17.2) and 1.9 times higher than those partially vaccinated (aHR 1.9, 1.3 – 2.6). Most pertussis cases were in children who were further away from their last DTaP dose.[17]

Key points

- Unvaccinated children (aged 3 months to 11 years) are 13 times more likely to have pertussis than fully vaccinated children and twice as likely as partially vaccinated children.
- Receiving at least one dose of aP vaccine provides 40% – 50% protection before the age of 12 months and halves the risk of hospitalisation.
- With a dose-dependent increase in effectiveness, three or four doses provide the best protection (at least 98% effective).

Effectiveness in special groups

An Australian cohort study investigated pertussis incidence and vaccine effectiveness in 1.3 million children in Western Australia and New South Wales during 2001 – 2012, followed for 18 months. The children were stratified by risk factors: 4.9% were Aboriginal children and 3.6% (consisting of 5.6% Aboriginal and 3.5% non-Aboriginal children) had at least one or more comorbidity or prematurity (born at <32 weeks or 32 – 37 weeks gestation). The most common comorbidities were respiratory, heart disease, kidney disease, prematurity <32 weeks.[6] Vaccine effectiveness against hospitalisation was similar between Aboriginal and non-Aboriginal children, but findings showed that improved timeliness and antenatal vaccination could improve pertussis protection in Aboriginal infants.

For those with comorbidity, dose one and two vaccination were much less effective against pertussis hospitalisation for those without comorbidities (dose 1: VE 0% vs 41%; dose 2: VE 30% vs 80%; dose 3: 70% vs 81%, respectively).[6] In infants born prematurely before 32 weeks gestion, no significant reduction in pertussis hospitalisation was shown until after the third dose compared with after dose two. Hospitalisation for pertussis was six times more likely post dose three (ie from 6 months of age) than for otherwise healthy infants.[6] Since antenatal vaccination or delays in timeliness have less of an effect beyond age 6 months, additional measures should be considered to prevent pertussis in infants with complex health conditions, such as additional doses or improved vaccines.

Similarly, the effectiveness of the first dose of vaccination against pertussis hospitalisation was less in Dutch preterm infants (born <37 weeks gestation) than those born at term (VE = 73% [95% CI 20 – 91%] preterm vs 95% [93 – 96%] for term infants).[4] The effectiveness of the second doses were comparable (93% vs 86%). The median age of hospitalisation for preterm infants was 3 months compared with 2 months for term infants (p<0.001).[4]

Key points

- Comorbidities increase the risk for severe pertussis in children.
- On-time vaccination and antenatal vaccination can improve the outcomes for these infants up to the age of 6 months.
- Hospitalisation risk is six times higher in children with comorbidities aged over 6 months than for healthy children.
- Children in New Zealand, including those with comorbidities, do not currently receive a booster dose in the second year of life – this is likely to increase the risk of severe pertussis in high-risk toddlers.
- Additional measures, in addition to three primary doses plus a booster in the second year of life, are likely to be needed to improve pertussis outcomes of infants and toddlers with complex health conditions.

Duration of protection

As mentioned above, the risk of pertussis increases with time since the last aP dose. In a large cohort study of almost half a million children in the US, pertussis risk was five times higher in children aged 19 months to under 7 years who were three years or more post vaccination than those less than one year post vaccination (aHR 5.0, 95% CI 1.8 – 13.8).[17] For older children aged 7 – 11 years, the risk of pertussis was doubled in those who were six years or more post vaccination compared with those less than three years. Children who had a booster dose in addition to being fully vaccinated for age with the primary course had a lower risk of pertussis than those who were fully vaccinated only (aHR 0.5, 0.3 – 0.7).[17] The authors noted that the results suggest that suboptimal vaccine effectiveness and waning immunity could play a major role in recent pertussis epidemics.[17]

The systematic review conducted by Wilkinson et al found that in children aged 0 – 10 years, vaccine effectiveness of aP vaccines in the first year was 98% (90–100, I^2 = 94%) and 81% (69–89%, I^2 = 0) by 5 years post vaccination.[19]

Another systematic review and meta-analysis by Gao et al (2022) found substantial waning in antibody immunity against pertussis and diphtheria follow vaccination with DTaP-containing vaccines.[18] Anti-pertussis toxin antibody geometric mean ratios declined rapidly within three years since the last dose.[18]

Key points

- Protection provided by pertussis vaccines lasts for a few years, but risk of infection increases with time since last dose.
- In young children (aged 19 months to under 7 years), who have received fewer doses than older children, protection wanes within three years.

- Additional doses after the primary course help reduce the risk of pertussis in children.

Summary of vaccine effectiveness in infants

- A three-dose primary course in infants is required to be optimally protected in the first year of life.
- Vaccine effectiveness significantly increases with each subsequent primary dose in infancy, a fourth dose in the second year of life provides a very high level of protection.
- Compared with fully vaccinated children, unvaccinated children were 13 times more likely to have pertussis and twice likely as partially vaccinated children. However, unvaccinated and partially vaccinated children are only a small proportion of the total pertussis cases.
- Children more distant from their vaccinations are at a higher risk of pertussis, which can be temporarily reduced by additional doses after the primary course.
- The need for a booster dose is especially important for young children with comorbidities or other factors, such as under-nourishment, that increase their risk of requiring hospital care for pertussis.

Pertussis vaccination given in pregnancy - infant's dose zero

Boosting maternal anti-pertussis antibody levels, by Tdap vaccination during pregnancy, provides passive immunity in the infant from birth through transplacental transfer of IgG. In addition, parents who accept vaccination during pregnancy are most likely immunise their child on time.[70] This section considers the latest evidence around the safety, immunogenicity and effectiveness of antenatal vaccination against severe pertussis in young infants and what impact this has on the infant's response to the primary course. See Table 9, Table 10 and Table 11 for further details.

As discussed in our 2018 review of evidence, the best timing for antenatal vaccination with Tdap appears to be around 20 – 33 weeks gestation for an optimal balance in the infant between antibody accumulation and postnatal waning.[2] At that time, only a few studies had investigated vaccination in the second trimester (ie before 27 weeks gestation). An interval of at least 15 days between vaccination and birth maximises the chance of protective levels of antibody transfer. Due to rapid waning of maternal antibodies after a booster dose, vaccinations are recommended to be repeated in each pregnancy. Initial recommendations commenced maternal vaccinations from 28 weeks to 38 weeks, but this resulted in infants being inadequately protected if born prematurely.[2]

Interference has been observed with some primary series vaccines containing diphtheria and pertussis antigens (and polio where TdaP-IPV is given in pregnancy) in the presence of maternal antibodies. A key question is whether there is any clinical significance for this interference in antibody response, and if so, whether it would be amplified in NZ with a primary Schedule commencing at age 6 weeks rather than 8 weeks, 2 months or 3 months as in other countries.

Delaying the infant primary schedule would only be appropriate if a very high proportion of mothers received a pertussis-containing vaccine in pregnancy. Data is limited to judge the ideal age to commence the primary series for antenatally vaccinated infants. A delayed start for all infants would increase the risk of pertussis in those born to unvaccinated mothers, particularly for Māori and

Pacific children in whom maternal uptake is lowest and who are already at higher risk of delayed immunisations.[2]

Vaccinating during pregnancy to provide passive antibody protection to young infants was first introduced in 2011 in the US, in 2012 in the UK and 2013 in NZ. More than 40 countries have implemented maternal Tdap vaccination, although uptake is suboptimal in many of these countries, including New Zealand. Recommendations around the timing of pertussis vaccination in pregnancy and the start of the infant immunisation programme vary widely around the world making it challenging to compare data.[20]

Safety in pregnancy

As a non-live, subunit vaccine, there are no theoretical, biologically plausible reasons why Tdap could pose a safety risk in pregnancy, to either the vaccinated person or to the infant before or after birth. But it is important review the current evidence to provide reassurance to parents (see Table 9 for more details of the studies presented here).

Amongst the published literature, there is consensus that Tdap vaccination can be safely used in pregnancy. No safety concerns have been raised for pregnancy, perinatal or infant outcomes, and the benefit has been well demonstrated.[20, 21] A previously described New Zealand safety study (Pertussis Immunisation in Pregnancy study, PIPS) provided reassurance that Tdap is not associated with unexpected safety risks in pregnancy and detected no biologically plausible vaccine-associated adverse maternal outcomes.[75]

The safety of vaccines used in pregnancy is not as well studied or monitored as it should be, especially since pregnancy is often an exclusion in clinical trials. In the past due to the lack of data, vaccine data sheets were conservative about the use of vaccines in pregnancy. However, with widespread use, the Boostrix (Tdap) data sheet was updated to indicate its use for the prevention of pertussis in infants born to women vaccinated during pregnancy.[76]

The Global Alignment on Immunisation Safety Assessment in Pregnancy consortium (GAIA) was established in 2014, to create a coordinated and standardise approach for monitoring safety of vaccines administered in pregnancy.[24] GAIA developed 26 standardised definitions to classify obstetric and infant adverse events, but these are not widely used in the literature.[24] Davies et al (2024) conducted a systematic review that included 116 papers about vaccine safety in pregnancy. Of these 25% were about influenza vaccine, 20.7% Tdap and 12.9% were COVID-19 vaccine related. The most frequently investigated adverse events of special interest (AESI) were preterm birth, small for gestation age and hypertensive disorders. Fewer than 10 reported GAIA definition use.[24]

Systematic reviews

A meta-analysis of three articles, conducted by Simayi et al (2022), found no significant increase in the risk of severe adverse events (SAE) related to pregnancy or infant outcomes between those vaccinated with Tdap in pregnancy and unvaccinated controls. For the pregnant woman, pooled odds (OR) of SAE was 1.26 (95% CI 0.78 – 2.05, p = 0.35), and for the infants, pooled odds was 0.61 (0.37 – 1.01; p = 0.053).[77]

Chorioamnionitis

A systematic review and meta-analysis by Anderson et al (2022) investigated the risk of chorioamnionitis and non-pertussis infections in women who received pertussis vaccine in

pregnancy.[22] Pooled data from six retrospective observational studies (two studies with statistical significance) showed an association between pertussis vaccination, and no other non-live vaccines, and chorioamnionitis (risk ratio [RR] 1.24, 95% CI 1.14 – 1.42). There was no significant difference in non-pertussis infections (RR 1.12, 0.43 – 2.91), spontaneous abortion or still-birth (RR 1.04, 0.92 – 1.16) or neonatal death (RR 0.32, 0.02 – 4.69). The prevalence of chorioamnionitis in non-vaccinated groups was almost 3% and an additional eight cases were predicted per 1,000 vaccinated women.[22] However, the clinical relevance of this association was uncertain, since there was no strong association between receipt of a pertussis-containing vaccine in pregnancy and the known clinical consequences of chorioamnionitis, such as sepsis and preterm birth.[22] An early study in the US investigating 24 years of Vaccine Adverse Event Recording System (VAERS) data found that 1% of pregnancy-related reports to VAERS were for chorioamnionitis following vaccination in pregnancy (with HPV, Tdap or influenza vaccines). In most of these reports, the vaccine recipient had at least one risk factor for chorioamnionitis. Based on these findings, no safety concerns were raised.[78]

Repeat vaccinations

Another systemic review by D'Heilly et al (2019) reported no increase in acute adverse events among pregnant women who receive separate doses of a tetanus-containing vaccine less than two years, two to five years, or more than five years apart.[23] The rates of systemic and local reactions, including fever, in those who received Tdap were similar between those who had and those who had not received a tetanus-containing vaccine within the previous one to five years (based on two studies). No evidence of any enhanced safety risk was shown when Tdap was given concomitantly with influenza vaccine. The review concluded that maternal immunisation does not adversely affect pregnancy, birth or neonatal outcomes, and its findings support recommendations for pertussis vaccination in each pregnancy.[23]

Summary of safety in pregnancy

- Safety data support the recommendations to be vaccinated against pertussis in pregnancy.
- Pregnancy is associated with complications unrelated to vaccination, making it more challenging to decipher any adverse events that may temporally but not causally be associated with vaccination.
- Unfortunately, monitoring of vaccine safety in pregnancy suffers from a lack of standardisation because, despite established definitions for adverse events (GAIA) recognised by the Brighton Collaboration, these are rarely used in studies. Despite this, no safety concerns have arisen and robust data support Tdap given in pregnancy.
- Reassuringly, in relation to the recommendation to repeat Tdap vaccination in each pregnancy, the systemic and local reactions were not increased following repeat vaccinations given from one to five years apart in subsequent pregnancies.

Immunogenicity – antibody transfer to infants

The primary role of pertussis vaccination in pregnancy is to provide infants with passive immunity to protect them against pertussis until they can be actively immunised with their own vaccines. Transplacental transfer of IgG commences at around 13 weeks gestion but, as the placenta grows, the rate of transfer increases. The ideal timing of vaccination before birth requires a balance between the peak in maternal antibody levels with waning after birth. Without a defined correlate of protection for pertussis, it is difficult to determine the precise timing to achieve the optimally

protective antibody levels in the infants. See Table 10 for further details of the evidence presented below.

Timing of vaccination

A systematic review by De Weerdt et al (2024) of 26 papers on immunogenicity found that antibody titres at delivery were affected by timing of vaccination in pregnancy. Vaccination administered in the early third trimester rather than late third trimester achieved the highest titres.[20] Antibody titres were positively correlated with time between vaccination and birth, and maximal protection occurred around the early third trimester or at least 8 weeks prior to birth. However, since very few studies have evaluated immunogenicity when vaccinating prior to 20 weeks gestation, a role for earlier vaccination cannot be excluded.

A Dutch cohort study found that infants born early or at term (≥37 weeks gestation) to mothers vaccinated during the mid-second trimester (20 – 24 weeks gestation) had around two-fold lower anti-pertussis toxin antibody levels at birth and at age 2 months than those vaccinated in the mid-third trimester (30 – 33 weeks gestation) (see Table 4).[25] Anti-FHA antibodies in cord blood were also significantly lower following earlier vaccination. For neonates who were born prematurely (25 – 35 weeks gestation), cord blood anti-PT antibody titres were not significantly different to those born at term when maternally vaccinated in the mid-second trimester.[25] There were also significant differences in maternal tetanus and diphtheria toxoid antibodies, between those born at term or preterm delivery, but this was not related to timing of vaccination. The authors proposed that when vaccination occurs prior to 24 weeks, the peak in maternal antibody response after vaccination may not coincide with the optimal time for maternal antibody transfer. This appears not to be compensated for with a longer gestation time. The clinical relevance of these lower antibody levels is unknown without a correlate of protection or epidemiological study.[25] This study did not compare the antibody levels in infants born prematurely between maternal vaccination in the second or third trimester.

The risk of severe pertussis in premature infants is very high[26] and therefore early vaccination is substantially better than no vaccination.

Table 4: Anti-pertussis toxin antibody titres following maternal vaccination in second or third trimester at birth (adapted from Immink et al 2024)

Blood sample	GMC anti-PT IgG (IU/ml, 95% CI)		GMR (95% CI)	P value
Preterm / term infants	**Maternal Tdap in 2nd trimester (study cohort)**	**Maternal Tdap in 3rd trimester (reference cohort)**	**study vs reference**	
Maternal	32.9 (26.0-41.6)	61.8 (46.8-81.7)	0.53 (0.35-0.80)	< 0.001
Neonate cord blood	58.6 (46.4-74.2)	125.1 (94.0-166.3)	0.47 (0.31-0.72)	< 0.001
Infant age 2 months	14.7 (10.6-20.4)	27.3 (20.1-37.1)	0.54 (0.34-0.85;)	= 0.005
Maternal vaccination in second trimester	**Preterm infants**	**Term infants**	**preterm vs term**	
Maternal	60.4 (44.1-82.7)	32.9 (26.0-41.6)	1.84 (1.24-2.72)	= 0.002
Neonate cord blood	52.8 (40.7-68.6)	58.6 (46.4-74.2)	0.90 (0.63-1.30)	= 0.63
Infant age 2 months	11.2 (8.1-15.3)	14.7 (10.6-20.4)	0.76 (0.48-1.20)	= 0.23

Abbreviations: GMC – geometric mean concentrations; GMR – geometric mean ratio; PT – pertussis toxin; Tdap – tetanus, diphtheria acellular pertussis vaccine.

Preterm – born <35 weeks gestation; Term – born ≥37 weeks gestation. Maternal vaccination given at 20-24 weeks gestation or 30-33 weeks gestation.

A comparison of Tdap vaccination during or prior to pregnancy showed that Tdap vaccination during the late second or third trimester of pregnancy resulted in higher cord blood antibody levels against pertussis, tetanus and diphtheria antibodies than when Tdap was given before pregnancy. For pertussis antibodies, levels were 0.5 – 1 Log higher in maternal and cord blood when vaccinated during pregnancy ($p < 0.001$). This was especially evident for anti-diphtheria antibodies: seroprotective levels were reached by 100% of infants whose mothers were vaccinated during pregnancy compared to 62.5% of those vaccinated before pregnancy (Tdap timing before pregnancy was not given). Tdap before or during pregnancy vaccination did not affect the transfer of non-Tdap antibodies (hepatitis B, rubella or influenza). In this study, all participants received influenza vaccination in pregnancy.[29]

Repeat vaccinations

The immunogenicity of Tdap was assessed in 27 women following vaccination in two successive pregnancies (mean interval between pregnancies 2.4 years, range 1.4 – 3.9 years).[27] It found that although Tdap-specific IgG levels in the maternal sera were comparable in both pregnancies, the total IgG was reduced in the cord blood at the second delivery compared with the first (Table 5). It concluded that Tdap given in each pregnancy remains beneficial and that infants born to vaccinated mothers were better protected than unvaccinated infants (based on levels from a previous study).[27]

Table 5: Geometric mean concentrations (IU/ml) for Tdap-specific total IgG in maternal and cord serum at successive deliveries (De Weerdt 2024, open access)

	GMC (95% CI)		
	Delivery 1	Delivery 2	*P*[a]
Anti-PT	1.3 (1.2-1.6)	0.7 (0.4-1.1)	0.06
Anti-FHA	1.4 (1.2-1.6)	1.0 (0.7-1.4)	0.14
Anti-PRN	1.4 (1.2-1.7)	1.2 (1.0-1.5)	0.71
Anti-DT	1.4 (1.2-1.6)	1.0 (0.8-1.2)	0.03
Anti-TT	1.3 (1.1-1.5)	1.1 (0.9-1.2)	0.05

GMC, geometric mean concentration; 95% CI, 95% confidence interval; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; TT, tetanus toxoid; DT, diphtheria toxoid; [a]By the paired Wilcoxon signed-rank test.

Coadministration

A pilot study conducted in Taiwan found that protection against pertussis following Tdap was not influenced by vaccination with influenza or COVID-19 vaccines in pregnancy. It examined the immunogenicity of a third or fourth dose of COVID-19 vaccine (mRNA vaccines) with Tdap alone or Tdap plus influenza in 71 pregnant women (timing of vaccination not stated, except that Tdap and influenza were given concomitantly).[28] It found no significance difference in pertussis IgG in the vaccinated women with the addition of influenza or COVID-19 vaccinations. No interference was

seen from Tdap ± influenza vaccines in COVID-19 neutralising antibody SARS-CoV-2 inhibition rate.[28] High antenatal Tdap coverage rate meant the study did not included comparator groups without Tdap.

Summary of immunogenicity and antibody transfer

- Data is limited around different timing of Tdap vaccination in pregnancy, particularly when given in early than the late second trimester.
- Infants born prematurely benefit the most from earlier vaccine administration in pregnancy. These infants are at highest risk of severe pertussis and would not receive any protective antibody if vaccinations were given later in pregnancy.
- Antibody levels at birth in infants born at term appear to be lower if the vaccine is given earlier, but without a defined correlate of protection, the clinical relevance cannot be extrapolated.
- Likewise, antibody transfer in a second pregnancy, after being vaccinated previously, appears to be slightly reduced but the clinical relevance is unknown. Vaccination is better than no vaccination, especially since infants are at risk of being exposed to pertussis from their older siblings.
- Coadministration with influenza and COVID-19 vaccines did not significantly affect pertussis antibody titres to Tdap.

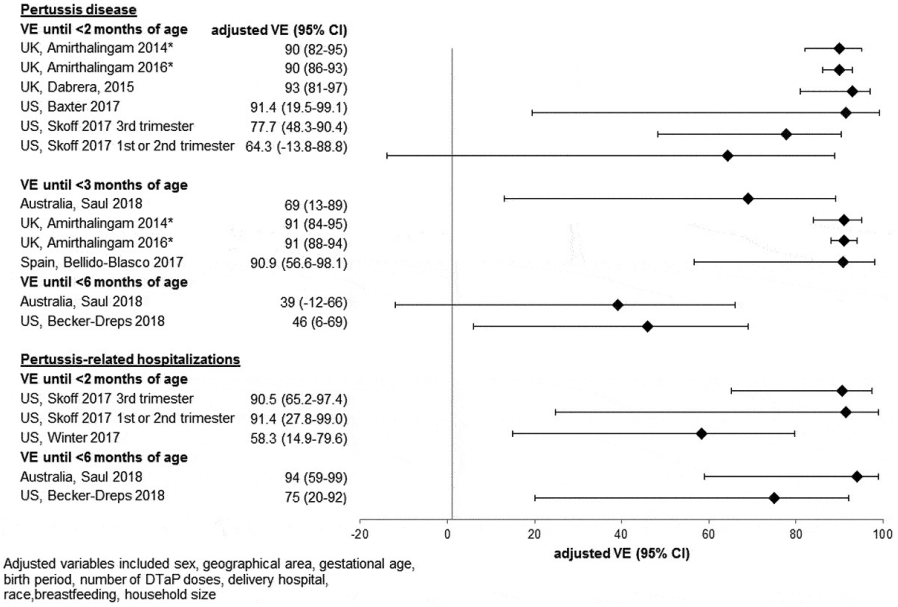
Effectiveness of antenatal vaccination

The following assesses the evidence for the effectiveness of antenatal vaccination in preventing pertussis in infants. See Table 11 for further details.

Recent literature

Maternal Tdap vaccination is highly effective at preventing pertussis and pertussis-associated hospitalisation of infants aged under 6 months. A Pharma-authored systematic review, of 11 articles published between 2011 and 2018, showed the adjusted vaccine effectiveness (VE) against confirmed pertussis in infants aged under 2 months ranged from 78% to 93% (see Figure 6).[3] Wide error bars are due to the small numbers of cases in the individual studies.

Figure 6: Effectiveness of maternal Tdap against pertussis disease and hospitalisation in infants age <6 months, systematic review (open access, Kandeil et al 2020)



The PERTINENT study in six European countries evaluated the effectiveness of maternal vaccination against pertussis hospitalisation in infants aged under 2 months using a test-negative design.[30] It demonstrated that vaccination in pregnancy effectively fills the gap in immunity prior to the infants first pertussis vaccinations. The study included 829 infants aged under 1 year who were hospitalised with pertussis-like symptoms; 336 cases were aged 4 days to 2 months. Laboratory-confirmed pertussis cases were compared with controls without any detectable *Bordetella* species infection. Of the infants aged under 2 months, nine of 75 (12%) cases and 92 of 199 (46%) controls were vaccinated in pregnancy. The median gestation age at vaccination for cases was 30.5 weeks (range 23 – 36) and controls 30.1 weeks (20 – 37). Vaccine effectiveness, adjusted for study site, time of onset and age group, was 75% (95% CI 35 – 91). When cases diagnosed only by nasopharyngeal swab were excluded, rather than a more reliable aspirate, VE increased to 88% (57 – 96%).[30]

The Australian Link2HealthierBubs study, conducted across Northern Territory, Western Australia and Queensland, evaluated the effectiveness of maternal vaccination in 279,418 mother-infant pairs over three years. The study assessed maternal vaccine effectiveness in infants up to the age of 18 months (total of 331 pertussis cases). Overall, maternal vaccination was 65.1% (95% CI 49.5–76.0) effective against pertussis infection and 60.2% (-18.3 to 86.6) effective against pertussis hospitalisation of infants aged up to 6 months. Effectiveness decreased with increasing age, from 70% in those aged under 2 months to 62% at age 5–6 months, with no significant protection after the age of 8 months. Antenatal vaccination significantly increased the median age for pertussis notifications ($p < 0.001$) from 7.5 months (IQR 10 months) in infants born to unvaccinated mothers to 11 months (IQR 8.75 months) in those who were vaccinated antenatally.[31]

Key points on antenatal vaccine effectiveness

- Antenatal vaccination against pertussis has been shown to be around 90% effective, overall, in preventing pertussis in young infants aged under 2 months.
- The greatest effectiveness (over 90%) is observed against pertussis hospitalisations in infants under 2 months old, with substantial protection maintained for up to 6 months.

- Infants born to vaccinated mothers tend to develop pertussis at a later age, which allows them more time to become fully vaccinated and for their airways and immune system to mature, thereby, likely to reduce disease severity.

Effectiveness with timing of vaccination in pregnancy

When pertussis vaccination was first introduced in pregnancy, recommendations were for vaccine to be administered in the third trimester from 28 – 38 weeks. Following the findings of studies in the UK and Switzerland,[79-81] this was reviewed and recommendations in some countries, including New Zealand, changed to second and third trimester. The New Zealand schedule recommends Tdap vaccination from 16 weeks gestation (and funded from 13 weeks gestation).

The Global Pertussis Initiative reviewed the status of pertussis vaccination in pregnancy at its 2021 Annual Meeting, noting various strategies, recommendations and adherence rates around the world.[21] Based on antibody concentrations at birth, the evidence supported vaccination in the late second and early third trimester over later in the third trimester. Definitive conclusions around widening the vaccination timeframe to earlier in the second trimester require further elucidation. Additionally, more data are required to confirm whether antibody level differences translate to differences in vaccine effectiveness in infants, and what, if any, impact maternal antibodies have on the effectiveness of the infant primary course.[21]

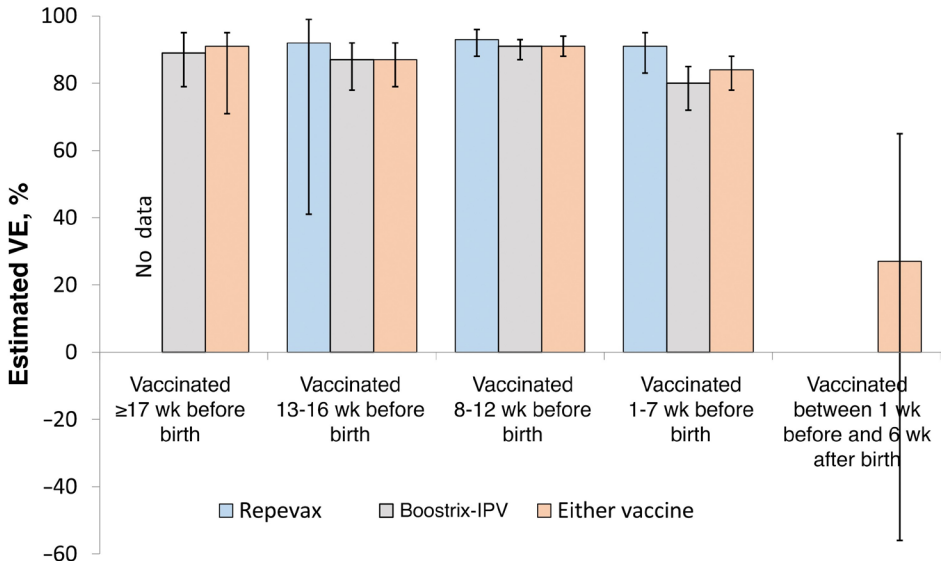
Presented below are some recently published data to support these questions. For further details see Table 11 and Table 6 for selected international pertussis immunisation schedules.

Recent literature

A systematic review by De Weerdt et al (2024) found that vaccination given late in pregnancy was associated with lower effectiveness against pertussis in infants than when given earlier.[20] The findings were mixed and some studies only compared early third and late third trimester timing, but overall, these studies found reduced effectiveness when the vaccine was given late in pregnancy.[20]

When the timing of the maternal vaccination was compared in the UK, vaccine effectiveness against pertussis in infants was equivalent for different gestational periods (except in those born to mothers vaccinated less than 7 days before birth to up to 41 days after delivery) (see Figure 7).[32] A population-based data linking study covering 6% of the UK population investigated the effectiveness of the maternal pertussis vaccination programme, for up to six years post implementation, in infants born from 1 October 2012 to 31 December 2019.[32] Across the whole programme, the vaccine effectiveness against confirmed pertussis infection was 88% (85 – 91%) up to age 2 months and 97% (81 – 100) against infant deaths due to pertussis.[32] Similar to NZ, in 2016, the recommended timing of maternal vaccination changed from the third trimester (from 28 weeks gestation) to the second trimester (from 16 weeks gestation). From its introduction in the UK, maternal Tdap vaccination coverage ranged from 60% – 75%. It was consistently high from 2016, demonstrating a clear impact of changing the recommendation to earlier timing with 40% of vaccinations being received more than 13 weeks prior to birth.[32]

Figure 7: Estimates of effectiveness of maternal vaccination in prevention of laboratory-confirmed pertussis in infants aged <93 days, by vaccine product and timing of maternal vaccination (Amirthalingam, 2023, CID open access)



The Link2HealthierBubs study in Australia also found no significant differences between the timing of maternal vaccination and vaccine effectiveness (at <28 weeks, 28 – 31 weeks or over 32 weeks gestation).[31] Likewise, a Spanish study found that maternal vaccination prior to 32 weeks gestation was as effective against pertussis in infants aged under 2 months as those vaccinated after 32 weeks gestation (88.5% vs 87.8%).[82]

Key points on timing of vaccination in pregnancy

- The timing of antenatal vaccination does not seem to significantly affect vaccine effectiveness in infants up to age 6 months, if administered more than seven days before delivery.
- A longer interval before delivery may enhance effectiveness slightly.
- Offering pertussis vaccination earlier in pregnancy has been shown to increase vaccine uptake.
- Early vaccination also provides protection against pertussis for infants born prematurely.

Conclusions

Maternal vaccination is highly effective at protecting infants against pertussis prior to completing their primary course, up to the age of 6 months. This age group is at the highest risk of severe pertussis and death due to pertussis. Timing of administration does not appear to significantly affect protection, except when given within a week of birth. Further data is required to find the ideal timing.

Antibody interference with the infant immune response.

Passively transferred, maternal antibodies can interfere with infants' immune responses to primary vaccinations. Thus, it is essential to strike a balance between the protective benefits of passive antibodies transferred via the placenta and ensuring infants mount a strong response to their own vaccinations. Maternal antibodies diminish quickly in infants after birth, making it crucial to time the infant's first vaccination before this protection wanes completely.

In Aotearoa New Zealand, due to a historically high incidence of severe and fatal pertussis in infants aged under 2 months, the immunisation schedule begins at age 6 weeks. A key concern is whether infants born to vaccinated mothers are sufficiently protected after completing the primary course from age 6 months when the course is commenced at a younger age. Low population immunity and reduced exposure to circulating *B. pertussis* in recent years could play an important role in the pertussis incidence in young children in New Zealand, whether vaccinated in pregnancy or not.

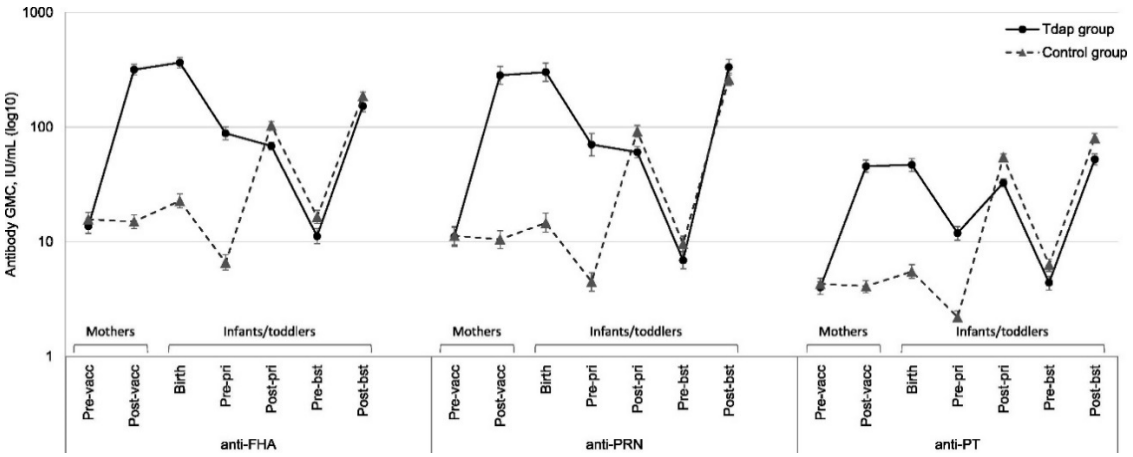
The following includes recent evidence to assess the impact of this potential interference. See Table 12 for further details of this evidence.

Immunogenicity of the infant primary course after vaccination in pregnancy

An individual participant meta-analysis involving eight studies revealed that when pre-immunisation IgG levels for certain vaccine antigens were doubled, there was a corresponding 8% – 17% reduction in IgG levels after primary immunisation, regardless of whether the infants were born to women immunised in pregnancy or not.[33] In infants born to Tdap vaccinated mothers, two-fold higher anti-PT and anti-DT antibody levels pre-immunisation were associated with 9% and 10% lower post-primary immunisation antibody levels, respectively. Spacing of the primary course (at 2-4-6 or 2-3-4 months) did not alter the primary or booster IgG levels for most Tdap antigens.[33]

A series of three phase IV RCT, conducted in Australia, Canada and Europe, followed approximately 600 infants born either to mothers vaccinated with Tdap (Tdap group) or placebo (control group) in pregnancy until the infants were 18 months of age (NCT02377349, NCT02422264 and NCT02853929).[38, 83, 84] The first trial investigated antibody levels at birth;[83] the second, the infant response to the scheduled primary course from ages 6 – 14 weeks;[84] and the third, the infant response to the toddler booster doses at ages 11 – 18 months.[38] At one month after the first DTaP-IPV-HepB/Hib and PCV13 doses, the seroresponse to the non-pertussis antigens was similar for both groups (at least 95%). For pertussis antigens, the vaccine response rates were lower in the Tdap than the control groups, but higher than the prevaccination lower detection limit, and all the infants were considered seropositive for all the pertussis antigens (see Figure 8).[84]

Figure 8: Geometric mean concentrations of pertussis antibodies in mothers before and after Tdap vaccination in pregnancy, and in infants before or after primary (pri) and booster (bst) vaccinations during phase IV clinical trial (Martinón-Torres, 2021, open access)



Blunting of the infant antibody response to the primary course was also demonstrated in an open-labelled, parallel RCT in the Netherlands.[34] The study enrolled 118 pregnant women aged 18 – 40 years, of which 58 were vaccinated with Tdap at 30 – 32 weeks gestation (Tdap group) and 50 were unvaccinated controls. Infants born to the Tdap group had high levels of maternal antibody to at least age 3 months (prior to first DTaP vaccination): only one of 54 (2%) of infants in the Tdap group had undetectable pertussis antibody levels compared with 34 of 50 (68%) infants in the control group. The anti-pertussis antibody concentrations were 16.6 times (95% CI 10.9 – 25.2) higher in the maternally vaccinated group than controls.[34]

By age 6 months, one month after completion of the two-dose primary course, the anti-PT IgG GMC ratio between Tdap group and controls had dropped to 0.4 (95% CI 0.3 – 0.6) and remained lower even after the 11-month booster (GMC ratio 0.5; 0.4 – 0.7).[34] Despite this, the antibody response to the booster dose was of similar magnitude between the groups. Although the antibody levels were reduced in the Tdap group, they were substantial and presumed to be protective (in the absence of a defined correlate of protection). The anti-PT levels in the Tdap group at age 3 months (prior to first DTaP vaccination) were 9.5 (6.1 – 14.9) times higher than those in the control group at age 2 months.[34] The study concluded that delaying the primary course until age 3 months for those who were vaccinated in pregnancy did not prevent maternal antibody interference, but it is likely that when maternal antibody levels were highest (ie age 2 months) greater interference is possible.[34]

Summary of immunogenicity of primary course

- The presence of maternal antibody results in some interference with the infant primary course, whether vaccinated in pregnancy or not.
- The implications of this interference on the level of protection are uncertain in the absence of a defined correlate of protection for pertussis.
- Evidence suggests that infants born to vaccinated mothers continue to be protected even with reduced antibody titres and that maternal vaccination provides passive antibody protection prior to completion of the primary course.
- Maternal antibody diminishes quickly in the infant, making it crucial to time the completion of the infants' primary vaccinations before this protection wanes completely.

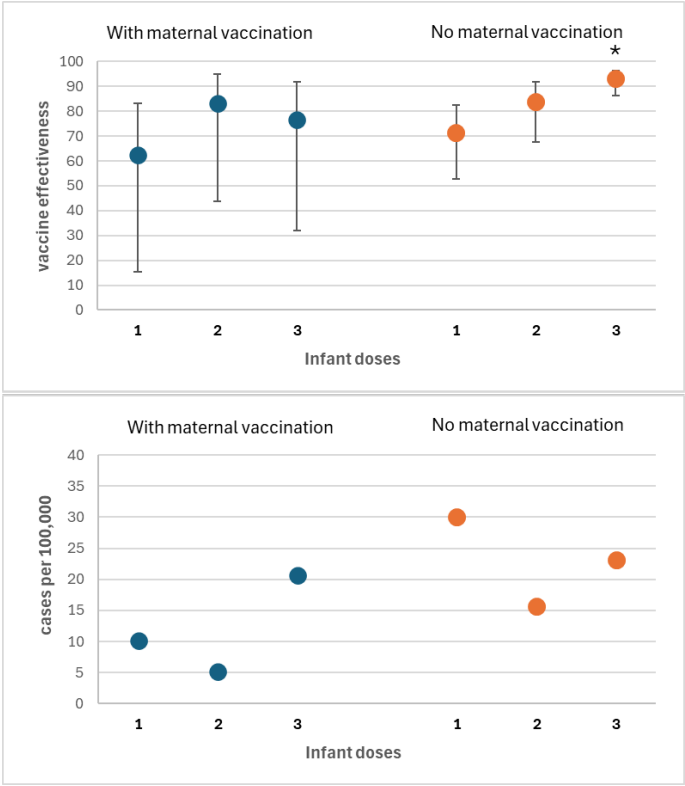
- For New Zealand, it is unclear whether moving the schedule from 6 weeks to 2 or 3 months would make a difference to pertussis control in infants born to mothers who are vaccinated in pregnancy.

Effectiveness of infant primary course after vaccination in pregnancy

As part of the PERTINENT test-negative study conducted in Europe, the vaccine effectiveness against pertussis hospitalisation was assessed in infants aged 2 to 11 months following maternal vaccination and at least one primary dose of pertussis vaccine.[30] Out of 376 infants eligible for pertussis vaccination, 123 were pertussis cases and 253 test-negative controls. Vaccinated infants were compared with a reference group of unvaccinated infants born to unvaccinated mothers (adjusted for site, time of pertussis onset and age). Regardless of the recommended schedule, at least one dose of pertussis vaccination in infants born to mothers who were vaccinated in pregnancy reduced the risk of pertussis hospitalisation by 74% – 95%. Vaccination in infants born to mothers not vaccinated in pregnancy reduced the risk by 68% – 94%. The limited sample size was not able to assess any effect of pregnancy vaccination on the effectiveness of infant vaccination. But these findings suggest good effectiveness of at least one dose of pertussis vaccine in infants aged 2 – 11 months, irrespective of vaccination status in pregnancy.[30]

The Australian Link2HealthierBubs study evaluated the effectiveness of maternal vaccination in 279,418 mother-infant pairs for three years.[31] It found maternal vaccination to be highly effective in infants up to the age of 8 months (see Figure 9). There was no indication of potential blunting by maternal antibodies until the infants' third primary dose (scheduled at age 6 months), with a significantly lower point estimate of effectiveness between those who were vaccinated or unvaccinated in pregnancy (76.5% vs 92.9%, p = 0.002). However, this was not associated with an increased risk of pertussis infection (HR 0.70, 0.61 – 3.39). This lower VE point estimate was not seen with doses one or two (given at age 6 – 8 weeks and age 4 months, respectively).[31]

Figure 9: Pertussis cases (per 100,000 population) and vaccine effectiveness of primary course in infants with and without maternal vaccination (adapted from data published by Regan et al, 2023)



Long-term impact of interference after the primary course

Data is limited on the long-term impact of maternal vaccination on vaccine effectiveness in infants. There is strong evidence of high pertussis antibody titres but some evidence of blunting of the primary course antibody response. Although during the phase IV clinical trials described above, infants vaccinated in pregnancy had a slightly lower baseline antibody level prior to a pertussis booster vaccination, given between the ages of 11 and 18 months, they were able to mount an amnestic response equivalent to those not vaccinated in pregnancy.[38] The groups did not differ in the antibody responses to other DTaP-IPV-HepB/Hib antigens and PCV13 serotypes.[38]

One systematic review and meta-analysis, which modelled the effectiveness of pertussis vaccination on pertussis transmission, found insufficient evidence to rule out modest reductions in effectiveness of the primary course following maternal vaccination.[35] It included four studies with six years follow-up, small sample sizes and large statistical uncertainty. The analysis gave a weighted mean relative risk of 0.7 (0.4 – 1.3) for pertussis after the third dose of primary immunisation in infants vaccinated in pregnancy, compared with those unvaccinated in pregnancy. Taking into consideration transmission dynamic modelling, the findings supported a role for maternal vaccination in protecting young infants most at risk from pertussis. Even in the presence of blunting, maternal immunisation was predicted to remain effective at reducing pertussis in unvaccinated newborns but could eventually (after more than a decade) result in an infection-control trade-off with older age groups. The study also highlighted large uncertainty and lack of research into effects of blunting on pertussis. It emphasised a need to disentangle the introduction of maternal vaccination programmes, the well-documented resurgence of pertussis incidence following the change from wP to aP vaccines, and recent influence from COVID-19 control measures on pertussis immunity.[35]

Summary of effectiveness of primary course

- The long-term impact of maternal vaccination and potential blunting of the infant antibody response to primary vaccinations is poorly understood.
- There is limited evidence to determine whether maternal vaccination an impactful effect on the effectiveness of infant immunisations.
- The primary course in infants is essential to provide long term protection against pertussis, after maternal protection has waned.
- Findings support the role of maternal vaccination in protecting infants, even in the presences of blunted primary course responses. This does not appear to increase the risk for disease overall.
- Continual monitoring, particularly now that pertussis cases are on the increase, is required to see if the antibody interference is clinically meaningful.

Immunogenicity and safety of toddler and preschool booster doses after vaccination in pregnancy

The third of the phase IV trials described above of the investigated whether these lower vaccine responses during the primary course affected the response to the toddler dose.[38] It found that the amnestic response was not affected by maternal vaccination. Infants born to vaccinated mothers had lower pertussis (FHA and PT) and diphtheria antibody levels than the control group, both before and after the booster dose (anti-PT 1.5-fold, anti-FHA 1.2-fold and anti-DT 1.4-fold difference). But

the booster response was equivalent in each group, despite a lower baseline level pre-booster in the Tdap group (see Figure 8). No differences in response to the other DTaP-IPV-HepB/Hib antigens and PCV13 serotypes were seen between the groups. A subgroup analysis did not find any differences by primary schedule or maternal vaccination timing.[38]

This clinical trial also found no increase in reactogenicity or change in safety profile when DTaP-IPV-HepB/Hib was given as a booster dose at ages 11 – 18 months following antenatal vaccination.[38]

The Dutch study described above[34] found that, although the antibody levels after a DTaP booster given at age 11 months (2+1 schedule) was lower in infants born to vaccinated mothers than in those not vaccinated in pregnancy, the magnitude of the response to the booster dose did not differ. The anti-PT IgG GMC ratio between Tdap group and controls remained at 0.5 (0.4—0.7) before and after the 11-month booster.[34]

The blunting effect of antenatal pertussis vaccination on pertussis vaccine responses in children was shown to persist beyond the age of 2 years and into early childhood in the UK. But this could be overcome by a booster dose preschool-age (at age 3 years 4 months).[37] A phase IV observational cohort study looked at the effects of maternal vaccination on the response to the preschool Tdap-IPV booster dose.[37] Overall, though pertussis-specific antibody levels tended to be lower in those vaccinated in pregnancy, both before and after preschool booster, there was no significant difference between the groups.[37] Only the anti-PT IgG concentrations were significantly lower prior to the preschool booster in children born to mothers vaccinated with Boostrix-IPV (GMR 0.42, 0.22 – 0.78, p = 0.03). At one month after the preschool booster, there were no significant differences between those vaccinated in pregnancy and those not. No significant difference were seen for diphtheria or tetanus antibodies and all achieved seroprotective levels.[37]

The blunting effect of maternal antibody appears to diminish after booster doses given in the second year of life, but for countries like NZ and UK where a booster dose is only given later (age 4–6 years), this is not reassuring.[32]

Summary of immunogenicity of booster doses

- In infants who received a three-dose primary course and booster at age 18 months, maternal antibody did not significantly impact infant pertussis titres post booster.
- In the absence of a toddler booster dose, lower antibody levels against pertussis toxin continue to be observed in preschool-aged children who were born to mothers vaccinated against pertussis in pregnancy. A preschool booster can remedy this.
- Furthermore, it is unclear whether this is clinically relevant since, although antibody levels trended lower in toddlers (even after a booster dose) or preschool children (in the absence of toddler booster) who were vaccinated antenatally, the absolute differences between titres were small.

Conclusions of maternal antibody interference

The limited evidence shows little impact of antenatal vaccination on the vaccine effectiveness of the infant primary course and early childhood booster doses against pertussis. Despite reduced antibody responses in infants and toddlers born to mothers who were vaccinated in pregnancy, it is unclear whether this is clinically relevant. Although antibody levels trended lower in toddlers (even after a booster dose) or preschool children (in the absence of toddler booster) who were vaccinated antenatally, the absolute differences between titres were small.

In the current NZ context, without a booster dose in the second year of life and starting the primary course at 6 weeks of age, this interference could be more impactful for infants and young children aged from 6 months to 4 years.

Immunisation schedules and booster doses

To achieve optimal control of pertussis with the current vaccines could mean adjusting the immunisation schedule. The following considers evidence around the infant primary course and for booster doses in toddlers, children and adolescents.

Primary course and toddler booster doses

Introduction

During the previous pertussis outbreak in NZ (October 2017 to May 2019, total 4,697 cases were notified), children aged 0–4 years were most seriously affected with the highest rates of cases in children aged under 1 year and ages 1–4 years.[72] Children with underlying conditions, including cardiac, respiratory or immune dysfunction, are at higher risk from pertussis hospitalisation. There are also ethnic and socioeconomic disparities in disease severity in young children.

Our 2018 review of evidence on pertussis assessed the question of waning immunity in childhood.[2] A further review was conducted in 2019 to specifically look at whether NZ needed a booster dose in the second year of life (toddler dose) to provide longer lasting protection through to the preschool dose given at age 4 years.[1]

Australia reinstated a toddler booster dose following evidence of waning pertussis protection from ages 2 to 4 years.[85] However, in a similar study, waning in vaccine effectiveness was not observed in New Zealand for notified pertussis under the current schedule (during 2006 – 2013, prior to maternal vaccination).[86] The waning seen in Australia was possibly associated with milder disease than assessed in the NZ study due to high levels of RT-PCR testing in Australia.

WHO recommends at least five doses of pertussis-containing vaccine before age 18 years and a booster dose in the second year of life is recommended for countries using acellular pertussis vaccines.[87] Furthermore, WHO also recommends six doses of tetanus-containing vaccine in childhood.[88]

Our 2019 review of evidence found that a toddler booster dose is likely to improve immunity of children until preschool booster at age 4 years.[1] It would be most beneficial to those with underlying health issues and for those born to mothers who received Tdap in pregnancy. By reducing the incidence of symptomatic pertussis in under 5-year-olds also helps to protect their younger siblings. Additionally, a toddler dose of DTaP improves diphtheria immunity and longevity of tetanus immunity in adulthood.

However, there is a safety concern for giving an additional dose of DTaP. One in ten children are at risk of extensive limb swelling after successive doses of DTaP. Although, this is usually painless, transient and benign, it can impact parental confidence in the safety of vaccines. Consideration could be given to administering Tdap instead of DTaP at the 4-year-old event, should an additional toddler dose of DTaP be implemented, to address this concern.

Recent evidence

For further details on the following literature, see Table 13.

A narrative systematic review, conducted in 2023, examined pertussis immunisation strategies and considered waning immunity in different countries.[39] Strategies examined were accelerated primary schedules (three primary doses within first 6 months) or extended schedules (three doses within 12 months), and compared booster doses given prior to or after 2 years of age.[39] The key findings were that:[39]

- the first dose of the primary course should be administered in a timely way, regardless of the primary schedules used in different countries
- completion of the schedule was critical for effectiveness of both primary and booster doses
- infants had suboptimal protection when scheduled doses were delayed
- a decline in natural boosting, particularly due to COVID-19 pandemic control measures, alongside a decline in immunisation coverage has led to a greater susceptibility in the population.

Additionally, although effective in providing direct protection, there was little evidence that booster doses in preschool children or adolescents provided indirect protection for other age groups. Hence children were a potential source of infection to younger siblings, putting young infants at risk, particularly where the schedule is extended.[39]

A change in the infant schedule in France from four doses, given at ages 2-3-4 months and a booster at 16 – 18 months, to three doses given at ages 2-4-11 months, was likely to have increased the risk for pertussis. At three years after vaccination, the risk of pertussis increased by 1.7 times (95% CI 1.4 – 2.0) and reduced pertussis antibody levels at ages 2 and 3 years by around 50% and 43%, respectively.[41]

A population-based retrospective cohort study conducted in Washington State, US, found that under-vaccination was significantly associated with a higher risk for childhood pertussis.[40] Of the 404 reported pertussis cases, 28.7% were unvaccinated, 36.9% were delayed and 34.4% were fully vaccinated on time. Those who had initiated the primary course late were 48% less likely to complete the primary series and under-vaccination was associated with a 3.5-fold higher (95% CI 2.3 – 5.5) risk of pertussis in the first year of life.[40] Based on a small sample size, no significant difference was shown in those who received three doses under the age of 2 years, either between a three-dose primary course (at 2-4-6 months) with no booster (3+0, as in NZ) or those given 2+1 course (at 2-4-11/12 months). The findings of this study also support the WHO recommendation for a booster dose in second year of life at age 18 months.[40]

Following antenatal vaccination

Pertussis antibody concentrations were significantly lower at a month after a booster dose (given at age 12 months) in infants born to mothers who were vaccinated in pregnancy and who received a two-dose primary course in Québec, Canada (ie 2+1 schedule). These were not significantly different for those who received a three-dose primary course with the booster given at 18 months. Impact of maternal vaccination on different immunisation schedules in infants against pertussis was assessed following the DTaP schedule change in June 2019 in Québec: from a 3+1 schedule (at 2-4-6-18 months) to a 2+1 schedule (at 2-4-12 months).[36] Post-booster antibody levels were compared for the different schedules and between those whose mothers did and did not receive Tdap in pregnancy.

Although the actual geometric mean concentrations of pertussis antibodies were lower, the clinical significance of the difference between the schedules in those vaccinated in pregnancy is unclear. Both schedules led to high antibody concentrations and the absolute differences were small.[36]

Conclusions

- New Zealand has a 3+0 pertussis immunisation schedule. These studies suggest that the addition of a booster dose given in the second year of life improves protection against pertussis in toddlers.
- Timing of the primary course appears to be less important than completing it, but timing differs in each country.
- Three-dose schedules (2+1 or 3+0) appear to be less protective in infants and young children than four dose (3+1) schedules.
- Most countries found a 2+1 schedule to be less protective under the age of 2 years than a 3+1 course, particularly for those born to mothers who were vaccinated in pregnancy.

Adolescent booster dose

Introduction

The benefit of an adolescent Tdap booster dose in preventing pertussis remains unclear. Currently, as part of the NZ Schedule, adolescents receive Tdap at the age 11 or 12 years. The protection from this booster is likely to be short-lived, particularly in those primed with aP as infants (ie, born in NZ since 2000). Additionally, the adolescent booster dose does not appear to provide herd immunity against pertussis to younger age groups.[89] However, it is likely to reduce disease severity, which is most important in adolescents with respiratory co-morbidities.[2]

Anti-pertussis toxin immunity wanes more rapidly following each booster dose in those primed with acellular pertussis (aP) vaccines. It is unclear whether omitting the adolescent Tdap dose will influence the response to any booster doses given in adulthood, particularly to those given in pregnancy. See Table 13 for further details.

Burden of pertussis in adolescents and young adults

During the change from whole-cell to acellular pertussis vaccines (in the late 1990s in the US), a shift in the burden of disease moved from infants and young children to adolescents and young adults.[8] From 2000 to 2016, these older age groups accounted for more than one quarter of all pertussis cases reported in the US. A booster dose of Tdap was introduced in 2006 for adolescents aged 11 or 12 years following a spike in cases aged 11 to 18 years during a pertussis epidemic in 2004 and 2005 in the US. The majority of these age groups had been primed in infancy with aP.[8] Although pertussis is not associated with high severity or mortality in this age group, it has a significant effect on morbidity related to insomnia, apnoea, weight loss, urinary incontinence, syncope, rib fractures and pneumonia.[8] Symptomatic pertussis also increases the risk of transmission to peers and infants too young to be immunised.

Recent evidence

The introduction of a Tdap booster at age 14 – 15 years in two Canadian provinces had an impact on pertussis incidence on those aged 15 – 19 years, as shown by significantly decreased incidence rate

ratios between adolescents and infants aged under 1 year. But the absolute impact on pertussis burden was likely to have been low since infant vaccination had already reduced the pertussis incidence and hospitalisations of young children.[43]

Decreases in pertussis cases were seen in Norway in those 8 – 15 years after introducing a booster dose at ages 7 – 8 years in 2006 (IRR 0.89; 95% CI 0.88 – 0.90), and similarly in those age 16 – 19 years after introducing a booster at age 15 – 16 years in 2013 (IRR 0.84, 0.82 – 0.86).[42] No significant changes were seen among children aged under 1 year during these times (who receive a primary course at 3, 5 and 12 months). Findings indicated some indirect protection to adults (ages 20 – 39 years and 40 years and over) but not in infants. Despite high vaccination coverage in the target groups, a steady increase in pertussis incidence rates was seen in children aged 1 – 7 years (from 63 to 86 / 100,000) and aged 8 – 15 years (from 88 to 122 / 100,000) during 2013 to 2019.[42] An earlier Norwegian study found that the seasonality of pertussis differed between preschool-aged children and school-aged children, and that indirect protection was seen within age cohorts but provided little protection for neighbouring age cohorts. Therefore, it concluded that booster doses given to adolescents provided indirect protection for unvaccinated adolescents but was not likely to protect infants.[89]

Safety of booster

A meta-analysis of six RCT comparing Tdap with Td, found an increased risk for gastrointestinal symptoms — nausea (RR 1.26; 95% CI 1.01 – 1.57) and vomiting (RR 2.08; 1.21 – 3.85) — in adolescents and adults.[90] No increased risk for fever was seen when Tdap was compared with Td, but a subgroup analysis showed an increased risk when comparing reduced-dose Tdap (8µg PT, as used in NZ) with TdaP containing more PT (> 8µg) (RR 1.61; 1.02 – 2.52).[90]

Key points

- The introduction of aP vaccines in the late 1990s shifted the burden of pertussis from young children to older children and young adults.
- A booster dose given in early adolescence helped to reduce this burden.
- Although symptomatic pertussis is not life-threatening in most young people, it can have high levels of morbidity and risks transmission to peers and infants, particularly if those infected are parents.
- A booster dose given to adolescents can provide direct protection to the individual and possibly to their age cohort, but provides limited indirect protection to younger age groups.
- Tdap has a very good safety profile, with few adverse events. Gastrointestinal symptoms, nausea and vomiting, have been reported at a higher rate than Td vaccine. Higher pertussis toxin doses can also increase the risk for fever.
- In our previous review, we noted that disease severity is reduced in vaccinated adolescents, and this would be particularly beneficial to those with respiratory comorbidities.

Booster doses in non-pregnant adults

Antenatal vaccination is the most effective way to protect young infants from pertussis, through passive immunity. It also prevents symptomatic infection in mothers, who are key sources of *B. pertussis* infection to their young infants. Additionally, unfunded booster doses are recommended

in New Zealand for healthcare workers (HCW),[87] other occupational carers and close household members of young infants.

Most people are unaware of nasopharyngeal carriage of *B. pertussis* or show minimal symptoms of pertussis. There is moderate evidence that booster doses of Tdap are protective against nosocomial transmission in HCW.[2] Since no correlate of protection for pertussis has been established, data around the requirements and timing for repeat boosters is limited. Although the current vaccines do not effectively prevent carriage of *B. pertussis*, vaccinating those in close contact with infants can help to prevent disease in infants by reducing the risk of exposure to active illness and coughing. The incremental benefit of vaccinating close contacts when the mother has been immunised in pregnancy is unclear.

General immunity post COVID-19

As described above (see *Pertussis following the COVID-19 pandemic*), post-COVID-19 studies have shown that the incidence of pertussis declined dramatically during the pandemic due to non-pharmaceutical strategies to control the spread of SARS-CoV-2.

When anti-pertussis antibody levels in paired blood samples from 18 healthcare workers of childbearing age were compared in Canada, there was a significant decline during 2021 compared 2020 due to low exposure to pertussis and the absence of recent boosting.[12] The incidence of pertussis during 2020 (3 cases per 100,000) and 2021 (<1 case per 100,000) was the lowest in British Colombia since 1990.

Similar findings were observed by a serosurvey conducted in 2020 in Zhejiang Province, China with low pertussis circulation during the COVID-19 pandemic.[10] Over 50% of participants aged over 7 years had undetectable anti-PT IgG (no preschool or adolescent boosters are given in China). Only small proportion (<1%) of adolescents and adults had evidence of recent infection.[10] It concluded that the immunity to pertussis is low in general, but infections continued to occur during the strict non-pharmaceutical interventions of the COVID-19 response.[10]

Occupational vaccination

Within the recent literature, several studies looked at attitudes and vaccine uptake, but few showed the risks of waning immunity, vaccine effectiveness or safety in health care or early childhood education settings.

Safety and immunogenicity

In terms of safety and immunogenicity, booster doses of Tdap given five or 10 years after a previous dose were immunogenic for all antigens and the safety profile was acceptable.[45, 46] A slightly higher proportion of those vaccinated reported a solicited adverse event when Tdap was given after five years than 10 years (94% vs 88%, respectively – from two separate studies). The five-year study participants were younger than those vaccinated after 10 years (aged from 15 years vs 18 years).[45]

Vaccine effectiveness

A case-control study in older adults (mean age 61 years, range 46 – 81 years) in Australia demonstrated modest protection (aVE 52%, 95% CI 15 – 73%) against PCR-confirmed pertussis for up to six years after Tdap (range 5.0 – 6.7 years). Of the PCR-confirmed pertussis cases, 20 had been vaccinated and 152 were unvaccinated. Although statistical power was limited, no significant waning

in vaccine effectiveness was observed up to six years post vaccination or with increasing age.[47] When compared with PCR-based diagnosis, the study found that pertussis serology was unreliable and led to misdiagnosis, likely due to the increase in antibodies following the use of Tdap vaccination in adults.

Other occupational groups

One occupational group often overlook for vaccination are early childhood education (ECE) employees working with infants too young to be fully immunised. A survey conducted in New Zealand, between late-January to mid-February 2020 among 4,021 ECE teaching staff, found that less than 50% of participants reported immunisation against pertussis within the last 10 years, compared with 85% who reported they were immunised against measles, mumps and rubella.[44] A small proportion (0.5%) declined to answer the question on immunisation and a few commented that they did not see immunisation as relevant to their role or strongly disapproved of being asked about their immunisation status. In a similar Australian study, 75% of ECE staff reported pertussis immunisation. In Australia, unvaccinated ECE staff can be required to only work with infants older than 12 months, to take antibiotics during a bacterial disease outbreak or be excluded from work during a vaccine-preventable disease outbreak.[44]

Cocooning and parental post-partum vaccination

Antenatal vaccination is by far the most effective approach for protecting young infants before they can be fully immunised against pertussis. Where maternal vaccination does not occur, the second line of defence is vaccination of household members, particularly parents, grandparents and other caregivers, as well as ensuring siblings are up to date with their routine immunisation. However, there is limited evidence that this approach is effectiveness. In part, this is due to incomplete protection from within or outside of the household. A Swiss study, conducted 2012 to 2013, found that although the majority of household vaccinations occurred within the perinatal period and within 2 months of the infant's birth, for 93% of families cocooning remained incomplete, and in most families (82%) less than half of the close contacts had received pertussis vaccination.[91]

During a pertussis epidemic in 2011 – 2012, the Department of Health in Western Australia implemented a postpartum cocooning policy offering Tdap to new parents, grandparents and other household carers. This strategy was ineffective in preventing pertussis in infants aged under 6 months.[92] Out of 53,149 infants born to parents who were vaccinated within 28 days of birth, 118 developed pertussis. There was no difference in the incidence of pertussis between those with both parents vaccinated postpartum or those with unvaccinated parents: 1.9 vs 2.2 infections per 1,000 infants, aHR 0.91 (0.55 – 1.53); and those whose mother was vaccinated postpartum (aHR 1.19, 0.82 – 1.72).[92]

Postnatal vaccination of mothers was also shown to not be as effective as maternal antenatal vaccination in the UK.[32] Vaccine effectiveness against pertussis in infants aged under 3 months born to mothers either vaccinated within 6 days of birth or 1 – 41 days after birth was 27% (-56 to 65). In comparison, for those born to mothers vaccinated at least 7 days before birth, vaccine effectiveness was 89% (86 – 91).[32] See Figure 7.

A survey conducted in 2016 in Melbourne, Australia, found that 22% of newborns were discharged to a household in which neither parent had been vaccinated against pertussis.[48] Of 589 women and/or their partners surveyed when admitted to maternity wards, 70% of the pregnant women and 66% of their partners reported having received pertussis vaccination according the national

recommendations (48% during pregnancy and 66% within 10 years). In families where antenatal vaccination did not occur, rates of vaccination of partners or other carers were lower than in those families where antenatal vaccination had occurred (26% vs 83%). This was especially seen in households where carers had come from overseas (18.5% vs 76%). The survey concluded that cocooning remained an important approach to protect newborns of mothers who were unvaccinated or vaccinated late in pregnancy.[48] When adjusting for the type of family member and residence status, the odds of a family member being vaccinated was 10 times higher in the households in which the mother had been vaccinated in pregnancy (OR 10.5, 5 – 20.1, $p < 0.01$).

Conclusion

Although the current vaccines do not effectively prevent carriage of *B. pertussis*, vaccinating those in close contact with infants, such those working in birthing units and neonatal care, does appear to help to prevent disease in infants. This review did not identify any recent papers investigating transmission of *B. pertussis* from health care workers to patients with time since vaccination. In the US, due to its limited ability to interrupt transmission, routine Tdap revaccination of healthcare workers is not generally used.

The incremental benefit of vaccinating close contacts (cocooning) when the infant has been immunised by vaccination in pregnancy is unclear. Over recent years, as a consequence of COVID-19 control measures, natural boosting of pertussis immunity has been reduced due to low exposure to circulating *B. pertussis*.[10, 12] Therefore, the use of booster doses could be more important in occupational and household settings than pre-2020.

Recent data on the safety and effectiveness of repeated occupational vaccinations is limited. Given the waning immunity seen following aP vaccination, it seems logical to maintain repeat booster doses every 5 – 10 years in those working closely with young infants and other high-risk groups. Although, this review was unable to determine the precise timing required. Booster doses are likely to becoming increasingly important for younger staff who were born since 2000 and primed solely with aP vaccines (see *Comparison of whole-cell and acellular pertussis vaccines*). Pertussis vaccination also needs to be encouraged in settings beyond health care, such as early childhood education and daycare centres.

To be an effective strategy, vaccination of all caregivers needs to be conducted preferably prior to the birth of an infant. Antenatal vaccination of the pregnant person is the most effective way to protect to the youngest infants. For any incremental benefit, other caregivers also should not wait until the birth to be immunised to provide an additional layer of protection. In many cases though, where maternal vaccination does not happen the other caregivers are also unvaccinated, particularly for those visiting from overseas. Ideally, caregivers need to be vaccinated least two weeks before engaging with the infant.

Key points

- The incremental benefit of vaccinating close contacts (cocooning) when the infant has been immunised by vaccination in pregnancy is unclear.
- To help to maintain immunity and protect young infants and high-risk groups, 5 – 10 yearly Tdap booster doses are recommended.
- The shorter timing between doses is likely to be most important for those born since 2000 and primed solely with DTaP.

- The use of pertussis booster vaccination is required beyond health care settings.
- Vaccination of all close contacts of newborns is best conducted prior to birth for most effective protection, in addition to antenatal vaccination of the pregnant person. This includes family members visiting from overseas.
- Apart from ensuring the infant is vaccinated on time, it is unclear what the most effective strategy is for parents, caregivers and those working with young infants if maternal vaccination is missed.

Comparison of acellular and whole cell pertussis vaccines

A major focus of research around pertussis vaccination is the difference between whole-cell pertussis (wP) and acellular pertussis (aP) vaccines, with a resurgence in pertussis potentially attributed to the change from whole cell pertussis (wP) vaccines following the introduction of aP vaccines in the late 1990s / early 2000s.

With success of the initial pertussis vaccination programmes starting in the 1940s, attention shifted from the severe effects of pertussis to the safety of wP vaccines and a decline in coverage.[8] Due to local reactogenicity, persistent crying in infants, hypertonic hyper-responsive episodes (HHE), and suggested associations with rare, severe neurological adverse events such as encephalopathy (now disproven[93]), wP vaccines were replaced in most high-income countries by aP vaccines. However, the evidence around safety has been contested and the WHO stated in its position paper on pertussis in 2015 that there is no evidence to contraindicate wP vaccines.[87] Because wP vaccines are cheaper, many lower and middle income countries continue to use wP vaccines in infants.[87] New Zealand replaced DTwP with DTaP in 2000.

Reactogenicity appears to increase with subsequent doses of wP and for this reason they are not generally used for booster doses in older children. Differences between acellular and whole-cell pertussis vaccines has emerged in terms of ability to prevent transmission and duration of protection.

As mentioned in the introduction of this review, increases in pertussis rates have been related to several factors (see Figure 1).[49] Notably, although aP vaccines induce strong antibody responses and are effective in preventing symptomatic disease, rapid waning in protective antibody levels and an inability to sterilise *B. pertussis* nasopharyngeal carriage are considered important drivers of this resurgence.

The reported duration of protection from natural infection is around 10 – 20 years, for wP around 10 – 12 years, and for aP around 3 – 5 years.[49] This short duration means that, prior to a booster dose, younger children are susceptible. One study reported the odds of pertussis increases by a factor of 1.33 (95% CI 1.23 – 1.43) for every year after a DTaP vaccination, regardless of number of doses in the primary series.[49, 94] Waning immunity has also been shown with wP vaccines despite a slightly longer duration of protection.

The following considers the evidence around differences in pertussis immunity following priming with either wP or aP vaccines. It also investigates the potential role of a mixed wP / aP schedule. See Table 15 for further details of the studies.

Immunogenicity

In recent years, differences in the immune response to wP and aP vaccines have been shown from the first dose. These differences persist following further exposure to pertussis antigens, through vaccination or infection. Furthermore, repeat boosters with the same vaccine formulation appears to result in dominant immunity against non-protective epitopes and more rapid waning of protection. For those primed with aP (ie born since 2000 in NZ), consequences are expected for booster doses in pre-schoolers, adolescents and mothers-to-be.[2]

Recent evidence

Antibody responses to *B. pertussis* infection differed between those immunised with wP or aP (PT-only) vaccines.[50] Sera from 36 Danish adolescents (aged 15 – 20 years), submitted for diagnosis of pertussis (anti-PT IgG) during 2014 – 2016, were analysed using a range of assays to detect antigen specificity of IgG and IgA. Two groups were defined: those born just prior to (wP group) and just after (aP group) the change to aP vaccines in 1997. These were further defined as having high or low anti-PT IgG titres (wP+, wP-, aP+, aP-; nine samples in each group). Those with high anti-PT IgG titres also had high levels of IgG and IgA against the other pertussis antigens (FHA, PRN or *B. pertussis* outer membrane vesicles [OMVs]), and there were no differences in these between the aP+ or wP+ groups. Those with low antibody titres (wP- or aP-) had low levels of anti-OMV antibodies only. Antibody profiling found some immunogenic antigens induced by *B. pertussis* infection had not been previously identified, and that the selection of these antigens was significantly different between the aP and wP groups for both serum IgG and IgA antibodies. Therefore, antibody specificity following a recent pertussis infection in adolescence was correlated with the pertussis vaccine received in childhood. This study found that the response to infection after vaccination was not limited only to the antigen(s) given in the vaccine (ie not limited to PT in those primed with single antigen aP vaccine).[50]

The T cell profile of adults immunised as children with wP vaccines was examined in Ireland.[51] Cells were collected from 20 patients (10 each vaccinated with wP or aP as children) undergoing tonsillectomy; and nasal tissue cell samples were collected by mid-turbinate swabs from 20 healthy volunteers. These were matched with peripheral blood samples. Tonsil mononuclear cells (TMCs) and peripheral blood mononuclear cells (PBMCs) were incubated with Staphylococcal enterotoxin B (positive control), heat-killed sonicated *B. pertussis* or purified FHA (which provided a more consistent T cell response than PT). A significantly higher frequency of $CD4^+$ T cells producing IFN-γ and IL-17A was found in the tonsils of adults primed as children with wP than with aP vaccines. Those primed with wP not aP vaccine had tonsil and nasal cells that produced IFN-γ and IL-17A in response to *B. pertussis*. These cells were identified as tissue-resident memory T cells (T_{RM}) and were shown to persist in the respiratory tract for decades after pertussis vaccination with wP vaccines.[51] This is consistent with studies of PBMCs showing Th1/Th17 polarised responses to wP and Th2-predominant aP responses.

Key points

- Differences in the T cell and antibody profile are shown between those primed with acellular or whole-cell pertussis vaccines.
- Those primed with whole-cell vaccine appear to have longer lasting immunity.

- The duration of pertussis protection is likely to be determined by tissue-resident memory T cells and an associated difference in the T cell polarisation in respiratory mucosal tissue and in peripheral blood.
- Antibody responses differ during infection depending on the type of vaccine used in priming.

Effectiveness

The relevance of differences in immune responses can only be measured by looking at the impact of the different vaccination programmes on pertussis incidence.

Recent evidence

A systematic review by Wilkinson et al (2021) of compared the effectiveness of aP and wP vaccinations and found the pooled estimate of effectiveness to be similar (79%).[19] However, there was a high degree of heterogeneity (of over 90%) between studies in the way vaccine effectiveness was determined. The review concluded that any pertussis vaccine provides short-term protection against pertussis but duration of protection is longer for wP vaccines.[19]

A case-control study in England found that the effectiveness pertussis vaccination differed in children depending on which vaccine was used first in their primary course.[54] Children were primed with either a three-component acellular pertussis vaccine (aP3), a five-component acellular pertussis vaccine (aP5) or whole-cell pertussis vaccine (wP). Some were primed with a mix of wP and aP vaccines after October 2004, when aP5 replaced wP on the immunisation schedule, and some children received wP priming and aP3 preschool booster. Using data from a pertussis outbreak involving 10,454 cases during 2011 – 2012, the study compared 403 cases aged 5 – 15 years with 581,971 age-matched controls (all vaccinated with four doses of pertussis-containing vaccine at least 60 days before symptom onset). It found that of the 403 cases, those who received three primary doses of aP3 had almost four-times greater odds of being a case than those who received three primary doses of wP (aOR 3.86, 95% CI 2.56 – 5.82). There was no significant difference between those who received aP5 or wP (aOR, 0.89; 0.29 – 2.73).[54] After receiving a preschool booster of aP, there was little difference between groups, except for those given low-dose aP5 in those primed with aP3 (with shorter follow-up). Although children who received aP5 priming were younger and less distant from their preschool dose than those primed with wP, their risk did not appear to differ from wP when adjusted for year of birth and type and year of preschool booster.[54] The authors concluded that a primary course with aP3 was associated with a higher risk for pertussis than those primed with wP.

Key point

Children vaccinated solely with aP3 vaccines (as used in NZ) appear to be less well protected from pertussis than those who were primed with wP vaccines or mixed wP/aP schedules.

Mixed whole cell / acellular vaccine schedules

In recent years, emerging evidence suggests a difference between wP and aP vaccine types as to how the immune system is primed. This difference in priming polarises the subsequent responses to vaccination or wild-type infection towards either a T helper-1 (Th1) type cell profile or a T helper-2 type response (Th2/Th17).[52] Further studies have shown that this difference affects the immune memory within mucosal tissue into adulthood.[51, 53]

The immunostimulatory liposaccharides on the surface of whole inactivated or live *B. pertussis* act as the adjuvant for wP vaccines[41] and induce a proinflammatory response. The advantage is that the response is driven through toll-like receptor 4 (TLR-4), which in turn activates Th1 cells and the generation of tissue-resident memory T cells (T_{RM}).[52] The disadvantage is that this inflammatory response increases vaccine reactogenicity. Acellular vaccines contain alum as the adjuvant. Alum is associated with a more Th2-type response that induces antibody and less reactogenicity but has also been associated with an increased risk of allergy.[56]

The first exposure to either vaccine determines the polarity of the immune response thereafter. Therefore, priming with one or the other vaccine drives the immune response to *B. pertussis* for life.

The difference in immunity and effectiveness profiles of wP and aP vaccine raises the question as to whether there is any value in returning to whole cell vaccines for the first dose of the primary course. Mixed schedules have been proposed since reactogenicity and adverse reactions increase with subsequent doses of wP. Priming with the first dose of wP and then following up with less reactogenic aP vaccinations could prevent the skewing of the T cell response towards the Th2 profile. The reactogenicity of wP vaccines increases with the number of doses received. Careful consideration is required in relation to vaccine confidence – it is known that adverse experiences during the first vaccination event can result in parental hesitancy to return for subsequent vaccinations.[59]

Safety

A Cochrane review in 2021 found no increased risk for vaccine-associated severe AE when either wP or aP were given as the first dose to infants (wP vs aP RR 0.94, 95% CI 0.77 – 1.16, 11 studies). No cases of encephalopathy were diagnosed in seven RCT involving 32,300 infants given wP and 83,003 aP recipients.[55]

An ongoing Australian RCT (OPTIMUM) is comparing the reactogenicity, immunogenicity and IgE-mediated response of the mixed wP/aP versus standard aP-only schedule.[57] Infants were randomised at age 6 weeks to either wP (DTwP-Hib-HepB) or aP (DTaP-IPV-HepB/Hib) vaccines, and all completed the schedule with aP vaccines (DTaP-IPV-HepB/Hib at 4 and 6 months, and DTaP-IPV at 18 months).[57] The most common response after the first dose given to 6-week-old infants was irritability in 65 out of 73 infants (88%) who received DTwP-Hib-HepB and 59 out of 72 (82%) given DTaP-IPV-HepB/Hib. Severe injection site pain was reported after dose one in 6/74 (8%) of wP group and none who received aP. Severe systemic reactions were more common in mixed wP/aP group after the first dose of wP (19% vs 11% in the aP-only group), but were similar after the 4-month and 6-month aP doses. Paracetamol use on more than one occasion after 6-week dose was more frequent in those who received wP (59/75, 79%) than aP (52/75, 69%). During this study, no cases of hypotonic hyporesponsive episodes were reported.[57] Reassuringly, parental acceptance of the mixed schedule was high with 71 out 73 (97%) of the mixed schedule group said they would agree to have the same schedule again, and this was comparable to 69 out of 72 (96%) of the aP-only group.[57]

Immunogenicity

The Cochrane review mentioned above found little reliable evidence around the incidence of allergic disease in young children following wP or aP vaccination use, or a mixed schedules.[55] A cohort study analysing linked administrative datasets of nearly 220,000 Australian children found a 53% lower risk of food-allergy related hospitalisations in those who were given a first dose of wP before 4 months of age.[56]

The ongoing two-stage RCT (OPTIMUM study) in Australia is examining the use of wP as the first dose of the immunisation schedule at age 6 weeks (DTwP-Hib-HepB) and completing the schedule with aP vaccines (DTaP-IPV-HepB/Hib at 4 and 6 months, and DTaP-IPV at 18 months).[57] The aim of the project is to compare the reactogenicity, immunogenicity and IgE-mediated response of the mixed wP/aP versus standard aP-only schedule.[57] Published data to date has shown non-inferiority in PT-IgG titres between wP or aP groups at age 7 months and no differences in tetanus toxoid IgE. Further analyses of the $CD4^+$ T cell polarisation against pertussis antigens and atopic phenotypes are anticipated.[57]

Effectiveness

The evidence for effectiveness of mixed wP/aP courses is limited. The UK study mentioned previously found that when the primary course commences with wP, the risk for pertussis remains higher when the course is completed with three-component aP compared with a complete wP course vaccine (pertussis OR 2.47 (1.71 – 3.56), $p < 0.001$).[54] The risk of pertussis is similar to wP when the course is completed with a five-component aP vaccine (OR 1.82 (0.52 – 6.37), $p = 0.35$). However, since the children vaccinated with aP5 were the youngest cohort, it is unknown whether this is due to less waning in protection with age.[54]

Key points

- There may be a role for giving infants a wP-containing vaccine as the first infant dose to improve pertussis control for the long term. Data is limited to determine whether this is valid strategy to overcome the challenges with aP priming.
- There appear to be no safety concerns when wP is given as a single first dose.
- Data suggest that a first dose with aP vaccine may increase the risk for food allergies compared with wP priming.

Maternal antibody interference with whole-cell primary course

The presence of maternal antibodies had a greater impact on the pertussis-specific response to wP primary vaccination in infants than aP vaccination during a clinical trial in Thailand. Infants born to mothers who receive Tdap in pregnancy received either aP or wP-containing vaccine at ages 2, 4, 6 and 18 months. These were compared with wP-vaccinated infants not vaccinated during pregnancy.[58] After maternal Tdap, 158 infants vaccinated with aP-containing primary course had significantly higher antibody levels ($p < 0.001$) against all test pertussis antigens than 157 infants who received wP-vaccines. Post-booster, only anti-PT and anti-PHA antibodies remined significantly higher in the aP groups ($p < 0.001$). Anti-PT and anti-FHA antibodies were significantly higher in wP-vaccinated infants born to unvaccinated mothers than in wP-vaccinated infants born to Tdap vaccinated mothers. At all stages, antibody functionality was greater in the wP-vaccinated infants.[58]

Conclusion

Waning antibody levels and a lack of sterilising immunity is associated with the aP programme introduction. Theoretically, a mixed wP/aP schedule could overcome the limitations of aP vaccines. In practice, several challenges remain.

- No wP-containing pertussis vaccines are approved for use in New Zealand.

- By having a different vaccine for the first primary doses from subsequent primary doses, is likely to cause confusion and errors in service delivery.
- It is uncertain that this approach will reduce reactogenicity and maintain immunogenicity of wP.
- Any signs of increased reactogenicity could be a significant barrier for uptake, reduce parental confidence after dose one, and result in delayed uptake of aP doses. It may be better accepted if given alongside the meningococcal B vaccine with paracetamol. But it is unknown whether the risk of adverse events would increase if wP and meningococcal B vaccines were given concurrently.

Recombinant and other pertussis vaccines

In addition to mixed schedules, using both the whole cell and acellular pertussis vaccines in the primary course (see above), other vaccine technologies are being evaluated to overcome the limitations of the current acellular vaccines. Thes include a recombinant genetically detoxified pertussis toxin vaccine, live attenuate whole cell pertussis and adjuvant technologies. See Table 16 for additional details.

Recombinant acellular vaccine

Introduction

To improve the immunogenicity of aP vaccines, vaccines are being used that contain genetically detoxified (PT_{gen}) recombinant pertussis toxin instead of the current chemically (hydrogen peroxide or formaldehyde) detoxified pertussis toxin. As described in our 2018 pertussis review of evidence,[2] clinical trial data showed that genetic inactivation of pertussis toxin using recombinant DNA technology significantly increased anti-pertussis seroconversion rates and antibody duration compared with the current chemically detoxified PT vaccine formulations.[95, 96] Despite increased immunogenicity, the reactogenicity profiles were similar between these vaccine types.

In addition, to reduce interference or adverse events associated with the tetanus or diphtheria toxoid components of DTaP and Tdap, a monovalent recombinant pertussis vaccine has been developed. A vaccine containing PT_{gen} and FHA has been licensed in Thailand since 2016, available as both a pertussis-only (monovalent) vaccine (aP_{gen}, Pertagen®; BioNet-Asia) and a reduced-dose TdaP combined vaccine ($TdaP_{gen}$, Boostagen®). These are used routinely from age 11 years as booster doses, in pregnancy and occupational boosters.[60] Pertagen is under regulatory evaluation by the Therapeutics Goods Agency in Australia and the European Medicines Agency.[97]

Safety of recombinant vaccine

Post-market surveillance of aP_{gen} and $TdaP_{gen}$, in 11,420 adolescents and adults and including 1,778 pregnant participants, showed the incident rate of adverse events (AE) to be 11.5 per 1,000 individuals (95% CI 9.7 – 13.6). The most common AE was local injection-site pain in after both vaccines and muscle pain after $TdaP_{gen}$. All AEFI were mild to moderate in intensity and resolved within a few days. AE rate in pregnancy was 1.1 per 1,000 (0.3 – 4.1), 91% of participants had uncomplicated pregnancies and 99% delivered healthy babies – exceeding rates generally reported in Thailand.[60]

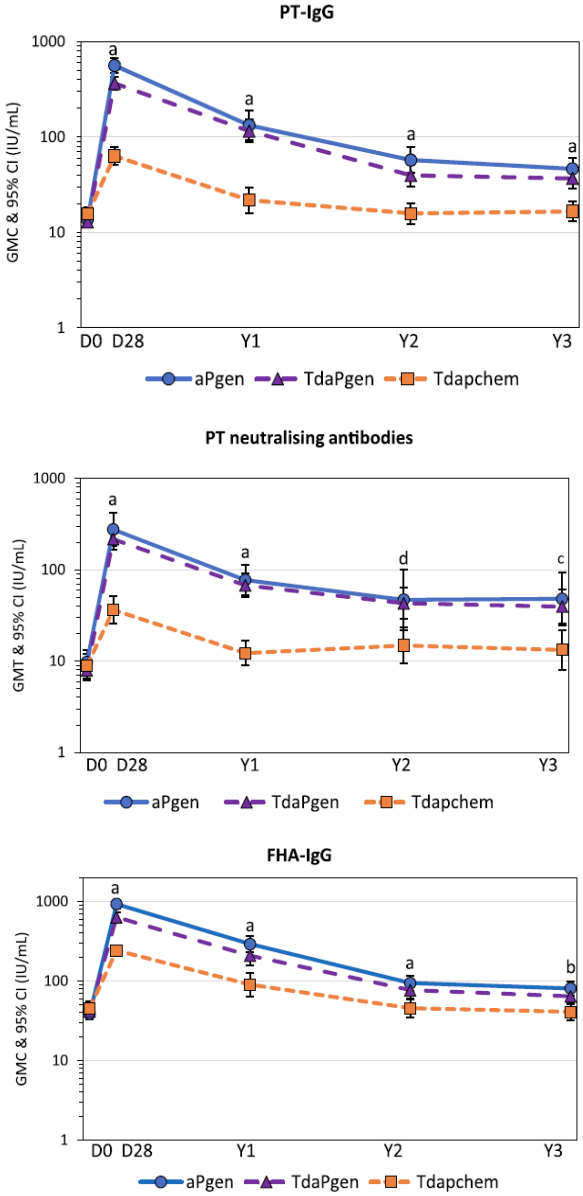


Figure 10: Pertussis antibody kinetics over three years post booster vaccination with genetically detoxified recombinant pertussis toxin (aP_{gen} or $TdaP_{gen}$) or chemically detoxified Tdap ($TdaP_{chem}$) vaccines. (Pitisuttithum, 2021, open access).

Immunogenicity of recombinant vaccine

In a follow-up study of phase II/III clinical trial, pertussis antibodies levels remained significantly elevated for three years in adolescents vaccinated at ages 12 – 17 years with aP_{gen} or $TdaP_{gen}$ in Thailand.[61] Antibodies against PT and FHA declined in the first year, but stabilised to levels significantly above baseline in the aP_{gen} and $TdaP_{gen}$ groups. Antibody levels were significantly higher in these groups at all time points compared with the $TdaP_{chem}$ (chemically detoxified PT) group, as shown in Figure 10. None of the $TdaP_{chem}$ recipients remained seroconverted (defined as ≥4-fold change from baseline) after three years, compared with 65% (95% CI 44.1% – 85.9%) of aP_{gen} and 55% (33.2% – 76.8%) of the $TdaP_{gen}$ recipients. After three years, PT neutralising antibodies in the aP_{gen} and $TdaP_{gen}$ groups remained elevated by 4.6-fold (2.6 – 8.1) and 3.7-fold (2.2 – 6.1), respectively. In the $TdaP_{chem}$ groups, the PT antibody levels returned to prevaccination levels within two years.[61] All participants in both $TdaP_{gen}$ and $TdaP_{chem}$ groups remained seroprotected for three

years against tetanus toxoid; and 86% and 88%, respectively, remained seroprotected against diphtheria toxoid. Follow-up studies are planned after five years.[61]

Maternal vaccination with recombinant vaccine

A post-marketing observational study in Thailand recruited pregnant women who were vaccinated in the second or third trimester with aP_{gen} or $TdaP_{gen}$ (n = 508), or Td only (n = 76).[62] High levels of anti-pertussis antibodies were shown in maternal and cord blood samples at birth in both of the recombinant vaccine groups. The use of the monovalent vaccine enabled women to opt for pertussis-only vaccination if they had received Td earlier. Both vaccines were well tolerated and did not alter pregnancy outcomes. Commencing in 2024, Thailand became the first country to offer recombinant aP_{gen} in pregnancy.[62]

Birth dose of monovalent recombinant vaccine

Recombinant aP_{gen} vaccine has also been considered to be given as a birth dose in infants whose mothers were not given Tdap during pregnancy.[63] A previously described[2] RCT recruited healthy infants in Australia aged less than 5 days, of whom, 221 were given monovalent aP_{gen} plus hepatitis B (HepB) vaccine and 219 controls were given HepB vaccine alone. Infants were also vaccinated at ages 6, 10 and 16 weeks with DTaP-IPV-HepB/Hib and 10-valent pneumococcal vaccine. At 10 weeks of age, 93.2% (192/206) of infants who received a birth dose had detectable anti-PT and anti-PRN antibodies, compared with 50.8% (98/193, $p < 0.001$) of the controls; anti-PT antibody GMC were four-fold higher in the aP birth-dose group. By 32 weeks, the only significant difference in PT and FHA antibody levels between the groups was seen in infants born to mothers who had not received Tdap within the previous 5 years. A blunting of antibody responses to other concomitant antigens (DT, HepB, Hib) was seen, but these exceeded defined protective levels. No difference were seen between groups for pneumococcal vaccine serotypes.[63] The study concluded that a birth dose of aP_{gen} could provide active pertussis protection to infants born to unvaccinated mothers too young to receive their primary course.[63]

This review found no evidence around the use of this recombinant aP in a DTaP vaccine for use in routine immunisation of children.

Key points

- Pertussis-only or combined recombinant aP vaccines are a safe and immunogenic option for pertussis booster vaccination in adolescents and adults, including in pregnancy.
- The safety and immunogenicity of aPgen-containing monovalent and Tdap vaccines were favourable. There were no safety concerns in pregnant and non-pregnant recipients.
- Mild to moderate localised injection-site pain and muscle pain were the most reported reactions.
- The immunogenicity of genetically detoxified PT appeared to be superior to chemically detoxified PT, with longer lasting and higher pertussis neutralising antibody levels.
- The use of the aPgen vaccine in infants looks promising as a birth dose for those not vaccinated in pregnancy, but data is limited to date.

Other vaccine types

Other new pertussis vaccine strategies in development include live attenuate vaccines, outer membrane vesicle (OMV)-based vaccines, and alternative delivery systems and adjuvants. Clinical data on these is limited to date.

- **Intranasal live attenuated vaccine**: An intranasal live attenuated pertussis vaccine (BPZE1) was found to be well tolerated and immunogenic in healthy adults aged 18–50 years.[65] It induced pertussis-specific IgG and IgA antibodies with broad specificities and a Th1 phenotype. BPZE1-induced antibodies had greater opsonising and bactericidal function than those induced by aP vaccine.[64-66]
- Adjuvants:
    - Preclinical studies have examined the use of saponin and semi-synthetic saponin adjuvants to advance the immunogenicity of aP vaccines.[67]
    - A small-molecule imidazoquinoline adjuvant to induce toll-like receptor (TLR7/8) responses has been investigated to overcome neonatal hyporesponsiveness and skewed T cell profiles seen with aP vaccines.[98]
- **OMV:** Similar to some meningococcal B vaccines, *B. pertussis* outer membrane vesicle-based vaccines have also been considered as a strategy to improve pertussis vaccination.[99, 100]
- Development of pertussis vaccines is also focussing on identifying new epitopes to improve the efficacy and duration of protection of pertussis immunity.[101-103]

Key points

- Improvements to pertussis vaccination strategies likely require alternative approaches to vaccine design and reverse vaccinology to improve the ability of these vaccines to prevent transmission (sterilising immunity) and produce longer lasting immunity without increased reactogenicity and risk for severe adverse events.
- Intranasal vaccination is being investigated to induce a sterilising mucosal response.
- Recombinant technology is being used to identify different epitope targets and other technologies to produce novel adjuvants.

Summary of evidence tables

Table 6 International pertussis immunisation recommendations

Country	Group	Vaccine	Schedule	Comments
Australia	Pregnancy	Tdap	Ideally 20 – 32 GW	
	Infants and children	DTaP-IPV-HepB/Hib DTaP DTaP-IPV	Age 2, 4, 6 months 18 months 4 years	First dose can be administered from 6 weeks
	Adolescents	Tdap	Age 12-13 years	
	Adults	Tdap		Anyone wishing to reduce likelihood of becoming ill with pertussis
	HCW / ECE	Tdap	Every 10 years	
	Older adults	Tdap	≥ 65 years	If have not had Tdap in last 10 years
	Carers and household members of infants <6 months	Tdap		Given at least 2 weeks before contact with infant
Canada	Pregnancy	Tdap	27 – 32 GW	ideally
	Infants and children	DTaP-IPV-HepB/Hib or DTaP-IPV-Hib DTaP-IPV or Tdap-IPV	Age 2, 4, 6 months 12-23, ideally 18 months Age 5 years	Alternative schedules mix these vaccines
	Adolescents	Tdap	Age 15 years	10 years after last DTaP or Tdap.
	Adults	Tdap	1 dose in adulthood	regardless of interval since last Td.
Norway	Pregnancy	Tdap	2nd or 3rd trimester	Regardless of time since last vaccination and every pregnancy
	Infants and children	DTaP-IPV-HepB/Hib Tdap-IPV	Age 3, 5, 12 months 7 years	Infants born ≤32 weeks received additional dose of DTaP-IPV-HepB/Hib at age 6 weeks.
	Adolescents	Tdap-IPV	Age 15 years	
	Adults	Tdap	Every 10 years	
United Kingdom	Pregnancy	Tdap	From 16 GW	Ideally before 32 weeks but can be given after.
	Infants and children	DTaP-IPV-HepB/Hib TdaP-IPV	Age 8, 12, 16 weeks 3 years 4 months or soon after	
	Adolescents	Td-IPV	Age 14 years	No pertussis
	HCW	Tdap	One dose if been >5 years since a pertussis vaccination.	3 levels of priority: Priority 1 regular and close clinical contact with severely unwell infants (<3 months) and women in last month of pregnancy repeat doses 5 years apart.
US	Pregnancy	Tdap	24 – 36 GW	Tdap postpartum only for those who have never previously received Tdap.
	Infants and children	DTaP	Age 2, 4, 6 months, 15-18 months 4-6 years	
	Adolescents	Tdap	Age 11 – 12 years	
	Adults	Tdap	For those who have never received Tdap	Td only given 10-yearly
	Older adults	Tdap	Age ≥65 years	
	HCW	Not suggested	Revaccination may be considered if healthcare associated transmission occurs	Tdap has limited effect to interrupt transmission or curtail an outbreak.

Abbreviations: DTaP – combined diphtheria, tetanus, acellular pertussis vaccine; ECE – early childhood education; GW – gestation weeks; HepB – hepatitis B; HCW – health care workers; Hib – *Haemophilus influenzae* type B vaccine; IPV – inactivated poliovirus; Td – combined tetanus and diphtheria toxoid vaccine; TdaP – tetanus, reduced dose diphtheria and pertussis vaccine
Sources: Australia Immunisation Handbook Pertussis (whooping cough); Canadian Immunization Guide; Helse Norge Vaccines and vaccination; UK Health security agency; UK Green book chapter 24 Pertussis; US CDC Pertussis recommendations

Table 7: Burden of disease

Outcomes	Ref	Participants	Results	Findings
Burden of disease in infants and young children				
Pertussis severity related to gestational age	4	676 medical records for children aged <2 yr hospitalised for pertussis during 2005–2014 in Netherlands	prematurity <37 GW: • 12% of pertussis hospitalisation vs 8% of Dutch birth cohort. • median age of admission = 3m for preterm vs 2m for term infants (p<0.001) • required longer ICU stays (15 vs 9 days). • oxygen supplementation and ICU admission were similar between the groups • artificial respiration (aOR 2.8, 1.3-6.0) and apnoea (1.8, 1.0-3.3) were more frequent in preterm infants when adjusted for age and presence of coinfections. VE against pertussis hospitalisation preterm vs term: • 1st dose age 2m = 73% vs 95% • 2nd dose at age 3m = comparable 99% vs 86%	The rate of hospitalisation of premature infants was higher than the overall birth cohort. They were of an older age (median age 3m) than full term infants (2m). The severity of pertussis was similar between the groups, but preterm infants required longer ICU admissions and were more likely to require artificial respiration.
Burden in aP era	5	1402 paediatric (≤16y) hospitalisation for pertussis in Canada 1999-2015	Infants <2m highest mean annual incidence (/ 100,000 population) for: • pertussis hospitalisation 116 (95% CI 85-148) • ICU admission 33.5 (26.3-40.6). Overall, 25% children require ICU admission, majority in infants <2m (38%) • independent risk factors: age <16 weeks, prematurity, encephalopathy and confirmed pertussis diagnosis • 21 deaths – risk factors age <4 weeks, prematurity, female sex. Hospitalisation incidence from age 6mlarge reduction – from 28 to 5/100K population between age 4-5m and 6-11mand 0.8/100K for those aged 1-4 years.	In aP vaccine era, pertussis continues to contribute to childhood morbidity and death, particularly for infants under 2 months prior to vaccination. Maternal vaccination has potential to reduce this burden. Infant vaccinations also contribute significantly to protection
Pertussis burden in Australia	6	1.3 million children in WA and NSW 2001-2012, followed for 18 months. stratified by Aboriginal (4.9%), prematurity (<32 vs 32-<37 GW), ≥1 comorbidities (3.6% of total, of these 3.5% non-aboriginal and 5.6% were aboriginal – most common respiratory, heart disease, kidney disease, premature <32GW.	3,771 first episode of pertussis notified age <18m 1,207 (32.0%) pertussis-coded hospitalisation – 101 admitted to ICU and 3 died. ICU – 68 (67.3%) were aged <2mand 86 (85.1%) were < 4m. • Aboriginal – 10.6% notification, 14.6% hospitalised cases, 15.8% of ICU admissions = over-represented. • Proportion with ≥1 comorbidity increases with pertussis severity – notified 199 (5.3%), hospitalised 84 (7.0%) and 23 in ICE (22.8%).	Aboriginal children had a significantly higher rate of pertussis notifications prior to any vaccine doses than either those with comorbidity or non-Aboriginal infants. Children with comorbidity had lower VE even after 3rd primary dose.

Outcomes	Ref	Participants	Results	Findings
Severe LRTI caused by pertussis	7	Prospective study, Cape Town, S. Africa, conducted over 1y, enrolled 460 children median age 8m (IQR 4-18m) admitted to hospital with acute lower respiratory tract infection.	Pertussis infection confirmed 32/460 (7%) of children. Adjusted risk increased if: • Age <2m: aRR 2.37 (95% CI 1.03-5.42) • HIV exposed uninfected: aRR 3.53 (1.04-12.01) • HIV infected: 4.35 (1.24-15.29) • Undernutrition: mild aRR 2.24 (1.01-5.09), moderate 2.7 (1.13-6.45) • *B. pertussis* detected in caregiver: aRR 13.82 (7.76-24.62) Significant protection if completed ≥3 primary vaccine doses: aRR 0.28 (0.10-0.75)	Nasopharyngeal carriage of *B. pertussis* in caregivers, HIV infection or exposure, under-nutrition and younger age were significantly associated with increased risk of severe pertussis in infants. Primary course was highly protective. Pertussis vaccination in pregnancy is a high priority, especially in HIV infected women.
Levels of immunity post COVID-19 non-pharmaceutical control measures				
Impact of pandemic on pertussis incidence	9	England, laboratory confirmed cases Lockdown March 2020 then masking wearing/social distancing to 18 July 2021.	Incidence in pertussis dropped from April 2020, despite anticipating a peak year. Incidence rates in July 2020 to June 2021 (after lockdown) vs July 2014-June 2019 /100,000 • infants <1y= 0.5 vs 24.5 • 1-4y= 0.19 vs 3.13 • 5-14y = 0.11 vs 9.41 • Over 15y = 0.13 vs 7.37 • Total = 0.13 vs 7.60 Total incidence rate ratio between 2020/21 and 2014/19 was 0.02 (0.01-0.02) Vaccine coverage: • Prenatal – dropped 2.7% lower than in 2019/2020 financial year (from 76.8% to 70.5%) • For infants – some data sources showed an increase, but timeliness affected as age 6m coverage decreased by 3%.	Lockdown measures due to COVID-19 pandemic had a significant impact on pertussis transmission. But also led to a decline in pertussis vaccine coverage. Also concerns that pertussis is going undiagnosed as similar cough symptoms to COVID-19. Unclear of the situation 2 years on.
Serosurvey in China	10	Blood samples collected across Zhejiang Province, China in 2020 from 4,459 participants aged 0-59 years, 30 participants per age group (ages <1, 1-2, 3-4, 5-6, 7-9, 10-14, 15-19, 20-29, 30-39 and 40-59 years). Children aged 1-14 years – 98.9% received 3 primary doses pertussis vaccination; 97.3% had 4 doses.	Seropositivity (≥20 IU/ml anti-PT IgG), by age: • Highest 1-2y = 81.44% • Lowest 10-14y = 4.7% • Sharp drop from age 3-4y (67.7%) to 9.8% at ages 5-6y and low for subsequent groups (4 – 6 %). Low immunity 5 years after last dose. • 50% had undetectable (<5 IU/ml) anti-PT IgG from ages 7y to 39y. • Modelling based on time of blood sample since 4th dose, showed a decline within the first year for anti-PT, -FHA and -PRN antibodies. Decline in anti-PRN antibodies was not as significant as for PT and FHA. • Based on antibody titre of ≥80 IU/ml from age 5y, a minority of preschool, adolescent and adults might have had recent infection – lower than a study conducted in 2014. Estimated infection rates were much higher than notifications, particularly in adolescents and adults.	Although prevalence of pertussis decreased during 2020/COVID-19 pandemic, a proportion of adolescents and adults had evidence of recent pertussis infection but not identified by diagnosis/routine surveillance. A high proportion of population are susceptible, and half may not retain immunity beyond age 7y (no pertussis vaccine beyond preschool age in China).

Outcomes	Ref	Participants	Results	Findings
maternal immunity post COVID-19 NPI	12	18 paired blood samples of childbearing age female HCW at start (May-June 2020) and 1 year into COVID-19 pandemic (Feb-May 2021) in British Columbia, Canada. None of the HCW had Tdap since 2017. Matched to 26 first trimester samples taken in 2018 and 2019 age groups selected (median 37 years, IQR 28-41) – homogenous wP primed population (ie born 1974-1997)	• Pertussis incidence during 2020 (3/100,000) and 2021 (<1/100,000) were the lowest since 1990. Compared with 2018/19, 2020 levels were not significantly lower (slightly). Anti-pertussis IgG levels declined in 2021 vs 2020 o Anti-PT: 6.8 IU/ml (4.2-10.9) vs 8.4 (5.1-13.9); p = 0.004 o Anti-FHA: 18.8 (10.9-32.2) vs 23.6 (13.2-42.1) p<0.001 o Anti-PRN: 371 (18.1-75.9) vs 47.3 (24.8-89.9) p = 0.092 • Proportion of women with anti-PT IgG in 2021 vs 2020 o ≥5 IU/ml – 55.5% (10/18) vs 66.6% (12/18), p=0.73 o ≥15 IU/ml – 27.8% (5/18) vs 33.3% (6/18), p = 1 o ≥30 IU/ml – 11.1 vs 16.7% (3/18), p = 1 o ≥40 IU/ml – 5.6% (1/18) vs 5.6% (1/18), p = 1	Showed a significant decrease in pertussis antibody levels in 18 healthcare workers of childbearing age with low exposure and absence of recent boosting. Clinical implications are uncertain.

Abbreviations: aP – acellular pertussis vaccine; FHA – filamentous haemagglutinin; GW – gestation weeks; HCW – health care workers; IgG – immunoglobulin G; IQR – interquartile range; m – months; NPI – non-pharmaceutical interventions; PT – pertussis toxin; PRN – pertactin; SR – systematic review; wP – whole-cell pertussis vaccine; y – years

Table 8: Childhood immunisation – effectiveness of pertussis vaccine

Outcomes	Ref	Participants	Results	Findings
Childhood DTaP schedule				
Dose dependent effectiveness in infants <1 year	15	Case controlled study. Active surveillance (PERTINENT study) during Dec 2015-2019, 35 hospitals in 6 EU/EEA hospitals. Hospitalised pertussis cases (259 cases vs 746 controls) aged 2-11m at time of discharge. Case = lab-confirmed +ve *B. pertussis* test. Regardless of year, August had the highest mean number of pertussis cases over the 4 years vs Feb/March for pertussis-negative controls.	• After ≥1 dose (210 cases and 476 controls): VE = 59% (36-73) • VE after only 1 dose ≥14 days before symptom onset: o Age 2-11m – 56% (28-73) o Age 2-5m – 48% (5-72) • VE after two doses (175 cases and 476 controls aged 2-11 months) o For any dose, age 2-11m – 73% (50-86) o 2nd dose only, age 3-10m – 76% (43-90)	Findings suggest that for infants aged 2 -11 months having received at least one dose of aP vaccine reduces the risk of being hospitalised with pertussis by almost 60%. Only one dose halves the risk of hospitalisation if aged 2-5 months. After two doses VE increases to more than 73%.
	16	Population based case-control study. Swiss paediatric surveillance unit assessed immunisation status of children aged 2.5 months to 2 years hospitalised for pertussis. Cases - 327 children during 2006-2010 and 196 during 2013-2017 vs 20,633 controls. routine aP3 vaccination given at age 2, 4, 6, and 15-24m, (±2wks coverage: 80%, 74.9%, 65.2%, 86.5%). By age 2y 94.2% (15,461) had 3 doses and 86.5% (17,865) 4 doses.	VE against pertussis hospitalisation increased with each consecutive dose. Doses: 1. 42% (95% CI 11.3-62.6) 2. 84% (70.2-92.1) 3. 98% (96.1-99.3) 4. No cases after dose 4 – 100% (96.0-100)	Study demonstrated an incremental improvement in VE with each dose (with 42% point-estimate after dose 1 and further dose-by-dose increases).
DTaP effectiveness in childhood, US	17	469,982 children followed from age 3 months until +ve pertussis, received Tdap or turned 11 years (average follow-up 4.6 years per child). Born between 1999-2016 at KPNC. Routine five doses DTaP given at ages 2, 4, 6, 12–18 months and 4–6 years.	Total 738 pertussis cases: o 99 unvaccinated o 36 under-vaccinated o 515 fully vaccinated for age o 88 fully vaccinated plus one dose • Risk of pertussis aHR (95% CI): o Vaccinated vs unvaccinated: 13.53 (10.64–17.21) o Vaccinated vs under-vaccinated: 1.86 (1.32-2.63) o Fully vaccinated plus one dose vs fully vaccinated: 0.48 (0.34-0.68) • See below for duration of protection data.	Unvaccinated and under vaccinated children accounted for less than 20% of the pertussis cases (4% of person years follow-up). Most cases were fully vaccinated, especially those most distant from vaccination. Suboptimal VE and waning are possible factors associated with epidemics.

Outcomes	Ref	Participants	Results	Findings
Systematic review pertussis VE and duration of protection	19	SR/MA (to Nov 2019) – wP and aP, included 47 VE [32 aP, 22wP and 14 mixed] and 15 duration studies. See below for duration of protection data.	Pooled estimate VE: • aP – 79% (95% CI 73-83; I^2 =93%) • wP – 79% (69-86; I^2 = 93%) • mixed – 84% (75-90; I^2 = 92%) • VE altered by study design, case definition, high statistical heterogeneity (I^2 > 50%), age groups, epidemic period, country. • Pooled estimate VE against severe pertussis (hospitalisation or death) = 91% (87-94%; I^2 = 67%)	Evidence that any pertussis vaccine confers protection against pertussis disease, but wanes rapidly for aP vaccines. High degree of heterogeneity was not fully explained – there were differences in timing, magnitude and pertussis activity trends, vaccine schedules and products across jurisdictions. Decisions made around vaccine policy based on these studies should carefully consider sources of heterogeneity.
Special groups				

Effectiveness in Premature infants, Netherlands	4	676 medical records retrieved of patients age 0-2 years with pertussis during 2005-2014 linked to vaccination data. 12% were preterm (born <37 GW) and median age at admission 3m for preterm vs 2m for term (p<0.001)
		Note – schedule 6w-2m, 3, 4, 11m but unclear how long after vaccination that hospitalisation occurred.
			Preterm vs term
			• Median age at admission: 3m vs 2m (p<0.001)
			• Vaccinated: 62% vs 44% (p=0.01)
			• Co-infections: 37% vs 21% (p=0.01)
			• VE
			  ○ first dose (age 2m at admission): 73% (20-91%) vs 95% (93-96%)
			  ○ second dose (age 3m at admission): 86% (9-96%) vs 93% (85.96%)
				Premature infants accounted for 12% of pertussis hospitalisation but only 8% of Dutch birth cohorts. Effectiveness of first dose was lower than term infants, despite this cohort being more likely to have received the first vaccinations. Premature infants required longer ICU care and more likely to have co-infections than hospitalised term infants.

Effectiveness in high-risk children, Australia	6	1.3 million children in WA and NSW 2001-2012, followed for 18 months. stratified by Aboriginal (4.9%), prematurity (<32 vs 32-<37 GW), ≥1 comorbidities (3.6% of total, of these 3.5% non-aboriginal and 5.6% were aboriginal – most common respiratory, heart disease, kidney disease, premature <32 GW.	VE against hospitalised pertussis
			• Aboriginal vs non-aboriginal
			• dose 1: 51% vs 25%
			• dose 2 69% vs 74%
			• dose 3: 76% s 80%
			• with vs without comorbidities
			  ○ dose 1: 0% vs 41%
			  ○ dose 2: 30% vs 80%
			  ○ dose 3: 70% vs 81%
			• with comorbidities dose 3: hospitalised 70% (29-87) vs non-hospitalised (24%, -49 to 61)
			• children with comorbidities had a 6-fold higher rate of hospitalised notified pertussis.
				For Aboriginal and non-Aboriginal children, improved timeliness and antenatal vaccine coverage should improve pertussis protection.
				For highest risk children (<32 weeks gestation or significant comorbidities), measures such as extra doses or vaccines with improved immunogenicity are required (particularly in settings where a 2+1 schedule is used).

Duration of protection				

DTaP effectiveness in childhood, US	17	Cohort study - 469,982 children followed from age 3 months until +ve pertussis, received Tdap or turned 11 years (average follow-up 4.6 years per child). Born between 1999-2016 at KPNC. Routine five doses DTaP given at ages 2, 4, 6, 12–18m and 4–6y.	Total 738 pertussis cases
			See above for vaccination effectiveness data.
			• Risk of pertussis aHR (95% CI):
			  ○ Age 19m to <7y, ≥ 3 years vs <1 years since vaccination: 5.04 (1.84-13.8)
			  ○ Age 7 to 11y, ≥6 years vs <3 years since vaccination: 2.32 vs 0.97-5.59
			  ○ children aged >18m with longer intervals between recommended doses were at highest risk.
				Most cases were fully vaccinated, especially those most distant from vaccination. Suboptimal VE and waning are possible factors associated with epidemics.

Outcomes	Ref	Participants	Results	Findings
Systematic review - Pertussis VE and duration of protection	19	SR / MA (to Nov 2019) – wP and aP, included 47 VE [32 aP, 22wP and 14 mixed] and 15 duration studies. See above for aP VE data and Table 15 for VE of mixed and wP schedules.	Duration of protection, aP VE: • Ages 0 – 10 years: ○ 1st year VE = 98% (90-100; I^2 = 94%) ○ By 5 years post vaccination = 81% (69–89; I^2 = 0%) • Ages 11 – 20 years ○ 1st year VE = 72% (66-76; I^2=0%) ○ 4 years post vaccination = 42% (16–60; I^2 = 2%)	Evidence that any pertussis vaccine confers protection against pertussis disease, but wanes rapidly for aP vaccines. High degree of heterogeneity was not fully explained – there were differences in timing, magnitude and pertussis activity trends, vaccine schedules and products across jurisdictions.
Systematic review - waning immunity	18	SR / MA – DTP-containing vaccines. 59 articles in SR and 30 acellular pertussis articles in MA (also 16 diphtheria, 16 tetanus and 10 polio).	Pooled RR • with time since last dose (compared with control period): ○ 1-2 years = 1.65 (1.33-2.05) ○ 2-3 years = 2.06 (1.62-2.62) ○ 5-6 years = 5.50 (4.33-6.98) ○ 8-9 years = 8.43 (5.06-14.03) • Compared with unvaccinated groups ○ 0-1 years = 0.09 (0.05-0.16) ○ 2-3 years = 0.23 (0.16-0.33) ○ ≥8 years = 0.30 (0.20-0.43) Based on GMR estimates diphtheria antibodies waned • 25% participants did not have seroprotective Ab levels 2-6 years from last dose • at 5-6 years post vaccination, titres were not significantly different to prevaccination levels (GMR 1.21, 0.68-2.17). Tetanus and polio – persistent antibody levels in almost all participants at 10 years.	Found evidence of substantial waning in antibody immunity against pertussis and diphtheria after vaccination. No defined correlate of protection but levels reached prevaccination levels suggesting decreased immunity. Saw sustained long-term immunity against tetanus and polio. Requires further evaluation to predict the need and optimal timing between pertussis and diphtheria boosters.

Abbreviations: aP – acellular pertussis vaccine; aHR – adjusted hazard ratio; DTP – diphtheria, tetanus and pertussis; GMC – geometric mean concentration; GMR – geometric mean ratio; GW –gestation weeks; KPNC – Kaiser Permanente North California; NSW – New South Wales; PERTINENT - Pertussis in Infants European Network; PT – pertussis toxin; RR – risk ratio; SR/MA – systematic review and meta-analysis; VE – vaccine effectiveness; wP – whole-cell pertussis vaccine; WA – Western Australia

Table 9: Vaccination in pregnancy – safety

Outcomes	Ref	Participants	Results	Findings
Timing in pregnancy	20	SR 11/45 publications on safety	No indication of increased safety concerns with timing of pertussis vaccination in pregnancy. Studies found no association between reactogenicity (fever or local reactions), adverse pregnancy outcomes (stillbirth and miscarriage) or adverse infant outcomes (preterm birth, low birth weight or birth defects) with timing of Tdap administration in pregnancy.	
Meta-analysis of safety and immunogenicity of Tdap given in pregnancy	77	Published literature to Oct 2021. Out of six RCT, three reported safety of Tdap in pregnancy for infant and pregnancy. Limitation – did not perform meta-analysis on obstetric or foetal complications.	Pooled OR (0% heterogeneity): • Pregnancy outcomes/pregnant women SAE = 1.26 (95% CI 0.78-2.05, p = 0.35) • infants = 0.61 (0.37-1.01; p = 0.053).	Data support the recommendation for routine Tdap vaccination in pregnancy to improve protection for infants against pertussis before primary immunisations.
Chorioamnionitis, non-pertussis infections and other AE in pregnancy	22	SR/MA of 13 observation and 6 RCT, published up to Jan 2021. Pooled data from 6 observational studies on chorioamnionitis. Excluded studies with 0 events.	Increased risk of chorioamnionitis in women vaccinated with pertussis vaccine but not with other non-pertussis, non-live vaccines given in pregnancy – RR = 1.24 (1.141-1.42) (2/6 studies showed statistical significance). Prevalence of chorioamnionitis in non-vaccinated groups was 2.9%; out of 1000 vaccinated an additional 8 will have chorioamnionitis. No signif difference for other outcomes: • non-pertussis infection (1 OS and 2 RCT): RR 1.12 (0.43-2.91) • spontaneous abortion or still birth (4 OS): RR 1.04 (0.92-1.16) • neonatal death (1 OS) RR 0.32 (0.02-4.69)	A lack of a strong association between maternal immunisation with a pertussis-containing vaccine and known clinical consequences of chorioamnionitis, such as sepsis and preterm birth, may indicate a lack of clinical relevance for this association. But does not discount an association. Limitation: Based on retrospective studies of ICD-10 codes. In high-income countries the negative outcomes of chorioamnionitis are less easily detected with high standard of care. Those who are vaccinated likely to follow better care but also may be more likely to have issues detected and elect for epidural delivery which also has an association with chorioamnionitis/similar symptoms.
Repeat vaccinations	23	SR – safety in pregnancy,27 articles included.	Frequency of systemic and local reactions to Tdap, including fever, were similar 1-5 years apart to those who did not have previous Td vaccine. No increase in acute AE or adverse birth outcomes following previous Td containing vaccine given <2 years, 2-5 years or >5 years. Nor between infants born to mothers who received single or multiple doses of Tdap in <5 years.	

Abbreviations: GW – gestation weeks; m – months; OS – observational study; RCT – randomised controlled trial; RR – risk ratio; SR/MA – systematic review and meta-analysis; Tdap – tetanus, diphtheria, acellular pertussis vaccine; Td – tetanus and diphtheria vaccine; y - years

Table 10: Vaccination in pregnancy – immunogenicity of antibody transfer from mother to infant

Outcomes	Ref	Participants	Results	Findings
Passive antibody transfer				
Timing in pregnancy	20	SR of 26/45 publications on immunogenicity	Vaccination in early third trimester or at least 8 weeks before delivery is suggested to provide maximal protection. Higher antibody levels were reported in several publications when immunisation was administered in early third compared with late third trimester. Some studies found no difference with timing in pregnancy. Most reported a positive correlation between time interval between vaccination and delivery and antibody titres at delivery. No studies considered relationship between timing of vaccination and antibody titres in breastmilk or cellular immunity. Few studies investigated first or second trimester vaccination.	
Maternal antibody transfer	25	Multicentre cohort study, Netherlands between Aug 2019-Nov 2021. Total 221 women delivered 239 offspring. Maternal Tdap given either 20-24 GW (mid-2nd trimester) or 30-33 GW (mid-3rd trimester). 1. Premature birth (<33 weeks), mother vaccinated 20-24 GW (73 infants) 2. Early to late term (born ≥37 GW), aged 2 months, mother vaccinated 20-24 GW (66 infants) 3. Early to late term (born ≥37GW), aged 2 months, mother vaccinated 30-33GW (reference cohort of 55 infants recruited Jan 2014- Feb 2016) Blood samples at delivery from mother and umbilical cord, and from infants at age 2m	See Table 4 for data • Maternal TT and DT antibody GMRs were significantly different between preterm and term delivery and the GMR for anti-FHA antibody in cord blood between early and later vaccination (p=0.06 and 0.09, respectively). • Sensitivity analysis did not find significant difference between maternal antibody levels in preterm cohort who delivered before COVID-19 restrictions or during.	Anti-pertussis toxin antibody levels approximately two-fold lower at age 2 months in infants born to mothers vaccinated with Tdap in mid-2nd trimester compared with mid-3rd trimester. When vaccination occurs prior to 24 weeks, the peak in antibody after vaccination may not coincide with the optimal time for maternal antibody transfer and appears not to be compensated for with longer time to delivery. Clinical relevance of these lower antibody levels is unknown without a correlate of protection or epidemiological study.
immunogenicity and transplacental transfer	83	phase IV RCT, 687 healthy pregnant women given Tdap vaccine at 27-36 GW or placebo control (age 18-45y). Europe, Canada and Australia. NCT02377349	GMC ratios of maternal antibodies in cord blood (Tdap/control): • anti-FHA = 16.1 (13.5-19.2) • anti-PRN = 20.7 (15.9-26.9) • anti-PT = 8.5 (7.0-10.2) • somewhat higher anti-pertussis antibodies in those vaccinated at 27-32 GW vs 33-36 GW	Tdap vaccination in pregnancy produced high levels of pertussis antibodies in the cord-blood at birth.

Outcomes	Ref	Participants	Results	Findings
Tdap Prior to or during pregnancy	29	Cohort study, 3 arms, 58 maternal/cord blood pairs collected 2011-2017. All received influenza vaccine and 25 (43%) received Tdap in pregnancy. Remained vaccinated prior to pregnancy (no timing given) Arm 1 – 2/25 received Tdap 31 and 32 GW in 2011-2012 Arm 2 – 9/19 Tdap between 28-33 GW in 2013/2014 Arm 3 – 2/14 Tdap at 26.6-26.9 GW & 12/14 Tdap 28.7-33.6 GW.	Tdap Ab were higher in mother and cord blood in those vaccinated in pregnancy: 0.5-1 Log higher against all 3 Ags (PT, FHA and PRN) than before pregnancy ($p<0.001$). Tetanus Ab – during pregnancy vaccination marginally higher in mothers, significantly higher infants vs pre pregnancy vaccination ($p = 0.0059$) Influenza antibodies were comparable between groups. No correlation between maternal IgG and placenta transfer efficiency (ratio 0.9 and 1.1 for all IgG types vaccinated during vs prior) – higher levels in infants due to maternal antibodies not increased rate of transfer.	Efficiency of antibody transfer was similar between those vaccinate prior to or during pregnancy. Did not affect transfer of non-Tdap antibodies. Pertussis IgG antibody levels were higher in those vaccinated in pregnancy
Tdap immunity after two successive pregnancies	27	27 women given Tdap in first pregnancy enrolled in follow-up for 2nd pregnancy. Mean interval between deliveries 2.4 years (1.4-3.9). Mean gestational age at vaccination – 29.5 (1st pregnancy) and 28.8 GW (2nd pregnancy).	Tdap-specific total IgG in maternal serum were comparable but reduced in cord blood at 2nd delivery compared with first. (See Table 5) Transfer ratios were reduced for total IgG and IgG1 IgG1 – comparable for FHA, DT and TT Abs but lower for anti-PT and PRN in maternal serum. In cord blood – transfer efficiency was lower for FHA, DT and TT compared with first delivery. No difference for other IgG subclasses.	Tdap in each pregnancy remains beneficial but transfer was reduced for subsequent pregnancy. At both deliveries, infants born to vaccinated mothers were still better protected than those unvaccinated.
Coadministration of influenza, COVID-19 and pertussis vaccines	28	Pilot study in Taiwan, 71 participants received 3 and 4 doses of mRNA COVID-19 vaccine (final dose in current pregnancy) plus Tdap/Influenza (TI) or Tdap alone (T). Maternal blood samples collected at birth. No indication of timing of vaccination in pregnancy. High antenatal Tdap coverage in Taiwan meant no pregnant comparators without Tdap.	No significant difference in pertussis IgG between 3 and 4 COVID-19 vaccine doses, and no difference with addition of influenza vaccination • 3TI vs 3T = 17.69 vs 18.64 U, p=0.971 • 4TI vs 4T = 15.98 vs 13.89 U, p=0.973 • No interference in COVID-19 neutralising antibodies observed. • Suggestion of cross-protection/indirect protection against influenza A with COVID-19 vaccination but not influenza B in the groups who didn't receive influenza vaccine.	Protection from pertussis is not influenced by vaccination with influenza or COVID-19 in pregnancy.

Abbreviations: DT – diphtheria toxoid; FHA – filamentous haemagglutinin; GMC – geometric mean concentration; GMR – geometric mean ratio; GW –gestation weeks; PRN – pertactin; PT – pertussis toxin; RCT – randomised controlled trial; Td – tetanus diphtheria vaccine; Tdap – tetanus diphtheria acellular pertussis vaccine; TT – tetanus toxoid

Table 11: Vaccination in pregnancy – effectiveness against pertussis in infants

Outcomes	Ref	Participants	Results	Findings
Effectiveness of antenatal vaccination up to age 6 months				

SR burden of pertussis in infants and effectiveness maternal immunisation	3	Infants aged <6 months, 11 articles published 2011-2018
		Outcome: VE of maternal Tdap preventing pertussis in infants, and impact of programme (3 studies age <12m).
			• Infants <2m: adjusted VE against confirmed pertussis in infant ranged from 77.7% to 93%.
			• infants <3m:
			  ○ similar, ¾ studies ranged 90.9-91%, one Australian study VE 69% (13-89)
			  ○ deaths<3m vaccinated ≥10 day prior to birth: VE 95% (79-100)
			• Infant age <6m: lower than in young infants
			  ○ VE against infection 39% not significant
			  ○ VE hospitalisation of 46%
			VE to reduced severity of pertussis (by preventing hospitalisation):
			• crude VE 75.4% (49.8 -88.9) significant
			• no significant when adjusted 52.1% (-0.16-80.3) for chronological age, gestational age and paediatric aP vaccination.
			Impact – greatest reduction infants <3 months
			• Argentina: by 78% (72-83%), from 328 cases in 2012 to 72 in 2013 with 78% maternal coverage.
			• UK – 234/100K in 2012 vs 30 cases /100K in 2018
				Effectiveness of maternal Tdap against pertussis disease and hospitalisation in infants up to age 6 months.
				Maternal vaccination currently is the most effective means to protect newborns and young infants against pertussis prior to primary immunisation.

Effectiveness of maternal vaccination <age 2 months.	30	PERTINENT study in six European countries. TND, Dec 2015-2019 829 infants aged <1 year (336 aged 4 days - <2months and 493 aged 2-11 months) hospitalised with pertussis-like symptoms – cases *B. pertussis* or controls without any *Bordetella* sp infection. Median gestational age of vaccination cases 30.4 GW (range 23-36) and controls 30.1 GW (20-37)	Effectiveness of vaccination in pregnancy in infants aged <2 months • 9/75 (12%) cases and 92/199 (46%) controls were vaccinated in pregnancy. • Adjusted VE (for study site, time of onset and age group) = 75% (35-91) and when diagnosed by aspirate = 88% (57-96%).	Vaccination in pregnancy reduces the risk of infants to young to be vaccinated (ie aged <2 months) being hospitalised with pertussis by around 80% (75-88%). Vaccination in pregnancy is an effective strategy to fill the immunisation gap prior to the infant's first vaccinations.

Outcomes	Ref	Participants	Results	Findings
Effectiveness of maternal vaccination in infants aged up to 8 months.	31	Australia, population-based cohort study NT, WA and QLD (Link2HealthierBubs), 279,418 mother-infant pairs, linked health records. 57% received Tdap 28 – 31 GW. total 331 cases up to age 18 months, 118 cases per 100,000 infants First 3 years, estimated 52% pregnant individuals received aP.	82 per 100,000 antenatal vaccinated infants (119 cases) and 157 per 100,000 antenatal unvaccinated (213 cases). • 49/331 (14.8%) aged <2m • 124/331 (37.5%) aged <6m, of these 12.9% hospitalised, 4.8% ICU and 2 deaths (1.6%) Overall, VE maternal vaccination: • Infection < 6m = 65.1% (49.5-76.0) • Hospitalisation <6m = 60.2% (-18.3 to 86.6) 2.8 cases /100K vaccinated vs 8.9/100K unvaccinated • By age group, VE against infection: ○ <2m = 70.4% (50.5-82.3) ○ 3-4m = 65.7% (41.8-79.8 ○ 5-6m = 61.6% (37.5-76.4) ○ 7-8m = 43.3% (6.8-65.6) ○ Not significant after 8 months. Median age notified (p <0.001, predominantly in QLD) • vaccinated antenatally = 11 m (IQR 8.75) • unvaccinated antenatally = 7.5m (IQR 10)	Pertussis vaccination around 28 GW was associated with lower risk of pertussis infants to 8 months. No significant differences observed in timing of maternal vaccination on infant antibody levels at birth. Also see Table 12.
Timing of vaccination in pregnancy				
Timing in pregnancy	20	SR – 9/45 publications on effectiveness. All studies either conducted in UK or Argentina, total of 133,275 mother-infant pairs included but some duplication of participants	Mixed findings – some found no difference in effectiveness in infants aged less than 2 or 3 months between second and third trimester vaccination. US study favoured early third trimester (but didn't investigate second trimester).	Recommendations around the timing of maternal vaccination implemented worldwide differ widely. Timing of vaccination in pregnancy seems to impact immunogenicity and vaccine effectiveness. Notably, effectiveness is reduced if vaccine is given late in pregnancy compared with earlier in pregnancy.
Effectiveness of timing of maternal vaccination	32	Routine data collected from the General practice information system (ImmForm) and clinical practice research datalink (CPRD) covering 6% of UK population. Pertussis vaccination only counted if given >300 days before birth and ≤8 days after. Children born 1 Oct 2012 to 31 Dec 2019. VE – pertussis onset <62 days (before vaccination) or if vaccination was delayed for infants aged <93 days. VE calculated for maternal vaccination ≥17 weeks, 13-16 weeks, 8-12 weeks or 1-7 weeks before birth, and 1wk before and 6wk after birth [perinatal].	• Maternal coverage 60-75%, consistent from 2016 – clear impact of earlier timing recommendations on uptake with 40% receiving Tdap ≥13 weeks before delivery. • 1162 lab-confirmed pertussis cases in children between 2012-2016., 599 aged <93 days, 463 (77%) unvaccinated mothers, 136 (23%) vaccinated mothers. 19 infants died, none after earlier vaccination was introduced, 2 were vaccinated 4 and 8 days before delivery. VE against infection • age <3m = 89% (86-91) • age < 2m = 88% (85-91) • VE against death – 97% (81-100) • Equivalent VE for different time periods (except for perinatal) comparison of vaccines: • VE Td3ap-IPV < Td5ap-IPV (87%; 84-90 vs 92%; 88-95)	Maternal vaccination is highly effective against pertussis infection and against pertussis-associated death up to age 3 months providing protection prior to infant's immunisations. VE was equivalent with different gestational periods except those born between 7 days before and 41 days after delivery.

Outcomes	Ref	Participants	Results	Findings
Effectiveness of maternal vaccination in infants aged < 6 months.	31	Australia Link2HealthierBubs (described in Table 11), 279,418 mother-infant pairs, linked health records. 57% received Tdap 28 – 31 GW.	Gestation age VE % (95% CI) • <28 weeks: 78.4 (12.3-94.7) • 28-31 weeks: 62.2 (76.8- [38.7]) • ≥32 weeks: 70.5 (43.2-84.7) Time from vaccination to birth • 2-6 weeks: 74.8 (12.3-94.7) • 7-11 weeks: 61.7 (38.3-76.2) • ≥12 weeks: 70.6 (20.0-89.2) • Similar findings when weighted by inverse probability of receiving Tdap in pregnancy.	No significant differences between timing of maternal vaccination and vaccine effectiveness in infants aged < 6 months.
Effectiveness of maternal vaccination in Spain	82	Case-control study – 47 cases infants aged 8 weeks at time of disease onset and 124 controls born within 15 days of matched case. (Jun 2016-2018, northern Spain)	Mothers of cases were less frequently vaccinated in third trimester than controls (59.6% vs 83.9%, p<0.001). VE maternal vaccination 88.0 (53.8-96.5) and slightly higher for those vaccinated before 32 GW than after = 88.5% vs 87.8%	Vaccination in pregnancy is very effective in reducing pertussis in infants ≤2 months. Vaccination before and after 32 weeks gestation was equally effective.

Abbreviations: 100K – 100,000 population; GW – gestation weeks; NT -Northern Territory; PERTINENT - Pertussis in Infants European Network; QLD – Queensland; SA – South Australia; SR – systematic review; TdaP-IPV – combined tetanus, diphtheria, acellular pertussis and inactivated poliovirus vaccine; VE – vaccine effectiveness

Table 12: Vaccination in pregnancy – maternal antibody interference on infant immunity

Outcomes	Ref	Participants	Results	Findings
Immunogenicity of the infant primary course and booster after vaccination in pregnancy				
Meta-analysis, post-immunisation IgG response in infant	33	Individual-participant meta-analysis of 8 studies, post-immunisation IgG in infants born to mothers immunised Tdap or unimmunised in pregnancy	Tdap immunised group: • 2-fold higher pre-immunisation vs post primary immunisation GMR: ○ anti-PT – 0.91 (0.88-095, n=494) ○ anti-DT – 0.90 (0.87-093, n=519) • 2-folder higher pre-immunisation vs post-booster GMR: ○ anti-PT – 0.91 (0.85-0.97, n=224 ○ anti-FHA – 0.92 (0.85-0.99, n=232) Unimmunised group: • 2-fold higher pre-immunisation vs post primary immunisation GMR: ○ anti-PT – 0.92 (0.88–0.97, n = 373) ○ anti-FHA – 0.88 (0.85–0.92, n = 378) ○ anti-PRN - 0.84 (0.81–0.88, n = 367) ○ anti-TT - 0.88 (0.83–0.93, n = 241) ○ anti-DT - 0.83 (0.79–0.87, n = 278) • 2-fold higher pre-immunisation vs post-booster GMR ○ anti-FHA – 0.92 (0.86-0.99, n=138) • 2-3-4 months primary schedule resulted in 78% lower PT response than 2-4-6 months post booster (GMR 0.22m 0.08-0.61)	Two-fold higher anti-PT and anti-DT antibodies preimmunization were associated with 9% and 10% lower post-primary immunisation levels. Increased levels of IgG pre-primary immunisation were associated with a reduce post-primary and booster immunisation level for some antigens - regardless of whether women were immunised or not in pregnancy. Spacing of the primary course did not affect primary and booster IgG levels for most vaccine antigens. Current study does not suggest there is any clinical relevance of the lower antibody levels in infants born to mothers vaccinated in pregnancy but if this was shown in the future, modification of the infant primary course timing would need to be considered for these infants.
Immunogenicity of infant primary response following maternal vaccination	84	Follow-up of phase IV trial above, see Table 10 (NCT02422264). Immunogenicity of DTaP-IPV-HepB/Hib antigens. 601 Infants aged 6-14 weeks old born to mothers who received Tdap or placebo, vaccinated according to national schedules.	• For diphtheria, tetanus, hepB, polio, Hib – both groups had seroresponse at 1 month post vaccination ≥95% (94.5 -100%). • no interference was seen for PCV13 serotypes. • Pertussis antigen vaccine response rates (>than pre-vaccination lower limit) Tdap vs placebo ○ Anti-FHA – 36.9% vs 94.8% ○ Anti-PRN – 37.5% vs 90% ○ Anti-PT – 77.1% vs 99.2% • At one month post primary vaccination all infants were seropositive for all the pertussis antigens.	Maternal pertussis antibodies interfere with the infant's antibody response to pertussis antigens (particularly anti-FHA and anti-PRN antibodies) but the clinical significance is unknown as all infants were considered to be seropositive according to the study cut-off.

Outcomes	Ref	Participants	Results	Findings
Delayed infant vaccinations following maternal dose	34	Open-label parallel RCT Netherlands. 118 pregnant women aged 18-40 yr Tdap at 30-32GW or <48h postnatal (control). Infants vaccinated at 3, 5, 11m +/- maternal Tdap. Infant blood samples – cord, 2, 3, 6, 11, 12m Post-hoc analysis also compared with historical data for 2, 3, 4 and 11m without maternal vaccination – samples taken at 5m, 11m and 12m.	At age 3 months, 34/50 (68%) of infants in the control group had undetectable pertussis IgG levels compared with 1/54 (2%) Tdap group • The infant pertussis antibody concentrations were similar between the control group vaccinated with 2+1 schedule starting at age 3 months were compared with historical cohort given 3+1 doses starting at age 2 months. Tdap group at 3m vs control at 2m – anti-PT GMC ratio at 3m = 9.5 (6.1-14.9) Tdap vs control anti-PT IgG GMC ratio (similar for FHA and PRN antibodies): • Age 2m – 15.7 (9.9-24.8) • Age 3m – 16.6 (95% CI 10.9-25.2) • Age 6m – 0.4 (0.3-0.6) • Age 11m – 0.5 (0.4-0.7) • Age 12m – 0.5 (0.4-0.7)	Infants born to vaccinated mothers had 9.5 times higher pertussis antibody at age 3 months than controls at age 2 months (age first dose given in Netherlands). After primary series the Tdap group had significantly reduced antibody levels than controls. The effect of a booster dose was equivalent. Although antibody levels remained reduced, they were substantial. Delaying primary course until 3 months doesn't prevent blunting, more blunting is likely when vaccinated at 2m when maternal antibody levels were higher. It was suggested that this data support a 2+1 schedule for DTaP for those born to Tdap mothers, depending on maternal vaccination coverage and timeliness of maternal vaccination.
Impact of maternal vaccination on toddler booster response	38	Additional follow up of trials above – up to 18 months of age NCT02853929 263 (Tdap) and 277 (control) toddlers received DTaP-IPV-HepB/Hib and PCV13 boosters at age 11-18 months.	Before the booster dose, antibody GMCs ~1.4-1.5 times higher for anti-pertussis and diphtheria antibodies in the controls than Tdap group. Other DTaP-IPV-HepB/Hib and PCV13 antigens were comparable. One month post booster response rates: • pertussis ≥92.1-98.1% Tdap group vs 96.7-99.6% controls Seroprotection rates for other DTaP-IPV-HepB/Hib antigens >99.2% in both groups. PCV13 >98% for both groups (except serotype 3 ~79% both) • Pertussis antigens GMC control vs Tdap ○ Anti-FHA – 1.2-fold higher ○ Anti-PT – 1.5-fold ○ Anti-DT – 1.4-fold • All other antigens equivalent. • No difference in findings when analysed by primary schedule timing or maternal vaccination timing.	Likely due to maternal antibody interference to infant's response to the primary course, toddlers born to mothers vaccinated in pregnancy continued to have lower antibody levels than those not vaccinated in pregnancy for pertussis and diphtheria antigens. But the booster response was equivalent in both groups, just started at a lower baseline. The clinical relevance is unclear but other studies have not shown reduced protection in toddlers when vaccinated in pregnancy.

Outcomes	Ref	Participants	Results	Findings
Preschool booster	37	UK phase IV study. 64 children given $Tdap_5$-IPV at age ~3y 4m following antenatal $Tdap_3$-IPV (Boostrix-IPV) or $Tdap_5$-IPV (Repevax) or no vaccination. (note, UK does not provide a toddler booster doses, median time since last DTaP dose was 36 months) Boostrix has higher PT levels than Repevax.	Antibody prior to booster: • No significant difference between vaccinated groups • Anti-PT IgG were significantly lower in children born to Boostrix vaccinated compared with unvaccinated mothers. (GMR 0.42, 0.22-0.78, p=0.03). Overall no significant difference but tending to be lower for all pertussis antigens. No difference for TT and DT antibodies. 1 month post preschool booster • No significant difference, only apparent lower trend for lower anti-pertussis IgG vaccinated vs unvaccinated antenatally.	Blunting effect of antenatal pertussis vaccination on pertussis response in children persists beyond the age of 2 years into early childhood but can be overcome by a booster dose.
Safety of booster doses after primary course				
Safety of booster dose in toddlers born to mothers vaccinated in pregnancy	38	Phase IV clinical trial as described above.		No increase reactogenicity or change in safety profile of DTaP-IPV-HepB/Hib when given as a booster dose to toddlers (aged 11-18 months) born to mothers vaccinated with Tdap in pregnancy.
Effectiveness of infant primary course after vaccination in pregnancy				

Effectiveness of maternal and primary course age 2-11 months.	30	PERTINENT study, as above
		376 infants eligible for pertussis vaccine aged 2-11 months, 123 cases and 253 test-neg controls.
		Median gestational age of vaccination cases 30.1 GW (range 19-36) and controls 30.6 GW (14-36)
		Reference group unvaccinated infants and mothers
			Vaccination status:
			• in pregnancy and ≥1 dose PV: 31 cases (25%) and 98 (39%) controls
			• PV only: 27 cases (22%) and 53 controls (21%)
			• Pregnancy only: 9 cases (7%) and 38 controls (15%)
			Vaccine effectiveness (n=376,) adjusted for site time of onset and age:
			• Preg and ≥1 dose PV: 74% (95% CI 33-90)
			• PV only: 68% (27-86)
			• Preg only: 36% (-85-78)
			• Aspirate diagnosis:
			  ○ Preg/PV: 88% (62-96)
			  ○ PV only: 81% (62-96)
			  ○ Preg only: 44% (-109-85)
				Regardless of the recommended schedule, ≥1 dose of pertussis vaccination in infants born to mothers who were vaccinated in pregnancy reduced the risk of pertussis hospitalisation by 74-95%. Vaccination in infants born to mothers not vaccinated in pregnancy reduced the risk by 68-94%.
				The limited sample size was not able to assess any effect of pregnancy vaccination on the VE of infant vaccination. But these findings suggest good effectiveness of ≥1 doses of PV in infants aged 2-11 months, irrespective of vaccination status in pregnancy.

Effectiveness of maternal vaccination up to 8 months	31	Australia, population-based cohort study NT, WA and QLD (Link2HealthierBubs), described in Table 11	Lower point estimate after 3rd infant vaccination in maternally vaccinated vs unvaccinated (76.5% vs 92.9%, p=0.002) – no increase in pertussis infection (HR 0.70, 0.61-3.39). Not seen with dose 1 and 2.	Pertussis vaccination around 28 GW was associated with lower risk of pertussis infants to 8 months. Lower effectiveness in maternally vaccinated infants after 3rd dose didn't translate to a greater risk of disease compared with those who received no antenatal vaccination.

Outcomes	Ref	Participants	Results	Findings
Modelling impact of maternal immunisation on pertussis transmission	35	SR/MA – 4 studies with 2-6 years follow-up. Included modelling of transmission dynamics.	Weighted mean RR of pertussis of infants born to vaccinated and unvaccinated mothers, after primary immunisation: • 1st dose = 0.26 (0.11-0.67) • 2nd dose = 0.73 (0.39-1.34) • 3rd dose = 0.71 (0.38-1.32)	Findings support a role for maternal vaccination in protecting young infants most at risk from pertussis. Even in the presence of blunting, maternal immunisation was predicted to remain effective at reducing pertussis in unvaccinated newborns but may eventually (after more than a decade) result in an infection-control trade-off with older age groups. The study highlighted large uncertainty and lack of research into effects of blunting on pertussis. There is a need to disentangle the introduction of maternal vaccination with the resurgence of pertussis incidence and more recently the impact of COVID-19 control NPIs.

Abbreviations: SR/MA – systematic review and meta-analysis; VE – vaccine effectiveness; PV – primary vaccination; NT – Northern Territory; QLD – Queensland; SA – South Australia; NPIs – non-pharmaceutical interventions; RR - risk ratio; GW – gestational weeks; DT – diphtheria toxoid; FHA – filamentous haemagglutinin; GMC – geometric mean concentration; GMR – geometric mean ratio; GW –gestation weeks; PCV13- 13-valent pneumococcal conjugate vaccine; PRN – pertactin; PT – pertussis toxin; RCT – randomised controlled trial; Td – tetanus diphtheria vaccine; Tdap – tetanus diphtheria acellular pertussis vaccine; TT – tetanus toxoid

Table 13: Effectiveness and impact of different childhood immunisation schedules

Outcomes	Ref	Participants	Results	Findings
Primary course and infant boosters				
Narrative SR pertussis immunisation strategies	39	98 studies including observation, VE and modelling studies from 24 countries. • Accelerated – 3 doses age <6m • Extended – 3 doses age <12m • Booster – on, before or after 2nd year of life.	Recurrent themes of studies: timing of vaccination, vaccine coverage, waning immunity/vaccine effectiveness, direct and indirect effectiveness, switching from accelerated to extended schedules, impact of changes in testing. • Timeliness of delivery and completion of the schedule is key – first dose is important in reducing pertussis in infants, regardless of the schedule. • Protection from booster doses, whether given before or after 2nd year of life, wanes at similar rates. Delaying boosters to pre-adolescence may result in increased pertussis in young children. • Increases in testing and pertussis notification could in-part explain the observed increase in cases. WHO reported 5/19 countries had a true surge.	Challenging to compare schedules. Insufficient evidence to determine if one schedule was better than another. Countries need to select a schedule to obtain and maintain high coverage and reduce the risk of delay in delivering vaccines to infants. Booster vaccination did not indirectly protect infants.
Pertussis risk associated with timelines and number of doses	40	Retrospective cohort study Washington State, US, based on 316,404 children aged 3m to 9 years 2008-2017. Schedule 2-4-6, 15-18, and 4-6 years. (min age 38 days)	• 6.3% had no DTaP recorded • 36.7% were delayed for >1 dose • 56.9% were fully vaccinated with no delay. Higher proportions of the unvaccinated and delayed vaccinated children lived in areas of low SES. Those who delayed primary course were 48% (47-49%) less likely to complete the primary course and under vaccination was associated with a 3.5-fold higher (2.3-5.5) risk of pertussis in the first year of life. Of 404 pertussis cases: • 28.7% were unvaccinated • 36.9% were delayed • 34.4% were fully vaccinated on time. Under vaccination risk of pertussis (aRR, 95% 95% CI): • primary (ie <3 doses at 19 months) = 4.8 (3.1-7.6) • 1st booster (<4 doses at 5 years) = 3.2 (2.3-4.5) • 2nd booster (<5 doses at 9 years) = 4.6 (2.6-8.2) • Under/delayed vs age appropriate/timely: o aged 7-19 months, 4.8 (3.1-7.6) o not statistically significant at ages 19-60m (aRR 3.2, 2.3-4.5) and 5-9y. 3+0 vs 2+1 primary course – aRR 3.9 (0.5-28.8) (small sample size for 2+1)	Under vaccination was significantly associated with higher risk for pertussis. Delay in children who received the recommended number of vaccine doses did not increase pertussis risk.

Outcomes	Ref	Participants	Results	Findings
Modelling, change in schedule in France	41	Negative binomial regression model for no. of pertussis cases by year and age relative risk depending on schedule. Schedule pre 2013 – 2-3-4m and 16-18m; new schedule 2-4-11m. Data collected Jan 2012-Dec 2019, 7493 PCR+ symptomatic pertussis cases aged 2-20 years.	Fasting waning of immunity following vaccination with new schedule. Risk of pertussis 3 years after vaccination was 1.7 (1.4-2.0) times higher for children vaccinated according to new schedule. Anti-PT IgG – 50% lower at age 2 years under new schedule and 43% lower at age 3 years.	New schedule likely resulted in shorter-lived protection with an increase in pertussis cases seen in children aged 2-5 years. Schedule choice is a key component in pertussis control strategies.
Impact of maternal antibody				
Effect of maternal antibody on pertussis and pneumococcal antibodies after 2+1 and 3+1 primary course	36	Blood samples used from 378 children collected during another clinical trial. Quebec, Canada Vaccinated with a combination of Infanrix and Pediacel, PCV10 and PCV13. 3+1 at 2-4-6-18 months, blood sample at 19 months 2+1 at 2-4-12 months, sample at 13 months.	Pertussis analysis: • 2+1 schedule – Tdap vaccinated mother had lower anti-pertussis Abs than unvaccinated mothers (aGMR) at age 13 months (post 12m-booster): • Anti-PT = 0.77 (0.65-0.90) • Anti-FHA = 0.66 (0.55-0.79) • Anti-PRN = 0.72 (0.52-0.99) • 3+1 schedule vaccinated vs unvaccinated mothers (19m) – no significant difference aGMR o Anti-PT = 0.77 (0.65-0.90) o Anti-FHA = 0.66 (0.55-0.79) o Anti-PRN = 0.72 (0.52-0.99) • After adjusting for maternal vaccination, 3+1 had higher anti-pertussis Ab levels than 2+1. Infanrix hex booster induced higher levels. • Pneumococcal – PCV10 vaccinated 2+1 schedule, maternal vaccination only had small, non-significant effect on response to serotypes. • PCV10-only vs mixed PCV10 2+1/PCV13 booster - significantly lower 19A 79% seroconversion vs 100% among Tdap vaccinated.	Possible blunting of pertussis response after maternal vaccination, more pronounced in DTaP 2+1 schedule than 3+1. No significant interference of pneumococcal vaccination. Although 2+1 resulted in significantly lower pertussis Abs, the absolute differences in GMCs were small.
Adolescent booster doses				
Impact on pertussis incidence	43	British Colombia and Quebec, Tdap since 2004 in adolescents aged 14-15 years. aP vaccines had been used across all analysis periods in BC but only a proportion in Qb during 2000-2003.	ages 15-19 years to <1 year olds IRR decreased during 2009-2012 post Tdap vs 2000-2003 pre-Tdap: • BC 0.15 vs 0.3, p=0.001 • Qb 0.03 vs 0.05, p=0.006.	Adolescent boosters may have significantly reduced pertussis incidence in older teenagers (15-19 years) but the absolute impact on the burden of pertussis was likely to have been minimal due to already reduced in pertussis and serious outcomes in younger children.

Outcomes	Ref	Participants	Results	Findings

School age and late adolescent boosters	42	74,675 pertussis cases notified to Norwegian Surveillance System 1998-2019.	Booster introduction IR /100,000 and IRR (95% 95% CI)
			• 2006-2012 Age 8-15y = 433 to 199; 0.89 (0.88-0.90)
			• 2013-2019 Age 16-19y = 171 to 77; 0.84 (0.82-0.86)
			• Age <1 year
			  ○ 2006/2012 IRR 0.99 (0.95-1.04)
			  ○ 2013-2019 IRR 0.96 (0.91-1.02)
			• Adults ages 20-39 years – IR decreased both periods (0.94 and 0.92)
			• Children – IR increased (1.05 and 1.08) despite high coverage
				Pertussis booster doses offered direct protection to targeted groups. Potential indirect protection to adults. Infant incidence unchanged.

Safety of booster doses in adults and adolescents	90	SR/MA – 6 RCT Td vs Tdap and 3 RCT aP vs placebo in adolescents and adults	• Incidence of nausea and vomiting was significantly higher in Tdap than Td group
			  ○ Nausea – RR 1.26 (1.01-1.57)
			  ○ Vomiting – RR 2.08 (1.21-3.58)
			  ○ Fever – RR 1.06 (0.58-1.94) (greater with higher PT content vaccine 8µg; PT 8µg vs >8µg RR=1.61)
			• No statistical difference between aP and Placebo for headache or injection site erythema.
				Meta-analysis found gastrointestinal symptoms were increased with Tdap but at low incidence.

Abbreviations: 3+0 – three primary and no booster; 3+1 – three primary and one booster; 2+1 – two primary and one booster; aGMR – adjusted geometric mean ratio; BC – British Colombia; DT – diphtheria toxoid; FHA – filamentous haemagglutinin; GMR – geometric mean ratio; GW –gestation weeks; IR – incidence rate; risk ratio; IRR – incidence rate ratio; m – month; PRN – pertactin; PT – pertussis toxin; PCV10 – 10-valent pneumococcal conjugate vaccine; Qb – Québec; RCT – randomised controlled trial; SR/MA - systematic review and meta-analysis; Td – tetanus diphtheria vaccine; Tdap – tetanus diphtheria acellular pertussis vaccine; TT – tetanus toxoid; y – year

Table 14: Booster doses in non-pregnant adults

Outcomes	Ref	Participants	Results	Findings
Pertussis immunity post COVID-19				

Pertussis antibody in health care workers	12	BC, Canada – 18 paired samples HCW of childbearing age.	Pertussis incidence:
			• 2020 – 3 cases per 100,000
			• 2021 <1 case per 100,000.
			Antibody levels (IU/ml)
			• 2021 vs 2020
			  ○ Anti-PT = 6.8 (4.2-10.9) vs 8.4 (5.1-13.9); p=0.004
			  ○ Anti-FHA = 18.8 (10.9-32.2) vs 23.6 (13.2-42.1); p<0.001
			  ○ Anti-PRN = 37.1 (18.1-75.9) vs 47.2 (24.8-89.9); p=0.092
			• In 2020, Ab levels didn't differ significantly to early-gestation pregnant women in 2018/2019 but noted that HCW are usually more likely to have received vaccine or exposure to *B. pertussis* than general population.
				Significant decline in pertussis immunity due to low case numbers, pathogen exposure and absent boosting.
				The decline in cases was also seen across the population, including in infants under 1 year who are more likely to have severe illness, and therefore, not attributed to under reporting.

Serosurvey	10	Serosurvey in 2020, Zheijian Province, China (with no preschool or adolescent boosters) Anti-PT IgG putative seroprotective cutoff at 20 IU/ml and undetectable <5 IU/ml.	Age >7 years – 50% had undetectable anti-PT antibody Proportion of population with evidence of recent infection (anti-PT IgG titres of ≥80 IU/ml) • Age 10-14 years – 0.9% • 15-29 years – 0.3% • 40-59 years – 1.1% Attenuation model – 5 years after previous vaccination predicted to reach unprotective levels (anti-PT 5.6 IU/ml)	Pertussis immunity was low in general. Infections continued to occur during COVID-19 response restrictions. Although lower than seen during previous study in 2014, estimated infection rates were higher than the notified rates.
Adult booster doses / occupational boosters				
Tdap given 5 years after previous dose	45	Post-marketing study, 2nd dose Tdap given 4-5 years after previous dose to 545 participants aged 15-69 years	• 94.2% reported at least 1 solicited AE – injection-site pain (87.6%), redness and swelling (<30%) and systemic AE myalgia (61.0%), headache, malaise, fever (6.5%). Slightly more frequent than initial dose. • 100% Seroprotection for TT, 95% diphtheria. • Based on ≥50 EU/ml threshold for pertussis – 82.1% PT, 96.7% FHA, 95.6% PRN, 99,8% FIM2/3.	Second dose of Tdap given 5 years after previous Tdap dose was well tolerated and immunogenic.

Outcomes	Ref	Participants	Results	Findings
Immunogenicity after 10 y ears	46	RCT 1330 adults aged 18-<65 years Tdap or Td given 8-12 years after previous dose of Tdap.	Solicited AE reported by 97.7% Tdap and 88% Td. No significant different rates of reactions. Robust antibody response, all pertussis antigens met prespecified non-inferiority thresholds, GMR pre/post vaccination: • PT = 8.1, FHA = 5.9, PRN = 6.4, Fim 2/3 = 5.2 • Post vaccination titres of TT and DT antibodies were similar between Td and Tdap groups. With >99% achieving seroprotective levels. • High antibodies pre-vaccination might have affected the ability to induce a booster response against PRN, FIM2/3 and TT.	Second dose of Tdap given 10 years after previous dose was well tolerated and immunogenic. Similar safety profile to Td.
Effectiveness in older adults	47	Case-control study in adults aged 46-81 years (mean 61 years). Pre-specified analysis population - 333 cases and 506 controls. PCR-only 172 cases and 266 controls.	• 17% of cases and 16% of controls had pertussis vaccination on average 3.0 (range 0.8-8.8) years prior. • Overall there was no evidence of VE (8%, -36-37%) for all cases (diagnosed using serology and PCR testing) but when looking at those diagnosed by PCR-only the adjusted VE was 52% (15-73%) and a greater time since vaccination (5.9 years, 5.0-6.7 years).	Among older adults, VE against PCR-confirmed pertussis was around 50% and no evidence of waning protection was seen with increasing age nor time since vaccination. Although the statistical power was limited, the VE point estimate showed no declining trend for up to 6 years. This population primed either with wild-type infection or whole cell vaccines. Serological diagnosis was likely misclassifying cases and unreliable where adults are increasingly receiving Tdap.
Early childhood educators	44	Survey of 4,000 ECE in NZ	• <50% of participants received Tdap in last 10 years • 85% reported vaccinated with MMR • 0.5% declined to respond	Early childhood educators and carers are under immunised for pertussis, putting infants at risk.
Cocooning and post-partum vaccination				

Parents of newborns	91	Cross-sectional survey, 884 (25% response rate) parents of newborns born May-Sept 2012 and 2013, Basel, Switzerland, 3 questions exploring pertussis knowledge.	• 64% of mothers and 59% fathers accepted pertussis vaccination when recommended (by health professional)
			• Overall 204/884 (23%) mothers and 147 (17%) 887 fathers were accurately protected according to cocooning strategy.
			• Only 7% of newborns were protected by a complete cocoon (all close contacts immunised) and 18% were ≥50% cocoon coverage. With only 79% of siblings up to date.
			• Most vaccinations occurred within 1 or 2 months after birth:
			  ○ 88 (47%) / 178 immunised mothers and 61 (48%) / 126 immunised fathers.
			  ○ 31 mothers and 24 father immunisation delayed by >2m after birth.
				In absence of new vaccines or alternative strategies, cocooning strategy is highly suboptimal. Intensifying efforts, such as improving knowledge among health professionals and population.
				Improve provision and acceptance of pertussis vaccine by pregnant women and other close contacts.
				Update of siblings immunisation could be addressed while mother was pregnant.

Outcomes	Ref	Participants	Results	Findings
Household cocooning	92	Data linkage study in WA – 64,364 live births in 2011-2012 linked to parental pertussis vaccination and notified pertussis cases. Vaccination post-partum ≤4 weeks after birth.	• 43,480 (68%) had ≥1 vaccinated parent (60% mothers and 36% fathers) • After excluding those who were vaccinated prior to birth or absent vaccination data, 118/53,149 developed pertussis. • Pertussis incidence – not significantly different: o Both parents vaccinated post-partum vs unvaccinated (1.9 vs 2.2 cases / 1000) – aHR 0.91 (0.55-1.53) o Maternal only post-partum – aHR 1.19 (0.82-1.72)	Vaccinating parents during 4-weeks postpartum did not reduce pertussis incidence in infants.
Effectiveness of timing of maternal vaccination	32	UK study see Table 11 Perinatal vaccination = 1wk before and 6wk after birth	See Figure 7 VE against pertussis in infants aged <3 months when mother vaccinated perinatally = 27% (-56 to 65)	Maternal vaccination is highly effective against pertussis infection in infants up to 3 months except when given too close to birth or postpartum.
Cocooning – partner vaccination	48	Survey of 689 women and/or partners in maternity wards in Melbourne Aug -Dec 2016. 37% of adult carer contacts, other than parents, came from overseas.	• 70% women and 66% partners reported pertussis vaccination according to national recommendations (48% during pregnancy and 66% within last 10 years). • 22% newborns discharged with neither parent vaccinated • Compared with those with vaccinated mothers, lower rates of vaccination in household where mother was not vaccinated: o Partners vaccinated – 83% vs 26% o Other carers – 76% vs 18.5% (particularly when carer usually reside overseas). o Adjusting for family member and residency status: OR 10.5 (5-20.1), p<0.01 if mother vaccinated. • Odds of reporting vaccination was 94% lower in overseas resident contacts – OR 0.06 (95% CI 0.04-0.11), p<0.01	Main findings 1. One third of pregnant women and partners are not vaccinated according to guidelines 2. Lower rates of vaccination of contacts if maternal vaccination does not occur 3. Adults carers from overseas are less likely to be vaccinated than those resident in Australia. Antenatal care should promote maternal vaccination and also encourage vaccination of partners and contacts, particularly if maternal vaccination does not occur.

Abbreviations: aHR – adjusted hazard ratio; BC – British Colombia; ECE – early childhood education; OR – odds ratio; FHA – filamentous haemagglutinin; PCR – polymerase chain reaction; PRN – pertactin; PT – pertussis toxin; VE – vaccine effectiveness; WA – Western Australia

Table 15: Comparison of whole cell and acellular pertussis immune responses

Outcomes	Ref	Participants	Results	Findings
Immune response				
Antibody response in adolescents	50	Serum analysis, left-over samples used to diagnose pertussis from 36 adolescents aged 15-20 years, from 2014-2016 Denmark Defined groups: wP or aP primed with high (+) or low (-) anti-PT IgG [wP+, wP-, aP+, aP-]	Those with high PT IgG also had high IgG and IgA titres against other pertussis antigens (FHA, PRN and OMV) – no difference between aP and wP groups. Antibody response to other previously undefined immunogenic pertussis antigens showed a difference between wP and aP groups in both IgA and IgG against these antigens.	Antibody specificity to pertussis antigens in response to a recent pertussis infection correlates with pertussis vaccine received in childhood.
T cell profile adults immunised as children	51	Cells obtained from tonsillectomy (10 adults wP and 10 aP vaccinated as children), nasal cells from mid-turbinate swab from 20 healthy volunteers. All matched with peripheral blood samples. None had recent pertussis infection.	Of CD4 cells, a greater proportion were T_{RM} in nasal tissue than tonsil. Detectable pertussis-specific T_{RM} in 80-90% of nasal cell donors. Higher frequency of IFN-γ and IL-17+ CD4 T_{RM} in nasal mucosa of adults vaccinated with wP than aP as infants. IL-13 producing T cells dominate in those aP primed.	IFN-γ and IL-17+ *B. pertussis*-specific CD4 T_{RM} can persist in the respiratory tract for decades after pertussis vaccination and is more prevalent in adults who received wP primary doses. CD4+ memory T cells that respond to *B. pertussis* are found in the respiratory tissue and not in circulation.
Effectiveness				
Effectiveness comparing wP and aP	19	SRMA (to Nov 2019) – wP and aP, included 47 VE [32 aP, 22wP and 14 mixed] and 15 duration studies. See Table 8	Pooled estimate VE: • aP – 79% (95% CI 73-83; I^2 =93%) • wP – 79% (69-86; I^2 = 93%) • mixed – 84% (75-90; I^2 = 92%) • VE altered by study design, case definition, high statistical heterogeneity (I^2 > 50%), age groups, epidemic period, country.	Evidence that any pertussis vaccine confers protection against pertussis disease, but wanes rapidly for aP vaccines (See Table 8).
effectiveness of 3 & 5 component aP with wP vaccines	54	Case-control study, England. Ages 5-15 years, primed with 3 doses of either wP, aP3, aP5 or a mix and given aP preschool booster at age 4 years. Switch from wP to aP in 2004 (continued with mixed schedules due to supply) 403 pertussis cases vs 581,971 controls. Limitation - shorter period after aP5 vaccination than wP and aP3.	Compared with 3 doses of wP primary course, odds of pertussis (OR, 95% CI): • 3 doses aP3 – 3.86 (2.56-5.82) p<0.001 • 3 doses aP5 – 0.89 (0.29-2.73) p=0.85 • wP/aP3 mix – 2.47 (1.71-3.56), p<0.001 • wP/aP5 mix – 1.82 (0.52-6.37), p=0.35 When adjusting for year of birth and preschool booster, risk in aP5 group did not differ from wP group. Preschool booster (with any aP vaccine) gave similar protection when wP primed (p=0.9); marginally increased odds of pertussis in aP5-low group vs aP3 when primed with aP (p=0.04).	Confirmed that aP5 would produce similar protection as wP. A primary course with aP3 was associated with a higher risk for pertussis than those primed with wP. Further data required to compare duration of protection as aP5 primed children were the youngest.

Outcomes	Ref	Participants	Results	Findings
Mixed whole cell and acellular primary course				
Safety	55	Cochrane review	Risk of SAE following first dose in infants = wP vs aP RR 0.94 (0.77-1.16) 11 studies No cases of encephalopathy in 7 RCT (32,300 infants wP and 83,003 infants given aP)	No increased risk for vaccine-associated severe adverse events with either wP or aP first doses
wP vs aP nasal colonisation	53	Study in mice – respiratory tissue-resident memory (T_{RM}) cells – aP, wP and previous infection. Mice challenged 6 and 2 weeks prior to aerosolised live B. pertussis challenge.	• aP had delayed clearance in lungs and significantly higher bacterial count at 7 days post challenge. wP cleared infection rapidly. • wP reduced bacterial in nasal cavity in 3 days and completely by day 14. But aP had not cleared infection by d14 and had similar bacterial counts to unvaccinated mice. • wP vaccinated mice had IFN-γ and IL-17 production from spleen and lung tissue; aP produced IL-5 not IFN-γ and IL-17. • wP – induced significant more *B. pertussis*-specific CD4 T cells (not enhanced CD8 or B cells) in lung and nasal tissue. • Long-term protection and prevention from colonisation after wP vaccination was longer than aP but less than natural infection. • When compared higher antigen content aP Infanrix with Boostrix – Infanrix induced more complete protection against lung infection (but timing of vaccination differed – 4wk), but not against nasal colonisation.	Most persistent protection is provided by natural infection – through accumulation and stimulation of *B. pertussis*-specific IL-17 secreting T_{RM} in the lung and nasal tissues. There was a highly significant correlation between number of IL-17/IFN-γ T_{RM} cells and long-term protection against nasal colonisation and IL-17 T_{RM} and lung infection. aP protected against lung infection but not against nasal colonisation. Polarised Th2 / antibody-dominant response may suppress T_{RM} induction and clearance of bacteria from nasal tract after challenge.
Allergy				

Food anaphylaxis hospitalisations	56	NSW administrative data of 218,093 Australian children 1997-1999, 86 children aged 5-15 years hospitalised. Comparison of food-induced anaphylaxis hospitalisation of those given wP vs aP first dose. Comparison with venom induced anaphylaxis and all-cause anaphylaxis.	Incidence rate / 100,000 child-years for food-induced anaphylaxis:
			• wP first dose – 3.5 (2.6-4.6)
			• aP first dose – 5.1 (3.5-7.1)
			• aHR – 0.47 (0.26-0.83)
			• Venom anaphylaxis:
			  ○ wP – 4.9 (3.9-6.2)
			  ○ aP – 5.1 (3.5-7.1)
			  ○ aHR wP vs aP = 0.92 (0.53-1.60)
			all-cause anaphylaxis
			  ○ wP – 10.6 (0.9-12.4)
			  ○ aP – 12.8 (10.2-15.8)
			  ○ aHR = 0.92 (0.53-1.60)
				Vaccination with wP in infancy was associated with lower risk for food-induced anaphylaxis hospitalisation (severe IgE-mediated food allergy) than aP.

Mixed wP/aP schedule, IgE-mediated responses	57	OPTIMUM RCT, Australia.
		Comparison of wP first dose with aP only schedule – 75 infants per arm. Australia vaccinated at ~6w with either DTwP-Hib-HepB or DTaP-IPV-HepB/Hib, then 2 and 4m (DTaP-IPV-HepB/Hib) and DTaP-IPV at 18m
			Mixed schedule no-inferior for PT-IgG at 1m after 6m dose. No difference in tetanus toxoid IgE at 7 months.
			• Irritability was most common response after the first dose:
			  ○ in wP group - 65/73 88%
			  ○ aP only group - 59/72 (82%)
			• Severe systemic reactions:
			  ○ First dose wP/aP group = 19% vs 11% aP only
			  ○ Similar between groups for subsequent aP doses at 4 and 6 months.
			• Paracetamol use ≥1 after first dose – wP (59/75, 79%) vs aP (52/75, 69%).
			• Parental acceptance was high – 97% agreed they would have wP/aP schedule again compared with 96% of aP-only group.
				Mixed schedule had acceptable immunogenicity and reactogenicity profile.

Outcomes	Ref	Participants	Results		Findings
Maternal antibody interference with wP					
Interference of maternal antibody on wP vs aP primary course	58	RCT 155 infants vaccinated with wP and 158 infants with aP containing vaccines at 2, 4, 6, 18 months born to Tdap vaccinated mothers. 79 control wP vaccinated / unvaccinated mothers (EPI wP group).	• aP v wP primed ○ higher pertussis Ab post primary course (p<0.001) • wP (+Tdap) group vs EPI wP group (no Tdap) ○ lower anti-PT and anti-FHA titres (p<0.001) ○ somewhat lower anti-PRN (p=0.03) ○ Interference persisted after booster. • EPI wP vs aP post priming and post booster: ○ higher anti-PT ○ lower anti-FHA and anti-PRN.	All groups – antibody had waned substantially at 18 months prior to booster and increase post booster with comparable anti-PT levels. Differences in PT, FHA and PRN antibody levels may be associated with low amounts of FHA and PRN in the wP vaccine (not specified). Maternal antibody blunting did not appear to affect the inhibition of *B.pertussis* growth by the sera from wP vaccinated infants. Bactericidal ability of wP primed infants was stronger than aP post booster.	The presence of maternal antibodies had a greater impact on the antibody response to wP than aP primary course vaccines.

Abbreviations: aHR – adjusted hazard ratio; aP – acellular pertussis vaccine; EPI – Expanded programme for immunisation; IgE – immunoglobulin E; IFN-γ – interferon gamma; IL-17 – interleukin 17; FHA – filamentous haemagglutinin; OR – odds ratio; PCR – polymerase chain reaction; PRN – pertactin; PT – pertussis toxin; RCT – randomised controlled trial; SAE – serious adverse events; TRM – tissue resident memory T cells; wP – whole cell pertussis vaccine

Table 16: Recombinant pertussis vaccine

Outcomes	Ref	Participants	Results		Findings
Recombinant genetically detoxified PT vaccine					

Safety	60	Post-marketing surveillance in Thailand, 11,420 adolescents and adults, including 1,778 pregnant people	Incidence rate of AE per 1000 recipients
			• Total – 11.5 (95% CI 9.7-13.6)
			• aP_{gen} – 7.3 (4.2-12.7)
			• $TdaP_{gen}$ – 12.2 (10.2-14.6)
			• 131 / 11429 surveyed reported AEFIs
			• 1 AEFI reported by 77 /131 (58.8%)
			• 2 AEFI reported by 31/131 (23.7%)
			  • Most were injection site pain - rate 8.7/1000 (7.2-10.6)
			  (aP 12 cases and TdaP 87 cases)
			  • $TdaP_{gen}$ only
			  ○ myalgia – 3.0 (2.0-2.9) (32 reports)
			  ○ injection site swelling (1.8)
			  ○ rate ~1/1000 – malaise, headache, fever, fatigue
				• 1 case of lymphadenitis
				• All were mild and resolved in a few days without sequelae; most were reported after $TdaP_{gen}$
				• For pregnant participants, incidence of AEFI with either vaccine was lower than for overall study population at 1.1 per 1,000 (0.3-4.1)
				• Rate of congenital abnormalities was 1.3% in this cohort and lower than Thai prevalence rate of 8%.
					Post marketing surveillance showed that aP_{gen} and $TdaP_{gen}$ vaccines are safe in adolescents and adults, including those who are pregnant.

Immunogenicity and duration of adolescent booster	61	Observational 2-year follow-up of phase II/III clinical trial of $TdaP_{gen}$ and aP_{gen} given to adolescents vaccinated at age 12-17 years. Compared with chemically detoxified Tdap vaccine ($Tdap_{chem}$)	At 3 years after booster vaccination
			Antibody waning stabilised 2- and 3-years post $TdaP_{gen}$ and aP_{gen} boosters significantly above baseline.
			(see Figure 10)
			• Anti-PT GMR above baseline
			• $TdaP_{gen}$ – 2.5-fold (1.9-3.3)
			• aP_{gen} – 3.0-fold (2.2-4.1)
			• $Tdap_{chem}$ – back or below baseline.
			At all timepoints, $TdaP_{gen}$ and aP_{gen} PT-specific IgG and neutralising Abs were significantly higher than $Tdap_{chem}$ group.
				Pertussis seropositivity for anti-PT IgG:
				• aP_{gen} – 95.2 (89.8-100)
				• $TdaP_{gen}$ – 96.6% (92.0-100)
				• $Tdap_{chem}$ – 85.0% (76.0-94.0)
				• Anti-FHA IgG – similar between groups (>95%)
				• Pertussis booster response (≥20 IU/l)
				  ○ aP_{gen} - 80.7% (70.8-90.5)
				  ○ $TdaP_{gen}$ – 74.6% (63.5-85.7)
				  ○ $Tdap_{chem}$ – 40.0% (27.6-52.4)
				• All participants who received Td vaccines were seropositive for tetanus toxoid. And >85% for DT.
					Recombinant aP vaccines were associated with anti-PT antibody responses sustained well above baseline for at least 3 years, longer than that seen with a chemically detoxified aP vaccine. Anticipated that a longer duration of protection is also maintained.

Outcomes	Ref	Participants	Results	Findings
Maternal vaccination	62	Post-marketing observational study – given in pregnancy – 199 aP_{gen} and 200 $Tdap_{gen}$, 54 Td only.	• 74% vaccinated at 27-36 weeks (mean 28.5 weeks). • Cord blood pertussis antibody levels were 18- to 32-fold higher in the aPgen exposed groups than Td only. • Proportion of cord blood with anti-PT IgG >30IU/ml ○ aP_{gen} – 87.9 (83.4-92.5) ○ $TdaP_{gen}$ – 91.0% (87.0-95.0) • Pregnancy, birth and neonatal outcomes were similar between groups. No complications were vaccine-associated. • Timing in pregnancy – before 27GW > 27-36GW and both around 20-fold greater Ab levels than >36 weeks.	Immunisation with aP_{gen} and $TdaP_{gen}$ is safe and effective for pertussis antibody transfer to infants. Antibody levels tended to be higher for monovalent aPgen.

Abbreviations: AE – adverse event; AEFI – adverse events following immunisation; aP_{gen} – recombinant acellular pertussis vaccine (genetically detoxified); FHA – filamentous haemagglutinin; GMR – geometric mean ratio; PRN – pertactin; PT – pertussis toxin; $TdaP_{gen}$ – tetanus, diphtheria and recombinant pertussis vaccine; $Tdap_{chem}$ – tetanus, diphtheria and chemically detoxified acellular pertussis vaccine

Literature review

SCOPUS

- Pertussis vaccine 2018-1 July 2024 = 5108 documents
- Limit to English, keywords vaccination and pertussis 3997
- Selected 44 just in 2024 – decided to revisit search terms

MEDLINE

1. **Pertussis vaccine** – focussed - 7500
2. Limit English, 2019-current (3 July), 593
3. Deduplicate 498
4. **Maternal** – 13718222
5. 3 AND 4. Combined – 129, selected 67, removed duplicates = 46

6. **Occupation*** (limited English, humans, 2019-current) 245235
7. 3 AND 6 = 5
8. Health care workers 98517
9. (limited English, humans, 2019-current) 33205
10. 3 AND 9 = 0
11. Early childhood education 6027
12. limited English, humans, 2019-current) = 2395
13. 3 AND 11 = 0

14. Pertussis 10,9917
15. 13 AND 9 = 18, selected 6
16. 9 AND 14 = 178

17. 'monovalent pertussis vaccine', limit 2018-current, English = 11
18. Recombinant pertussis vaccine = 14 – selected 1
19. Occupational vaccin* limit 2019-current = 32, deduplicate 23 selected 4

Pubmed

- pertussis vaccination cocooning strategies (2016-2024) -34 found, 22 selected
- birth dose pertussis vaccine 2018 – 2024 – 97 results, selected 14

Further papers were found through other papers and published since this literature search was conducted. Total library 379 after removing duplicates. Includes reports, product information (data sheets), and webpages.

References

1. Nowlan M. Review of evidence: Is there a gain for adding a pertussis-containing vaccine booster dose in the second year of life? Immunisation Advisory Centre 2019 October 2019.Available from: on request
2. Nowlan ML. Review of evidence to inform the New Zealand National Immunisation Schedule, 2018: Pertussis. Immunisation Advisory Centre; 2018 10 April 2019.Available from: https://www.immune.org.nz/publications/review-of-evidence-to-inform-the-new-zealand-national-immunisation-schedule-2018-pertussis
3. Kandeil W, van den Ende C, Bunge EM, et al. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. Expert Rev Vaccines. 2020;19(7):621-38.doi: 10.1080/14760584.2020.1791092
4. van der Maas NAT, Sanders EAM, Versteegh FGA, et al. Pertussis hospitalizations among term and preterm infants: clinical course and vaccine effectiveness. BMC Infectious Diseases. 2019;19(1):919.doi: 10.1186/s12879-019-4563-5
5. Abu-Raya B, Bettinger JA, Vanderkooi OG, et al. Burden of children hospitalized with pertussis in Canada in the acellular pertussis vaccine era, 1999-2015. J Pediatric Infect Dis Soc. 2020;9(2):118-27.doi: 10.1093/jpids/piy128
6. Sheridan S, McIntyre P, Liu B, et al. Pertussis burden and acellular pertussis vaccine effectiveness in high risk children. Vaccine. 2022;40(9):1376-82.doi: 10.1016/j.vaccine.2021.10.013
7. Muloiwa R, Dube FS, Nicol MP, et al. Risk factors for *Bordetella pertussis* disease in hospitalized children. PLoS One. 2020;15(10):e0240717.doi: 10.1371/journal.pone.0240717
8. Zerbo O, Fireman B, Klein NP. Lessons from a mature acellular pertussis vaccination program and strategies to overcome suboptimal vaccine effectiveness. Expert Rev Vaccines. 2022;21(7):899-907.doi: 10.1080/14760584.2021.1984891
9. Tessier E, Campbell H, Ribeiro S, et al. Impact of the COVID-19 pandemic on *Bordetella pertussis* infections in England. BMC Public Health. 2022;22(1):405.doi: 10.1186/s12889-022-12830-9
10. He H, Zhu Y, Jin M, et al. The decline in immunity and circulation of pertussis among Chinese population during the COVID-19 pandemic: A cross-sectional sero-epidemiological study. Vaccine. 2022;40(48):6956-62.doi: 10.1016/j.vaccine.2022.10.020
11. Khalil A, Samara A, Campbell H, et al. Recent increase in infant pertussis cases in Europe and the critical importance of antenatal immunizations: We must do better...now. Int J Infect Dis. 2024;146:107148.doi: 10.1016/j.ijid.2024.107148
12. Reicherz F, Golding L, Lavoie PM, Abu-Raya B. Decay of anti-Bordetella pertussis antibodies in women of childbearing age following COVID-19 non-pharmaceutical measures. Vaccine. 2022;40(27):3746-51.doi: 10.1016/j.vaccine.2022.04.086
13. McIntyre PB, Best E, Byrnes CA, et al. Pertussis deaths in New Zealand without community transmission—an infant immunity gap? The Lancet Regional Health - Western Pacific. 2023;37:100850.doi: 10.1016/j.lanwpc.2023.100850
14. Torjesen I. Whooping cough: Doctors are urged to encourage vaccination as eight infants die in England amid case surge. BMJ. 2024;385:q1265.doi: 10.1136/bmj.q1265
15. Merdrignac L, Ait El Belghiti F, Pandolfi E, et al. Effectiveness of one and two doses of acellular pertussis vaccines against laboratory-confirmed pertussis requiring hospitalisation in infants: Results of the PERTINENT sentinel surveillance system in six EU/EEA countries, December 2015 - December 2019. Vaccine. 2024;42(9):2370-9.doi: 10.1016/j.vaccine.2024.02.090
16. Mack I, Erlanger TE, Lang P, et al. Dose-dependent effectiveness of acellular pertussis vaccine in infants: A population-based case-control study. Vaccine. 2020;38(6):1444-9.doi: 10.1016/j.vaccine.2019.11.069
17. Zerbo O, Bartlett J, Goddard K, et al. Acellular pertussis vaccine effectiveness over time. Pediatrics. 2019;144(1):e20183466.doi: 10.1542/peds.2018-3466
18. Gao H, Lau EHY, Cowling BJ. Waning immunity after receipt of pertussis, diphtheria, tetanus, and polio-related vaccines: A systematic review and meta-analysis. J Infect Dis. 2022;225(4):557-66.doi: 10.1093/infdis/jiab480
19. Wilkinson K, Righolt CH, Elliott LJ, et al. Pertussis vaccine effectiveness and duration of protection - A systematic review and meta-analysis. Vaccine. 2021;39(23):3120-30.doi: 10.1016/j.vaccine.2021.04.032

20. De Weerdt L, Herzog SA, Van Damme P, Maertens K. Timing of pertussis vaccination during pregnancy: Evidence and implementation – A systematic review. Vaccine. 2024;42(21):126152.doi: 10.1016/j.vaccine.2024.07.053
21. Olson-Chen C, Swamy GK, Gonik B, et al. The current state of pertussis vaccination in pregnancy around the world, with recommendations for improved care: Consensus statements from the Global Pertussis Initiative. Int J Gynaecol Obstet. 2024;165(3):860-9.doi: 10.1002/ijgo.15311
22. Andersen AR, Kolmos SK, Flanagan KL, Benn CS. Systematic review and meta-analysis of the effect of pertussis vaccine in pregnancy on the risk of chorioamnionitis, non-pertussis infectious diseases and other adverse pregnancy outcomes. Vaccine. 2022;40(11):1572-82.doi: 10.1016/j.vaccine.2021.02.018
23. D'Heilly C, Switzer C, Macina D. Safety of maternal immunization against pertussis: A systematic review. Infect Dis Ther. 2019;8(4):543-68.doi: 10.1007/s40121-019-00265-6
24. Davies HG, Thorley EV, Al-Bahadili R, et al. Defining and reporting adverse events of special interest in comparative maternal vaccine studies: a systematic review. Vaccine X. 2024;18:100464.doi: 10.1016/j.jvacx.2024.100464
25. Immink MM, Bekker MN, de Melker HE, et al. Maternal pertussis immunization and immunoglobulin G levels in early- to late-term and preterm infants. JAMA Netw Open. 2024;7(7):e2424608.doi: 10.1001/jamanetworkopen.2024.24608
26. Byrne L, Campbell H, Andrews N, et al. Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England. Arch Dis Child. 2018;103(3):224-9.doi: 10.1136/archdischild-2016-311802
27. De Weerdt L, Thiriard A, Leuridan E, et al. Immunogenicity at delivery after Tdap vaccination in successive pregnancies. Frontiers in Immunology. 2024;15.doi: 10.3389/fimmu.2024.1360201
28. Chen WC, Hu SY, Cheng CM, et al. Pilot study on evaluating the impact of tetanus, diphtheria, and pertussis (Tdap), influenza, and COVID-19 vaccinations on antibody responses in pregnant women. Vaccines (Basel). 2024;12(3).doi: 10.3390/vaccines12030312
29. Post AL, Li SH, Berry M, et al. Efficiency of placental transfer of vaccine-elicited antibodies relative to prenatal Tdap vaccination status. Vaccine. 2020;38(31):4869-76.doi: 10.1016/j.vaccine.2020.05.036
30. Merdrignac L, Acosta L, Habington A, et al. Effectiveness of pertussis vaccination in pregnancy to prevent hospitalisation in infants aged <2 months and effectiveness of both primary vaccination and mother's vaccination in pregnancy in infants aged 2-11 months. Vaccine. 2022;40(44):6374-82.doi: 10.1016/j.vaccine.2022.09.054
31. Regan AK, Moore HC, Binks MJ, et al. Maternal pertussis vaccination, infant immunization, and risk of pertussis. Pediatrics. 2023;152(5):e2023062664.doi: 10.1542/peds.2023-062664
32. Amirthalingam G, Campbell H, Ribeiro S, et al. Optimization of timing of maternal pertussis immunization from 6 years of postimplementation surveillance data in England. Clin Infect Dis. 2023;76(3):e1129-e39.doi: 10.1093/cid/ciac651
33. Abu-Raya B, Maertens K, Munoz FM, et al. Factors affecting antibody responses to immunizations in infants born to women immunized against pertussis in pregnancy and unimmunized women: Individual-Participant Data Meta-analysis. Vaccine. 2021;39(44):6545-52.doi: 10.1016/j.vaccine.2021.09.022
34. Barug D, Pronk I, van Houten MA, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. The Lancet Infectious diseases. 2019;19(4):392-401.doi: 10.1016/s1473-3099(18)30717-5
35. Briga M, Goult E, Brett TS, et al. Maternal pertussis immunization and the blunting of routine vaccine effectiveness: a meta-analysis and modeling study. Nature Communications. 2024;15(1).doi: 10.1038/s41467-024-44943-7
36. Febriani Y, Mansour T, Sadarangani M, et al. Tdap vaccine in pregnancy and immunogenicity of pertussis and pneumococcal vaccines in children: What is the impact of different immunization schedules? Vaccine. 2023;41(45):6745-53.doi: 10.1016/j.vaccine.2023.09.063
37. Sapuan S, Andrews N, Hallis B, et al. An observational, cohort, multi-centre, open label phase IV extension study comparing preschool DTAP-IPV booster vaccine responses in children whose mothers were randomised to one of two pertussis-containing vaccines or received no pertussis-containing vaccine in pregnancy in England. Vaccine. 2022;40(49):7050-6.doi: 10.1016/j.vaccine.2022.10.005

38. Martinón-Torres F, Halperin SA, Nolan T, et al. Impact of maternal diphtheria-tetanus-acellular pertussis vaccination on pertussis booster immune responses in toddlers: Follow-up of a randomized trial. Vaccine. 2021;39(11):1598-608.doi: 10.1016/j.vaccine.2021.02.001
39. Tessier E, Newport D, Tran A, et al. Pertussis immunisation strategies to optimise infant pertussis control: A narrative systematic review. Vaccine. 2023;41(41):5957-64.doi: 10.1016/j.vaccine.2023.08.073
40. Rane MS, Rohani P, Halloran ME. Association of diphtheria-tetanus-acellular pertussis vaccine timeliness and number of doses with age-specific pertussis risk in infants and young children. JAMA Netw Open. 2021;4(8):e2119118.doi: 10.1001/jamanetworkopen.2021.19118
41. Paireau J, Guillot S, Ait El Belghiti F, et al. Effect of change in vaccine schedule on pertussis epidemiology in France: a modelling and serological study. The Lancet Infectious diseases. 2022;22(2):265-73.doi: 10.1016/S1473-3099(21)00267-X
42. Seppälä E, Brathen Kristoffersen A, Bøås H, et al. Pertussis epidemiology including direct and indirect effects of the childhood pertussis booster vaccinations, Norway, 1998-2019. Vaccine. 2022;40(23):3142-9.doi: 10.1016/j.vaccine.2022.04.038
43. Brousseau N, Skowronski DM, Bellemare D, et al. Impact of the adolescent pertussis booster dose on the incidence of pertussis in British Columbia and Quebec, Canada. Vaccine. 2020;38(3):427-32.doi: 10.1016/j.vaccine.2019.10.063
44. Prasad N, Turner N, Alexander S. Early childhood education staff are falling through a vaccination policy gap in New Zealand. New Zealand Medical Journal. 2022;135(1548):96-102.doi:
45. Halperin SA, McNeil S, Langley J, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011;29(46):8459-65.doi: 10.1016/j.vaccine.2011.07.068
46. Halperin SA, Donovan C, Marshall GS, 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. 2019;8(2):105-14.doi: 10.1093/jpids/pix113
47. Liu BC, He WQ, Newall AT, et al. Effectiveness of acellular pertussis vaccine in older adults: Nested matched case-control study. Clin Infect Dis. 2020;71(2):340-50.doi: 10.1093/cid/ciz821
48. Krishnaswamy S, Wallace EM, Cheng AC, et al. Protecting newborns from pertussis: The role of partner vaccination in the era of maternal immunization. European journal of obstetrics, gynecology, and reproductive biology. 2017;216:159-63.doi: 10.1016/j.ejogrb.2017.07.031
49. Szwejser-Zawislak E, Wilk MM, Piszczek P, et al. Evaluation of whole-cell and acellular pertussis vaccines in the context of long-term herd immunity. Vaccines (Basel). 2022;11(1):1.doi: 10.3390/vaccines11010001
50. Raeven RHM, Van Der Maas L, Pennings JLA, et al. Antibody specificity following a recent bordetella pertussis infection in adolescence is correlated with the pertussis vaccine received in childhood. Frontiers in Immunology. 2019;10(JUN):1364.doi: 10.3389/fimmu.2019.01364
51. McCarthy KN, Hone S, McLoughlin RM, Mills KHG. IL-17 and IFN-gamma-producing respiratory tissue resident memory CD4 T cells persist for decades in adults immunized as children with whole cell pertussis vaccines. J Infect Dis. 2024.doi: 10.1093/infdis/jiae034
52. Saso A, Kampmann B, Roetynck S. Vaccine-induced cellular immunity against *Bordetella pertussis*: Harnessing lessons from animal and human studies to improve design and testing of novel pertussis vaccines. Vaccines (Basel). 2021;9(8):877.doi: 10.3390/vaccines9080877
53. Wilk MM, Borkner L, Misiak A, et al. Immunization with whole cell but not acellular pertussis vaccines primes CD4 T_{RM} cells that sustain protective immunity against nasal colonization with *Bordetella pertussis*. Emerging Microbes & Infections. 2019;8(1):169-85.doi: 10.1080/22221751.2018.1564630
54. Carvalho CFA, Andrews N, Dabrera G, et al. National outbreak of pertussis in England, 2011-2012: A case-control study comparing 3-component and 5-component acellular vaccines with whole-cell pertussis vaccines. Clin Infect Dis. 2020;70(2):200-7.doi: 10.1093/cid/ciz199
55. Pérez Chacón G, Ramsay J, Brennan-Jones CG, et al. Whole-cell pertussis vaccine in early infancy for the prevention of allergy in children. Cochrane Database Syst Rev. 2021;9(9):CD013682.doi: 10.1002/14651858.CD013682.pub2
56. Pérez Chacón G, Fathima P, Jones M, et al. Infant Whole-Cell Versus Acellular Pertussis Vaccination in 1997 to 1999 and Risk of Childhood Hospitalization for Food-Induced Anaphylaxis: Linked Administrative Databases Cohort Study. J Allergy Clin Immunol Pract. 2024;12(3):670-80.doi: 10.1016/j.jaip.2023.12.048

57. Pérez Chacón G, Estcourt MJ, Totterdell J, et al. Immunogenicity, reactogenicity, and IgE-mediated immune responses of a mixed whole-cell and acellular pertussis vaccine schedule in Australian infants: A randomised, double-blind, noninferiority trial. PLoS Med. 2024;21(6):e1004414.doi: 10.1371/journal.pmed.1004414
58. Wanlapakorn N, Maertens K, Vongpunsawad S, et al. Quantity and quality of antibodies after acellular versus whole-cell pertussis vaccines in infants born to mothers who received tetanus, diphtheria, and acellular pertussis vaccine during pregnancy: A randomized trial. Clin Infect Dis. 2020;71(1):72-80.doi: 10.1093/cid/ciz778
59. Betsch C, Bödeker B, Schmid P, Wichmann O. How baby's first shot determines the development of maternal attitudes towards vaccination. Vaccine. 2018;36(21):3018-26.doi: 10.1016/j.vaccine.2018.04.023
60. Fortuna L, Chaithongwongwatthana S, Soonthornworasiri N, et al. Enhanced post-licensure safety surveillance of a new recombinant acellular pertussis vaccine licensed as a monovalent (aP, Pertagen(R)) and tetanus, reduced-dose diphtheria combination (TdaP, Boostagen(R)) vaccine for immunization of adolescents and adults in Thailand. Vaccine. 2020;38(51):8194-9.doi: 10.1016/j.vaccine.2020.10.070
61. Pitisuttithum P, Dhitavat J, Sirivichayakul C, et al. Antibody persistence 2 and 3 years after booster vaccination of adolescents with recombinant acellular pertussis monovalent aP(gen) or combined TdaP(gen) vaccines. EClinicalMedicine. 2021;37:100976.doi: 10.1016/j.eclinm.2021.100976
62. Chaithongwongwatthana S, Wijagkanalan W, Wanlapakorn N, et al. Transplacental transfer of maternal antibodies following immunization with recombinant pertussis vaccines during pregnancy: Real-world evidence. Int J Infect Dis. 2024;144:107047.doi: 10.1016/j.ijid.2024.107047
63. Wood N, Nolan T, Marshall H, et al. Immunogenicity and safety of monovalent acellular pertussis vaccine at birth: A randomized clinical trial. JAMA Pediatr. 2018;172(11):1045-52.doi: 10.1001/jamapediatrics.2018.2349
64. Lin A, Apostolovic D, Jahnmatz M, et al. Live attenuated pertussis vaccine BPZE1 induces a broad antibody response in humans. Journal of Clinical Investigation. 2020;130(5):2332-46.doi: 10.1172/JCI135020
65. Keech C, Miller VE, Rizzardi B, et al. Immunogenicity and safety of BPZE1, an intranasal live attenuated pertussis vaccine, versus tetanus-diphtheria-acellular pertussis vaccine: a randomised, double-blind, phase 2b trial. Lancet. 2023;401(10379):843-55.doi: 10.1016/S0140-6736(22)02644-7
66. Jahnmatz M, Richert L, Al-Tawil N, et al. Safety and immunogenicity of the live attenuated intranasal pertussis vaccine BPZE1: a phase 1b, double-blind, randomised, placebo-controlled dose-escalation study. The Lancet Infectious diseases. 2020;20(11):1290-301.doi: 10.1016/S1473-3099(20)30274-7
67. Buzz C, Ragupathi G, Bennett SR, et al. The novel semisynthetic saponin adjuvant TQL1055 enhances the antibody response to pertussis vaccine with an improved tolerability profile over QS-21. Open Forum Infectious Diseases. 2020;7(SUPPL 1):S638.doi: 10.1093/ofid/ofaa439.1423
68. Nowlan M, Turner N, Kiedrzynski T, et al. 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.doi:
69. Australian Government. Table. Minimum acceptable age for the 1st dose of schedule NIP-funded vaccines in infants.: Department of Health and Aged care; 2024 [updated 19 July 2024; cited 2024 Nov 29]. Available from: https://immunisationhandbook.health.gov.au/resources/tables/table-minimum-acceptable-age-for-the-1st-dose-of-scheduled-nip-funded-vaccines-in-infants
70. Young A, Charania NA, Gauld N, et al. Knowledge and decisions about maternal immunisation by pregnant women in Aotearoa New Zealand. BMC Health Services Research. 2022;22(1):779.doi: 10.1186/s12913-022-08162-4
71. Edwards KM, Decker MD, Heath Damron F. Pertussis vaccines. In: Orenstien W, Offit P, Edwards KM, editors. Plotkin's Vaccines [Internet]: Elsevier; 2023 [cited 12 December 2024]. 762-815.
72. Institute of Environmental Research and Surveillance. ESR Pertussis report, May 2019. Porirua, Wellington, New Zealand: ESR; 2019 10 June 2019.Available from: https://www.esr.cri.nz/digital-library/pertussis-monthly-report-may-2019/
73. UK Health Security Agency. Confirmed cases of pertussis in England by month 2024 [updated 10 Oct 2024; cited 6 Nov 2024]. Available from: https://www.gov.uk/government/publications/pertussis-epidemiology-in-england-2024/confirmed-cases-of-pertussis-in-england-by-month

74. NHS England. Childhood vaccination coverage statistics, England, 2023-24 2024 [updated 17 Sept 2024; cited 6 Nov 2024]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-immunisation-statistics/england-2023-24
75. Griffin JB, Yu L, Watson D, 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.doi: 10.1016/j.vaccine.2018.07.011
76. GSK. New Zealand datasheet: Boostrix [Internet]. Medsafe; 2023 [cited 6 December 2024]. Available from: https://www.medsafe.govt.nz/profs/datasheet/b/Boostrixinj.pdf
77. Simayi A, Zhu L, Jin H. Safety and immunogenicity of pertussis vaccine immunization during pregnancy: A meta-analysis of randomized clinical trials. Journal of Tropical Medicine. 2022;2022:4857872.doi: 10.1155/2022/4857872
78. Datwani H, Moro PL, Harrington T, Broder KR. Chorioamnionitis following vaccination in the Vaccine Adverse Event Reporting System. Vaccine. 2015;33(27):3110-3.doi: 10.1016/j.vaccine.2015.04.097
79. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clin Infect Dis. 2016;62(7):829-36.doi: 10.1093/cid/ciw027
80. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, et al. Pertussis antibody transfer to preterm neonates after second- versus third-trimester maternal immunization. Clin Infect Dis. 2017;64(8):1129-32.doi: 10.1093/cid/cix046
81. 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
82. Godoy P, Garcia-Cenoz M, Rius C, et al. Effectiveness of maternal pertussis vaccination in protecting newborn: A matched case-control study. J Infect. 2021;83(5):554-8.doi: 10.1016/j.jinf.2021.08.022
83. Perrett KP, Halperin SA, Nolan T, et al. Immunogenicity, transplacental transfer of pertussis antibodies and safety following pertussis immunization during pregnancy: Evidence from a randomized, placebo-controlled trial. Vaccine. 2020;38(8):2095-104.doi: 10.1016/j.vaccine.2019.10.105
84. Perrett KP, Halperin SA, Nolan T, et al. Impact of tetanus-diphtheria-acellular pertussis immunization during pregnancy on subsequent infant immunization seroresponses: follow-up from a large randomized placebo-controlled trial. Vaccine. 2020;38(8):2105-14.doi: 10.1016/j.vaccine.2019.10.104
85. 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.doi: 10.1542/peds.2013-3181
86. Radke S, Petousis-Harris H, Watson D, et al. Age-specific effectiveness following each dose of acellular pertussis vaccine among infants and children in New Zealand. Vaccine. 2017;35(1):177-83.doi: 10.1016/j.vaccine.2016.11.004
87. World Health Organization. Pertussis vaccines: WHO position paper - September 2015. Releve epidemiologique hebdomadaire. 2015;90(35):433-58.doi:
88. World Health Organization. Tetanus vaccines: WHO position paper - February 2017. Weekly Epidemiological Record [Internet]. 2017;92(06). Epub 10 February 2017. Available from: https://www.who.int/publications/i/item/WHO-WER9206
89. Lavine JS, Bjørnstad ON, de Blasio BF, Storsaeter J. Short-lived immunity against pertussis, age-specific routes of transmission, and the utility of a teenage booster vaccine. Vaccine. 2012;30(3):544-51.doi: 10.1016/j.vaccine.2011.11.065
90. Xu J, Liu S, Liu Q, et al. The effectiveness and safety of pertussis booster vaccination for adolescents and adults: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(16):e15281.doi: 10.1097/MD.0000000000015281
91. Urwyler P, Heininger U. Protecting newborns from pertussis - the challenge of complete cocooning. BMC Infect Dis. 2014;14:397.doi: 10.1186/1471-2334-14-397
92. Carcione D, Regan AK, Tracey L, et al. The impact of parental postpartum pertussis vaccination on infection in infants: A population-based study of cocooning in Western Australia. Vaccine. 2015;33(42):5654-61.doi:
93. Ray P, Hayward J, Michelson D, et al. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. Pediatr Infect Dis J. 2006;25(9):768-73.doi: 10.1097/01.inf.0000234067.84848.e1
94. McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics. 2015;135(2):331-43.doi: 10.1542/peds.2014-1729

95. Pitisuttithum P, Chokephaibulkit K, Sirivichayakul C, 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;18(11):1260-8.doi: 10.1016/s1473-3099(18)30375-x
96. Sricharoenchai S, Sirivichayakul C, Chokephaibulkit K, et al. A genetically inactivated two-component acellular pertussis vaccine, alone or combined with tetanus and reduced-dose diphtheria vaccines, in adolescents: a phase 2/3, randomised controlled non-inferiority trial. The Lancet Infectious diseases. 2018;18(1):58-67.doi: 10.1016/s1473-3099(17)30612-6
97. BioNet's Recombinant Pertussis Vaccine Submitted to European Medicines Agency (EMA) [press release]. Lyon, France: BioNet Europe, 31 July 2024 [cited 12 December 2024]. Available from: https://bionet-asia.com/bionet-recombinant-pertussis-vaccine-submitted-to-ema/
98. Dowling DJ, Barman S, Smith AJ, et al. Development of a TLR7/8 agonist adjuvant formulation to overcome early life hyporesponsiveness to DTaP vaccination. Sci Rep. 2022;12(1):16860.doi: 10.1038/s41598-022-20346-w
99. Elizagaray ML, Gomes MTR, Guimaraes ES, et al. Canonical and non-canonical inflammasome activation by outer membrane vesicles derived from *Bordetella pertussis*. Frontiers in Immunology. 2020;11:1879.doi: 10.3389/fimmu.2020.01879
100. Yılmaz Çolak Ç, Tefon Öztürk BE. *Bordetella pertussis* and outer membrane vesicles. Pathogens and Global Health. 2022;117(4):342-55.doi: 10.1080/20477724.2022.2117937
101. Hernandez G, Shamseldin M, Verzani E, et al. Discovering and assessing novel epitopes of Bordetella pertussis to improve the whooping cough vaccine through immunopeptidome analysis and immune recognition assays. Journal of Biological Chemistry. 2023;299(3 Supplement):S42.doi: 10.1016/j.jbc.2023.103148
102. Ghasemnejad A, Bazmara S, Shadmani M, Bagheri KP. Designing a new multi-epitope pertussis vaccine with highly population coverage based on a novel sequence and structural filtration algorithm. IEEE/ACM transactions on computational biology and bioinformatics. 2021;18(5):1885-92.doi: 10.1109/TCBB.2019.2958803
103. Shamseldin MM, Hernandez G, Verzani E, et al. Development of a next generation pertussis vaccine: An unbiased biochemical approach to identify novel CD4+T cell recognized antigens from. Journal of Immunology. 2023;210(1).doi: 10.4049/jimmunol.210.Supp.223.15