2012 Antigen Review for the New Zealand National Immunisation Schedule: Pertussis

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Executive summary

Despite widespread gains in disease control with immunisation programmes, pertussis remains a major global public health problem. Pertussis is a disease that occurs across the age spectrum. Young infants remain at risk of serious disease which continues to cause fatalities in both developed and developing countries.

The primary focus of pertussis immunisation policy internationally is to reduce the risk of severe pertussis in infants. This requires both a complete and timely delivery of the primary immunisation series and the appropriate use of booster doses of pertussis vaccine. The worldwide priority is to achieve greater than 90 per cent coverage for the primary infant series of three doses with a high quality pertussis vaccine in infants. Universal implementation of infant immunisation has reduced the number of infant deaths and the incidence of pertussis disease in younger children. The contribution that older age groups make to the spread of pertussis to infants has been increasingly recognised in recent decades and has become a key consideration in contemporary refinements of national and international immunisation recommendations.

Whole-cell pertussis vaccines have been in use since the 1940s. Their effectiveness is shown by the 150 to 200 fold decrease in incidence rate of pertussis seen in the United States between the 1940s and the 1970s. While effective, they are among the more reactogenic of vaccines and have never been considered appropriate for use in older children and adults. Since the 1990s many countries have moved to using acellular pertussis vaccines which have better reactogenicity profiles than whole cell vaccines and can be used across the age range. The most efficacious acellular vaccines are, at best, only as efficacious as the most efficacious whole-cell vaccines. The duration of vaccine induced immunity from acellular pertussis vaccines appears to be shorter than what was achieved when immunisation schedules consisted solely of whole-cell vaccines. There is considerable concern that immunisation schedules, which consist solely of acellular pertussis vaccine, are less effective at controlling pertussis than were whole cell vaccine schedules.

Natural immunity to pertussis is incomplete, and hence, pertussis is a recurrent disease in humans. Our incomplete understanding of the pathogenesis and immunology of \textit{Bordetella pertussis} infection and pertussis disease continues to limit our capacity to develop vaccines that provide sustained protection against disease or effective prevention of transmission of \textit{B. pertussis}.

Epidemiology

Pertussis remains an international problem with considerable disease burden, particularly in infants and young children. Increasingly, disease is being identified in older children, adolescents and adults. This is due to increasing awareness of disease in these age groups, better diagnostic testing, and waning immunity from vaccines particularly with acellular vaccines. There is also the possibility of emergence of new strains that are more resistant to acellular vaccines.

Diagnosis

The development and widespread use of PCR testing has enabled the increased recognition of pertussis. However, the successful use of PCR in clinical laboratories needs to be associated with rigorous quality-assessment programmes and disease categorization needs to be based on appropriate clinical case definitions and not just on PCR positivity alone.

It is recommended that new case definitions for pertussis are applied to improve sensitivity and specificity, recognising the different clinical presentations in three different age groups: zero to three months, four months to nine years, and 10 years and older. These recognise the atypical presentation of pertussis in infants and that pertussis is now commonly a vaccine-modified disease in most age groups.

New Zealand is experiencing a significant increase in pertussis. Increases in pertussis notifications have been seen previously and occur over a four to five year cycle in New Zealand. The underlying reasons for such a cycle are unknown. The under-one year old infants are the most vulnerable with a cumulative notification rate in 2012 of 606/100,000. In 2012, ethnicity data show that the highest notification rate was amongst the European ethnic group (148.5 per 100,000 population) followed by Māori (126.8 per 100,000).
Hospitalisations are highest for Pacific Peoples (24.1% of cases) then Māori (14.7%). Geographically, the rate of notifications is highest in the Nelson-Marlborough DHB (452.5 per 100,000) followed by the West Coast (421.7 per 100,000). Almost one third (541) of notifications were not vaccinated including 22 cases of infants aged less than six weeks old (not eligible for vaccination).

Over the past 10 years there has been a shift in the serotype of the New Zealand *B. pertussis* population from almost 90% serotype 1, 3 to an equal mixture of serotype 1, 2 and 1, 3. Further characterisation of the toxin promoter from some of the strains in the current outbreak has shown them to contain the *ptxP3* allele.

**Safety profile of acellular vaccines**

The safety profile of acellular vaccines is well established. In comparison with whole-cell vaccines, acellular vaccines are less likely to cause febrile convulsions and hypotonic-hypo-responsive episodes (HHE). There is a small increase in the frequency of fever, and of redness and swelling localised to the injection site from the first to the third dose in a primary infant immunisation series. Injection site reactions are more common after the fifth dose, but still significantly less frequent than with whole-cell vaccines. Adding Hib vaccine to combination vaccines that also contain diphtheria, tetanus, acellular pertussis vaccine (DTaP) increases the frequency of pain and of localised redness. There is a small increased risk of febrile convulsions on the day of administration of the first two doses in a primary course given at three and five months, but the absolute risk is small. It is unknown if the same effect is seen with a primary course starting at six weeks of age.

Tdap booster doses appear well tolerated in all age groups. Local reactions are similar to DTaP when used as a fourth dose in children aged four to six years, and Tdap vaccines are less reactogenic compared to DTaP vaccines when used for booster doses in older children and adolescents. Reactions may be slightly more frequent in adults receiving ten-yearly boosters of Tdap following a primary course of DTaP.

Tdap booster doses can be used safely from weeks following the delivery of a Td vaccine. Tdap vaccines appear safe in pregnancy based on safety data from the US Vaccine Adverse Event Reporting System (VAERS) to date.

Pertussis-containing vaccines do not appear to increase the risk of Guillain-Barre Syndrome, encephalopathy/encephalitis/meningitis, paralytic syndromes, seizures, cranial nerve disorders or coeliac disease. There was a higher incidence of cough seen in VAERS data with Tdap vaccinees compared to Td vaccinees. Case studies have shown that examples of previously alleged vaccine encephalopathies were due to genetic syndromes and inborn errors of metabolism. One case report has been published of femoral neuropraxis in an infant who received diphtheria, tetanus and acellular pertussis/inactivated poliovirus/*Haemophilus influenzae* type B vaccine.

**Immunogenicity**

There are a number of challenges in measuring vaccine immunogenicity, efficacy and effectiveness due to there being no established correlates of protection, limitations with case definitions, and difficulties in comparing vaccine efficacy estimates calculated using different study designs.

Booster Tdap vaccines appear to elicit good immune responses in children, adolescents, adults and the elderly, and are non-inferior to DTaP vaccines. Adding a Hib component to a combination vaccine appears to reduce the Hib antibody response, but not the responses to the other antigens.

Infants of mothers vaccinated with Tdap vaccines show good immunogenicity responses. Based upon observations from the initial whole cell vaccine efficacy trials, conducted in the UK and USA in the 1940s showing immunisation prior to age four weeks was less immunogenic, there has been concern that maternally acquired antibody in infants may interfere with the active immune response to the primary immunisation series. Whether this occurs significantly with acellular vaccines, and if so, whether it is a clinically relevant effect, is as yet unknown. Early data from vaccination of newborns at birth and one month of age demonstrate that good immune responses are induced and no interference with subsequent responses to the primary course was apparent.
Efficacy and Effectiveness

As a primary immunisation series, the acellular pertussis vaccines with three or more components are more likely to be effective than one or two component vaccines. The efficacy of multicomponent vaccines is 84% to 85% in preventing typical whooping cough and from 71% to 78% in preventing mild pertussis disease. In contrast, the efficacy of one and two component vaccines varies from 59% to 78% against typical whooping cough and from 41% to 54% against mild disease. There is insufficient data to determine whether there is a clinically significant difference in efficacy between three and five component vaccines.

Protection against pertussis following booster doses of acellular pertussis wanes rapidly. Vaccine efficacy for children that have received a three dose infant primary series and two preschool boosters is estimated to be 71%. Vaccine effectiveness data suggest that following a primary course and booster dose a gradual waning of vaccine-induced protection occurs over four to six years. In a population given five doses of DTaP prior to the age of seven years rapid waning of protection against pertussis is seen with the risk of pertussis disease increasing by an average of 42% per year post the last dose.

Adolescent booster doses of Tdap vaccines are effective, with vaccine effectiveness measures from around 66% to 79% against diagnosed pertussis, but there are no accurate efficacy measurements.

Immunity after vaccination has been thought to be of shorter duration than after the natural disease. Immunisation provides more sustained protection against disease than it does against infection with B. pertussis.

While herd immunity has been demonstrated with pertussis vaccines, the amount of herd immunity delivered with current acellular vaccines and schedules appears small. The lack of impact of national schedules on the periodicity of pertussis epidemics implies that they have had little effect on the circulation of B. pertussis in the population as a whole.

To date, cocoon strategies have not been shown to be effective. This is likely to be due to logistical challenges in implementation of such strategies. Vaccination in pregnancy has been shown to be immunogenic. Passive transfer of maternal antibody to infants occurs, but as yet, there is no data on the effectiveness of this strategy for the prevention of pertussis disease in infants.

In several countries where acellular pertussis vaccines have been in use for a decade or more, genetic changes have occurred over time in three pertussis antigens – pertussis toxin (PT), PRN and fimbriae. Acellular vaccines may be driving selection among strains, enabling wider circulation of B. pertussis strains for which current acellular vaccines have lower efficacy. However, whether these changes are from significant vaccine pressure or random genetic drift remains unclear. The contribution of strain variability may be of less importance than the accumulation of susceptible individuals due to waning immunity.

Age-specific concerns

While pertussis disease occurs across the whole population the most severe disease is in newborns, infants too young to be vaccinated or those who have not completed their primary immunisation series on time. Current strategies remain focused on preventing severe disease in young infants. While the development of vaccines that can be delivered across the age range raises the possibility of herd immunity, the effectiveness of such strategies has not yet been proven. Reasons for this include the limited duration of vaccine induced protection, the lower coverage that is achieved when immunising older age groups and the relatively short period of time that such strategies have been in place.

Vaccine Options

Acellular vaccines are multicomponent usually consisting of two to five components. There are no monovalent pertussis vaccines available internationally; all are in combination with at least diphtheria and tetanus toxins. Acellular vaccines contain three or more antigens overall are considered to have better efficacy than one or two component vaccines. As of early 2013, the major international manufacturers of acellular pertussis vaccines are Baxter International, Crucell NV, GlaxoSmithKline, Merck and Co, Novartis, Sanofi Pasteur and Pfizer.
Summary of schedule options

Discussion is on-going internationally with regard to the ideal vaccination programme for pertussis. Options and objectives for each option are listed below based on a summary of Pertussis Strategies adapted from the Consensus on Pertussis booster vaccination in Europe initiative (COPE) recommendations 2011.

• Reinforce high coverage and timely delivery of the primary infant immunisation series.
  The primary objective of this strategy is to reduce disease in infants.

• Preschool or school boosters
  Primary objectives are to reduce disease in this age group and reduce spread to infants.

• Universal adolescent booster
  Primary objective is to reduce transmission to infants; secondary objective is to reduce disease in adolescents and young adults and develop herd immunity.

• Healthcare worker vaccination
  Primary objective is to reduce transmission to patients; secondary objective is to reduce disease in healthcare workers.

• Cocoon vaccination
  Primary objective is to reduce transmission to infants; secondary objective is to reduce disease in adults.

• Childcare vaccination
  Primary objective is to reduce transmission to infants; secondary objective is to reduce disease in staff.

• Universal adult vaccination
  Primary objectives are to reduce transmission to infants and reduce disease in children; secondary objective is to reduce disease in adults and to develop herd immunity.

Economic evaluations, in general, favour pertussis booster vaccination in adults and adolescents, although, there is uncertainty around which age-groups to vaccinate and the exact epidemiological conditions under which vaccination would be cost effective.

In view of the uncertainties about the feasibility of adult vaccination strategies, some current international commentary favours focusing more on pregnancy and cocoon strategies to protect the most vulnerable and the development of improved vaccines, which have longer lasting immunity, and less on adult strategies with the available vaccines.

Targeted vaccination of pregnant women is predicted to halve the risk of infant pertussis infection. Other potential cocooning strategies include using the birth of a child as a reminder to ensure all siblings are immunised and the immunisation of other close caregivers, such as fathers. The cost and logistical barriers to widespread implementation of cocooning are major limitations.

Vaccination of pregnant women may be a more effective strategy. The use of maternal vaccination to provide temporary passive immunity to infants is well established and considered safe. However, further studies are awaited to clarify whether the theory that maternally-derived antibodies may interfere with the infant’s immune response to the primary course of pertussis vaccine applies to the available acellular vaccines. As yet, no studies showing effectiveness of this strategy have been published in the peer-reviewed literature.
Implementation issues

Adverse reactions after multiple simultaneous vaccinations are only slightly more frequent than would be expected for the most reactogenic vaccine alone. Reduced immunogenicity to the pertussis antigens has occasionally been seen when given in combination or in association with another vaccine, but no data exists to suggest that this decreases the efficacy of pertussis vaccines. There are no concerns with concomitant delivery with other current vaccines on the NZ schedule. Concomitant delivery has been shown to be safe and effective alongside meningococcal C conjugate tetanus toxoid vaccines and a multicomponent protein meningococcal B vaccine (4CMenB).

Those who have had previous anaphylactic reactions to the vaccine or any component should be evaluated with a skin test to the vaccine and its components. There are no longer concerns about increased reactogenicity with giving of Tdap vaccines within two years of previous receipt of a tetanus/diphtheria containing vaccine.

It is not recommended to change the vaccine brand used in a primary course; however, interchangeability for the booster dose appears to be safe and effective.

Recently published international recommendations, around strategies for improving immunisation coverage that have relevance to the NZ context, include a focus on improving vaccination to high risk neonates via better integrated service and performance initiatives for neonatal units; better protocols, such as the use of standing orders, to improve postpartum vaccination in medically underserved women; a stronger focus on vaccination of staff in child care settings via utilisation of accreditation or licensing processes and education to the directors of the centres; and a recommendation to focus strategies for junior doctors (medical residents) around the issue of ‘lack of time’ to obtaining a vaccination. It is unknown, but worthy of consideration, whether the same considerations around time constraints are an issue in the NZ context. Mandatory vaccination approaches do not appear to be necessary in countries with existing high immunisation coverage.
2012 Antigen Review for the New Zealand National Immunisation Schedule: Pertussis

Prepared as part of a Ministry of Health contract

by

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

January 2013 (edited July 2014)
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<th>Description</th>
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<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunisation Practices (US)</td>
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<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
</tr>
<tr>
<td>aP</td>
<td>Acellular pertussis containing vaccines - two antigen, three antigen or five antigen brands</td>
</tr>
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<td>B. pertussis</td>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>COPE</td>
<td>Consensus on Pertussis booster vaccination in Europe initiative</td>
</tr>
<tr>
<td>DTaP</td>
<td>Diphtheria, tetanus, acellular pertussis vaccine</td>
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<tr>
<td>FHA</td>
<td>Filamentous haemagglutinin</td>
</tr>
<tr>
<td>GMC</td>
<td>Geometric Mean Titre</td>
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<tr>
<td>HEP B</td>
<td>Hepatitis B vaccination</td>
</tr>
<tr>
<td>HHE</td>
<td>Hypotonic hyporesponsive episode</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenzae type B vaccine</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PCV13</td>
<td>Pneumococcal conjugate vaccine containing antigens from 13 pneumococcal serotypes</td>
</tr>
<tr>
<td>PCV7</td>
<td>Pneumococcal conjugate vaccine containing antigens from 7 pneumococcal serotypes</td>
</tr>
<tr>
<td>PT</td>
<td>Pertussis toxin</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Tdap</td>
<td>Tetanus, diphtheria, acellular pertussis booster vaccine</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Event Reporting System</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>wP</td>
<td>Whole-cell pertussis containing vaccines</td>
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1. Background –

Pertussis and vaccination

Pertussis is a common and potentially serious disease of childhood. It is also increasingly recognised in older age groups, albeit usually with less severe consequences. Despite widespread gains in disease control pertussis remains a major public health problem.

The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infants. The worldwide priority is to achieve greater than 90% coverage with a high quality pertussis vaccine in infants (1).

Universal implementation of infant immunisation has reduced disease among the younger age groups, but has shifted the age distribution of disease to older age groups (2). However, pertussis has always been a disease that has affected the full age spectrum.

Whole-cell pertussis vaccines have been in use since the 1940s and remain the most effective and most widespread vaccines used worldwide (3). Since the 1990s, many developed countries have moved to using acellular pertussis vaccines which have a better reactogenicity profile, although may be less effective than traditional whole-cell vaccines. Efficacy varies between different whole cell and acellular pertussis vaccines. The lack of a clear serological correlate of protection makes it difficult to interpret the immunogenicity data from different vaccines in terms of their vaccine effectiveness. The major current limitation of all pertussis vaccines is the short duration of immunity, enabling pertussis to recur in older age groups as immunity wanes (2).

This review evaluates the literature on vaccination against rotavirus published since the writing of the New Zealand (NZ) Immunisation 2011 Handbook from 2009 to 2012. During an edit of this review in 2014 prior to publication, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.
2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for pertussis vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around pertussis vaccines for New Zealand.

- General specifications.
  - Safety.
  - Effectiveness.
- Implementation issues (practicality and possible impact on uptake).
- The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination.
- Different options of placement on the schedule, based on international findings and best practice.
- Different vaccine options and comparisons between the options.
- Specific service specifications for pertussis vaccines.
  - Evidence for providing the vaccine for mothers immediately after giving birth, and evidence for extending this to both parents.
  - Investigation of recommended groups for pertussis control coverage, including: pregnant women, healthcare workers, 45-65 year age group (i.e. inclusion with the 45/65 Td scheduled vaccine).
  - Duration of protection provided by vaccines.
- Investigation of strain changes internationally.
- Investigation of whether a booster dose should be included in the schedule, and if so international evidence for when this should be administered.
- Duration of protection provided by vaccines.

2.2 Literature search strategy

1. The points below have formed the focus of the literature search:
   1. Safety
      a. Safety of pertussis vaccine in infants.
      b. Safety in pregnant women.
      c. Anything new in safety over the past few years.
   2. Effectiveness in disease control.
      a. Children
      b. Adults
      c. Indirect effects/herd immunity
      d. Duration of protection
   3. Implementation issues (practicality of and possible impact on uptake).
      a. Value of a catch-up/supplementary dose in infant schedule.
   4. Differences that need to be considered for each age group, for example the variable severity of disease and immunisation concerns that differ with age.
   5. Different option for placement on the schedule, based on international findings and best practice.
   6. Different vaccine options for each disease and comparison between the options.
   7. Current international research and evidence around use of vaccines.
      a. Consider this point covered in 1 to 6.

Other areas of special interest

- Evidence for providing the vaccine for mothers immediately after birth and evidence for extending this to both parents.
- Investigation of recommended groups for pertussis control coverage, including pregnant women, healthcare workers, 45 to 65 year age group (i.e. inclusion with the 45 to 65 tetanus, diphtheria scheduled vaccine).
- Investigation of strain changes internationally
- Investigation of whether a booster dose should be included in the schedule, and if so international evidence for when this should be administered.
- Duration of protection provided by vaccines.
2.2.1 Medline search terms and strategy

**MeSH term: Pertussis, focus, all subgroups**

5037
Limit to Humans, English, 2009 – current
390 (Keep and view)

2.2.2 Cochrane Library search terms and strategy

Search term Pertussis Vaccin*
Limit to Cochrane Reviews, Other Reviews, and Trials
2009-present
4 results (keep and view)

2.2.3 Scopus search terms and strategy

Pertussis Vaccin* Published 2011 – present
1268
Limit to: Medicine, humans, vaccination, pertussis vaccine, journals
347
Exclude Letter, Short survey, editorial and erratum
340 (keep and view)
Reject social science articles. Delete duplicates

Final EndNote library after literature search and revisions 400

2.2.4 Grey literature

Conference abstracts were sought to include data that had not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012. No conference abstracts and posters were accessed.

2.2.5 Additional searches

Where questions arose, additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further six articles were accessed.

2.2.6 Final library

The final library includes 409 references. Where systematic reviews and/or meta-analysis were available, the preceding literature has been excluded from the review.

**Figure 1. Flow of selection of articles for review**

2.3 Participants/populations

The population for a potential universal programme are all ages

2.4 Interventions

The interventions included are combination vaccines that include:

- Whole cell pertussis containing vaccines (wP)
- Acellular pertussis containing vaccines (aP) – two antigen, three antigen or five antigen brands

The controls are usually a non-pertussis containing vaccine, such as diphtheria, tetanus vaccines.

2.5 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.
3. Recent epidemiology

Worldwide pertussis remains an important problem, particularly in young children. It is a significant cause of morbidity and mortality in infants and is a significant cause of death in infants younger than two months of age in high income countries (4).

In many countries, despite sustained high coverage for childhood pertussis vaccines, the disease remains inadequately controlled. The WHO estimates that in 2008 about 16 million cases occurred worldwide, 95% of which were in developing countries. In 2008 approximately 195,000 children died from pertussis (5).

Widespread pertussis vaccination of children and the consequent reduction in disease incidence in this age group has not affected the epidemic peaks which continue to occur typically every three to four years. This implies that childhood immunisation has had no significant impact upon the circulation of pertussis in the human population. While a chronic carrier state has not been demonstrated, more recent use of highly sensitive PCR assays shows that in outbreak situations the organism can also be identified in people with no clinical evidence of disease (5).

In the past 10 years or so, increases in disease have been reported in many Western countries - even those with sustained high immunisation coverage. Age groups where rates have been particularly high include adolescents and adults and, more recently, primary school aged children (4, 6). Much of the international increase in pertussis disease rates over the past decade have been in adults, adolescents and infants too young to have been immunised (7).

United States (US) data has reported that adults and adolescents have accounted for over 50% of cases in recent years (8). In 2012 the UK reported nearly 10 times the number of older children and adults in England and Wales than when the disease last peaked in 2008 (9).

The Netherlands has experienced increasing pertussis rates since 1996 in the context of sustained very high infant immunisation coverage. In a serological surveillance study undertaken in 2006-2007 approximately 9% of the entire population above nine years of age had a pertussis infection in that time interval, twice the frequency observed a decade earlier (10). About one quarter of the adolescents and adults with presumptive pertussis infection reported to have had at least two weeks of coughing symptoms in the preceding year (10). With young infants, 76% - 83% of transmission is from household members (11). A higher seroprevalence is seen in low income groups (10).

In the Asia-Pacific region establishing accurate incidence data has been difficult (12). In the majority of countries, children less than five years bear the greatest disease burden, however Australian epidemiology has shown that the cohort contributing to the greatest disease burden is broader, including infants, children and adolescents (12). The detection of this in Australia may in part be due to extensive use of better laboratory diagnostics and heightened awareness among the medical profession and public. A study in Singapore noted that 97% of adults aged 18-45 were seropositive for pertussis (13).

Explanations for the increased disease rates and changing age distribution include a greater awareness among health providers, improved access to more sensitive and specific diagnostic tests, the reduced potency of acellular vaccines compared to whole-cell vaccines and adaptation of the causative organism leading to the emergence of new strains (3, 9, 10).

3.1 Diagnosis

PCR assays identify unique gene sequences of *B. pertussis* in respiratory secretions. Although bacteria can no longer be cultured after 5 days of antibiotic therapy the PCR can remain positive for a further week. Although it requires scrupulous technique to avoid cross-contamination this rapid, highly sensitive and specific diagnostic method is now the gold standard for diagnosis (5). The development and widespread use of PCR testing has enabled the increased recognition of pertussis. The successful use of PCR in clinical laboratories needs to be associated with rigorous quality-assessment programmes and disease categorization needs to be based on appropriate clinical case definitions and not just of PCR positivity alone (5).
3.1.1 Case definitions for pertussis disease

Traditional case definitions were based mostly on clinical presentations, however, there is increasing recognition of milder and less typical presentations particularly in adolescents and adults. The Global Pertussis Initiative (GPI) has developed an algorithm for the signs/symptoms of pertussis most common to three age groups: zero to three months, four months – nine years and 10 years and older (15). It is hoped that the utilisation of these new definitions for pertussis will increase both the sensitivity and specificity in its diagnosis. As per the Figures 1 and 2 below:

**Figure. 2. Algorithm for the Diagnosis of Pertussis reproduced from Cherry et al. (15)**

**Figure. 3. Clinical Case Definition of pertussis for surveillance purposes reproduced from Cherry et al. (15)**
3.2 New Zealand epidemiology

New Zealand is experiencing a significant increase in pertussis. The number of notified cases rose dramatically from July 2011 and remained high throughout 2012 (Figure 3). Increases in pertussis notifications have been seen previously and occur over a four to five year cycle in New Zealand (Figure 4). The underlying reasons for such a cycle are unknown.

Figure 4. Number of pertussis notifications by week reported 2010 – 2012
(Source from surv.esr.cri.nz)

The under-one year old infants are the most vulnerable with a cumulative notification rate in 2012 of 606.1 per 100,000, the highest of any age group (Table 1). Notification data up to the 7th December 2012 indicate there were 378 cases of pertussis in this age group in 2012, of which 167 were hospitalised. There were 40 notifications of infants under six weeks old, 36 of which were hospitalised.
Table 1. Cumulative notification rate of Pertussis in 2012

<table>
<thead>
<tr>
<th>Age group (Years)</th>
<th>Cumulative notifications¹</th>
<th>Rates²</th>
<th>Hospitalisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>378</td>
<td>606.1</td>
<td>167</td>
</tr>
<tr>
<td>1-4</td>
<td>836</td>
<td>331.9</td>
<td>27</td>
</tr>
<tr>
<td>5-9</td>
<td>688</td>
<td>239.5</td>
<td>9</td>
</tr>
<tr>
<td>10-14</td>
<td>498</td>
<td>170.0</td>
<td>5</td>
</tr>
<tr>
<td>15-19</td>
<td>253</td>
<td>79.7</td>
<td>6</td>
</tr>
<tr>
<td>20-29</td>
<td>482</td>
<td>77.9</td>
<td>4</td>
</tr>
<tr>
<td>30-39</td>
<td>622</td>
<td>110.5</td>
<td>11</td>
</tr>
<tr>
<td>40-49</td>
<td>692</td>
<td>109.6</td>
<td>13</td>
</tr>
<tr>
<td>50-59</td>
<td>439</td>
<td>79.0</td>
<td>17</td>
</tr>
<tr>
<td>60-69</td>
<td>308</td>
<td>73.8</td>
<td>13</td>
</tr>
<tr>
<td>70+</td>
<td>193</td>
<td>47.4</td>
<td>15</td>
</tr>
<tr>
<td>Overall</td>
<td>5389</td>
<td>122.3</td>
<td>287</td>
</tr>
</tbody>
</table>

¹. Cumulative notifications excluding cases under investigation from 31st Dec 2011 to 7th December 2012
². Rate per 100,000 population using 2011 mid-year population estimates

Ethnicity data show that the highest notification rate was amongst the European ethnic group (148.5 per 100,000 population) followed by Māori (126.8 per 100,000). In the under-one year old age group, Māori had the highest notifications (862.4 per 100,000), followed by Pacific people (742.0 per 100,000). The European ethnic group had the highest notifications across all other age groups. The highest proportion of cases hospitalised by ethnic group were for Pacific people (24.1% of cases) then Māori (14.7%). While higher notification rates have been evident in Europeans since pertussis became a notifiable disease in 1996, hospital admission rates are higher for Māori and Pacific children (16, 17).

In 2012, two pertussis deaths were reported; one in an unimmunised three-year old with underlying health issues and one in a premature infant aged less than six weeks old.

Geographically, the rate of notifications in 2012 was highest in the Nelson-Marlborough DHB (452.5 per 100,000), followed by the West Coast (421.7 per 100,000).

The vaccination status was known for 1513 of the 2305 confirmed notified cases with known age. Almost one third (541) were not vaccinated, including 22 cases of infants aged less than six weeks old (not eligible for vaccination). One hundred and sixteen cases reported were fully vaccinated (Table 2).

Table 2. Immunisation status¹ of confirmed pertussis cases in 2012²

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total cases N</th>
<th>Doses N (%)</th>
<th>Vaccinated (no dose info) N (%)</th>
<th>Not vaccinated N (%)</th>
<th>Unknown N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 w</td>
<td>25</td>
<td>0 0 0 0 0</td>
<td>22 (88)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>6 w to 3 m</td>
<td>87</td>
<td>47 (54) 1 (1)</td>
<td>0 0 0 0 3 (3)</td>
<td>30 (34)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>3 m to 4 m</td>
<td>43</td>
<td>8 (19) 18 (42)</td>
<td>0 0 0 0 0</td>
<td>15 (34)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>5 m to 3 y</td>
<td>374</td>
<td>6 (2) 10 (3)</td>
<td>161 (43) 32 (9) 1 (0) 21 (6) 111 (30)</td>
<td>32 (9)</td>
<td></td>
</tr>
<tr>
<td>4 y to 10 y</td>
<td>572</td>
<td>10 (2) 4 (1)</td>
<td>37 (6) 144 (25) 75 (13) 79 (14)</td>
<td>161 (28)</td>
<td>62 (11)</td>
</tr>
<tr>
<td>11+ y</td>
<td>1204</td>
<td>55 (5) 6 (0)</td>
<td>15 (1) 22 (2) 40 (3) 177 (15) 202 (17)</td>
<td>687 (57)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2305</td>
<td>126 (5) 39 (2)</td>
<td>213 (9) 198 (9) 116 (5) 280 (12) 541 (23)</td>
<td>792 (34)</td>
<td></td>
</tr>
</tbody>
</table>

¹. Information derived from Episurv; ². Up to 7th December 2012

Cases of pertussis are confirmed by culture of the organism, detection of B. pertussis DNA by PCR from nasopharyngeal swabs or epidemiologically linked to a confirmed case. The majority of pertussis cases are confirmed by PCR, but some culture isolates are sent to ESR for further characterisation and storage. Over the past 10 years there has been a shift in the serotype of the New Zealand B. pertussis population from almost 90% serotypes 1, 3 to an equal mixture of serotypes 1, 2 and 1, 3. Further characterisation of the toxin promoter from some of the strains in the current outbreak has shown them to contain the ptxP3 allele, an allele associated with increases in pertussis seen in some other parts of the world.
3.3 Summary of epidemiology

Pertussis remains an international problem with considerable disease burden, particularly in infants and young children. Increasingly disease is being identified in older groups, adolescents and adults. This is due to a combination of increasing awareness of disease in these age groups, better diagnostic testing, and waning immunity from vaccines, particularly with acellular vaccines. There is also the possibility of emergence of new strains that are more resistant to acellular vaccines.

New Zealand is experiencing a significant increase in pertussis incidence. Increases in pertussis notifications have been seen previously and occur over a four to five year cycle in New Zealand. The underlying reasons for such a cycle are unknown.

The under-one year olds are the most vulnerable with a cumulative notification rate in 2012 of 606.1 per 100,000. Ethnicity data show that the highest notification rate was amongst the European ethnic group followed by Māori. Hospitalisations are highest for Pacific Peoples (24.1% of cases) then Māori (14.7%). Geographically the rate of notifications is highest in the Nelson-Marlborough DHB followed by the West Coast. Almost one third of notifications were not vaccinated including 22 cases of infants aged less than six weeks old who were not eligible for vaccination.

Over the past 10 years there has been a shift in the serotype of the New Zealand \textit{B. pertussis} population from almost 90% serotype 1, 3 to an equal mixture of serotype 1, 2 and 1, 3. Further characterisation of the toxin promoter from some of the strains in the current outbreak has shown them to contain the \textit{ptxP3} allele.
4. Vaccine safety

4.1 Objective
The objective of this section is to review the most recent safety data for currently licenced pertussis-containing vaccines. Only Adverse Events Following Immunisation (AEFI) that have been considered subsequent to the pivotal clinical efficacy trials are reviewed here and any major clinical differences between vaccine types.

4.2 Outcomes
Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE).

4.3 Review

4.3.1 Safety of Whole-Cell vaccines
There is a well-established safety profile for whole cell pertussis vaccines, and whole-cell vaccines are recognised as being generally very reactogenic. There is robust evidence that whole-cell vaccines have prevented much death and severe diseases, but some uncertainty remains about the potential for the whole-cell vaccine to have some deleterious non-pertussis specific effects (5). Listed below are the more recent publications on this issue, while this is not pertinent to the NZ context they are added for completeness in terms of recent publications on pertussis vaccines.

4.3.1.1 Overall mortality in low income countries with whole-cell vaccines
Studies have suggested that that DTwP may have negative effects on overall child survival. Recently, results were published from an observational study undertaken in Guinea-Bissau during 1993 to 1995, utilising data from a vitamin A trial in which vaccination status was registered at the time of measles vaccination at nine months of age. In this study 141/455 (31%) of children were missing one or more DTP vaccinations and were likely to receive them after the measles vaccine was delivered. They examined whether missing DTwP vaccine, at this time point, was associated with effects on overall mortality and found that in female children missing DTwP was associated with 3.55 times higher risk of dying before 36 months of age (95% CI 1.23-10.26), whereas there was no difference in male children (0.97; 95% CI 0.34-2.80). As an observational study confounding could have played a role. Children missing DTwP at enrolment tended to have lower nutritional status, but this tendency was strongest for male children. The authors conclude that, despite the limitations of the data and based on the available evidence, DTwP delivered after standard measles vaccination has a negative effect for female children (18).

A WHO-sponsored study in Guinea-Bissau reviewed 2320 low birth weight infants and examined survival until the six month visit. Over this time there were 50 deaths. Children vaccinated with DTwP had better health status for all indices than unvaccinated, but despite this, the death rate ratio for DTwP vaccinated children differed significantly for girls; overall early DTwP vaccination was associated with a threefold higher mortality between two to six months for girls despite the better nutritional status than those unvaccinated. The authors proposed that DTwP may deregulate the female immune system so that subsequent unrelated infections are fought less efficiently (19).

Aaby et al concludes that these observational trials are incompatible with DTwP merely protecting against the targeted diseases and appears to be associated with higher mortality in girls. They recommend that Randomised Controlled Trials (RCT) of DTwP are warranted in developing countries to measure the true impact on survival (20).

4.3.2 Safety of acellular vaccines
There are numerous studies that have established the safety profile of acellular vaccines. These have demonstrated their superior safety profile in comparison with whole-cell pertussis vaccines (5). Recent studies on new combination vaccines such as hexavalent DTaP-IPV-HepB-PRP-T continue to support the excellent safety profiles of acellular vaccines (21).

4.3.2.1 Cochrane review 2012
A 2012 Cochrane review of acellular pertussis vaccines pooled the safety data using a random effects meta-analysis model from 52 safety trials with a total of 136,541 participants (22). Overall, acellular vaccines were superior to whole-cell vaccines for all minor reaction outcomes for the primary course and booster doses. Acellular vaccines are less likely to cause febrile
convulsions and hypotonic-hyporesponse episodes (HHE). When comparing acellular vaccines with placebo (usually DT vaccines), there was no significant difference in the incidence of adverse events, with the exception of injection site swelling being more common among recipients of acellular vaccines after the third dose in the primary series. The authors cautioned that, given the uncommon occurrence of severe adverse reactions, there may not be enough statistical power to detect small but clinically relevant differences, and therefore, continuing surveillance for rare severe adverse reactions with acellular pertussis vaccines is warranted.

With acellular vaccines, a significant increase in the incidence from the first dose to the third dose during the primary series is observed for some minor adverse events; fever, local redness and swelling. The rate of reported injection site reactions continues to increase after the fifth consecutive dose of aP vaccine at four to six years of age. However, injection site tenderness after five doses of acellular vaccine is significantly lower than after five doses of whole-cell vaccine. The incidence of adverse reactions in children boosted with acellular vaccines after whole-cell priming is lower than if whole-cell vaccines had been used for every dose.

4.3.2.2 Cochrane review of combination vaccines

A 2012 review was undertaken on adding Hib to a combination vaccine reviewed DTP-HPV vaccination versus DTP-HPV-Hib vaccines, both in whole cell and acellular combinations. It included 20 studies with 5232 participants for safety surveillance. There were no serious adverse events reported, but a significant increase in pain and redness was observed in those given the combination vaccine with Hib (23).

4.3.2.3 DTaP Safety in Preterm infants

A population based case series examined data on 834,740 children in Ontario, Canada. They compared the frequency of emergency room visits and admissions in the three days post the first infant vaccination event at two months in small for gestational aged children (those in the lowest 10th percentile) and in very preterm infants versus term children. When compared with all term children there was a small non-significant reduction in frequency of emergency room visits and admissions in the three days after the first vaccine event at two months of age in small for gestation age near term infants (RR 0.89; 95% CI 0.74-1.07) and more so for very preterm infants (RR 0.67; 95% CI0.49-0.93). The authors speculate that the immune response is attenuated in preterm children resulting in reduced adverse events, but this may be masked because the reduced birth weight results in a comparatively increased dose of vaccine given (24).

4.3.2.4 Safety of booster acellular vaccines (Tdap)

The reduced antigen combined diphtheria, tetanus and acellular pertussis vaccines (Tdap) are designed to avoid the increasing reactogenicity seen with the fourth and fifth doses from the higher dose DTaP and DTwP vaccines (25). Tdap vaccines are now widely used in many countries as booster vaccines, generally licensed for individuals from four years of age and above in European schedules, and 10 years of age and above in the US schedule.

4.3.2.4.1. Review of Tdap safety

A 2012 review article summarising all the original clinical trials and additional prospective studies for the three-component Tdap vaccine Boostrix® (GlaxoSmithKline) concluded that this vaccine was safe and well tolerated in all age groups, including adults and the elderly, with similar patterns of adverse events across the broad age groups (25).

Key summary points from this review article are listed below:

- Local injection site reactions are the most common adverse events with the majority occurring within two days of vaccination. Most adverse events were mild or moderate intensity and transient. Fatigue and headache are the most common systemic adverse events. Extended follow up for six months showed no evidence of serious vaccination-related adverse events of an autoimmune nature or of new chronic disease, although there is one case report of a person being diagnosed with type 1 diabetes within 20 days of vaccination.

- One study focused on the use of Tdap as the sixth dose given to adolescents aged 10-12 years following five previous DTaP doses. The incidence of local swelling was significantly lower than was seen previously after the fifth DTaP dose although local pain was occurred more frequently.

- In a study of children aged four to six years (n=54) who had a history of a significant injection-site reaction to a fourth dose of DTaP in their second year, a booster dose of Tdap or DTaP produced a recurrence of injection-site reaction in 41 (75%), of which nearly half were extensive, although only 11 (2.6%) reported the highest score (severe pain) for a three-point pain grading scale.
• Local reactions occur less frequently with Tdap compared with DTwP administered to children aged four to six years.

• In children aged four to eight years reactogenicity to Tdap did not differ compared with DT or DTaP although there was a trend towards reduced reactogenicity with Tdap compared with DTaP.

• In adults receiving Tdap 10 yearly the vaccine was well tolerated, although local reactions tended to be reported slightly more frequently.

A three year observational study followed adolescents aged 10-18 years comparing 13,427 who had received Tdap vaccination with 12,509 who had received Td vaccination. There were no significant differences between the cohorts for medical attended neurological or haematological events. Interestingly the incidence of allergic reactions, mostly urticarial, within 30 days of vaccination was higher with the Td group, and the Td group had a higher incidence of asthma.

US Vaccine Safety Datalink information assessing 660,000 subjects aged 10-64 years who had received Tdap showed that the vaccine did not significantly increase the risk of Guillain-Barre Syndrome above the background incidence, nor the risk relative to Td of encephalopathy, encephalitis or meningitis, paralytic syndromes, seizures, or cranial nerve disorders.

The US Vaccine Adverse Event Reporting Service (VAERS) data on subjects aged ≥ 65 years, who were given Tdap vaccine during 2005-2010, showed 243 reports of which 41% were local reactions, 4% allergy, and 2% neurological events with one case of Guillain-Barre syndrome. The only difference found in comparison with those given Td was a disproportionately higher incidence of cough.

4.3.2.4.1.1 Booster doses in pre-school children
An Italian RCT examined the safety of booster vaccination for 305 children aged five to six years who had been primed with three doses of DTaP vaccine and then given Tdap-IPV (dTap-IPV; Boostrix™-IPV three component from GSK) versus DTaP-IPV (Tetravac™, two component from sanofi-pasteur-MSD). The most commonly reported reactions were pain at injection site in 63.6% of the Tdap-IPV and 63.2% of the DTaP-IPV and fatigue in 26.5% of the Tdap-IPV and 23.7% of the DTaP-IPV children. No major adverse events were reported and the authors concluded that both vaccines were well tolerated (26).

4.3.2.4.2. Safety with using shorter intervals for Tdap vaccines
Two studies in a total of 387 adults aged 18 – 76 years have shown that when using Tdap vaccines after Td vaccines intervals as short as three weeks do not lead to an increased risk of local reactions when compared with the traditional schedules of keeping a two year spacing (27, 28).

4.3.2.5. Febrile convulsions
A Danish study reviewed the risk of febrile convolution and epilepsy after the introduction of the DTaP-IPV-Hib vaccine on the childhood schedule at three, five and 12 months with a population-base cohort study of 378,834 children born between Jan 2003 and Dec 2008. Overall, children did not have higher risk of febrile convulsions during the seven days after each of the three primary course vaccines when compared to a reference cohort of children who had not received these vaccinations in the previous seven days. However, a high risk of convulsion was seen on the day of the first and second vaccinations (HR 6.02; 95% CI 2.86-12.65; HR 3.94; 95% CI 2.18-7.1, respectively), but not on the day of the third vaccination (HR 1.07; 95% CI 0.73-1.57) versus the reference cohort. There was no association between receipt of DTaP-IPV-Hib vaccines and the risk of epilepsy. The authors concluded that there is an increased risk of febrile convulsions (seizures) on the day of the first two vaccines in the primary course given at three and five months but the absolute risk is small. These results apply to a schedule where the first dose is given at three months of age, it is unknown if the same incidence is seen with a primary schedule started at six weeks of age (29).

4.3.2.6. Tdap safety in pregnancy
A review of the VAERS reporting data from Jan 2005 to June 2010 identified 132 reports of Tdap administered to pregnant women of which 55 (42%) described no adverse event. There were no maternal or infant deaths reported and the most frequent pregnancy-specific adverse event reported was spontaneous abortion in 22 (16.7%) of cases. The authors concluded that “during a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning patterns in maternal, infant or fetal outcomes” (30).
4.3.2.7 Rare events

4.3.2.7.1 Coeliac Disease

Using an ecological approach, a Swedish population-based incident case-referent study analysed changes over time in the national immunisation vaccination programme and the incidence of coeliac disease. Exposure information was obtained via a questionnaire and child health clinic records. The introduction of pertussis vaccine coincided in time with decreasing coeliac disease incidence rates. Vaccination against pertussis was not associated with coeliac disease (OR 0.91; 95% CI 0.6-1.4), nor was vaccination against Haemophilus influenzae or measles, mumps/rubella. A note of interest: BCG was associated with a reduced risk for coeliac disease (OR 0.54; 95% CI 0.31-0.94) (31).

4.3.2.7.2 Encephalopathy

A case report was published of a patient subsequently diagnosed with Angelman syndrome at 47 years of age who had intellectual disability and epilepsy from infancy. His condition had previously been assumed to be the result of a vaccine encephalopathy following smallpox vaccine. This case highlighted that genetic syndromes need to be considered and include a genetic work-up in alleged vaccine encephalopathy (32). Other cases previously attributed to pertussis vaccination have subsequently been diagnosed as Dravet syndrome (severe myoclonic epilepsy of infancy).

4.3.2.7.3 Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) cases were identified from the Kaiser Permanente Northern California databases from 1995 to 2006 using hospital discharge codes. There were 550 cases identified in over 33 million person years (33). There were no cases of GBS identified as occurring within six weeks of any vaccine.

4.3.2.7.4 Other

A case report from 2011 reported a three month old who developed femoral neuropathy after vaccination with DTaP-IPV-HPV-Hib vaccine (34). Good neurological recovery was made within eight weeks post vaccination.

4.4 Summary vaccine safety

Whole cell pertussis containing vaccines have a well-established safety profile. Observational data in this area raise concerns around the possibility of increased overall mortality in developing countries with female infants when given a primary course of DTwP, and this area requires further research.

The safety profile of acellular vaccines is well established. In comparison with whole-cell vaccines acellular vaccines are less likely to cause febrile convulsions and hypotonic-hypo-responsive episodes (HHE). There is a small increase in the frequency of fever, and of redness and swelling localised to the injection site from the first to the third dose in a primary infant immunisation series. Injection site reactions are more common after the fifth dose, but still significantly less frequent than with whole-cell vaccines. Adding Hib vaccine to combination vaccines that also contain DTaP increases the frequency of pain and of localised redness. There is a small increased risk of febrile convulsions on the day of administration of the first two doses in a primary course which is given at three and five months but the absolute risk is small. It is unknown is the same risk is seen with a primary course starting at six weeks of age.

Tdap booster doses appear well tolerated in all age groups. Local reactions are similar to DTaP when used as a fourth dose in children aged four to six years, and Tdap vaccines are less reactogenic compared to DTaP vaccines when used for booster doses in older children and adolescents. Reactions may be slightly more frequent in adults receiving ten yearly boosters.

Tdap booster doses can be used safely from three weeks following the delivery of a Td vaccine. Tdap vaccines appear safe in pregnancy based on VAERS data to date.

Pertussis-containing vaccines do not appear to increase the risk of Guillain-Barre Syndrome, encephalopathy/encephalitis/meningitis, paralytic syndromes, seizures, cranial nerve disorders or coeliac disease. There was a higher incidence of cough reported with the use of Tdap vaccines in VAERS data compared to Td vaccines.

Case studies have shown that examples of previously alleged vaccine encephalopathies were due to genetic syndromes and inborn errors of metabolism. A case report has been published of femoral neuropathy in an infant who received diphtheria, tetanus and acellular pertussis/inactivated poliovirus/Haemophilus influenzae type B vaccine.
5. Immuneogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective
The objective of this section is to review the most recent performance data for currently licensed pertussis-containing vaccines. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute new evidence to the current understanding of the effectiveness of pertussis-containing vaccines and evidence of their impact in populations.

5.2 Outcomes
The outcomes considered for this review are:

- Serological markers of immune response to pertussis: IgG antibodies to pertussis toxin (PT), pertactin (PRN), fimbriae (FIM2/3) and filamentous haemagglutinin (FHA)
- Vaccine efficacy and effectiveness against severe or typical pertussis: defined as three weeks or more of a paroxysmal cough with laboratory proven pertussis or clear epidemiological link
- Vaccine efficacy and effectiveness against mild pertussis: one week or more of a cough illness with laboratory proven pertussis

5.3 Review
While there is substantial variation with different vaccines in general the whole cell pertussis vaccines have efficacy estimates against typical pertussis ranging from 36% to 94% in infants and young children after three to four doses and acellular vaccines have efficacy estimates of 36% to 93% (5, 35-37).

Earlier efficacy estimates of acellular vaccines may have been inflated, both due to limitations of case definitions and methodological limitations with observer bias in early pivotal trials (38).

5.3.1 Immunogenicity
There is on-going debate around serological correlates of protection. It is generally thought that antibody titres to PRN (>7 EU/mL) and PT (66 EU/mL) in particular, are significantly associated with protection. Anti-PRN, anti-FIM 2/3 and anti-PT antibodies are used as surrogate markers of protection against pertussis for multicomponent acellular and whole-cell vaccines (5). However, Plotkin et al. caution that established efficacious one or two-component pertussis vaccines were not included in the studies to establish correlates of protection (5).

5.3.1.1 Whole-cell pertussis vaccines

Originally, it was thought that all whole-cell vaccines had similar immunogenicity, however as reported by Plotkin et al., significant differences have been noted with different whole-cell vaccines produced in different countries and in the same country at different points in time (5).

5.3.1.2 Acellular pertussis vaccines

Data on the more recent acellular combination vaccines relies on non-inferiority of immunogenicity data compared to existing licensed vaccines. For example, a recently reported study shows that a hexavalent DTaP-IPV-HepB-PRP-T vaccine containing a two component pertussis vaccine shows non-inferiority of immunogenicity based on measurement of the PRP titre compared to a licensed DTwP-HepB/Hib and oral poliovirus vaccine (21).

The immunogenicity of Tdap vaccines as a single dose in children aged four to eight years, adolescent, adults and the elderly have been assessed predominantly by measurement of serum levels of anti-PT, anti-PRN and anti-FIM. As serological correlates of protection have not been established the results are difficult to assess. Summarised results from all published research show that in all age groups, short-term antibody responses to booster vaccination were seen. In children aged four -six years, previously vaccinated with DTaP or DTwP, the immunogenicity responses to a booster dose of Tdap were similar to a DTaP or DTwP booster. Following a booster dose of Tdap in adolescents, adults and the elderly, antibody concentrations to three pertussis antigens were non-inferior to antibody levels achieved with DTaP vaccine booster. Seropositivity rates begin to decline within five years after a booster dose in adolescents and adults. The Tdap formulation with the greatest aluminium content (0.5 mg/dose) gave highest anti-PT geometric mean concentrations (GMC) supporting an enhanced immune response seen with greater amounts of this adjuvant (25).
A randomised controlled trial (RCT) conducted in Italy investigated the immunogenicity of booster vaccination in 305 children aged five to six years who had been primed with three doses of DTaP vaccine during infancy. Children were randomly assigned to receive one of two boosters: Tdap-IPV (dTap-IPV; Boostrix™-IPV, three-component from GSK) versus DTaP-IPV (Tetravac™, two-component from sanofi-pasteur-MSD). At one month post vaccination, all subjects were seropositive for anti-PT and anti-FHA. Anti-PRN seropositivity was seen in 99.3% of the Tdap-IPV groups and 60.4% of the DTaP-IPV group. The authors concluded that the reduced diphtheria antigen content Tdap-IPV was non-inferior to the full strength DTaP-IPV with respect to immunogenicity (26).

5.3.1.3 Cochrane review of combined vaccines adding Hib

A 2012 review of adding Hib to a combination vaccine compared DTP-HPV vaccination with DTP-HPV-Hib vaccines, both whole cell and acellular combinations. Twenty studies involving 5874 participants were included. There was no significant difference in serological responses to pertussis antigens, however in nine studies, poor antibody responsiveness was seen to Hib with anti-PRP measures below the assay cut-off points of 1.0 µg/ml (RR 2.14; 95% CI 1.48-3.10) (23).

5.3.1.4 Vaccination in pregnancy

A study compared antibody concentrations to five *B. pertussis* antigens (PT, PRN, FHA and FIM2/3) in umbilical cord samples from neonates born of 52 mothers who had received and 52 who had not received Tdap vaccination in pregnancy. It showed that the infants from mothers who had been vaccinated in pregnancy had significantly higher concentration of antibodies against all five antigens (PT p<0.001, FHA p=0.002, PRN p<0.001, FIM 2/3 p<0.001) (39).

Commentators have speculated, and some earlier studies have suggested, that maternal antibodies against PT interfere with the active immunity of the infant (40). However, maternal antibodies against PT have not been shown to interfere with the immune response to acellular pertussis vaccine given as a primary series starting at two months of age. Even if interference occurs, it may not be clinically relevant (41).

5.3.1.5 Vaccination of newborns

A study conducted in Australia randomised 76 newborn infants to one of three groups: aP at birth and one month, aP at birth, or control. All infants received the standard Australian Hep B at birth, followed by DTap-Hep B-Hib-IPV and PCV 7 at two, four and six months of age. By two months of age, 22/25 (88%) of the two-dose recipients had detectable IgG antibodies to PT compared with 9/21 (43%) who received a birth dose only and 3/20 (15%) of controls; geometric mean antibody titres were significantly higher in the two-dose group. At eight months of age, antibodies to PT had plateaued, however, antibodies to FHA and PRN increased with successive doses. The authors concluded that giving two doses of aP, at birth and a month of age, induces significantly higher antibody levels against pertussis antigens by two months of age than one dose at birth, without reducing subsequent pertussis antibody responses (42).

5.3.2 Efficacy/Effectiveness

5.3.2.1 Whole-cell pertussis vaccines

Efficacy estimates vary with the type of vaccine used from 36% to 94% with duration of efficacy varying up until eight years of age following a primary series (5).

5.3.2.2 Acellular pertussis vaccines

Summary data from nine acellular vaccine efficacy trials with components varying from one to six and a case definition similar to the WHO definition of ≥ 21 days paroxysmal cough with positive culture or PCR, is reported in Plotkin et al. (5). These data show a wide range of vaccine efficacy results from 36% to 93%.

Summary conclusions from Plotkin et al. are that the monocomponent vaccine, which has 50% more PT, appears to be more effective than the two-component vaccine in preventing the most severe manifestations of disease. On the other hand, the two-component vaccine appeared to be more effective in preventing mild or moderate disease. Earlier efficacy results suggested that acellular vaccines were substantially less efficacious than whole-cell, although, later studies suggested that efficacy would have been higher had a standard three-dose schedule been used and a whole-cell control group had been included (5).

The multiple component vaccines with three or more components are more effective than the known lower efficacy whole-cell vaccines, but may be less effective than the highest efficacy whole-cell vaccines (22).
It is still very difficult to assess efficacy of different vaccines due to lack of comparability between studies with respect to the range of case definitions used, variability in antigenic components and in quantities of each antigenic component. Most recently, due to the trend towards combination vaccines without thiomersal and consolidation in the vaccine industry, there are now three broadly distributed acellular pertussis vaccines: the French two-component vaccine, the Belgian three-component and the Canadian five-component vaccines. National surveillance data support the effectiveness of each of these vaccines (5).

### 5.3.2.3 Whole-cell pertussis vaccine priming and acellular boosting

Cohort data from 58,233 children born in Queensland in 1998 was used to compare the effectiveness of a primary infant series of an Australian produced DTwP vaccine with an acellular vaccine. A total of 40,694 (69.9%) of the children had received at least three doses of a pertussis-containing vaccine during their first year, and overall, 267 cases of pertussis were reported from within this cohort between 1999 and 2011. Children who had received a three dose DTaP primary course (n= 9827) had higher rates of pertussis than those who had received a three dose DTwP primary course (RR 2.53, 95% CI 1.06-6.07). Possible explanations for this finding included antigenic shifts in circulating strains of *B. pertussis* or different immune responses from acellular versus whole-cell priming, possibly via “linked epitope suppression”, whereby, the initial immune response may be locked to certain epitopes and the response to other linked epitopes on subsequent exposure is inhibited. The authors suggested that a primary course using a moderately effective DTwP vaccine may be more protective than an acellular vaccine (43).

### 5.3.2.4 2012 Cochrane Review

A Cochrane review of acellular vaccines, published in 2012, concluded that differences in trial design precluded a meta-analysis of the efficacy data. The analysis included six efficacy trials with a total of 46,283 participants and made a range of conclusions, despite not undertaking a meta-analysis (22).

Since not all whole-cell vaccines have the same efficacy, it is difficult to make comparisons with whole-cell vaccines. Acellular vaccines with three or more components are more effective than the known low-efficacy whole-cell vaccines, but appear to be less effective than the highest efficacy whole-cell vaccines in preventing whooping cough.

Comparisons across the studies suggest that multicomponent (> three component) vaccines have greater efficacy than one and two component vaccines against both typical whooping cough (21 or more days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a confirmed household member case) and mild disease (seven or more consecutive days of cough with confirmation by culture or serology). The efficacy of multicomponent vaccines varied from 84% to 85% in preventing typical whooping cough and from 71% to 78% in preventing mild pertussis disease. In contrast, the efficacy of one and two component vaccines varied from 59% to 78% against typical whooping cough and from 41% to 54% against mild disease. The five component vaccines have been shown to be superior to two component vaccines in preventing typical whooping cough. There is insufficient data to determine whether there is a clinically significant difference between three and five component vaccines.

Where data were available for the population who did not complete all schedule doses, efficacy was only marginally lower than in those who had received all vaccine doses. Studies from Japan, the US and Canada have all confirmed the effectiveness of national programmes with acellular pertussis vaccines.

### 5.3.3 Duration of protection

Immunity after vaccination was thought to be of shorter duration than after the natural disease. There is a range of evidence from German adults of frequent natural infections that challenges this concept. However, it is possible that vaccine-induced immunity is less vigorous, and vaccines appear to provide more protection against disease than against infection (5).

Cell-mediated immunity is an important function of immunity to pertussis. Infants require multiple doses of vaccine, because the duration of protection in infants is shorter than for adults. The cellular immune response to DTaP in infants is functionally and phenotypically dissimilar to the response generated by these vaccines in adults. In infants, the percentage of polyfunctional T helper 1 (Th1) and T helper 2 (Th2) cells is less than in adults and a narrower CD4 cell phenotype is observed (44). Protective immunity from wP vaccines is mediated largely by Th1 cells, whereas aP vaccines induce strong Th2 and Th17 responses, which are likely to result in shorter duration of protection (45).

Immunogenicity studies suggest that antibody responses to Tdap booster vaccines in adolescents and adults start to wane after five years (25). Duration of
protection with whole-cell pertussis vaccines wanes by 50% over a period of six to 12 years (5).

Vaccine effectiveness data for the DTaP vaccine Infanrix® (GlaxoSmithKline) suggest that following a primary course and booster dose a gradual waning of vaccine-induced protection occurs over four to six years (46).

A US study examined the incidence of pertussis in a well-vaccinated, well-defined community during a large outbreak in California (47). From a population base of 135,000 patients, a total of 171 people with a cough illness of at least seven days duration were PCR positive for *B. pertussis* from March to October 2010. There was a notable increase in cases among those aged eight to 12 years, proportionate to the interval since the last scheduled vaccine dose. The authors concluded that the current US schedule of an infant primary course of three and a booster at 15 to 18 months was insufficient to prevent outbreaks of pertussis.

The duration of protection after five doses of DTaP was assessed in California with data from 2006 to 2011 using a case-control study. The fifth dose of DTaP was given prior to the age of seven years. During the study, 277 children PCR positive for pertussis aged four to 12 years were compared with 3318 PCR-negative matched controls. Rapid waning of protection against pertussis was evident within five years of the fifth dose, and the odds of pertussis increased by an average of 42% per year the post last dose (48).

A case-control study evaluated the effectiveness of five doses of DTaP vaccine, by time since the fifth dose, in 15 Californian counties looking at all suspected, probably and confirmed pertussis cases among children aged four – 10 years in 2010. At five years or longer since the fifth dose, the estimated VE was 71.2% (95% CI 45.8 – 84.8%) (4).

Similar results were seen in Iraq, where a seroprevalence study of 595 individuals aged one to 35 years was undertaken. Iraq has high coverage with a primary series of three doses of DTwP in infancy followed by boosters at 18 months and four to six years (49). In this study, school aged children aged seven to 10.9 years had the lowest frequency of seroprotection against pertussis. Based on serological diagnosis, high rates of pertussis infection were seen among adolescent and young adults, including asymptomatic/subclinical infections.

A Turkish seroprevalence study was undertaken in 2008/2009 on 385 health children, aged 18 months to eight years, all vaccinated against pertussis with a primary course and one booster. The lowest seropositivity incidences were in the four to five year old age group (28.1%) and highest in the 16 to 18 year old age group (64.2%). The authors concluded that antibody concentrations against *B. pertussis* antigens decreased four to six years after vaccination, then increase again, which is most likely to be as a result of natural infection (50).

A recent seroepidemiology study in Singapore, undertaken between August 2008 and July 2010 on 1200 children aged one to 17 years, showed that the concentrations of antibodies to pertussis antigens declined with age. Almost half of the adolescents aged 13 to 17 years were seronegative for pertussis IgG antibody to PT, FHA and lipopolysaccharide. Overall, 15% of children who had received their last pertussis vaccination did not show measurable antibody levels within one year, and more than one third of children, who had completed the primary course, had low levels of antibody within two to three years of the last vaccination (51).

A Norwegian study used the national vaccine registry, from 1996-2010, merged with case reports to assess duration of vaccine-induced immunity. The study found that an estimated 15% of vaccinated individuals lost their immunity within five years after vaccination. The process of waning began soon after vaccination in a substantial proportion of people, but quantifying the amount of time it takes for immunity to be fully lost is difficult. The authors concluded that the acellular pertussis vaccine prevents both disease and transmission, however, this protection is short-lived and variable (52).

**5.3.4 Herd immunity**

While herd immunity has been demonstrated with pertussis vaccines, the amount of herd immunity achieved with the current pertussis vaccines remains unclear (5). There is some evidence that herd immunity contributes to the effectiveness of large-scale vaccination programmes and in doing so improves the overall effectiveness of the less efficacious vaccines such as two-component vaccines as seen in Japan (22).

Two studies, one in Norway and one in Massachusetts, US, in populations with high immunisation coverage and good surveillance, showed that the addition of a booster dose of vaccine at aged seven years provides indirect (herd) immunity by reducing transmission within age groups, but minimal prevention of transmission between age groups. Lavine et al. speculate that these findings indicate strong mixing within age groups and between parents and offspring, but weaker contact patterns elsewhere (52).
5.3.5 Effectiveness of partial courses
A Swedish study evaluated the vaccination status of all children with laboratory-confirmed pertussis among a population of approximately one million infants born between 1996 and 2007. For infants three to less than five months old the incidence of pertussis disease with at least 14 days of cough decreased from 264/100,000 for unvaccinated infants to 155/100,000 for those who had received one dose of pertussis vaccine. For infants aged five to less than 12 months the incidence of pertussis was 526/100,000 for unvaccinated, 95/100 000 for a single dose and 24/100 000 for two doses. The authors calculated that if all infants had been vaccinated exactly on schedule there would be 28% fewer pertussis cases with a 14 day cough, and 38% fewer hospitalisations due to pertussis (53). This study clearly demonstrated the effectiveness of partial courses and the importance of vaccination on time.

5.3.6 Effectiveness of adolescent schedules
Several publications have assessed the effectiveness of adolescent schedules. A pertussis outbreak in 2007 in a nursery and school in the Virgin Islands in the US was analysed, which found that there were 51 confirmed or probable cases among 499 students giving an attack rate of 10%. Overall, 41 (18%) unvaccinated students had confirmed or probable pertussis compared with two (6%) of the vaccinated students; the relative risk of pertussis associated with non-vaccination of 2.9. Vaccine effectiveness of the adolescent Tdap was 65.6%, but with wide confidence intervals (95% CI 35.8 to 91.3%, p=0.092) (54). In a similar study in Australia, conducted during a pertussis epidemic in 2008 – 2009, the incidence rate ratio among adolescents receiving Tdap was 0.6 (95% CI 0.6-0.7). A study in Western Australia, where annual school-based immunisation of each entering cohort is conducted, observed sustained decreases in pertussis incidence both in adolescents and infants younger than six months (RR 0.4; 95% CI 0.3-0.6), suggesting that when high rates of immunisation in adolescents are consistently maintained, both adolescent and infant disease is reduced (7). With similar methodology, a US study reviewed cases of pertussis reported to the CDC comparing various age groups before and after the implementation of universal Tdap recommendations for adolescents in 2005 (55). Following the introduction of the adolescent booster, there was a decline in pertussis incidence in adolescents but not in other age groups. However, there was a range of limitations in this study, including probable underestimation of cases, no data on vaccinations status to report actual VE and low Tdap coverage in adolescents (50%).

5.3.7 Effectiveness of vaccination during pregnancy and cocooning strategies
Immunising mothers and other family members in the postpartum period to protect the infants from pertussis exposure is called cocooning. The effectiveness of cocooning strategies has not been established as these strategies have been difficult to implement widely and effectiveness is difficult to measure (7).

A cross-section study in four hospitals in Houston was undertaken to evaluate the number of laboratory-confirmed pertussis cases admitted in children <6 months of age from July 2000 to December 2007, before and after the introduction of the US cocooning strategy in 2006. A total of 514 infants were admitted with pertussis, 378 pre-cocooning intervention and 136 after the intervention. During the intervention period, 67% of postpartum women received Tdap vaccine. Overall, there were identical proportions of infants born during the two study periods who were diagnosed with pertussis. The authors concluded that immunising only post-partum mothers with Tdap vaccine did not reduce pertussis illness in infants under six months of age (36).

The rationale for vaccinating in late pregnancy is based on data from the 1940s and 1950s which showed that IgG, produced by mothers who received whole cell pertussis vaccine in late pregnancy, was transferred to the infants (56). Studies since have confirmed that pertussis-specific IgG is efficiently transported across the placenta (39, 56). To date, no studies have been conducted to confirm the effectiveness of this strategy (40).

5.3.8 Vulnerable populations
There are several studies showing that children and young adults with chronic kidney disease, including those on dialysis, have sub-optimum seroconversion following immunisation with DTwP vaccines (57). It is recommended that children with chronic kidney disease are to receive pertussis-containing vaccines; protective antibodies for diphtheria and tetanus toxoids have been demonstrated in these children, although, as of early 2013, there are no data on the effectiveness of acellular pertussis vaccines (57).

A Korean study measured diphtheria, tetanus and pertussis antibody titres after antineoplastic treatment in 146 children aged three to 17 years with haematological malignancies, such as leukaemia.
and lymphoma (58). All of the children had been fully immunised for age prior to treatment. Of these patients, 62.3% had non-protective anti-PT antibody titres after treatment, and the rate of completely protective immunity was decreased by 43.6% compared with age-matched healthy populations. A decrease in pertussis immunity was significantly greater in a chemotherapy group than in a haematopoietic stem cell transplantation (HSCT) group (p = 0.039); this may have been due to more widespread use of re-immunisation after HSCT than after standard chemotherapy. The study found no significant correlation between levels of serum antibody titres with the severity of the illness, treatment or age of the patient. The authors stressed the importance of re-immunisation after completion of treatment, although there is still no clear agreement on the strategy to do this.

5.3.9 Antigenic variability

The Netherlands has experienced a steady increase in pertussis disease incidence since the introduction of acellular vaccines in 2001 to replace whole-cell vaccines; this is despite high childhood immunisation coverage. The increase in incidence started prior to the introduction of acellular vaccines and has been considered likely to be due to a decrease in the DTP dose and a change in the predominant pertussis fimbrial serotype in the vaccine from Fim3 to Fim2 (7).

In Australia, a primary course of a whole-cell vaccine has been shown to be more effective than a contemporaneous acellular vaccine course. A potential explanation for this is the possibility of antigenic shifts in circulating *B. pertussis* strains (43).

An analysis of 82 isolates of *B. pertussis* conducted in Israel in 2007-2008 showed two predominant closely related strains of pertussis with minimal DNA heterogeneity (59). Israel has high immunisation coverage rates. This study suggests that high pertussis vaccination coverage correlates with low genetic diversity of circulating strains. The authors suggest that positive selection of strains that are not included in the pertussis vaccine may occur and lead to increased pertussis disease.

A *B. pertussis* strain, deficient in pertactin (PRN), has increased in prevalence in Japan. This PRN-deficient isolate was first discovered in 1997. In isolates collected from 1990 to 2009, 33 of 121 (27%) isolates were PRN-deficient. The authors suggest the most likely explanation is vaccine-driven selection (60). In Japan, four pertussis vaccines are used currently; two contain PRN1 and two do not. Since the introduction of these vaccines in 1981, PRN1 strains have been gradually replaced by PRN2 strains, particularly since the mid-1990s, and PRN-deficient strains have significantly increased since the early 2000s. This suggests that PRN1 strains are most affected by vaccination with vaccines containing PRN1, whereas PRN2 strains producing non-vaccine type PRN are not (60).

A study from Finland analysed 85 *B. pertussis* strains identified from 2006 to 2011, and in 2011, found two non-PRN expressing isolates, for the first time, eight years after the introduction of the acellular vaccine (61).

Acellular pertussis vaccines were introduced in France in 1998, initially as an adolescent booster, and then rapidly introduced to the whole population. All *B. pertussis* and *B. parapertussis* isolates collected since 2000 have been analysed. An increasing number of isolates lacking expression of pertactin was observed, particularly in the areas of high immunisation coverage. The authors concluded that whole-cell pertussis vaccine-induced immunity leads to a more ‘monomorphic’ population, whereas acellular vaccines appear to promote evolution and selection among strains, enabling an increase in the number of circulating isolates (62).

Australia has experienced a prolonged epidemic of *B. pertussis* that started in 2008. From 2008 to 2010, 194 isolates collected from four regions showed that two newly emerged strains carrying PRN2 and PT3 had become predominant. These strains types accounted for 81% of the isolates, in contrast to an analysis of isolates from 2000 to 2007, in which they had accounted for 31%. The authors considered that these newly emerging types were the predominant cause of the prolonged epidemic. The emergence of these strains appeared to be due to the selective pressure from vaccine-induced immunity with the acellular vaccine, which has been used in Australia since 1997 (63).

The epidemiology of pertussis continues to differ between countries. It is unclear whether the changes in *B. pertussis* strain dominance are from significant vaccine pressure or a natural genetic drift (35). However, the contribution of strain variability is considered to be of less importance than the accumulation of susceptible individuals due to waning immunity among cohorts of children receiving acellular vaccines (35). Cherry has summarised the data and reports that some data suggest that decreased efficacy may be as a result of high antibody levels to PT having a blocking effect in the presence of high
antibody values to PRN or to FIM (38). It is evident that genetic changes have occurred over time in three pertussis antigens: PT, PRN and fimbriae. However, Cherry considers that there is currently no evidence to support the hypothesis that circulating B. pertussis strains are evolving to escape from vaccine-produced antibodies. His reasoning is that, as yet, this has not been observed in Denmark where a single antigen PT toxoid vaccine has been in use for approximately 15 years (3).

### 5.4 Summary of immunogenicity/efficacy/effectiveness

There are considerable challenges in measuring immunogenicity, efficacy and effectiveness due to there being no established correlates of protection, limitations of case definitions and difficulties in study methodologies. There is substantial variation between individual vaccines. Whole cell pertussis vaccines have efficacy estimates against typical pertussis ranging from 36% to 94% in infants and young children after three to four doses. For acellular vaccines, the comparable estimates of vaccine efficacy cover a similar range (36% to 93%).

Results of immunogenicity studies are difficult to interpret as serological correlates of protection have not been established. However, it is generally accepted that antibodies to PT, PRN and FIM are the best markers of immunogenicity. Booster Tdap vaccines appear to elicit good immune responses in children, adolescents, adults and the elderly and are non-inferior to DTaP vaccines. Adding a Hib component to a combination vaccine appears to reduce the Hib antibody response, but none of the other antigens.

Infants of mothers vaccinated with Tdap vaccines show good immunological responses. There is a possibility, as yet unproven, that maternally acquired antibody in infants may interfere with the active immune response to the primary course. Whether this occurs, and if so, whether it is a clinically relevant effect, is as yet unknown. Early data from vaccination of newborn infants at birth and one month of age shows good immune responses and no interference with subsequent responses to the primary course.

A primary course using a moderately effective DTwP vaccine may be more protective than an acellular vaccine primary course. The multiple component acellular vaccines with three or more components are expected to be more effective than one or two component vaccines, and the known low-efficacy whole-cell vaccines, but may be less effective than the highest efficacy whole-cell vaccines in preventing whooping cough.

The efficacy of multicomponent acellular vaccine varies from 84% to 85% in preventing typical whooping cough and from 71% to 78% in preventing mild pertussis disease. In contrast, the efficacy of one and two component vaccines varies from 59% to 78% against typical whooping cough and from 41% to 54% against mild disease. There is insufficient data to determine whether there is a clinically significant difference between three and five component vaccines. Use of Tdap vaccines in adolescents is effective but there are no accurate efficacy measurements; current estimates are that they are 66% effective against confirmed pertussis disease.

Immunity after vaccination has been thought to be of shorter duration than after the natural disease. However, this concept is being challenged. It is possible that vaccine-induced immunity is less vigorous, and/or that it provides more protection against disease than against infection.

Infants have different cellular immune responses to DTaP vaccines, which are likely to result in shorter duration of protection. In all age groups vaccine-induced antibody concentrations start to wane soon after vaccination and the degree of protection against symptomatic disease decreases gradually as the immunity wanes. Immunity to pertussis is not a binary concept (present or absent) but the degree of protection against symptomatic disease decreases gradually. Immunogenicity studies suggest that antibody responses to DTaP in children and Tdap booster vaccines in adolescents and adults start to wane after four to six years. In a population given five doses of DTaP prior to the age of seven years rapid waning of protection against pertussis is seen with the risk of pertussis disease increasing by an average of 42% per year post the last dose.

Adolescent booster disease of Tdap vaccines are effective with measures from around 66% to 79% against diagnosed pertussis but there are no accurate efficacy measurements.

While herd immunity has been demonstrated with pertussis vaccines, the amount delivered with current pertussis vaccines and schedules appears small. The lack of impact of national schedules of pertussis immunisation on the periodicity of pertussis epidemics implies that they have had little effect on the circulation of B. pertussis in the population as a whole.
Cocoon strategies have not, to date, been shown to be effective. This is likely due to logistical challenges in implementation and evaluation. Vaccination in pregnancy has been shown to be immunogenic. Passive transfer of maternal antibody to infants occurs, but as yet there is no data on the effectiveness of this strategy for the prevention of pertussis disease in infants.

Children and young adults with chronic kidney disease are at higher risk of pertussis, but there is no data on the effectiveness of pertussis vaccines in this group. Children with haematological malignancies who have received chemotherapy have lower antibody concentrations and require re-boosting with pertussis vaccines.

In several countries where acellular pertussis vaccines have been in use for a decade or more, genetic changes have occurred over time in three pertussis antigens – PT, PRN and fimbriae. Acellular vaccines may be placing evolutionary pressure and driving selection among strains, enabling a wider number of circulating isolates to increase. However, epidemiology of the disease differs across countries and whether these antigenic changes are from significant vaccine pressure or genetic drift remains unclear. The contribution of strain variability may be of less importance that the accumulation of susceptible individuals due to waning immunity.
6. Age-specific issues

6.1 Objective
This section reviews the factors that need to be considered for various age groups. Literature for age-related morbidity and mortality is included. Issues around the use of available vaccines in age groups other than infants and young children are also considered.

6.2 Review

6.2.1 Burden of disease by age
While the incidence of pertussis is increasing, it is recognised that the most recent outbreaks are particularly in adolescents and young adults, and newborns and infants too young to have completed their primary course of immunisation. Current international strategies are directed at reducing severe disease in young infants by focusing on timeliness of delivery of the current schedule vaccines, adding booster doses for preschool and school aged children and adolescents, vaccination of women in pregnancy and cocoon strategies to protect newborns (64). While herd immunity is possible, there is no international evidence to date of a universal strategy effective enough to reduce the burden of disease in young infants.

6.2.2 Protection of infants
Infants are recognised as the group as highest risk of morbidity and mortality from pertussis disease. Cocooning strategies and vaccination of pregnant women (as described in section 8.2.5) and vaccination of newborns are strategies designed to respond to this concern. As of early 2013, there is no effectiveness data on the strategies around vaccination of pregnant women, and cocoon strategies have been found to be difficult to implement and need further evaluation (65). Newborn vaccination strategies have early promising data, but further research is awaited.

6.2.3 Vaccine issues for different age groups
While pertussis disease is becoming more recognised in the elderly and immunogenicity data exists for the use of Tdap vaccines in the elderly, data on the effectiveness of pertussis vaccines in the elderly is not yet available (66).

Australian seroprevalence data from 2007 highlights reduced immunity in the 35 to 44 year old age group, which is particularly of concern, since parents of young infants are frequently within this age group (67).

6.3 Summary of age-specific issues
While pertussis disease occurs across the whole population age range the most severe disease is in newborns, and infants too young to be vaccinated or those who have not completed their primary immunisation series on time. Current strategies remain primarily focused on preventing severe disease in young infants. While the development of vaccines that can be delivered across the age range raises the possibility of herd immunity, there is no data as yet to show that such strategies are effective. Reasons for this include the limited duration of vaccine induced protection, the lower coverage that is achieved when immunising older age groups and the relatively short period of time that such strategies have been in place.
7. Vaccine options

7.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules.

7.2 Review

Internationally whole-cell vaccines remain the most widely used vaccines as they have been shown to be efficacious, inexpensive to produce, and in many regions of the world, produced locally. Most Western countries have moved to acellular vaccines due to their better safety profile (5, 37). Acellular vaccines are multicomponent, and usually consist of two to five components. There are no monovalent pertussis vaccines available internationally; all come in combination with diphtheria and tetanus toxoids, at least (37). Acellular vaccines, that contain three or more antigens overall, are considered to have better efficacy than one or two component vaccines. The five component vaccines may have better efficacy than three component vaccines (38).

7.2.1 Design of acellular pertussis vaccines

7.2.1.1 Key components

The *Bordetella pertussis* antigens that are considered to be important components to the pertussis organism virulence, and hence to vaccine design, are listed below (5):

- Pertussis toxin (PT) is generally believed to play an important role in the induction of clinical immunity. PT has both local and systemic effects, including the inhibition of monocyte and neutrophil migration, and is immunogenic. Antibodies to PT are associated with clinical immunity to pertussis and many investigators believe these antibodies to be the most important mediators of clinical protection.

- Filamentous haemagglutinin (FHA) is an immunogenic adhesion molecule that facilitates binding to monocytes and macrophages.

- Fimbriae (FIM) are filamentous protein cell-surface structures - type 2 and 3 are considered the most important - but there are as many as eight FIM found in *B. pertussis*. There is accumulating evidence regarding the role of antibodies to fimbriae in clinical immunity. The WHO recommends that whole-cell pertussis vaccines contain fimbriae types 2 and 3. There is also evidence that a change in serotype can occur during the course of clinical pertussis, in some cases, and there are unproven suggestions that this change may result from use of vaccines that contain relatively little of fimbrial agglutinogen 3.

- Pertactin (PRN) is a surface-associated protein and is highly immunogenic. There is some animal evidence that mice immunised with PRN are protected only when also immunised with FHA.

- Adenylate cyclase is a toxin that has a hemolytic effect, and acts as an anti-inflammatory and antiphagocytic factor during infection. In mouse models, PT and adenylate cyclase appear to be the two most important virulence factors.

- Tracheal cytotoxin induces paralysis and destruction of respiratory ciliated epithelium.

- The role of heat-labile toxin on the pathogenesis of pertussis is unknown, although, it is a weak immunogen.

- *Bordetella*-resistance-to-killing genetic locus, frame A (BrkA) is an outer membrane protein, similar in structure to PRN, which protects the bacterium against classical pathway complement-mediated killing.

- The role of the endotoxin, lipopolysaccharide, in pathogenesis of disease or in recovery is unclear. The endotoxin content of the whole-cell vaccines may contribute to the immediate adverse systemic and local reactions to these vaccines.

During infection, *B. pertussis* binds strongly to ciliated respiratory epithelial cells and overcomes mucosal defences. For pathogenesis of pertussis, PT and FHA are important attachment proteins, and fimbrial proteins, PRN and BrkA also participate. PT enters the bloodstream and acts systemically. PT, adenylate cyclase and BrkA have marked effects of host immune function (5).

Studies in several countries using acellular vaccines have shown that minor genetic variations in PRN and PT exist, with a shift over time in the circulating strains towards variants not represented in the pertussis vaccine used in that community. Further studies are needed on this topic. Refer to Section 5.3.9.
7.2.1.2 Vaccine manufacturers/producers

There has been considerable change in the vaccine industry recently, some long established companies have merged or acquired new start-up companies. As of early 2013, the major international vaccine manufacturers are Baxter International, Crucell NV, GlaxoSmithKline, Merck and Co, Novartis, Sanofi Pasteur and Pfizer. The key characteristics of the commonly available acellular pertussis vaccines are given in Table 3.

Table 3. Key characteristics of the most common international acellular pertussis vaccines (adapted from Plotkin et al.)

<table>
<thead>
<tr>
<th>Manufacturer or distributor</th>
<th>Vaccine</th>
<th>PT µg/dose</th>
<th>Diphtheria toxoid limit of Flocculation units per dose</th>
<th>Tetanus toxoid limit of Flocculation units per dose</th>
<th>FHA µg/dose</th>
<th>PRN µg/dose</th>
<th>FIM µg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur (Canada)</td>
<td>Tripacel; Daptacel</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Sanofi Pasteur (Canada)</td>
<td>HCPDT</td>
<td>20</td>
<td>20</td>
<td>3</td>
<td>5</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Sanofi Pasteur (France)</td>
<td>Triavax; Triaxim</td>
<td>25</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Sanofi Pasteur (USA)</td>
<td>Tripedia</td>
<td>23.4</td>
<td>23.4</td>
<td>—</td>
<td>—</td>
<td>6.7</td>
<td>5</td>
</tr>
<tr>
<td>Baxter Laboratories</td>
<td>Certiva</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Chiron Vaccines</td>
<td>Acelluvax</td>
<td>5</td>
<td>2.5</td>
<td>2.5</td>
<td>—</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Infanrix</td>
<td>25</td>
<td>25</td>
<td>8</td>
<td>—</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Japan NIH</td>
<td>NIH-6</td>
<td>23.4</td>
<td>23.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Japan NIH</td>
<td>JNIH-7</td>
<td>37.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GlaxoSmithKline*</td>
<td>SKB-2</td>
<td>25</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Wyeth Pharmaceuticals</td>
<td>Acel-Imune*</td>
<td>3.5</td>
<td>35</td>
<td>2</td>
<td>0.8</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Key: FHA - filamentous haemagglutinin; FIM - fimbrial proteins; HCPDT - hybrid component pertussis-diphtheria-tetanus vaccine; PRN - pertactin; PT - pertussis toxin.

Trade names (most common trade names, if multiple names exist): HCPDT is the “hybrid” formulation of Tripacel.
NIH – National Institutes of Health; 1. formerly SmithKline Beecham Biologicals; * discontinued 2001

7.2.2 New vaccine possibilities

Aluminium adjuvanted acellular pertussis vaccines generally mediate their protective immunity via antibody generation through Th2 and Th17 pathways, thereby inducing shorter duration responses and possibly less effective vaccines. Commentary has called for new generation acellular vaccines that induce more Th1 responses, to extend the duration of protection, create more effective herd immunity and reduce the need for boosters.

Clark et al. comment that the regulatory pathways for approval of new or modified pertussis vaccines remain a significant hurdle – it is not possible to undertake RCTs now that all countries vaccinate with either traditional whole cell or acellular pertussis vaccines, and immunogenicity markers of protection have not been established.

7.2.2.1 New adjuvants

In 2012, a commentary article discussed the limitations of the current adjuvants in the acellular pertussis vaccines. Aluminium phosphate and aluminium hydroxide skew the immune response towards an antibody-driven dominated response, which may be limiting vaccine effectiveness. Alternative adjuvants are being considered, such as a triple-adjuvant formulation from Scott Halperin and colleagues at the Canadian Center for Vaccinology in Halifax, that focuses more on the cell-mediated immune responses.

7.2.2.2 Vaccines for newborns

Young infants are the age group most at risk of severe morbidity and mortality from pertussis. One approach is to design a vaccine for newborns. Vaccines do not elicit strong immune responses in young infants so vaccine technology will need to overcome this challenge before this strategy can be considered.
A French team have designed a live attenuated pertussis vaccine, designated BPZE1, which is to be given intranasally to newborns in the first few days of life (69). BPZE1 completed a phase I trial in 2011 in which it was found to be safe in adults (70).

7.3 Summary for vaccine options

Acellular vaccines are multicomponent, usually consisting of two to five components. There are no monovalent pertussis vaccines available internationally - all pertussis vaccines are in combination with diphtheria and tetanus toxins at least (37). Acellular vaccines that contain three or more antigens overall are considered to have better efficacy than one or two component vaccines (38). The five component vaccines may have better efficacy than three component vaccines. As of 2013, the major international manufacturers are Baxter International, Crucell NV, GlaxoSmithKline, Merck and Co, Novartis, Sanofi Pasteur and Pfizer.

The key antigenic components of the *B. pertussis* organism include important attachment proteins, pertussis toxin (PT), which also enters the bloodstream and has systemic effects, and filamentous haemagglutinin (FHA). Other important components include fimbrial proteins, PRN and BrkA.

There are significant hurdles to the development of new vaccines. However, in view of the short duration of immunity in particular, new possibilities need to be explored to create more effective vaccines with longer duration. This includes trialling different adjuvants and vaccines tailored to the newborn.
8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of pertussis vaccine on the childhood immunisation schedule, adult schedules, pregnancy and cocoon strategies.

8.2 Review

The increased recognition of pertussis in older persons, both adolescents and adults, and cost-effective studies have stimulated international interest in approaches to boosters.

The US have reported an increase in pertussis disease since 2000 in children aged seven to 10 years, the first birth cohorts to have received primary acellular vaccines, and the Australians have reported an increased incidence of pertussis among three year olds following discontinuing their fourth acellular vaccine given at 18 months of age, suggesting rapid waning of immunity from the primary series when acellular vaccines are used (35).

WHO recommendations in 2011 were for a three-dose primary course with the first dose administered at six weeks, subsequent doses four to eight weeks apart at age 10-14 weeks, and 14-18 weeks with completion of the primary course by six months of age (1). A booster dose is recommended for children aged one to six years, preferably during the second year of life. Vaccination is recognised as being able to prevent pertussis in adolescents and adults, but it was felt there was insufficient evidence to support the addition of booster doses in these age groups in order to achieve the primary goal of reducing severe pertussis in infants. Only acellular pertussis vaccines are recommended in ages six years and older. Further studies were awaited prior to recommendations for maternal vaccination and the relative merits of neonatal vaccination versus maternal vaccination. Vaccination of healthcare workers to prevent nosocomial transmission to infants and immunocompromised persons was considered likely to be cost effective if high coverage rates can be obtained.

Discussions are on-going internationally around the ideal vaccination pertussis immunisation schedule. All immunisation strategies continue to aim to prevent severe disease in infants. Universal adult and/or adolescent booster strategies aim to reduce morbidity in vaccinated populations and create herd immunity, whereas pregnancy vaccination and cocoon booster strategies, for selected individuals, such as parents and caregivers of infants, and vaccination of healthcare workers, aim at further reducing transmission to infants (71).

Recent commentary from the US recommends immunising all members of the population with extended pertussis immunisation of children, adolescents and adults (72). Cherry recommends that as there is circulating pertussis in all age groups there is a need to universally vaccinate all age groups at frequent intervals (38). However Norwegian commentary recognises the complexity of a system where the duration of immunity is short lived in the vaccines, there is little transmission between age groups so herd immunity may be fairly restricted to within cohorts, and vaccinating teenagers and adults may potentially erode existing immunity in adults of child bearing age and possibly increase disease circulation in this age group (52).

The Global Pertussis Initiative (GPI), an expert scientific forum, was formed in 2001 in response to the rising rates of pertussis internationally, and part of its brief is to focus on developing effective immunisation strategies for pertussis control (12). The GPI has hosted two meetings in the Asia-Pacific region, in Singapore in December 2006 and Hong Kong in February 2011: New Zealand was part of the 22 delegates from 12 countries. The 2011 recommendations took a focus on strategies to reduce transmission to infants, to develop broad immunity within a population and to reduce morbidity and mortality in all age groups. The recommendations from this initiative include:

- Reinforcement and/or improvement in current infant and toddler immunisation strategies
- Selective immunisation of childcare workers
- Selective immunisation of healthcare workers
- Cocoon immunisation (selective immunisation of new mothers, family and close contact of newborns)
- Universal pre-school booster doses (at four to six years of age)
- Universal adolescent immunisation
- Universal adult immunisation
The initiative notes that not all strategies should be weighted evenly in all geographic locales. The primary focus should be on reinforcing and improving immunisation rates in infants and toddlers. NZ recommendations based on this advice were to focus on improving coverage of all pertussis scheduled vaccines, 10-yearly vaccination of those who work with neonates and young children, and to pilot the promotion of cocoon immunisation around newborns. Universal adult immunisation and immunisation of childcare workers were not supported at this forum in 2011 (73).

8.2.1 Booster doses

The Netherlands have had a high incidence of pertussis since an outbreak in 1996. The introduction of an acellular booster dose at four years of age in 2001 has not changed this pattern (10) and cases of disease in fully immunised school children are being reported (7). Recent research suggests that Dutch children primed with the whole cell pertussis vaccine show good memory based B lymphocyte boosting and good cellular memory immune response upon a second acellular booster at nine years of age suggesting second booster at adolescence might improve long term immunity against pertussis (74).

Modelling based on their epidemiological data from 1996 to 2000 has been undertaken in the Netherlands (75). Their current schedule is a primary course at two, three and four months and booster doses at 11 months and four years. This model concluded that the optimal age for an additional booster dose in the 10 to 15 year age range and implementation of this dose would reduce both symptomatic and asymptomatic infections. However, the incidence of symptomatic infections in older age groups is expected to increase.

Studies are generally in favour of pertussis booster vaccination, although, an ideal cost-effective strategy has not yet been identified (76).

8.2.2 Schedules for adolescents

A number of countries recommend routine vaccination of adolescents with reduced-dose acellular vaccines (Tdap) in an effort to directly reduce disease in adolescents and adults and to indirectly reduce disease in infants. Refer to 5.3.5.

A review of the worldwide evaluations of pertussis booster vaccination looked at thirteen cost-effectiveness, cost-utility and economic impact models. Overall the most frequently studied strategies were adolescent boosters, adult boosters and cocoon strategies. All studies evaluating adolescent boosters suggested this was cost-effective or cost-saving compared with no booster vaccination (71).

Based on the results of a large cohort Norwegian study, the authors concluded that as the age mixing-patterns lead to little contact between teenagers and infants in this community they suggest that teenager booster vaccine campaign would likely provide strong protection for teenagers but little protection for infants (52). This lack of mixing of age bands may vary between countries and within different subgroups depending on issues such as family and household sizes.

8.2.3 Schedules for adults

The Netherlands experiences have shown that improvements in the childhood vaccination programme have reduced pertussis disease in childhood, but not affected the increase in adolescent and adult pertussis (7). There is even speculation that the high circulating rates of pertussis in adolescents and adults may even have limited the effectiveness of paediatric vaccination (10). Adult boosters have been suggested as a response, however this may reduce the opportunity for natural boosting which appears to take place frequently in the adult population and results in relatively mild adult infections (10). In view of the uncertainty some current international commentary favours focusing more on cocoon strategies to protect the most vulnerable, and the development of improved vaccines which have longer lasting immunity, and less on adult strategies with the current vaccines (10).

As previously mentioned in section 8.2.2, Millier et al. reviewed 13 cost-effectiveness, cost-utility and economic impact models. In general, economic evaluations favour pertussis booster vaccination in adults and adolescents, but there are divergences around which age groups to vaccinate and the exact epidemiological conditions under which vaccination would be cost effective. Furthermore, the fact that the epidemiology of pertussis varies so much over time, between countries and within countries creates further uncertainty. Millier et al. commented that “there remains uncertainty concerning the optimal vaccination policy to adopt, and further cost-effective studies should explore and compare a wider range of strategies” (71).

In 2008 and 2009, the European expert advisory group, Consensus on Pertussis booster vaccination in Europe initiative (COPE), met to discuss the evidence. It concluded that as immunity both from disease and vaccination is not long lasting, timing of booster doses
8.2.4 Herd immunity

There is uncertainty regarding the degree of indirect protection provided by pertussis containing vaccines (71). The fact that booster vaccination may generate herd immunity seems to be well accepted, despite limited data (71).

Modelling based on epidemiology can estimate how much additional vaccination coverage is required to obtain herd immunity effects. For example, a herd immunity assessment in Catalonia Spain showed that additional pertussis vaccination coverage of 25-46% in school-aged children, adolescents and adults would produce effective herd immunity (78).

8.2.5 Pregnancy and Cocoon Strategies

8.2.5.1 Pregnancy Vaccination

Antibodies to PT and FHA readily cross the placenta and are found in concentrations in infant sera as high as in maternal sera. The half-life of transplacental antibodies for the newborn is approximately six weeks. The use of maternal vaccination to confer passive immune protection to the infant has been well shown (5). However, there are concerns that high pre-existing pertussis antibody levels in young infants suppress the immune responses to the infant schedule vaccines; this is expected to be less of a concern with acellular vaccines than with whole-cell vaccines (5). Further research is needed and clinical studies are underway to evaluate the impact of safety, infant antibody levels and infant vaccine responsiveness.

8.2.5.1 Cocoon Strategies

There are a range of definitions of cocoon strategies: at different times, cocooning has been defined as vaccination of both parents immediately after birth of the child, vaccination of mothers after birth plus another adult caregiver after the first child, or vaccination of primary caretakers of infants less than one year of age (71). Data on transmission of pertussis within households was collected in a nationwide prospective study performed in the Netherlands between February 2006 and December 2009 (79). The study utilised the transmission rates of pertussis in 140 households with a clinically confirmed infection to model the effectiveness of using cocoon strategies. They showed that overall transmission rates in households were high, with mothers being the most infectious, other household members less so, and fathers, the least. Targeted vaccination of mothers would be expected to halve the probability of infant pertussis infection. While vaccination of siblings would be less effective in preventing household transmission, it may be effective overall, because siblings frequently introduce an infection into the household. Vaccination of fathers is expected to be the least effective strategy. The authors concluded that selective vaccination of those in a household with a young infant has the potential to substantially reduce disease burden of pertussis by reducing transmission within the household.

A modelling study, using computer simulations to test the potential impact of six immunisation strategies on the burden of pertussis in young infants, included 1) routine infant primary course at two, four and six months with boosters at 12-15 months and four to six years; 2) routine childhood vaccines and Tdap booster at 12 years of age; 3) routine childhood vaccines and cocooning of infants by immunisation of household contacts; 4) routine childhood vaccines plus adolescent immunisation at 12 years of age and cocooning and 5) routine infant course plus Tdap of adolescent and adults at 10 yearly intervals and cocooning (80). These simulations showed that the incidence of typical pertussis in young children 0-23 months decreased with all strategies, but significant reductions in the very young children were projected only with the cocoon strategy. On the basis of this the US CDC recommended universal ‘cocooning’ in 2006.

A study in Canada used surveillance and epidemiological data from 2000 to 2009, to model the effectiveness of six immunisation strategies (81). The proportion of infant pertussis attributed to a parent was estimated at 35%, and adult VE estimated at 85%. At least one cyclical peak was included in the data. The number needed to vaccinate (NNV) for parental immunisation was at least one million to prevent one infant death, approximately 100,000 to reduce one ICU admission, and greater than 10,000 to reduce one hospitalisation. The authors concluded, that in the context of low pertussis incidence, the parental cocoon programme would be inefficient and resource intensive for the prevention of serious infant outcomes.
They advised of the importance of considering local epidemiology before giving consideration to cocoon strategies.

Recent editorial commentary on cocoon strategies by Libster and Edwards suggests that the cost and logistical barriers to widespread implementation of cocooning are major limitations and suggest that cocooning is not the best overall approach to reduce the burden of pertussis in young infants (72). Gall et al. consider that the cocooning strategy has several serious problems – firstly, that the concept was never field tested prior to being recommended in the US in 2006; secondly, that the research shows that over 50% of disease in neonates is from non-identifiable sources; thirdly, the challenges around who can fund and administer for a whole family group if they are easily located; and finally, the challenge ensuring that vaccination is implemented at least two weeks prior to being in contact with the infant (82).

Vaccination of pregnant women may be a more effective strategy than cocoon vaccination, and is considered safe (82). Further studies are awaited to clarify whether the concerns regarding maternally derived antibodies interfering with the infant’s immune response to the primary course of pertussis vaccine applies with the currently used acellular vaccines. This is of particular relevance to NZ where the first dose of the primary course is administered at six weeks of age.

In June 2011, the ACIP revisited their recommendations for the prevention of pertussis in infants. They observed that, despite the five years since recommending cocooning, there had been very poor uptake; most hospitals had ignored it completely and parental awareness was essentially still very low. They concluded that postpartum vaccination is a “suboptimum national strategy to prevent infant pertussis morbidity and mortality” and that “vaccinating pregnant women in the late second or third trimester is acceptable and safe for both mother and fetus.” They noted that the programme cost of vaccinating during pregnancy is the same as post-partum, and there were not sufficient concerns about the blunting of the infant immune response not to recommend maternal vaccination during pregnancy (82).

Following meetings in 2008 and 2009, the European advisory group, COPE, recommended that cocoon strategies should continue and be further promoted until immunisation coverage in adults is sufficient to induce herd protection. Furthermore, in addition to targeting close family members, opportunities to provide Tdap boosters with other vaccines should be considered such as travel vaccination, occupational health and in place of tetanus prophylaxis for wound management.

8.2.6 Newborn vaccination

Administration of aP vaccines at birth and age one month have been shown to induce antibody responses in infants at the age of two months and not interfere with the response to the primary course (42). As of early 2013, WHO does not currently recommend neonatal vaccination until the results of further studies are available (1).

8.3 Summary of schedule options

Discussion is on-going internationally about the ideal vaccination programme for pertussis. Options and objectives for each option are listed below based on a summary of Pertussis Strategies adapted from COPE recommendations 2011 (77).

• Reinforce high coverage and timely delivery of the primary infant immunisation series.
  Primary objective is to reduce disease in infants; secondary objective is to reduce spread in infants and toddlers.

• Preschool or school boosters
  Primary objectives are to reduce disease in this age group and reduce spread to infants.

• Universal adolescent booster
  Primary objective is to reduce transmission to infants. Secondary objective is to reduce disease in adolescents and young adults and develop her immunity.

• Healthcare worker vaccination
  Primary objective is to reduce transmission to patients; secondary objective is to reduce disease in healthcare workers.

• Cocoon vaccination
  Primary objective is to reduce transmission to infants; secondary objective is to reduce disease in adults.

• Childcare vaccination
  Primary objective is to reduce transmission to infants; secondary objective is to reduce disease in staff.

• Universal adult vaccination
  Primary objectives are to reduce transmission to infants and reduce disease in children. Secondary objective is to reduce disease in adults and develop herd immunity.
Universal adult and/or adolescent booster strategies aim to reduce morbidity in vaccinated populations and to develop herd immunity, whereas pregnancy vaccination and cocoon booster strategies for selected individuals, such as parents and caregivers of infants, and vaccination of healthcare workers aim primarily at reducing transmission to infants.

Economic evaluations in general favour pertussis booster vaccination in adults and adolescents, but there are divergences around which age groups to vaccinate and the exact epidemiological conditions under which vaccination would be cost effective. Furthermore, the fact that the epidemiology of pertussis varies so much over time, between countries and within countries creates further uncertainty. Overall, the most frequently studied strategies were adolescent boosters, adult boosters and cocoon strategies. All the studies that evaluated adolescent boosters suggested this was cost-effective or cost-saving compared with no booster vaccination.

There is speculation that the high circulating rates of pertussis in adolescents and adults may have limited the effectiveness of paediatric vaccination. Adult boosters have been suggested as a response; however, this may reduce the opportunity for natural boosting which appears to take place frequently in the adult population and results in relatively mild adult infections.

In view of the uncertainty with adult vaccination strategies, some current international commentary favours focusing more on pregnancy and cocoon strategies to protect the most vulnerable, and the development of improved vaccines which have longer lasting immunity, and less on adult strategies with the currently available vaccines.

Targeted vaccination of pregnant women would be expected to halve the risk of infant pertussis infection. Other potential cocooning strategies include using the birth of a child as a reminder to ensure all siblings are immunised, and the immunisation of other close caregivers such as fathers. The cost and logistical barriers to widespread implementation of cocooning are major limitations.

While vaccination of siblings would be less effective in preventing household transmission, it may be effective overall, because siblings frequently introduce an infection into the household. Vaccination of fathers is expected to be the least effective strategy. In the context of low pertussis incidence, cocoon strategies are likely to be particularly inefficient and resource intensive for the prevention of serious infant outcomes. The cost and logistic barriers to widespread implementation of cocooning are major limitations and suggest that cocooning is not the best overall approach to reducing the burden on pertussis in young infants.

Vaccination of pregnant women may be a more effective strategy. The use of maternal vaccination to boost infant immune response is well established and considered safe. However, further studies are awaited to clarify whether the concerns regarding maternally derived antibodies interfering with the infant’s immune response to the primary course of pertussis vaccine applies with the currently used acellular vaccines.
9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data for currently licensed pertussis vaccines with respect to potential implementation issues in the NZ context. This includes the effect of pertussis-containing vaccines on the universal childhood schedule, co-administration, specific vulnerable population groups and adult schedules. The focus is on use of pertussis vaccines in the universal childhood programme, and for the adult populations, and consideration is given to any recent updates to the use of Tdap vaccines in adult schedules.

9.2 Review

9.2.1 Concomitant delivery

Whole cell and acellular vaccines are routinely delivered with polio, Hib, conjugate pneumococcal, hepatitis B, MMR and varicella vaccines. Most studies have found that the vaccine reactions after multiple simultaneous vaccinations are only slightly greater than would be expected for the most reactogenic vaccine alone. Reduced immunogenicity to the pertussis antigens has occasionally been seen when given in combination or association with another vaccine, no data exists to suggest that this decreases the efficacy of pertussis vaccines (5). Combination vaccines, including acellular pertussis, have been shown to reduce the immunogenicity of the Hib component when measuring the anti-PRP antibody geometric mean titres (83). Non inferiority of antibody response has been demonstrated with toddler booster doses at 18 months when using a hexavalent vaccine with an acellular pertussis component as compared to a pentavalent combination (84).

Tdap vaccine can be co-administered with IPV, or in combinations. Concomitant delivery with hepatitis A vaccine, tetravalent meningococcal conjugate vaccine, seasonal influenza vaccines and HPV vaccines are safe and effective (25). Concomitant delivery of meningococcal C tetanus toxoid conjugate vaccine with DTaP-HPV-IPV/Hib vaccines and PCV13 in the infant schedule at two, four, six and 15 months has been shown to be immunogenic for all antigens with a good safety profile (85). Similar results are seen with PCV10 (Synflorix®) (86). Co-administration of the rotavirus vaccine Rotarix™ and Infanrix-hexa™ does not affect immune responses (46).

Combination acellular pertussis vaccines can be safely delivered concomitantly with a multicomponent protein meningococcal B vaccine (4CMenB) producing good immunogenicity responses as a primary course of two, three and 4 months (87).

9.2.2 Catch-up programmes

The WHO recommends that children who have not been vaccinated should receive three doses of a pertussis-containing vaccine with intervals of two months between the first and second dose, and a six to 12 month interval between the second and third doses (1).

9.2.3 High risk groups

Asthma is associated with an increased risk of pertussis. An analysis of a 223 positive cases in a pertussis outbreak in Maine, US showed that, after adjusting for other variables, a history of asthma before the index date of pertussis was significantly associated with the risk of catching pertussis (OR 1.73, p=0.013) (88).

A study on immunoglobulin responsiveness in children receiving chemotherapy for acute lymphoblastic leukaemia showed significant loss of antibodies to vaccines. Levels of antibody against diphtheria, tetanus and pertussis all declined during the treatment period. Reduced treatment regimens result in higher specific antibody levels than intensive treatment. Observed antibody concentrations against pertussis, however, showed only small decline compared to large declines for diphtheria and tetanus. It is likely that this is a reflection of the rapid antibody decay seen after pertussis vaccination resulting in lower antibody concentrations prior to starting chemotherapy than with tetanus or diphtheria. The authors recommend reduced chemotherapy regimen for childhood acute lymphoblastic leukaemia and the need for revaccination (89).

A case study reported a pertussis infection in a two month old as being a plausible trigger for an atypical Haemolytic Uraemic Syndrome (HUS) case where there was no E. coli involvement (90). Pertussis infection has not previously been identified as a trigger for HUS.
9.2.4 Adverse reactions

The Joint Task Force of Practice Parameters (JTFPP) recently published practice parameters for adverse reactions to vaccines. This group represents the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology. Listed below are some of its recommendations pertinent to pertussis-containing vaccines (91):

• Anaphylactic reactions to vaccines should be evaluated with skin test to the vaccine and its components. If the skin tests are negative, subsequent doses can be administered in the usual manner but under observation. If the skin tests are positive, the vaccine can be administered in graded doses under observation.

• Measuring levels of IgG antibodies to the immunizing agents in a vaccine suspected of causing a serious adverse reaction to determine whether they are at protective levels can help determine whether subsequent doses are required.

• IgE mediated reactions to vaccines are more often caused by additive or residual vaccine components, such as gelatin, rather than the microbial immunizing agent itself.*

Based on the data from two published studies, increased reactogenicity is no longer considered to be a concern in giving of Tdap vaccines within two years of previous receipt of a tetanus/diphtheria containing vaccine (37).

9.2.5 Interchangeability

One published study, to assess changing from Tripedia™ to Infanrix™ during the primary series, found no adverse effect on safety or immunogenicity (92). In contrast, a recently published Canadian RCT evaluated a mixed primary infant schedule in 127 infants between May 2010 and January 2011. The double-blinded study randomised infants to either two doses of Pediacel™ (DTaP-IPV-Hib) at two and four months followed by one dose of Infanrix™-IPV/Hib (DTaP-IPV/Hib) at six months, or one dose of Infanrix™. IPV/Hib at two months followed by two doses of Pediacel™ at four and six months. Anti-pertussis toxin and anti-fimbriae 2 and 3 responses were statistically significantly higher in the second gr4oup than the first. Higher levels of filamentous haemagglutinin antibody were seen in the first group, and no difference in pertactin responses between the groups. Irritability and crying were common in the first group, as were overall systemic reactions after the third dose. The authors concluded that mixed schedules have different immunogenicity and reactogenicity; therefore it is preferable to complete the primary infant three-dose series with the same vaccine rather than considering the vaccines as interchangeable (93).

Interchangeability of pertussis containing vaccines for the toddler booster dose has been shown (94, 95). Despite limited data the ACIP has not felt there are expected to be any concerns about using different brands of acellular containing vaccines, following a primary course given in a different brand.

9.2.6 Is eradication possible?

In principle, pertussis can be eradicated since humans are the only reservoir for B. pertussis. However, interruption of transmission in a region has not yet been demonstrated. Plotkin et al. comment that “global eradication, although perhaps possible, is clearly many years away” (5).

9.2.7 Immunisation coverage

A review of integration of immunisation and other primary healthcare services in developing countries found a range of effective strategies for improving the delivery of other preventative and primary care services while maintaining good immunisation service delivery and high coverage (96).

9.2.7.1 Preterm and under-immunisation

Preterm infants are at particularly high risk of pertussis. A US retrospective cohort study reviewed immunisation status for all 668 infants discharged from six neonatal intensive care units in Northern California (97). Of these infants over half were not up-to-date at discharge. If all recommended vaccines had been given at the time of immunisation, the percentage of those up-to-date at discharge would have increased from 51% to 66%. Infants who had undergone abdominal, thoracic or neurological surgery were most likely to be under immunised. The authors speculated this may be due to multiple providers caring for a single infant, concerns about the effects of immunisation delaying surgery, or provider being more focussed on the surgical disease than the preventative needs. Infants with bronchopulmonary dysplasia or apnoea had higher rates of immunisation. They concluded that performance initiatives should consider including the evaluation of immunisation for infants at discharge as a potential target for quality assessments.
9.2.7.2 Pregnancy and cocooning
A study by Healy et al. providing Tdap vaccine to medically underserved, uninsured women postpartum in Houston, USA through a standing order protocol obtained 96% vaccination on women with no contraindications (98).

In summarising attitudinal and coverage data, Lessin et al. concluded that overall parents and family members are very receptive to be immunised to protect their infants from pertussis and other vaccine preventable diseases when they understand the issue (99).

9.2.7.3 Occupational vaccination
A French survey of 250 junior doctors (medical residents) in Paris revealed that only 65% were vaccinated with the recommended vaccine for pertussis (NB these results should be interpreted with caution as the questionnaire had only a 26% response rate) (100). The reported major reason for poor vaccination was “lack of time”. The authors concluded that improving vaccination strategies in this group needs to focus more attention on this issue.

Australian guidelines recommend pertussis vaccination for staff in childcare settings, although there is no regulation or licensing of this (101). A New South Wales survey of 319 out of 325 childcare centres in one region found that fewer than half of all the staff were vaccinated. The authors highlighted the importance of centre directors knowing the vaccination status of staff and the implementation of immunisation practices in accreditation or licensing processes.

9.2.7.4 Mandatory vaccination
A review of recommended and compulsory vaccination strategies in developed countries concluded that countries that have already succeeded in implementing sustainable and high rates of update with a voluntary approach, do not feel the need to implement mandatory approaches, which is more likely to be used in places with low coverage (102).

9.2.8 Pertussis testing and possible contamination
Pertussis diagnosis is now routinely PCR based in many countries. However, issues with contamination may arise. Two nasal wash specimens from a paediatrician’s office in the US tested positive for pertussis DNA; these were confirmed to be amplifiable DNA from the acellular pertussis containing vaccines Adacel™ and Pentacel™ (103). The contamination was found on the hands and nose of two healthcare professionals after they had administered the vaccine to multiple children. The authors hypothesised that aerosol transmission could give false positive PCR results.

A presumed outbreak of pertussis in a laboratory in 2008/2009, diagnosed by PCR and characterised by atypical cases, was shown to be as a result of specimen contamination with B. pertussis DNA from vaccines that occurred at the point of collection in clinics (104).

9.2.9 Bordetella parapertussis
With the more widespread use of PCR to diagnose pertussis, the diagnosis of Bordetella parapertussis has been shown to be more common than previously thought. In the US, nasopharyngeal samples were collected during a three year period (2008-2010) from patients with cough illnesses. PCR analysis showed that, of the 9.5% of samples that were positive for either B. pertussis or B. parapertussis, 14% were positive for B. parapertussis. A few samples were positive for both bacteria (105). Acellular vaccines are not expected to have a significant effect against B. parapertussis (38).

9.3 Summary for implementation issues
Most studies have found that reactions after multiple simultaneous vaccinations are only slightly greater than would be expected for the most reactogenic vaccine alone. Reduced immunogenicity to the pertussis antigens has occasionally been seen when given in combination or association with another vaccine, but no data exists to suggest that this decreases the efficacy of pertussis vaccines. There are no concerns with concomitant delivery with other current NZ schedule vaccines. Concomitant delivery has been shown to be safe and effective alongside meningococcal C conjugate tetanus toxoid vaccines and a multicomponent protein meningococcal B vaccine (4CMenB).

Recent recommendations concerning previous adverse reactions recommend that those who have had previous anaphylactic reactions to the vaccine or any component should be evaluated with skin test to the vaccine and its components. Measuring levels of IgG antibodies to the antigen in the vaccine suspected
of causing a serious adverse reaction to determine whether they are at protective levels can help determine whether subsequent doses are required.

There are no concerns about increased reactogenicity with giving of Tdap vaccines within two years of previous receipt of a tetanus/diphtheria containing vaccine.

It is not recommended to change the vaccine used for a primary course, however interchangeability for the booster dose appears to be safe and effective.

Strategies for improving immunisation coverage include: a focus on improving vaccination to high risk neonates via better integrated service and performance initiatives for neonatal units; protocols improvements, such as the use of standing orders to increase postpartum vaccination in medically underserved women; a stronger focus on vaccination of staff in childcare settings via utilisation of accreditation or licensing processes and the education of centre directors; and to improve vaccination in junior doctors by recommending focussed strategies to overcome this group’s concerns around ‘lack of time’ to obtain vaccination. Mandatory vaccination approaches do not appear to be necessary in countries with existing high immunisation coverage.

Pertussis testing with PCR can be contaminated with pertussis vaccine DNA. *B. parapertussis* is becoming more widely recognised with the use of PCR diagnostics. Current vaccines are not expected to be effective against *B. parapertussis*.

It is recommended that new case definitions for pertussis, which recognise the different clinical presentations in three different age groups, i.e. zero to three months, four months to nine years, and 10 years and older, are applied to assist with better sensitivity and specificity in diagnosis.
10. International policy and practice

10.1 Objective

The objective of this section is to summarise some of the important international experience on the use of acellular pertussis vaccines and position statements and policies from countries with comparable populations to NZ.

10.2 Review

Table 4. Pertussis Immunisation Schedules as of 2006, adapted Chapter 23 Plotkin et al. (5)

<table>
<thead>
<tr>
<th>Country</th>
<th>Primary vaccination schedule</th>
<th>Paediatric boosters</th>
<th>Adolescent-adult boosters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global: most countries in Africa, the Middle East, and Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPI Programs</td>
<td>6, 10, 14 weeks: DTwP</td>
<td>18 mo to 4yr: DTwP</td>
<td>No</td>
</tr>
<tr>
<td><strong>North America</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>2, 4, 6 mo: DTaP-IPV-Hib</td>
<td>18 mo: DTaP-IPV-Hib; 4-6yr: DTaP-IPV</td>
<td>14-16yr: Tdap (or Td)</td>
</tr>
<tr>
<td>United States</td>
<td>2, 4, 6 mo: DTaP or DTaP-IPV-HB</td>
<td>15-18 mo: DTaP or DTaP-Hib; 4-6yr: DTaP</td>
<td>11yr: Tdap</td>
</tr>
<tr>
<td>Mexico</td>
<td>2, 4, 6 mo: DTwP-Hib-HB</td>
<td>2 and 4yr: DTwP</td>
<td>No</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>3, 5, 7 mo: DTaP-IPV-Hib-HB</td>
<td>16 mo: DTaP-IPV-Hib-HB; 7yr: Td-IPV</td>
<td>13-16yr and decennially: Tdap</td>
</tr>
<tr>
<td>Belgium</td>
<td>2, 3, 4 mo: DTaP-Hib-IPV-HB</td>
<td>13-18 mo: DTaP-Hib-IPV-HB</td>
<td>14-16yr: Tdap (catch-up)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>9 weeks, 3 and 4 mo: DTwP/Hib</td>
<td>18-20 mo and 5yr: DTwP</td>
<td>No</td>
</tr>
<tr>
<td>Denmark</td>
<td>3, 5, 12 mo: DTaP-IPV-Hib</td>
<td>5yr: TdaP-IPV</td>
<td>No</td>
</tr>
<tr>
<td>Finland</td>
<td>3, 5, 12 mo: DTaP-HB-IPV</td>
<td>6yr: DTaP-IPV</td>
<td>14-15yr: Tdap</td>
</tr>
<tr>
<td>France</td>
<td>2, 3, 4 mo: DTaP-IPV-Hib or DTaP-IPV-Hib-HB</td>
<td>16-18 mo: DTaP-IPV-Hib or DTaP-IPV-Hib-HB</td>
<td>11-13yr: DTaP-IPV</td>
</tr>
<tr>
<td>Germany</td>
<td>2, 3, 4 m: DTaP-IPV-Hib-HB</td>
<td>11-14 m: DTaP-IPV-Hib-HB; 5-6yr: Tdap</td>
<td>9-17yr: Tdap</td>
</tr>
<tr>
<td>Greece</td>
<td>2, 4, 6 m: DTaP-IPV-Hib-HB</td>
<td>18 mo and 4-6yr: Tdap</td>
<td>No</td>
</tr>
<tr>
<td>Hungary</td>
<td>3, 4, 5 m: DTwP</td>
<td>3yr and 6yr: DTwP</td>
<td>No</td>
</tr>
<tr>
<td>Iceland</td>
<td>3, 5, 12 m: DTaP-IPV-Hib</td>
<td>4-5yr: DTaP-IPV</td>
<td>No</td>
</tr>
<tr>
<td>Ireland</td>
<td>2, 4, 6 m: DTaP-IPV-Hib</td>
<td>4-5yr: DTaP-IPV</td>
<td>No</td>
</tr>
<tr>
<td>Israel</td>
<td>2, 4, 6 m: DTaP-IPV-Hib</td>
<td>12 m: DTaP-IPV-Hib; 7yr: DTaP-IPV</td>
<td>No</td>
</tr>
<tr>
<td>Italy</td>
<td>3, 5, 11-12 m: DTaP-IPV-Hib-HB</td>
<td>5-6yr: Tdap</td>
<td>11-12yr or 14-15yr: Tdap</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>2, 3 m: DTaP-IPV-Hib-HB; 4 m: DTaP-IPV-Hib</td>
<td>11-12 m: DTaP-IPV-Hib-HB; 5yr: Tdap</td>
<td>12-15yr: Tdap</td>
</tr>
<tr>
<td>Country</td>
<td>Ages and Combination Dose Schedules</td>
<td>Additional Doses/Boosters</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2, 3, 4 m: DTaP-IPV-Hib 11 mo: DTaP-IPV-Hib; 4yr: DTaP-IPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>3, 5, 11-12 m: DTaP-IPV-Hib 6-8yr: DTaP-IPV</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Poland</td>
<td>2, 3-4, 5 m: DTwP 16-18 m: DTwP; 6yr: DTaP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Portugal</td>
<td>2, 4, 6 m: DTaP-IPV-Hib-HB 18 m: DTaP-Hib; 5-6yr: DTaP-IPV</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Russia</td>
<td>3, 4, 5, 6 m: DTaP or DTaP-IPV 18 m: DTaP or DTaP-IPV</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Slovak</td>
<td>2, 4, 10 m: DTwP-IPV-Hib 24 m: DTwP; 5yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Spain</td>
<td>2, 4, 6 m: DTaP-IPV-Hib-HB 15-18 m: DTaP-IPV-Hib; 13yr every 10yr: Tdap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>3, 5, 12 m: DTaP-IPV-Hib No 10yr: Tdap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>2, 4, 6 m: DTaP-IPV-Hib-HB 15-24 m: DTaP-IPV-Hib-HB; 11-15yr: Tdap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2, 3, 4 m: DTaP-IPV-Hib 3-5yr: DTaP-IPV</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

**Central and South America (most countries not shown follow a schedule similar to one of the following)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Ages and Combination Dose Schedules</th>
<th>Additional Doses/Boosters</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>2, 4, 6 m: DTwP-Hib 18 m: DTwP-Hib; 6yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Brazil</td>
<td>2, 4, 6 m: DTwP-Hib 15 m and 4-6yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Chile</td>
<td>2, 4, 6 m: DTwP 18 m and 4yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>El Salvador</td>
<td>2, 3, 6 m: DTwP-Hib-HB 15 m and 4yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>2, 4, 6 m: DTwP-Hib-HB 18 m: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Peru</td>
<td>2, 4 m: DTwP-Hib-HB; 3 mo, DTwP 3 mo: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Trinidad/Tobago</td>
<td>3, 4, 6 m: DTwP-Hib-HB 18 m and 5yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Uruguay</td>
<td>2, 4, 6 m: DTwP-Hib-HB 12 m: DTwP-Hib-HB; 5yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

**Asia (most countries not shown generally follow the EPI schedule)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Ages and Combination Dose Schedules</th>
<th>Additional Doses/Boosters</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>2, 4, 6 m: DTaP-IPV-HB or DTaP-IPV-Hib-HB 4yr: DTaP-IPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>3, 4, 5 m: DTwP 18-24 m: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2, 3, 4 m: DTwP or DTwP-HB 3-1-2 mo: DTaP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Japan</td>
<td>3-12 mo: 3 doses DTaP 15 mo: DTaP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Korea</td>
<td>2, 4, 6 mo: DTaP 15-18 mo and 4-6yr: DTaP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Republic of Malaysia</td>
<td>2, 3, 5 mo: DTwP-Hib 18 mo: DTwP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2, 4, 6 mo: DTaP 18 mo: DTaP</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Thailand</td>
<td>2, 4, 6 mo: DTwP or DTwP-HB 18-24 mo and 4-5yr: DTwP</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
10.2.1 United States

Acellular vaccines were introduced into the US in the primary paediatric course in 1996, and routinely using paediatric DTaP from 1997 as a five dose schedule for all children under seven years of age: recommended at ages two, four, six months with boosters at 15-18 months and four to six years (106).

Adolescents aged 11-18 years are recommended to receive a single dose of Tdap vaccine with the preferred age being 11-12 years. Adults aged 19 to 64 years are recommended to have a single dose of Tdap to replace the next booster dose of Td which is recommended every 10 years (107). Adults are also recommended to have a single dose of Tdap if they are in close contact with infants younger than 12 months, with priority to healthcare professionals.

The ACIP recommends that children aged seven to 10 years who are not fully vaccinated against pertussis should receive a single dose of Tdap.

In October 2012, the ACIP recommended Tdap during every pregnancy, preferably at 27 through to 36 weeks gestation (108). For women who fail to get vaccinated in pregnancy, it is recommended immediately postpartum. Cocoon vaccination for those around the newborn infant is also recommended at least two weeks prior to coming in contact with the infant (109).

Cocoon strategies to protect young infants by vaccinating pregnant women or early post-partum and other close household contacts are recommended in the US (110).

10.2.2 United Kingdom

The UK immunisation schedule for pertussis is the use of acellular pertussis containing vaccines at ages two months, three months, four months, and a booster at three years four months to five years old (111).

The primary course was changed in 1990 from ages three, five and 10 months to two, three and four months and effectively reduced the incidence of pertussis in infants aged three to 11 months (112).

In September 2012, in response to a national pertussis outbreak the Joint Committee on Vaccination and Immunisation (JCVI) recommended a temporary programme of immunisation of pregnant women, ideally between 28 and 38 weeks of pregnancy (113).

There are no vaccines that are routinely offered on the National Health Service to all adults. As of early 2013, the only adult recommendation for pertussis vaccine is for use in pregnant women.

10.2.3 Europe

An overview of immunisation schedule in European countries is provided by the European Centre for Disease Prevention and Control (114, 115).

All European countries except Poland offer acellular pertussis vaccine schedules. All offer a primary course of three doses. Several countries offer the third dose of the primary course at 12 months of age, and then only a single booster in childhood (Denmark, Iceland, Norway and Slovakia). The majority of European countries offer primary course of 3 and a booster at 12-18 months of age, and at around five years of age.

Despite high coverage with primary immunisation (>90%) but no booster at school entry the proportion of pertussis cases among immunised children in Denmark increase sharply after age five years. Three of the five European countries with the highest rates of pertussis have used little pertussis vaccine (Italy), have uneven usage (Germany) or interrupted the pertussis immunisation programme in the mid-1980s (Sweden) (116).

10.2.4 Australia

As of December 2012, the Australian schedule consists of a three-dose primary course at two, four and six months and booster doses for four years and 15-17 years old. A single dose of Tdap is recommended for all adults planning a pregnancy, for both parents as soon as possible after delivery of an infant, and for grandparents and other carers of young children (cocoon strategy) (117).

10.2.5 Asia-Pacific

All countries use a three-dose primary vaccination series and recommend completion by six months of age, expect for Japan where vaccination can commence as late as eight months of age (12). There is a mix of whole cell and acellular vaccines used across the region.

10.3 Summary of international policy and practice

A three dose primary course is used universally. The ages of delivery and number of booster doses are variable with many countries using toddler boosters, boosters at ages four to six years and adolescent boosters. The US and UK both currently recommend vaccination in pregnancy; for the UK this is a temporary programme for the duration of the current epidemic. Cocoon strategies are recommended in the US and Australia.
11. References


64. Gulland A. Teenagers and newborn babies in England and Wales may get pertussis jab as cases continue to rise. Bmj. 2012;345:e5919.


