Antigen Literature Review for the New Zealand National Immunisation Schedule, 2017:
Childhood Schedule

Prepared as part of a Ministry of Health contract for services by the Immunisation Advisory Centre

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

July 2017
Overview

Presented here is a review of published literature that considers the scheduling of national immunisation programmes in high income countries, with a particular focus on the needs for the National Immunisation Schedule in New Zealand (NZ). The main aim of this review, commissioned by the Ministry of Health, is to support evidence-based decisions relevant to the immunisation schedule in NZ for control of vaccine-preventable diseases, and to prevent associated morbidity and mortality, primarily, in children under the age of five years. Options, recommendations and potential issues are summarised.

Consideration around the timing of the primary series vaccination and the requirement for subsequent boosters is necessary for optimal disease control, but decisions also impact on the cost of and implementation requirements for such immunisation programmes.

The current NZ immunisation programme is, in general, providing good disease control. The major issues around the timing of the infant schedule are mostly driven by optimising prevention of severe early pertussis. Questions arise around the impact of maternal antibody on the effectiveness of the infant primary series, which currently starts at six weeks of age, particularly following maternal vaccination in pregnancy. Also considered are alternative strategies for pertussis control, since the current vaccines do not provide adequate protection against milder disease nor sufficiently prevent transmission. The effects of potential changes to the pertussis schedule are considered for other antigens that are administered concurrently with pertussis.

The NZ schedule offers fewer boosters for diphtheria and tetanus than is currently recommended by the World Health Organization (WHO), but there is no evidence of breakthrough disease. Similarly, despite WHO advice, hepatitis B vaccination is not offered universally at birth and there is, to date, no evidence of high-risk infants being missed. However, continued surveillance is required to ensure that antenatal screening is identifying all hepatitis B infected mothers. The current NZ hepatitis B schedule may not be ideal for spacing to ensure longevity of immunity.

Since measles and mumps outbreaks continue to occur, although these disease are not endemic in NZ, the scheduling of two doses measles-mumps-rubella vaccine is adequate, but only when coverage is sufficiently high to provide herd immunity. Meningococcal disease is currently of low endemicity in NZ, with occasional sporadic outbreaks. Meningococcal vaccines are not currently part of the routine immunisation schedule, but literature around their use is reviewed to assist in decision making.

This is not a systematic review and does not consider cost-effectiveness or vaccine safety in its evaluation. Literature published between January 2013 and July 2017 is included.
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Acknowledgements

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## Abbreviations

<table>
<thead>
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIES</td>
<td>Carrier-induced epitopic suppression</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-mediated immunity</td>
</tr>
<tr>
<td>DTaP-IPV-HepB/Hib</td>
<td>Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and <em>Haemophilus influenzae</em> type b vaccines.</td>
</tr>
<tr>
<td>DTwP</td>
<td>Combined diphtheria, tetanus and whole cell pertussis vaccine</td>
</tr>
<tr>
<td>ESR</td>
<td>Institute for Environmental and Scientific Research Ltd</td>
</tr>
<tr>
<td>EU/ml</td>
<td>ELISA (enzyme linked immunosorbent assay) units per millimetre</td>
</tr>
<tr>
<td>Fim2/3</td>
<td>Fimbriae 2 and 3</td>
</tr>
<tr>
<td>FHA</td>
<td>Filamentous haemagglutinin</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric mean titre</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline Ltd</td>
</tr>
<tr>
<td>GW</td>
<td>Gestational week</td>
</tr>
<tr>
<td>HepB</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>HIC</td>
<td>High income countries</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HSCT</td>
<td>Haematopoietic stem cell transplant</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon-gamma</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive pneumococcal disease</td>
</tr>
<tr>
<td>MMR</td>
<td>Combined measles, mumps, rubella vaccine</td>
</tr>
<tr>
<td>MMR1 / MMR2</td>
<td>First and second doses of MMR vaccine</td>
</tr>
<tr>
<td>MMRV</td>
<td>Combined measles, mumps, rubella, varicella vaccine</td>
</tr>
<tr>
<td>MSD</td>
<td>Merck Sharpe and Dohme Ltd</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>OMP</td>
<td>Outer membrane protein complex of <em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>OPA</td>
<td>Opsonophagocytic assay</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PCV (PCV7, -10, -13)</td>
<td>Pneumococcal conjugate vaccine – seven, ten or 13 valent</td>
</tr>
<tr>
<td>PBMC</td>
<td>Peripheral blood mononuclear cells</td>
</tr>
<tr>
<td>PRP</td>
<td>Polyribosylribitol phosphate</td>
</tr>
<tr>
<td>PRN</td>
<td>Pertactin</td>
</tr>
<tr>
<td>PT</td>
<td>Pertussis toxin</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
</tr>
<tr>
<td>Th1 / Th2 / Th17</td>
<td>T-helper-1 / T-helper-2 / T helper-17 cells</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</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>
</tr>
</tbody>
</table>
1 National Immunisation Schedules

The role of childhood immunisation schedules is disease control and is predominantly driven by the need to control of pertussis. Pertussis outbreaks occur every 3-5 years in New Zealand and have resulted in the deaths of infants, despite high immunisation coverage. Globally, in 2013, pertussis caused more than 63,000 deaths in children under the age of 5 years.1

Immunisation schedules vary by the age at which immunisation commences, the spacing of the doses, the number of doses in the primary series and the age and timing of subsequent booster doses. The nature of the vaccine and the number of antigens contained within each dose influences scheduling. Each country has different requirements in terms of disease control, how these affect the number of vaccines required for the schedule, and the ages requiring protection. The positioning of booster doses, in particular, is influenced by age that poses maximum risk for the specific vaccine-preventable disease and duration of protection afforded by the primary series. Complicated schedules or those that involve multiple injections in one visit can have adversely impact vaccine uptake and coverage. If vaccine coverage is sufficiently reduced, this can lead to outbreaks affecting individuals and reduce community immunity that can protect for infants too young to be immunised or children who do not respond adequately to vaccines, and may lead to a lack in confidence in immunisation for parents and health professionals. There are also cost implications for the number of doses and types of vaccines used.

1.1 Immunisation schedules in high income countries

Each country has its own immunisation schedule to meet the requirements for disease control and based on the advice of various immunisation advisory committees and funding agencies. Pertussis control is a key driver of immunisation scheduling. Pertussis vaccines are in mostly given in combination with other vaccine antigens, particularly tetanus and diphtheria. Other antigens are given as required for each country. A summary of various pertussis immunisation schedules used in high income countries (HIC) are given in Table 1.

For this review, where there is a gap of at least 6 months between doses the latter dose is considered a booster dose. For example, primary doses given at 2, 3, 5 months of age then a booster 12 months is 3+1, whereas a regime at 2, 4, 12 months is defined as 2+1.
Table 1: Summary of international immunisation recommendations for acellular pertussis vaccines by schedule type, as of February 2017 (adapted from European Centre for Disease Prevention and Control)

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of schedule</th>
<th>Pregnancy</th>
<th>Age of primary vaccination (months)</th>
<th>Booster doses months</th>
<th>Years</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand</td>
<td>3+1</td>
<td>Y</td>
<td>6 weeks, 3, 5</td>
<td>-</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>USA</td>
<td>3+1</td>
<td>R</td>
<td>2, 4, 6</td>
<td>15-18</td>
<td>4-6</td>
<td>5</td>
</tr>
<tr>
<td>Canada</td>
<td>3+1</td>
<td>Y</td>
<td>2, 4, 6</td>
<td>18</td>
<td>4-6</td>
<td>5</td>
</tr>
<tr>
<td>Australia</td>
<td>3+1</td>
<td>R</td>
<td>†6w/2m, 4, 6</td>
<td>18</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Examples in Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>15</td>
<td>5-7</td>
<td>5</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>10</td>
<td>5-6</td>
<td>5</td>
</tr>
<tr>
<td>Germany</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>11-13</td>
<td>5-6</td>
<td>5</td>
</tr>
<tr>
<td>Malta</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>18</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Netherlands</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>11</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>UK</td>
<td>3+1</td>
<td>Y</td>
<td>2, 3, 4</td>
<td>-</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cyprus</td>
<td>3+1</td>
<td>Y</td>
<td>2, 4, 6</td>
<td>15-18</td>
<td>4-6</td>
<td>5</td>
</tr>
<tr>
<td>Greece</td>
<td>3+1</td>
<td>Y</td>
<td>2, 4, 6</td>
<td>15-18</td>
<td>4-6y</td>
<td>5</td>
</tr>
<tr>
<td>Ireland</td>
<td>3+1</td>
<td>Y</td>
<td>2, 4, 6</td>
<td>-</td>
<td>4-6</td>
<td>4</td>
</tr>
<tr>
<td>Portugal</td>
<td>3+1</td>
<td>Y</td>
<td>2, 4, 6</td>
<td>18</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Austria</td>
<td>2+1</td>
<td></td>
<td>3, 5</td>
<td>12</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Finland</td>
<td>2+1</td>
<td></td>
<td>3, 5</td>
<td>12</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Norway</td>
<td>2+1</td>
<td></td>
<td>3, 5</td>
<td>12</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Sweden</td>
<td>2+1</td>
<td></td>
<td>3, 5</td>
<td>12</td>
<td>5-6</td>
<td>4</td>
</tr>
<tr>
<td>Italy</td>
<td>2+1</td>
<td></td>
<td>3, 5-6</td>
<td>11-13</td>
<td>5-6</td>
<td>4</td>
</tr>
<tr>
<td>France</td>
<td>2+1</td>
<td></td>
<td>2, 4</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Romania</td>
<td>2+1</td>
<td></td>
<td>2, 4</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Spain</td>
<td>2+1</td>
<td></td>
<td>2, 4</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

† Varies between states in Australia, National Immunisation Programme starts at 2 months
Y – funded, R - recommended
2 Options for New Zealand

2.1 Objective

The purpose of this review is to provide information to help inform evidence-based decisions around the optimum immunisation schedule in New Zealand (NZ) for control of vaccine-preventable diseases and to prevent associated morbidity and mortality. Based on a review of the literature around childhood immunisation scheduling, a summary of options, recommendations and potential issues are presented.

The review of the literature from which these options are summarised is presented in succeeding sections.

2.2 Pertussis

The prevention of severe pertussis, particularly in young infants, is the main driving force for setting the timing of immunisation schedules. When compared with most other high income countries, NZ commences its National Immunisation Schedule (the Schedule) at the youngest age of 6 weeks. However, with the introduction of tetanus-diphtheria-acellular pertussis (Tdap) boosters in pregnant women, it is unclear what effect the presence of higher maternal antibody levels will have on primary series vaccine effectiveness in the infant and the timing of future schedules.

2.2.1 Pertussis vaccines in New Zealand

The acellular pertussis (aP) vaccines used as part of the Schedule contain three pertussis antigens - pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). There are no stand-alone pertussis vaccines, all are combined with other antigens.

DTaP – full antigen doses of diphtheria toxoid, tetanus toxoid and acellular pertussis antigens

- DTaP-IPV (Infanrix®-IPV) – with inactivated poliovirus
- DTaP-IPV-HepB/Hib (Infanrix®-hexa) – with inactivated poliovirus, hepatitis B and conjugated Haemophilus influenzae type B antigens
- Tdap (Boostrix®) – tetanus toxoid and reduced antigen doses of diphtheria toxoid and acellular pertussis antigens

2.2.2 Timing of pertussis vaccine doses

Timeliness of primary series vaccinations is potentially important for disease control, although there is no consensus as to what spacing is optimum. Recommendations to start at 6 weeks of age may help enable earlier infant protection and to reduce any delay in the delivery of the first dose, which is offered at 2 or 3 months of age in most high income countries.

Immunoglobulin G (IgG) antibodies to PT and FHA readily cross the placenta and antibody concentrations in infant serum have been shown to be comparable to or higher than those in the mother. These passively transferred antibodies remain for at least 4-6 months. However, without maternal vaccination, low maternal pertussis antibody levels and rapid decay of passive antibody provide little protection against pertussis to the infant. Maternal vaccination is highly effective (>90%) in preventing severe pertussis in young infants and protection potentially continues for up to a year of age. To extend protection for a high proportion of preterm infants and for a greater accumulation of antibody, vaccination could be offered earlier than 28 weeks, in the second trimester.
Recent evidence suggests that the presence of maternal antibody in the infant has an inhibitory effect on pertussis antibody induced by DTaP vaccines during the primary immunisation series. It was estimated that this effect could be offset by a delay in commencement of the primary series. Although maternal vaccination strategies have the potential to influence established infant programmes, the effects of lower antibody responses have not been assessed clinically, to date.

Currently, vaccination coverage in pregnancy in NZ is not well quantified, but is likely to be too low to justify delaying the first infant dose, since the youngest infants are most vulnerable to pertussis. If maternal vaccination rates were higher and disease in the youngest infants was being controlled by maternal antibodies, a delay the timing of the first infant dose may be worth considering.

As an alternative, or for infants whose mothers who were not vaccinated during pregnancy, a birth dose with a monovalent aP vaccine has been proposed (not available commercially). However, the data on the effectiveness and effect on subsequent immunisations is currently unclear.

Acellular pertussis vaccines have been shown to induce permanent mixed T helper 2 (Th2) / T helper-1 (Th1) cell-bias of the immune response to pertussis antigens. In lieu of improved pertussis vaccines, first dose priming with wP containing vaccine (DTwP) may induce longer lived Th1 dominant immunity, help to more rapidly clear infection and thereby reduce transmission. Subsequent primary series doses, booster doses and pregnancy doses could continue with aP-containing vaccines. However, this strategy would need to be balanced against the concerns from the higher reactogenicity profile of wP-containing, which was the reason countries moved away from use of wP vaccines.

A booster dose in the second year life does not appear to be currently necessary in NZ, since there is no evidence of waning immunity prior to the age of 4 years. However, children with comorbidities may not be fully protected by the primary series, therefore to increase seroprotection, a booster dose in the second year of life could be beneficial for toddlers at higher risk, such as those born preterm, with immunodeficiency or with cardiorespiratory disease and chromosomal abnormalities. NZ vaccine effectiveness (VE) measurements are based on reported and hospitalised cases, and may not be measuring milder pertussis. It is, therefore, possible that mild pertussis circulating in young children and not being recognised or reported. Whether this has an effect on disease transmission to young infants is unclear, particularly as there is no clear evidence that aP-containing vaccines reduce carriage.

To maintain adequate anti-pertussis toxin antibody levels, a booster dose is required within 5 years of completion of the primary series before levels decline to baseline. Antibody wanes more rapidly if they have declined too low before boosting. Hence a preschool booster at 4 years of age would continue to be required.

If the presence of maternal antibodies was found to cause significant immune interference, particularly at 6 weeks of age, it is feasible that as maternal immunisation uptake increases fewer infants will have sufficient anti-PT antibody from the second year of life to protect against disease. Therefore a toddler booster dose would be required to maintain protection until preschool age.

Due to rapidly waning immunity within 5-8 years after the previous dose, boosters are generally seen as useful to prevent disease in older age groups, especially in adolescents aged 10-12 years and to help to reduce transmission to young children and infants. Sharing a household with adolescents aged 10-14 years has been associated with pertussis infection in older teenagers and adults, potentially as result of waning immunity in this age group. How frequently adolescents spread disease to vulnerable infants in the NZ setting is unknown.
2.2.3 Summary of options

- Continue with primary series of three vaccines
  - Currently reasonable protection with the current schedule
- Offer a 2+1 series with the third dose at around 12 months of age
  - Potentially, offers immunologically better spacing between second to third doses and enhances protection in the second year of life
- Begin maternal Tdap immunisation in second trimester to extend protection to preterm infants
- Delay start of infant schedule to reduce maternal antibody interference – only an option with high maternal immunisation coverage
  - Could consider offering two different schedule times, with earlier vaccination for those who missed a maternal vaccination dose
- Introduce whole cell pertussis vaccine as first priming dose to reduce disease transmission
  - The disadvantage is that wP vaccines have an increased reactogenicity profile.
- Birth dose of monovalent aP for infants whose mothers were not immunised in pregnancy
  - Awaiting further data on the effectiveness of this option
- Include a booster in second year of life, to protect higher risk infants and if more rapid antibody waning occurs due to interference from maternal antibody during priming
  - Unclear currently of the necessity of this
- Review the role and usefulness of adolescent boosters in disease control.

2.3 Haemophilus influenzae type b

Following the introduction of Haemophilus influenzae type b (Hib) conjugate vaccines to the Schedule, rates of invasive disease have dramatically decreased in a variety of settings. Hib vaccine is highly effective (>85%) in preventing invasive Hib disease when at least two doses are administered in infancy.

In immunised people, Hib vaccination prevents new nasopharyngeal colonisation, thereby reducing transmission, and where immunisation coverage is adequate, provides community / herd immunity. Even in areas with moderate coverage (60-75%) or where vaccine supply has been intermittently interrupted, invasive Hib disease has virtually disappeared.20

2.3.1 Hib vaccines in New Zealand

As part of the NZ Schedule, Hib vaccines are administered to infants at 6 weeks, 3 and 5 months of age, as a combination vaccine and with pneumococcal conjugate vaccine (PCV). A booster is given at 15 months of age concurrently with PCV, MMR and, from 1 July 2017, varicella vaccines.

- Hib-TT (Act-HIB or Hiberix®) - Haemophilus influenzae type b polyribosylribitol phosphate (PRP) conjugate to tetanus toxoid
- DTaP-IPV-HepB/Hib (Infanrix-hexa®) – includes Hib-TT conjugate
2.3.2 Timing of Hib doses

Booster doses in the second year of life extend and enhance seroprotection and vaccine effectiveness, and may compensate for incomplete primary series immunisation.20

Two doses of Hib vaccine are sufficient to provide good protection, when a booster is given at least 6 months after the second dose (2+1). This schedule provides better seroprotection than three doses without a booster (3+0), since the booster dose maintains seroprotective antibody, which is required to reduce carriage of the bacterium.21

There is no evidence of significant differences in immunogenicity following different primary and booster schedules in infants with two or three primary doses, the age of commencement of the schedule or one- or two-month intervals between doses. Seroprotection against Hib persists to at least 5 years of age in children who received three or four doses of DTaP-IPV-HepB/Hib or DTaP-IPV/Hib in infancy.22

Where there are populations with increased risk or earlier incidence of Hib, early doses using a 3+1 schedule are beneficial. No significant interference from maternal antibodies have been observed, although when first priming doses are given later the antibody responses to the priming doses and booster are higher.8 Since good disease control has been achieved in most populations, this effect is probably unlikely to be clinically significant.

Both Hib PRP-TT and PRP-OMP conjugate vaccines provide good protection for indigenous children in areas of higher risk.23 When Hib is used in TT conjugate vaccine, there is a risk of suppression of anti-PRP immunity due to competition with the tetanus component, and therefore Hib-TT should be given before or together with TT, not after.24

The current NZ immunisation schedule meets these criteria and is highly effective in preventing Hib. Since the schedule is commenced at 6 weeks of age, potentially higher risk Māori populations are better protected.

Continued surveillance is important, particularly in populations with higher risk or earlier onset Hib disease, to ensure that the current immunisation schedule, increased coverage of Tdap maternal immunisation (as potential source of anti-tetanus antibody interference) and changes to the vaccines given do not reduce seroprotection and effectiveness of the Hib immunisation.

2.3.3 Summary of options

- Reduce number of primary course doses from 3+1 to 2+1
- Continue with a booster dose in the second year of life

2.4 Hepatitis B

Hepatitis B immunisation has successfully reduced the development of chronic hepatitis B infection of young children and the incidence of acute infection in adolescents and adults in NZ. However, internationally, there are concerns that primary series immunisation of infants may not provide long lasting protection into adulthood since antibody levels wane during adolescence.

The importance of seroprotective antibody levels is unclear, since cell-mediated immunological memory is established by immunisation. Most adolescents retain cellular memory following receipt of a primary course given before the age of 12 months and seroprotective antibody responses can be induced by challenge doses.
2.4.1 Hepatitis B vaccines in New Zealand

Currently on the NZ National Immunisation Schedule, hepatitis B-containing vaccines are given in infancy at 6 weeks, 3 and 5 months of age. Only infants born to mothers who are hepatitis B surface antigen (HBsAg) positive, or whose hepatitis B status is unknown, receive a dose of single antigen hepatitis B vaccine at birth.

- DTaP-IPV-HepB/Hib (Infanrix-hexa®) – primary doses
- Recombinant HBsAg single antigen vaccine: HBvaxPRO® - used for toddler booster and eligible high-risk individuals, or unfunded Engerix® for occupational doses

2.4.2 Timing of hepatitis B doses

The timing of the hepatitis B vaccinations on the Schedule may not be providing optimal protection. A gap of at least 6 months between the second and third priming dose is more preferable to provide longer lasting seroprotection than a gap of less than 6 months. Increasing the spacing between the second and third HepB dose would reduce the potential need for a booster dose in adolescence and improve seroprotection in young adults.

The World Health Organization (WHO) recommendation is for all national immunisation programmes to include a monovalent HepB vaccine dose at birth. However, there is no indication that a birth dose is required for most infants in NZ, apart from those born to carrier mothers. Ongoing surveillance is essential to be sure that all high risk infants are offered a timely birth dose. Furthermore, it is possible that the introduction of a birth dose would then enable longer spacing to the final dose.

Currently, there is no apparent increase in the number of acute hepatitis B cases being notified in NZ in young adults and many of the cases notified are imported from overseas. Therefore, with limited data to date, an adolescent booster is probably not likely to be needed in individuals who are fully primed as infants. Research would be beneficial to examine seropositivity and cell-mediated immunity against HBsAg in older NZ adolescents to gauge how well they were primed with the shorter interval schedule.

2.4.3 Summary of options

- Two priming doses plus longer space to dose 3 (2+1) – dose three could be given any time after 9-12 months of age
- While there is currently no new indication that a birth dose is required, except for infants of infected mothers, ongoing evaluation is required to ensure that high risk infants are not being missed.

2.5 Tetanus

The scheduling of tetanus and diphtheria containing vaccines as part of the primary series sits alongside the schedule for pertussis, as they are usually combined into one vaccine that includes pertussis antigens (DTaP), or in combination boosters with reduced doses of diphtheria and pertussis antigens (Td or Tdap).

2.5.1 Tetanus vaccines in New Zealand

On the NZ National Immunisation Schedule, tetanus-diphtheria toxoid containing vaccines are administered at 6 weeks, 3 and 5 months of age (DTaP), with a booster at 4 years of age (DTaP), at 11-12 years of age (Tdap) and in women during pregnancy (Tdap). Boosters are funded at 45 and 65 years (Td), as well as for those with tetanus-prone injuries without up-to-date immunisation.
**DTaP** – full antigen doses of diphtheria toxoid, tetanus toxoid and acellular pertussis antigens

- DTaP-IPV (Infanrix®-IPV) – with inactivated poliovirus, given as preschool booster
- DTaP-IPV-HepB/Hib (Infanrix®-hexa) – with hepatitis B and conjugated *H. influenzae* type B antigens, used for primary series
- Tdap (Boostrix®) – tetanus toxoid and reduced antigen doses of diphtheria toxoid and acellular pertussis antigens, used for adolescent and pregnancy boosters
- Td (ADT™ Booster) – tetanus toxoid and reduced dose diphtheria toxoid, adult booster

### 2.5.2 Timing of tetanus booster doses

The NZ Schedule provides five doses of tetanus vaccine before adulthood. The WHO recommends six doses for life-long protection. It is not clear if an extra dose in the second year of life is required in NZ since the disease is not seen in childhood, except in unvaccinated children (four cases aged <10 years during 1997-2015), and tetanus control in immunised individuals appears to have been achieved. The primary course of tetanus immunisation induces long lasting memory.

The need for a six-dose regime, by adding a toddler dose, may be negated in NZ by the potential enhancing effect of TT conjugate vaccines on tetanus immunity. This effect may be dependent on the age at which the first dose was given. However, these conjugate vaccines cannot be used to substitute for a sufficient number and size of doses of dedicated tetanus vaccines.

If it is determined that DTaP vaccination to be required in the second year of life to improve pertussis control, then the number of tetanus (and diphtheria) doses would be increased by default.

### 2.5.3 Summary of options

- Options are determined by pertussis, and to some extent, diphtheria control
- Review immunisation status and booster requirements for elderly adults

### 2.6 Diphtheria

Cases of diphtheria are rare in NZ and appear as imported cases in from countries in which the disease is endemic (one or two cases of cutaneous toxigenic disease per year were seen in recent years but the last case of respiratory disease was in 1988). Diphtheria immunisation is provided by tetanus-diphtheria combined vaccines, as listed in section 2.5.1 (tetanus). As such, childhood diphtheria vaccination also sits alongside the schedule for pertussis immunisation.

#### 2.6.1 Timing of booster doses

Although long-lived, diphtheria immunity is not as long lasting as for tetanus, particularly in individuals who were not fully primed. Therefore, six childhood doses may be advantageous. However, the risk of diphtheria infection on NZ is very low and the five dose regime appears to be currently providing adequate protection.

The presence of maternal antibodies from Tdap-boosted mothers may reduce the infant response to conjugate vaccines containing diphtheria antigens, such as PCV10 or PCV13. Although seroprotection is retained, continued disease surveillance is essential as maternal immunisation uptake increases. Diphtheria-containing vaccines should be administered with or before diphtheria carrier protein conjugated vaccines.
Data do not support the need for decennial booster doses in adulthood in fully primed individuals.\textsuperscript{30}

2.6.2 \textbf{Summary of options}

- Maintain current schedule - dependent on pertussis control
- Add a second year of life booster to offer more effective diphtheria protection.

2.7 \textbf{Pneumococcal}

The introduction of pneumococcal conjugate vaccines (PCVs) to national immunisation schedules have resulted in significant declines in invasive pneumococcal disease (IPD) and pneumonia in infants.\textsuperscript{28}

2.7.1 \textbf{Pneumococcal vaccines in New Zealand}

Priming doses of pneumococcal conjugate vaccines are given concurrently with DTaP vaccines at 6 weeks, 3 and 5 months of age, with a booster dose at 15 months. PCV10 is used universally and PCV13 is given to high risk groups (as of 1 July 2017).

- PCV10 (Synflorix\textsuperscript{®})– ten pneumococcal polysaccharide serotypes, differently conjugated to diphtheria carrier protein variant CRM\textsubscript{197}, tetanus toxoid and non-typeable H. influenzae proteins
- PCV13 (Prevenar\textsuperscript{®} 13) – 13 pneumococcal polysaccharide serotypes conjugated to diphtheria carrier protein variant CRM\textsubscript{197}

A 23-valent polysaccharide pneumococcal vaccine (PPV-23, Pneumovax\textsuperscript{®}.23) is only used for high risk groups over the age of 2 years and is not considered in this review.

2.7.2 \textbf{Timing of doses}

The major differences in international schedules are between a two or three dose primary course, with or without a second year of life booster.

A booster dose is preferable to three priming doses without a booster as high antibody levels are maintained for longer.\textsuperscript{31} Both 3+1 and 2+1 regimes of PCV10 are effective in preventing invasive pneumococcal disease (IPD) in young children.\textsuperscript{32}

Inequities between ethnic groups have decreased since the introduction of PCV10 and PCV13 to the Schedule.\textsuperscript{33} The protection afforded by a third priming dose for children under 12 months of age may no longer be required as transmission of vaccine-type pneumococci is reduced. New Zealand has observed a significant decline in pneumococcal disease since PCV vaccines were introduced, therefore a 2+1 schedule may be most cost-effective and appropriate to provide longer lived protection in an already well protected population.

A booster dose in the second year of life provides greater seroprotection and reduces nasopharyngeal carriage in young children, thereby increasing herd immunity effects to older age-groups.\textsuperscript{34} Continued surveillance is required to ensure that a two-dose primary series sufficient to maintain disease control and does not result in increased transmission and disease in infants prior to the booster dose.

2.7.3 \textbf{Summary of options}

- Reduce number of doses from 3+1 to 2+1
2.8 Measles, mumps and rubella

To interrupt transmission of measles, a high level of population immunity is required with a herd immunity threshold of 89-94%. The Western Pacific Region was estimated to have 96% coverage for the first dose of measles vaccine in 2015, but only 85% for dose two. In New Zealand, 88% of 5-year old children are fully immunised and have received the second MMR dose.

2.8.1 MMR vaccines in New Zealand

Measles, mumps and rubella immunisation is provided by a combined MMR vaccine. As of July 2017, the Priorix® brand replaced M-M-R-II on the NZ programme. No differences in effectiveness are anticipated.

2.8.2 Timing of doses

On the NZ Schedule, the first dose of MMR (MMR1) is currently given 15 months and a second dose (MMR2) is administered as a preschool dose at 4 years of age. The purpose of the second dose is to protect children in whom the first dose does not induce sufficiently protective immunity. The requirement of a second dose appears to be particularly important to ensure a high level of immune protection against mumps, which is the weaker antigen.

Due to immune response immaturity, MMR is less immunogenic for measles and mumps in infants younger than 12 months of age.

The second dose appears to be effective given at any timing interval after the first dose (with at least a one month gap) – most high income countries provide MMR2 at preschool age (4-6 years) or in early adolescence (11-15 years). In the absence of circulating measles, the current NZ schedule timing appears reasonable, to provide protection during primary school and beyond for those who may not have sufficiently protected by the first dose.

However, there is a cohort of adolescents and young adults who may not be adequately immunised against measles, mumps and potentially rubella due to insufficient priming and poor coverage in the late 1990s and early 2000s. A booster campaign could potentially help to reduce the spread of imported outbreaks for those who did not receive two doses in early childhood. Going forward, increasing and maintaining coverage in infants with two doses of vaccines is likely to avoid this issue in the future.

2.8.3 Summary of options

- Maintain two dose schedule for infants
- Monitor MMR uptake following the introduction of varicella to the 15 month vaccination event.
- Temporary catch-up for potentially insufficiently primed adolescents, particularly for those who had not received two complete doses.

2.9 Varicella

One dose of varicella-containing vaccine given in the second year of life is highly effective in preventing severe varicella disease and reduces the incidence of all varicella disease.
second dose of varicella vaccine provide additional protection, whether given soon after the first dose or years later, and assists with maintaining herd immunity. Combined MMRV is as effective as coadministration with separate MMR and varicella vaccines in preventing varicella.

2.9.1 Varicella vaccines in New Zealand

Varicella vaccine was introduced to the routine NZ Schedule on 1st July 2017 as a single dose administered at 15 months of age concurrently with MMR1, Hib and PCV boosters. A catch-up campaign is provided for non-immune 11 year-olds. The vaccine is also funded for certain high-risk groups.

- Varicella (Varilrix®) – contains live attenuated Oka strain of varicella-zoster virus

The combined live attenuated MMR and varicella vaccine (MMRV; Priorix®-Tetra) is not currently used in NZ.

2.9.2 Timing of doses

One dose given at 15 months is expected to provide protection for the majority of toddlers against severe varicella, however, there is a possibility of mild breakthrough disease. With time, as the level of circulating virus declines, a second dose may be required to improve herd immunity and reduce the incidence of breakthrough disease, as now used in the US and Germany with good disease control. In an effort to improve coverage for both varicella and MMR2, in July 2013, Australia replaced a single dose of varicella vaccine at 24 months of age and MMR2 at 4 years of age with MMR1 at 12 months and MMRV at 18 months. An increased risk of febrile convulsions has been associated with the first dose of MMRV when given between the ages of 12-23 months compared with MMR alone and varicella vaccine. However, by administering MMR first, this is expected to be reduced. A systematic review of randomised controlled trials (RCTs) found comparable safety profiles for MMRV and MMR with or without varicella.

2.9.3 Summary of options

- Continued monitoring of hospitalisation reports is required to evaluate the impact of introducing varicella vaccine to the Schedule. Varicella is not a notifiable disease, therefore, reliable data on mild cases is not available
  - As the vaccinated cohort gets older and wild disease becomes less prominent, the addition of a second dose of varicella vaccine to the Schedule would need to be considered.

- If MMR is given earlier than the V, rather than at the same visit (as per the Australian schedule) then MMRV could be considered for the first dose of varicella as the reactogenicity for MMRV would then be expected to be lower
  - Further data is needed on the reactogenicity profile of MMRV being given following a first dose of MMR

- The second dose of varicella can be delivered as MMRV because the incidence of febrile events is lower with the second dose
  - Evaluation of vaccine uptake may be required prior to considering MMRV instead of separate MMR and varicella vaccination.
2.10 Meningococcal

Although, meningococcal vaccines are not currently included on the Schedule in New Zealand, except for certain high-risk groups and selectively during local outbreaks, the options for inclusion are reviewed. Local outbreaks of meningococcal disease occur regularly and are predominantly caused by serogroup B and C meningococci. The peak ages of disease incidence in NZ are in infancy, late teens and early adulthood. During 1991-2007, New Zealand experienced an epidemic of a single strain meningococcal B, which was successfully controlled by a specifically designed vaccine (MeNZB).

Both conjugate meningococcal vaccines, meningococcal serogroup C and quadrivalent meningococcal A, C, Y, W135 vaccines, provide good protection against invasive meningococcal disease when administered in infancy and to young adults.43

High levels of bactericidal serum antibody are important for disease control to prevent rapid progression of invasive disease and in reducing transmission. Since antibodies wane, booster doses are required in the second year of life and at least in early adolescence, if not earlier. A more effective strategy than frequent boosters is by means of using a mass catch-up programme, when the vaccine is first introduced to the schedule, to rapidly establish herd immunity. The establishment of herd immunity, particularly in adolescent age groups, has also been shown to be key in controlling meningococcal C disease.43

A conjugate vaccine is not feasible for meningococcal serogroup B (MenB) due to the low immunogenicity of its capsular polysaccharides. Early post-licensure data is demonstrating good effectiveness of a multicomponent recombinant MenB vaccine (4CMenB; Bexero®) against the most prevalent, predicted MenB strains in infants, when give as a two-dose priming regime. To maintain seroprotective levels of circulatory bactericidal antibodies during childhood, booster doses are required following a two-dose primary infant schedule. Since this vaccine has only recently been licensed, the long term impact on MenB disease, carriage and potential herd immunity is unknown.

2.10.1 Meningococcal vaccines in New Zealand

Only meningococcal conjugate vaccines are now available in NZ. Polysaccharide vaccines have been withdrawn. As of 2017, a licensed meningococcal B vaccine is unavailable.

- **Quadrivalent vaccines**
  - Meningococcal ACYW-135 (Menactra®)– conjugated to diphtheria toxoid protein; funded for special groups
  - Meningococcal ACYW-135 (Nimenrix®)– conjugated to tetanus toxoid, unfunded

- **Group C vaccine**
  - Meningococcal C (NeisVAC-C®)– conjugated to tetanus toxoid protein; funded for special groups

2.10.2 Timing and vaccine options

When disease rates are high in adolescence and early adulthood, booster doses are likely to be required to maintain seroprotective antibody levels to gain disease control. Adolescents have the highest meningococcal carriage rates, therefore, herd immunity may be achieved by initiating catch-up campaigns across adolescent age-groups but empirical evidence currently lacking.

The age and number of priming doses necessary for a universal programme in New Zealand may depend on the age at which meningococcal disease is most prevalent and whether New
Zealand choses to aim for herd immunity control by the introduction of meningococcal conjugate vaccine in a catch-up programme. In the United Kingdom, effective reductions in the number of priming doses given in infancy for its meningococcal C immunisation programme could only be achieved once herd immunity and low carriage rates had been established.\textsuperscript{44}

There is currently insufficient data to determine if the recombinant MenB vaccine, 4CMenB, is effective in reducing carriage of group B meningococci in teenage populations and whether herd immunity can be achieved through immunisation campaigns targeting adolescents and young adults.

Ten months following the introduction of 4CMenB in a two-dose infant priming schedule in the UK, the incidence rate of MenB cases halved in vaccine-eligible infants in the UK, irrespective of infant vaccination status or MenB strain coverage.\textsuperscript{45}

### 2.10.3 Summary of options

If introducing a conjugate vaccine to prevent meningococcal disease

- Start with a mass campaign across children and adolescents/young adults to establish herd immunity
- Introduce scheduled doses to the two age groups at highest risk – infants and adolescents.

There is insufficient data to determine the optimum schedule for the recombinant MenB vaccine. If herd immunity is achievable, the booster schedule is anticipated to be similar to the conjugate vaccines.

### 2.11 Coadministration

DTaP-containing vaccines should be given at the same time as conjugate vaccines, to avoid potentially immunosuppressive effects of epitope competition.\textsuperscript{24}

DTaP is known to have a suppressive effect on Hib-TT immunogenicity and therefore it is recommended that they are not given earlier (i.e. at birth) than the first Hib dose when using a Hib-TT vaccine. Although conjugate interactions are known, there appears to be no effect clinically on the population-wide effectiveness of these vaccines when conjugates are given simultaneously. In the majority of study cohorts, the antibody levels achieved were above protective thresholds.\textsuperscript{24, 46}

Effectiveness in disease control is the purpose of immunisation and protection should be targeted at the age groups most vulnerable to disease. Changes to schedules, made specifically to avoid possible changes to immunogenicity that do not alter clinical protectiveness, are not likely to be beneficial. Further data is required to assess the effects.
2.12 Conclusions

New Zealand had good disease control for most diseases. To further reduce burden on the health service, alternative schedules could be implemented which, for example, continue to improve disease control and/or to reduce the number of doses given. Potential immunisation schedule change suggestions are summarised in Table 2 based on findings of this literature review.

Table 2: Summary of alternative schedules for NZ

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Current schedule</th>
<th>Potential changes</th>
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| DTaP        | 3 +1 6w, 3m, 5m + 4y In pregnancy, from 28-38 weeks of gestation | • Extend maternal Tdap immunisation, e.g from 20 weeks  
• Delay start dose following maternal immunisation (e.g. start at 3m)  
• First dose with wP-containing vaccine  
• Included additional booster in 2nd year of life  
• Review option for a 2+1 schedule |
| Hep B       | 3+0 6w, 3m, 5m   | • Closely monitor the targeted birth dose to ensure all high risk infants receive vaccine at birth  
• >6m between dose 2 and 3 (2+1) (e.g. 6w, 3m, 9-15m) |
| Hib         | 3 +1 6w, 3m, 5m + 15m | • 2+1 (e.g. 6w, 3m, 9-15m) |
| PCV         | 3+1 6w, 3m, 5m + 15m | • 2+1 (e.g. 6w, 3m, 15m) |
| MMR         | 2 doses 15m and 4y | • Temporary catch-up dose for adolescents and young adults |
| Varicella   | 1 dose at 15m 11y catch-up | • Two doses are expected eventually to be required  
• Use MMRV instead of MMR+V (2 injections), depending on community acceptability, principally for second dose |
| Meningococcal | not included | For serogroups ACYW:  
• Infant and adolescent doses introduced depending on disease epidemiology  
• Adopt a herd immunity strategy, start with a mass catch-up campaign  
For serogroup B  
• Depending on disease epidemiology, introduce 2+1 infant schedule. |

DTaP = combined diphtheria, tetanus and acellular pertussis; HepB = hepatitis B; Hib = Haemophilus influenzae type B conjugate; PCV - pneumococcal conjugate; MMR = combined measles, mumps rubella; MMRV = plus varicella; w = week, m = month, y = year
Literature review

3 Literature review objectives

This literature review focuses on the usage, effectiveness in disease control and immunogenicity of the vaccination schedules of vaccines included on the National Immunisation Schedule (the Schedule) for children up to the age of 5 years in the New Zealand. The review considers data published or reviewed during January 2013 to June 2017. For details of the methodology for the literature search refer to the section 11.

The main objective of this review is to provide information around the use of vaccines and to help inform decisions relevant to immunisation programmes in NZ, it is not a systematic review. Cost effectiveness and vaccine safety are not reviewed.

4 Pertussis

4.1 Background

*Bordetella pertussis* is a bacterial infection that causes a paroxysmal cough, commonly known as whooping cough in children or the hundred-day cough in adolescents and adults. Infants are most vulnerable to this infection since it can result in brain damage caused by hypoxia during episodes of apnoea. A key virulence factor secreted by *B. pertussis* is pertussis toxin.47

Currently available pertussis vaccines do not provide long lasting protection, nor significant herd immunity, therefore the primary aim of pertussis immunisation is to reduce the risk of severe pertussis, particularly in infants in whom pertussis associated morbidity and mortality is the highest.1

During the most recent epidemic in New Zealand during 2011 to 2013, several hundred infants were hospitalised and three infants aged under 6 weeks died.48 To provide better protection for these youngest infants, maternal immunisation with a booster dose of tetanus, diphtheria and acellular pertussis (Tdap; Boostrix®) vaccine has been funded in the last trimester of pregnancy (gestational weeks 28-38) since 2013.

There are several challenges surrounding pertussis immunisation. The infants that are most at risk from the severity of pertussis are the very young, with naïve immature immune systems. The current pertussis vaccines appear to be inefficient at preventing transmission of the infection, therefore herd immunity and ring-fence protection are ineffective strategies and protection is only afforded to those who have personal immunity. Although there is no established serological correlate of protection, it is known that pertussis antibody levels wane rapidly, so that the duration of protection of these vaccines appears to be less than ten years, allowing recurrent outbreaks to occur. A protective role for cell-mediated immune memory has not been clearly identified, since reinfection of wild-type disease is known to occur.11

Pertussis is a complex extracellular and intracellular infection. How *B. pertussis* evades body defences and how the immune response works to prevent disease is poorly understood. The bacterium is able to adhere to and be internalised by the ciliated epithelial cells of the respiratory tract, cause signal changes within those cells and to locally and systemically modulate the innate and cellular immune system. Not only does the infection manifest as
respiratory disease, it is also able to cause metabolic disturbance, hypoglycaemia and toxicity in the brain.\textsuperscript{47}

One suggested cause for the apparent reduced effectiveness of the acellular pertussis vaccines is that over time there have been changes to the epitopes in the circulating strains of \textit{B. pertussis} and so that antigenic drift has occurred resulting in mismatch of the antigens in these vaccines. However, there is no evidence of diminished vaccine effectiveness against circulating strains.\textsuperscript{1}

4.2 Pertussis vaccination

In NZ, prior to the introduction of aP vaccines in 2000, whole cell pertussis (wP) was used in the infant vaccines. However, these had high reactogenicity and most HICs have elected to switch to the aP vaccines with a better reactogenicity profiles. This review has concentrated on acellular or mixed schedules as used predominantly in HIC rather than wP only vaccine schedules.

4.3 Immunogenicity of pertussis vaccines

4.3.1 Background

No correlate of protection has been established for pertussis antibody titres and high antibody titres do not necessarily translate to high vaccine effectiveness. It is not yet clear which pertussis antigens induce the most efficacious antibodies in preventing disease and disease transmission. The role of cell-mediated immunity, in particular for T cell subclasses, in immunity against pertussis is also undefined.

However, humoral responses to pertussis antigens were well characterised during the efficacy clinical trials conducted prior to the switch from wP vaccines to aP vaccines.\textsuperscript{1} It is known that the presence of anti-pertussis toxin antibodies can prevent severe pertussis in infants and it has recently been shown that this protection can be passively acquired from vaccinated mothers by transplacental transfer.\textsuperscript{5, 6}

Antibodies to PRN, Fim2/3 and PT have been identified as surrogate markers of protection against pertussis for multicomponent aP vaccines. Since the levels and specificity of antibodies induced vary between vaccines, together with variations in assay sensitivity, it is difficult to define a correlate of protection for pertussis.\textsuperscript{47}

The age at which vaccines are given can have consequences for the effectiveness of subsequent immunisations. For example, neonatal doses of DTaP may result in suppression of antibody response to Hib vaccines conjugated to diphtheria or tetanus toxoids. Also the presence of passively acquired maternal antibody can diminish the presence of antigen in an infant, therefore, if the vaccine is given at too young an age when maternal antibody levels are high, insufficient antigen is available for the infant to mount an immune response. This effect is less marked with inactivated vaccines than live vaccines.\textsuperscript{3}

The spacing of vaccine doses is important for the affinity maturation of the immune response to generate and maintain high affinity, antigen-specific memory. However, spacing of the doses needs to be balanced with the ability to give multiple vaccine antigens in one injection. For most vaccines, wide spacing of multiple doses is not critical in the development of immune memory, but may affect disease control prior to being fully immunised. The spacing requirements of schedules also varies with age and immune status.

Most inactivated vaccines are not known to interfere significantly with the immune response of other vaccines and can be given simultaneously or spaced between doses of other
inactivated vaccines or live vaccines. However, based on animal and human studies, there is the potential for immunological responses to inhibited when the interval is too short between two parenteral doses of the same or different live virus vaccines. Oral live vaccines do not interfere with immune responses to parentally administered live vaccines.3

In NZ, infants younger than 6 weeks of age are most vulnerable to severe pertussis, which can result in long term brain damage and death. Two strategies have been considered in the literature to provide immune protection for infants from birth. Firstly, passive transplacental transfer of pertussis antibodies from the pregnant mother prior to birth, and secondly, the administration of a pertussis-containing vaccine dose within a day of birth. The immunogenicity of these strategies are considered.

4.3.2 Maternal doses

IgG antibodies to pertussis toxin and filamentous haemagglutinin readily cross the placenta and antibody concentrations in infant serum have been shown to be comparable or higher than those in the mother. Vaccination in pregnancy with Tdap vaccine aims to boost immunity and IgG antibodies in mothers with immune memory to pertussis (as well as tetanus and diphtheria), to help to protect both mother and baby from pertussis infection.3

A RCT conducted in the US found that infant sera contained significantly higher concentrations of pertussis antibodies at birth and at 2 months of age following maternal immunisation with Tdap at 30 to 32 weeks gestation compared with infants of mothers who were vaccinated postpartum (anti-PT IgG in infants at birth: 68.8 EU/ml [95% CI 37.1-70.1] vs 14.0 EU/ml [7.3-26.9]; p<0.001). No significant differences in antibody responses were observed in infants from either group following the fourth dose of DTaP.49

When Tdap vaccine was given to 18 pregnant women (mean gestational age 29 weeks [range 25-32]), vaccine-specific IgG against all five components increased to the same extent as in 16 age-matched non-pregnant controls. However, the cellular immune response in the pregnant women was impaired. Non-pregnant women showed increased T cell proliferation and interferon-gamma (IFN-γ) production against tetanus toxin, PT and FHA antigens, whereas in pregnant women only T cell responses to TT were increased and were less than the controls. For both groups, the cellular responses returned to baseline by one year. Antibody levels had decreased by 1 year, particularly against PT, but remained significantly higher than prevaccination levels for all of the Tdap antigens.50

The timing of the maternal immunisation is important to consider – balancing the waning of PT antibody with the accumulation of sufficient antibody to protect the newborn. Preterm infants may not acquire sufficient antibody or may be born before the mother has been vaccinated. In a prospective observational study conducted in Switzerland between July 2014 and February 2016, cord blood samples were collected from preterm neonates of mothers who had received Tdap according to Swiss recommendations during the second trimester (gestational week [GW] 13 – 25, n=37) or third trimester (from GW 26, n=48 infant/mother pairs). Birth antibody levels were significantly higher for both anti-PT and anti-FHA antibodies following vaccination in the second trimester compared with vaccination in the third trimester: anti-PT 41.3 (29.6-57.5) vs 22.1 EU/ml (14.3-34.2), p=0.024; anti-FHA 201.1 (149.7-270.1) vs 120.2 (80.6-179.2) EU/ml, p=0.040. None of the 37 preterm infants born to mothers immunised in the second trimester were seronegative. Eleven infants born following third trimester immunisation were seronegative. Eleven infants born following third trimester immunisation were seronegative. 38% of these infants were born between GW 30-33 and 20% born GW 34-36. The study concluded that, although placental antibody transfer has been established as being most efficient during the third trimester, a longer transfer time appears to result in a greater accumulation of antibody in the fetus.7
Conclusions
Following booster immunisation of pregnant mothers with Tdap, anti-pertussis antibodies are effectively transferred to infants during pregnancy. Immunisation in the second trimester may result in a greater accumulation of protective antibody and provide earlier protection to infants born preterm.

A decline in antibody levels, within a year of vaccination, and impaired T cell responses in pregnant women support repeat booster doses during each pregnancy to provide adequate antibody to infants.

4.3.3 Birth doses
Studies in which wP vaccines were given at birth suggested immune tolerance was induced to pertussis antigens. Although later studies using aP vaccines at birth did not find any decrease in antibody response to pertussis antigens after the third dose of scheduled pertussis-containing vaccines, there was evidence of interference with Hib and hepatitis B vaccine responses.

4.3.3.1 DTaP at birth
As reviewed by Edwards and Berber in 2014, a study was conducted by Belloni et al (2003) to investigate the immunogenicity of birth doses of DTaP. Three-component aP vaccine was administered at birth and age 3, 5, 11 months (group 1) or at 3, 5, 11 months only (group 2). At 5 and 6 months of age, geometric mean titres (GMT) of anti-FHA and anti-PRN IgG were significantly greater in group 1, who had received two doses of vaccine, than group 2 who had only received one dose. However by the age of 12 months, the titres of anti-PT antibodies were significantly lower in group 1, suggesting that the birth dose suppressed anti-PT immune response.

In a study conducted by Halasa et al (2008) of infants who had received DTaP as neonates, lower diphtheria toxoid antibody GMTs were detected at 7 months of age. Fifty infants were given DTaP and hepatitis B vaccines or hepatitis B alone at 2-14 days after birth. Routine immunisation, including DTaP, was administered at 2, 4, 6 and 17 months to both groups. The infants who received DTaP at birth had significantly lower GMTs for anti-PT and anti-PRN IgG at 6, 7 and 18 months, anti-Fim at 6, 7, 17 and 18 months and lower anti-FHA at 18 months of age.51

A third study, conducted by White et al (2010), found that although neonatal vaccination induced earlier IgG response, a strong Th2 bias was seen in T-cell memory responses with high interleukin-5 (IL-5) and IL-13 production.51

4.3.3.2 Monovalent acellular pertussis at birth
Wood et al (2014) investigated antibody and cell-mediated immune responses at 4 years of age in Australian children who were administered monovalent aP at birth. In a previous study, they had shown that monovalent aP given at birth and at one month achieved higher pertussis IgG antibodies by 8 weeks of age compared with controls. A blunting of pertussis antibody responses was observed to booster doses given in the second year of life following birth doses of DTaP but not monovalent aP.9

At 4 years of age, those who had received monovalent aP at birth had a trend to lower anti-PT IgG compared with those who received the first dose of aP-containing vaccine at 8 weeks of age (GMT 28.7 versus 53.6 EI.U/ml) following DTaP-IPV booster, but the groups had identical anti-PRN and FHA antibodies. Group 1 received aP and HepB vaccines within 4 days of birth and aP at 4 weeks, group 2 received aP and HepB at birth only, and group 3 received HepB only at birth. All 52 infants received routine vaccinations of DTaP-IPV-HepB/Hib and PCV7 at 2, 4 and 6 months, followed by boosters at 4 years of age of DTaP-
IPV and MMR. Although group 1 had higher anti-pertussis antibody levels at age 8 months, by 2 years of age all groups had similar antibody levels. Less than 20% of the study participants had detectable PT and PRN IgG at 2 years of age, which declined to <15% prior to the 4 year-old booster. Across all groups, four-fold increases in PT IgG and PRN IgG were seen following DTaP-IPV booster at 4 years and all children had detectable anti-pertussis antibodies one month after the booster. Compared with the infants who did not receive birth doses, those who had received aP at birth had significantly more Th2 (IL-5, IL-9 and IL-13) cytokines with no differences in Th1 cytokines (IFN-γ, IL6 and TNF-α). A large multicentre trial is underway in Australia to examine humoral and cellular immunity, maternal antibody interference and bystander interference with concomitantly administered antigens, and safety of birth aP vaccine followed by DTaP at 6 weeks of age.

**Conclusions**

Birth doses of aP resulted in a Th2-biased immunity to further doses of aP-containing vaccines. Blunting of the anti-PT and anti-diphtheria antibody responses was observed in the second year of life following birth doses of DTaP but not with monovalent aP.

### 4.3.4 Immunogenicity of primary schedules in infants

The recent literature on the immunogenicity of different infant primary schedules is considered. Overall, various primary schedules of combination DTaP vaccine (for example 2-3-4, 2-4-6, 3-4-5 and 3-5 month schedules using DTaP-IPV-HepB/Hib vaccine) have been shown to be immunogenic for the antigens contained within them, including pertussis.52

#### 4.3.4.1 Antibody response to infant schedule vaccines

The Multicenter Acellular Pertussis Trial, a RCT conducted during the late 1990s, compared the immunogenicity of 13 DTaP and one DTwP vaccines in children receiving their fourth and fifth pertussis vaccine doses (following primary immunisations at 2, 4 and 6 months). Findings were reviewed by Edwards et al in 2014. They noted that significant increases in antibodies against all the included antigens were observed for all the vaccines. However there was a wide variation in antibody levels between vaccines, for example, mean PT IgG GMTs ranged from 29 to 180 EU/ml and for PRN ranged from 3.3-185 EU/ml. Another study also found that, although the GMTs varied between two DTaP vaccines, the pattern of decrease in antibody titres at one month and 15 months were consistent between the DTaP vaccines.51

#### 4.3.4.2 Duration of antibody persistence

The long term persistence of pertussis antibodies was assessed in 57 children aged 5 years in Sweden following scheduled immunisation with aP containing vaccines, either DTaP-IPV-HepB/Hib (Infanrix®-hexa, group 1) or DTaP-IPV/Hib (Infanrix®-IPV/Hib, group 2), at 3, 5 and 11-12 months. By 5 years of age, all antibody geometric mean concentrations had declined markedly compared with antibody levels after dose three. Antibodies against PT, FHA and PRN were detectable in 0, 12 and 8 of the 12 children in group 1, respectively. In comparison, seroprotective antibody levels were observed in 7 of the children for diphtheria, 10 for tetanus, 5 for HepB and 10 for Hib. Out of the 45 children in group 2, antibodies were detected in 9 children for PT, 41 for FHA, 34 for PRN. When compared with data from previous studies in children who had four doses by age 5 years, anti-diphtheria, tetanus and pertussis antibody seropositivity was similar. The low levels of anti-PT antibodies at age 5 years suggested a susceptibility to infection and little exposure to disease, and supported the administration of a preschool booster.53
4.3.4.3 Influence of maternal antibody

The immunogenicity and quality of the immune response to the first dose of an infant immunisation series depends on the presence of maternal antibody and the age at which the priming vaccine doses are given. An individual participant meta-analysis of de-identified clinical study data was conducted by Voysey et al. (2017) to investigate the influence that maternally-derived antibodies have on the infant vaccine responses. The study examined antigen-specific antibody concentrations prior to and at one month after priming doses and at one month after booster vaccinations of 7,630 infants from 32 immunogenicity studies of licensed and unlicensed vaccines across 17 countries. The mean age at baseline was 9 weeks (± standard deviation 2.3 weeks). NB: Any maternal antibodies were induced by natural exposure and these studies did not include any infants born to mothers who received antenatal vaccination.

Pre-existing maternal antibody was found to have an inhibitory effect on infant antibody responses to priming doses for 20 out of 21 vaccine antigens. For aP containing vaccines, the presence of two-fold higher maternal antibody concentration was associated with 11% lower post-vaccination antibody for PT and FHA and 22% lower anti-PRN antibody. No differences were seen between schedule spacing at 2-3-4 months or 2-4-6 months of age. The influences of maternal antibody remained at age 12-24 months prior to and after booster doses against aP antigens. When infants were immunised at an older age, higher antibody responses to priming doses were seen for 18 out of 21 antigens after adjusting for maternal antibody effects; for aP vaccines, there was a 1.06 fold increase in PT antibody per week of delay of the first infant dose, assuming a maternal antibody half-life of 26 days. Based on this, it was estimated that a delay of between 2.2 and 5.04 weeks would be required in infant immunisation to offset a 2-5 fold increase in infant levels of maternal PT antibodies to prenatal immunisation.8

Antibody responses to routine vaccinations in England were compared in infants of mothers vaccinated in pregnancy with infants of mothers who were not vaccinated. The study found that antenatal pertussis vaccination resulted in high infant pre-immunisation antibody concentrations. However, subsequent antibody responses to all three pertussis antigens, diphtheria and some CRM-conjugated antigens (PCV13 and some meningococcal C vaccines) were blunted, albeit above protective threshold levels. For PT antibodies, a 0.89-fold lower concentration was observed per 2-fold increase in pre-vaccination levels (95% CI 0.81-0.98; p=0.023) and 0.92-fold lower (0.86-0.98; p=0.011) for Fim antibodies. Whereas for FHA, antibody levels were enhanced 1.2-fold (1.11-1.31; p<0.001). Diphtheria antibody levels were 0.55-fold lower (0.46-0.66; p<0.001). Antibodies to tetanus and Hib were significantly higher in infants of vaccinated mothers by 1.24-fold (95% CI 1.05-1.46; p=0.011) and 2.3-fold (1.6-3.3; p<0.001), respectively. The study also found that infant antibody concentrations at 2 months of age were not affected by the timing of the antenatal pertussis immunisation in the third trimester. It was concluded that long-term follow-up of children of antenatally vaccinated mothers would be required in the absence of a serological correlate of protection for pertussis.54

Although these study concluded that maternal immunisation strategies have the potential to influence established infant programmes, the effects of lower antibody responses were not assessed clinically.

4.3.4.4 Concurrent administration

In a randomised open-label phase II clinical trial in Canada, when administered concurrently or one month apart, DTaPs-IPV-HepB/Hib and PCV7 elicited satisfactory antibody responses to all vaccine antigens in toddlers when given at 15 months of age after priming with routine immunisation.
three-dose primary series at 2, 4 and 6 months of age. Following concurrent administration, a ≥4-fold rise was seen in 99.3% of toddlers for PT antibodies, 88.9% for FHA, 92.4% for PRN and 99.3% for Fim-2/3 antibodies. Seroprotective booster responses were seen for the other vaccine antigens.55

Other recent papers on concurrent administration with pertussis-containing vaccines either evaluated the immunogenicity of antigens not currently included on the NZ immunisation schedule, such as meningococcal C, or were studies of unlicensed vaccines, such as the heptavalent DTaP-IPV-HepB-Hib-MenC vaccine or fully liquid Hib-containing multi-antigen vaccine. These have not been reviewed since they are not currently relevant to NZ.

**Conclusions**

Antibody levels against pertussis toxin decline more quickly than for other antigens following primary immunisation. Since PT is a key virulence factor in pertussis, the ability to neutralise the toxin is likely to be diminished by a decline in antibody. In DTaP primed toddlers, the levels of pertussis antibody could be increased by booster doses.

Although a blunting effect on immunogenicity to primary series immunisations has been observed due to the presence of maternal antibodies, particularly against pertussis and diphtheria, it is probably not sufficient to prevent priming of the immune response for the vaccines to be effective against severe disease. The long-term clinical significance is unknown, particularly for pertussis antigens. Seroprotective levels of antibody may be lost at a younger age where high antibody levels are not induced during priming, as seen for some vaccine brands, leading to a requirement for earlier booster doses. The role of maternal vaccination on this effect when starting the infant programme at 6 weeks of age remains unclear.

High coverage of maternal immunisation would be required to justify a delay to the start of infant immunisations to overcome any maternal antibody effects.

4.3.5 **Preschool booster responses**

In Norway, preschool boosters of DTaP are administered later than in many other countries, at 7-8 years of age rather than 4-6 years. In 2014, Norway was reported to have one of the highest incidence of pertussis in Europe, particularly in children aged from 5-19 years, despite 95% immunisation coverage. A cross-sectional study was conducted to investigate the antibody titres in 498 children, born between 1998 and 2003, who were primed at 3, 5 and 12 months of age with three component (PT, PRN and FHA) DTaP. Sera were obtained from stored routine laboratory samples and those with diagnosed immunodeficiencies were excluded. Anti-PT and FHA IgG antibody levels increased following the booster dose and were highest in those who had most recently been vaccinated: a peak within 100 days post booster was more than six times the prebooster levels of anti-PT antibodies (mean prebooster anti-PT = 7.3 IU/ml; peak within 100 days post-booster anti-PT = 45.6 IU/ml [95% CI 24.8-83.9]). These titres steadily declined, but remained significantly higher after the booster fourth dose than prior to the booster (including in samples collected 1001-1745 days after booster; p<0.05). The proportion of samples with anti-PT IgG falling to below 5 IU/ml increased from none in the first 300 days to 14-16% after 300 days and 18-30% by days 1001-1745. Anti-PT IgG was ≤5 IU/ml in 43% of the 104 subjects who had not received a booster dose (geometric mean of 6.4 years since primary DTaP immunisation). Of those who were unvaccinated, 31% had anti-PT IgG ≤5 IU/ml (GMT for group 11.8 IU/ml; 95% CI 6.0-23.2). The study concluded that antibody immunity against pertussis is low 5 years after primary vaccination and that a moderate immune response is induced by booster at 7-8 years, but this protection wanes to prebooster levels within a few years.17 In
2013, since the sera used in this study were collected, an adolescent Tdap booster given at 15 years of age was introduced in Norway.

**Conclusions**
To adequately boost anti-PT antibody levels to provide seroprotection, preschool doses are required within 5 years of the primary series before the levels decline to baseline.

### 4.3.6 Comparison between immune responses to pertussis vaccines and disease

Whole cell vaccines more closely mimic wild-type infection than acellular vaccines and induce similar T cell profiles with a Th1 predominance. Whereas, acellular vaccines only contain three or five pertussis antigens, understood to be pivotal in the immune response to pertussis, and induce a mixed T cell profile with Th2 predominance. However, the role of cell-mediated immunity in the prevention of pertussis is unknown and reinfection with wild disease can occur, suggesting incomplete memory.

#### 4.3.6.1 T cell response

Despite rapidly declining antibody levels following immunisation with aP, DTaP-containing vaccines were found to be better inducers of cell-mediated immunity (CMI) than DTwP vaccines and that this immunity persisted. When characterizing the cytokine profiles, DTaP were shown to induce both Th1 and Th2 type responses, whereas the DTwP response was as seen following the natural infection and predominantly Th1 driven. Both vaccines induced Th17-type cytokines, which have an important role in defence against extracellular pathogens.51

DTaP was shown to induce higher memory B cell responses following a booster dose at 4 years of age in aP primed children than those primed with wP. Conversely, pertussis-specific immune memory was longer lasting in children primed with wP. In aP primed children, T cell activation remained elevated after 3 years and responsiveness was not increased by booster doses. This was likely to be due to natural boosting by circulating infection in the older children.

#### 4.3.6.2 Th2-induced antibody responses

Since aP vaccines induce mixed Th cell responses against pertussis antigens, there is a likelihood of coproduction of vaccine-specific IgE as well as IgG antibodies, which contribute to an increased risk of delayed local reactions following a four-dose schedule of DTaP, such as transient and painless swelling of limb. Injection site reactions to preschool boosters have previously been shown to be attenuated if infant priming includes at least one dose of DTwP, or infants are primed with three doses of DTaP and a fourth dose (first booster dose) is given later than the second year of life. As well a risk of local reactions, a theoretical risk has been proposed of pathogen-specific IgE interfering with clearance mechanisms during infection.56

An Australian study confirmed generalised IgE-trophic activity of DTaP vaccine in preschoolers, and following the preschool booster at 5 years of age. Similar transient effects were also observed in infants (vaccinated at 2, 4, 6 months, with or without 18-month booster dose, with age-appropriate routine IPV or MMR vaccination). Transient food allergen-specific IgE responses were also more common in infants exclusively primed with DTaP; data related to symptoms of allergy were not available. A bystander IgE response to tetanus-derived antigen (TT) was also observed transiently during priming with DTaP but not with mixed DTwP/DTaP priming. The authors hypothesised that high levels of pertussis-specific IgE may serve as a biomarker of the risk for breakthrough pertussis infection amongst vaccinated children. As an alternative to reintroducing DTwP as a first dose, it was
suggested that an adjuvant, such as a defined toll-like receptor (TLR) agonist, would be a good option for aP vaccine to bind to the Th2-skewing alum component of these vaccines.56

**Conclusions**

There is concern that Th2 and/or Th17 predominant immunity may lead to hypersensitivity in DTaP primed children following repeat doses. It is plausible that the induction of Th2 type antibody subclasses, in particular IgE, could be associated with increased risk of allergic reactions in children primed with DTaP. Any associated food allergen sensitivity appeared to be transient, but bystander responses to tetanus-containing vaccines may be relevant, including the use of TT conjugated vaccines or repeated Td boosters given into adulthood.

**4.3.7 Whole cell and acellular pertussis vaccine priming and mixed schedules**

**4.3.7.1 T cell responses**

The differential pattern of T cell responses induced by wP and aP vaccines was shown to be maintained after booster vaccination, for up to several decades after the original priming. This suggests that childhood vaccination with aP or wP induces fixed responses to pertussis, unchangeable with boosting. Bancroft et al (2016) examined T cell and antibody responses to pertussis antigens of peripheral blood mononuclear cells (PBMCs) from healthy volunteers in the US, originally primed with either wP (n=13, born before 1991; median age 27 years [range 24-65]) or aP vaccines (n=20, born after 1997; median age 19 years [18-21]). Participants who had been diagnosed with pertussis infection at any time of their lives were excluded. Antibody titres to PHA, Fim2/3, PRN and PT antigens did not differ significantly and no antigen dominance was detected between the two groups.10

When cultured with IL-2, the T cell response in the aP-primed cohort was approximately two-fold greater than for the wP-primed cohort (median 6800 SFC/10⁶ PBMC per donor vs median 2900 SFC/10⁶ PBMC per donor, respectively; p=0.01). FHA accounted for 37-50% of the total response, and similar proportions of T cell responses were seen for both groups against PRN and PT (23% and 24% vs 32% and 20%, respectively, for aP vs wP primed). Fim2/3 responses were seen in 11% wP and 3% aP primed donors. Following aP booster vaccination, increases in antibody and T cell responses were observed after 3 months in both cohorts. However, there was a significantly higher frequency of pertussis-specific memory T cells in the aP primed donors at baseline than in those primed with wP. T cell responses to individual antigens were only significantly increased against PRN in the aP primed/aP boosted donors, whereas in the wP/aP donors, there was a significant increase in response to both PRN and PT.

This study also found that Th1 bias after wP priming was maintained in adults and adolescents, both before and after boosting with aP vaccine. After booster immunisations, an approximate 300-fold difference in pertussis-specific IFN-γ/IL-5 T cell ratio was seen between wP/aP donors and aP/aP donors – demonstrating the Th1 (IFN-γ dominant) bias in wP primed T cells and the Th2 (IL-5 dominant) bias of aP primed donors. Age was not found to be correlated to this difference between the cohorts.10

Alum-adsorbed aP vaccines generate strong antibody and Th2 responses. Alum was also shown to induce the innate immune system to produce IL-1β to activate Th17 cells and these, rather than Th2 cells, were shown in an experimental animal model to have critical the role in the protective immunity provided by aP vaccines. The protective immunity from wP vaccine and wild-type disease is predominantly Th1 and IFN-γ driven, activated by lipopolysaccharide through TLR. By using a TLR agonist instead of alum in aP, a more protective Th1 dominant response was induced in this animal model.57
4.3.7.2 Antibody responses of mixed DTwP/DTaP priming

As discussed above, bystander stimulation of Th2 cells is seen following DTaP immunisation in early infancy, which has been shown to result in transient vaccine-specific and total IgE production to unrelated antigens including food allergens. The study suggested that baseline pertussis-specific IgE titres may provide a mechanistic link to a susceptibility of pertussis in DTaP recipients. Further, findings demonstrated that mixed DTwP/DTaP priming schedules may improve resistance to disease and attenuate IgE effects on long-term vaccine-specific memory.56

Conclusions

Protective immunity against pertussis infection is afforded predominantly by Th1 cells. Priming with aP vaccines alter this to a less protective mixed T cell response involving Th2 and Th17 cells. This pattern of response is established after the first dose and is not altered following subsequent doses, therefore, immunity to pertussis is defined for life in aP primed individuals.

As summarised below, adapted from Edwards and Berber, 2014:

1. aP vaccines are immunogenic, but responses vary between different vaccines
2. Pertussis antibody wanes rapidly but promptly increases after booster vaccination with aP vaccines
3. wP vaccines also vary in immunogenicity and efficacy
4. Memory B cells persist in both aP and wP primed children
5. Neonatal immunisation with DTaP has been associated with some suppression of diphtheria and pertussis antibodies, this effect was less when monovalent aP was given at birth
6. T cell activation remains high in aP primed children and is not increased with aP boosters, whereas in wP primed children, the response increases with aP booster and natural infection.51

4.3.8 Role of immune response in prevention of transmission

There are two functions of the immune response against pertussis:

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

Questions remain around the role of T cell immunity to pertussis, although studies in mouse models have demonstrated that T cell immunity is required to protect against infection. B. pertussis has been shown to evade the immune system by inducing regulatory T cells and adhesion molecules allow it to enter the cells of the airway and to exist asymptptomatically as an intracellular infection. As well as the role for CD4 helper cells, particularly Th1 and Th17 cells, there is evidence that CD8 cytotoxic T cells may be important in the immune response to contain the disease.11

As reviewed by Fedele et al (2015), T cells were shown to be important in sterilizing immunity against pertussis. In a baboon model, transmission of infection to unvaccinated controls occurred from animals that were unable to clear the infection rapidly. The baboons vaccinated with aP vaccine were protected from pertussis disease, but not from bacterial colonisation, and were unable to prevent transmission of infection. Vaccination with wP induced rapid clearance of infection from the lungs which prevented colonisation and transmission.11
Conclusion

In terms of antibody responses, a sterilising function for IgA in the mucosa may be more important in preventing transmission than non-sterilising serum antibodies that reduce severity of the disease but not transmission.

4.3.9 Summary of pertussis immunogenicity

The immune response against pertussis is not well understood and differences in the response to acellular vaccines compared with whole-cell vaccines and wild disease, give rise to further questions. Bordetella pertussis is able to modify the immune response and cells of the respiratory tract to evade destruction, and even following wild-type infection, immune memory does not prevent reinfection throughout life.

The role of CMI and T cell memory is not well understood for pertussis. The Th1/Th17 dominant response induced by wild-type disease and wP rapidly clears infection and potentially helps to reduce transmission.

In contrast, acellular pertussis vaccines induce mixed T cell profiles, predominantly Th2 and Th17 driven. This pattern is established from the first dose of vaccine for life. Priming with wP then aP-containing vaccines may help to improve long lasting immunity to pertussis.

Antibodies against pertussis toxin wane more rapidly than against the other pertussis antigens particularly following immunisation with aP vaccines. Anti-PT antibodies play an important role in reducing disease severity by neutralising PT. To adequately boost anti-PT antibody levels to provide seroprotection, booster doses are required within 5 years of the primary series before the levels decline to baseline.

Currently, aP vaccines are protecting infants and toddlers from severe disease, but are not sufficiently effective to prevent recurrent disease outbreaks. Acellular vaccines are less able to prevent transmission. This and waning humoral immunity are thought to be two of the factors resulting in the apparent resurgence of disease.

The presence of maternally-derived antibody has a suppressive effect on the antibody levels induced by the primary immunisation of infants against aP antigens. Finding a balance between providing protection through infant immunisations early in life and the reducing the effect of maternal antibodies needs careful consideration. It is unclear if the effect of maternal antibodies is clinically relevant, and if a decision to delay infant immunisations was made to overcome this, then it could only be of clinical benefit to the most vulnerable and youngest infants if uptake of maternal vaccination coverage was high.

Birth doses are immunogenic, but lower antibody levels have been observed beyond the first year of life. Monovalent aP vaccines would be required at birth, since there is evidence that birth doses of DTaP interfere with subsequent immunogenicity of DTaP given during infancy against tetanus and diphtheria.

The introduction of a booster dose in the second year of life may be required in NZ as maternal immunisation coverage increases. Potentially, more rapid waning of anti-PT antibody may occur if the presence of maternal antibody interferes with the primary series response, thereby, increasing the risk of disease in young children prior to their preschool booster.
4.4 **Effectiveness of pertussis vaccines**

The effectiveness of pertussis immunisation is measured based on disease notifications and hospitalisation data. An apparent increase in notifications was observed since the introduction of aP vaccines. However, no evidence of a widespread resurgence was identified by a WHO review of high and middle-income country data. Increases were attributed to natural cyclic patterns of disease.\(^1\) Another factor to consider, as to whether these reflect a true increase in disease incidence and thereby reduced vaccine effectiveness (VE), is the improved detection of *B. pertussis* by polymerase chain reaction (PCR), which has led to improved surveillance and reporting of pertussis cases. Pertussis is often difficult to diagnose in adolescents and adults since it is not characterised by a ‘whooping’ cough and can be relatively mild with a prolonged, irritating cough. None-the-less, since the primary aim of pertussis immunisation programmes is to prevent severe disease resulting in hospitalisation and death, particularly of children and infants, monitoring the effectiveness of immunisation programmes is essential.

4.4.1 **Effectiveness of maternal doses**

A retrospective cohort study, conducted using data from the Kaiser Permanente Northern Californian medical data, found that maternal Tdap vaccination was highly effective against infant pertussis in the first 2 months and in the first year of life, even after DTaP infant doses. Effectiveness of maternal Tdap vaccination was 91.4% (95% CI 19.5-99.1) up to 2 months of age and 69.0% (43.6-82.6) over the first 12 months of life. The data time period, from 2010-2015 encompassed two pertussis epidemics, and the study population included 148,981 infants born from 2010 and of these 68,168 (45.8%) infants’ mothers had received Tdap after 20 weeks of pregnancy. There were 110 laboratory-confirmed pertussis cases aged ≤1 year including 17 cases aged ≤2 months.\(^6\)

The UK introduced maternal immunisation in October 2012 as part of an emergency response to rising pertussis-related hospitalisation and deaths of infants aged <3 months. Within the first year, an observational study conducted in England, found that the introduction of pertussis vaccination of pregnant women was highly effective in preventing pertussis in infants under 3 months of age (VE 91%; 95% CI 84-95). Effectiveness was greatest when given at least 28 days and 7-27 days before birth, but fell to 38% (95% CI -95 to 80) when mothers were vaccinated between 6 days before and up to 13 days after birth.\(^4\)

Since 2012, the level of maternal vaccination coverage has been maintained at around 60% in the UK. In light of reports of blunting of immune responses due to the presence of maternal antibodies in infants to primary immunisations, Amirthalingam et al (2016) demonstrated that the effectiveness of the maternal immunisation programme has been sustained for 3 years since its introduction (NB vaccine was changed from 5-component to 3-component aP in mid-2014). VE against infant deaths was estimated to be 95% (95% CI 79-100%) and 91% (88-94%) against disease overall. Protection was retained in infants following their first dose of primary series, however, after the third infant dose, there was no further evidence of maternal antibody protection. Infants of mother who received vaccine in pregnancy were not shown to be at increased risk of disease after primary immunisation. Therefore, any blunting in immune response due to the presence of maternal antibodies may not diminish the effectiveness of the primary series immunisations.\(^5\)

**Conclusions**

The presence of anti-pertussis toxin antibodies can prevent severe pertussis in infants and effective protection can be passively acquired from vaccinated mothers by transplacental
transfer. This passive protection overcomes the need for birth doses of aP, unless the mother has not received vaccination during pregnancy, for example, in the case of preterm infants. Immunisation earlier in pregnancy, in the second trimester rather than the third, could provide adequate protection to both full term and preterm infants.

4.4.2 Effectiveness of DTaP immunisation of children

A US based cohort study investigated the incidence of pertussis in children following immunisation with five doses of DTaP born during 1998-2003 in Minnesota and Oregon. Infants were immunised at 2, 4, 5 and 15-18 months and at 4-6 years. The incidence rates rose each year of follow-up of fully immunised children. The risk ratios for pertussis, during years 2 to 6 after DTaP immunisation, increased from 1.9 (95% CI 1.3-2.9) to 8.9 (6.0-13.0) and from 1.3 (0.6-2.8) to 4.0 (1.9-8.4) in Minnesota and Oregon, respectively. The incidence of cases among 7-10 year-olds rose more than six-fold from 2007 to 2009 in Minnesota. From 2006 to 2010, the number of cases also rose in Oregon but to a much lesser degree. Minnesota reported 6.5 times more cases of pertussis in children aged 7-10 years than Oregon during 2006 to 2010; likely due to surveillance and case identification differences.

A review of vaccination strategies to improve pertussis control in HIC countries was conducted by Chiappini et al in 2013, based on literature published between 2002 and 2013. It found that the most reasonable preventive measure was simultaneous use of more than one pertussis vaccination strategy, including immunisation of adolescents and adults and the use of cocooning of newborns. Across six RCTs (five included participants aged 2-3 months and one in those aged 15-65 years), the efficacy of three-component aP vaccine was 84-85% against typical whooping cough and 71-78% in preventing mild pertussis. There are wide variations in infant schedules and the use of booster vaccinations across Europe, Australia, New Zealand and North America (see section 1). Many countries include a preschool booster, with the aim of increasing herd immunity and reducing transmission. One reviewed study found that immunity to pertussis following a fifth dose waned within 5 years and the risk of disease increased by 43% each year. The effectiveness of a Tdap booster in adolescents was found to be around 78% in a cross-sectional study conducted for a year following a mass vaccination programme targeting high school students, in over 270,000 Australian adolescents aged 12-19 years, which was lower than the estimated 92% efficacy seen during clinical trials. This review did not discuss the effectiveness of the different infant schedules in preventing pertussis in children ≤12 months. It was noted that increased awareness and the use of PCR for diagnosis may have influenced the reporting of cases in HIC countries and the apparent resurgence of disease.

Conclusions

Effectiveness of DTaP immunisation declines rapidly with time since the last dose (probably within 5 years), particularly where there is a high level of disease in circulation as seen in Minnesota. The most effective control measures involve more than one immunisation strategy, including simultaneous administration of boosters given at preschool, in adolescence and during pregnancy.

Increased pertussis awareness and the use of PCR tests in diagnosis influence estimates of vaccine effectiveness and disease reporting.

4.4.3 Timeliness of infant schedule

A US-based study estimated that the timely administration of the first three pertussis vaccine doses to infants at exactly 60, 120 and 180 days of age could avoid 278 pertussis cases, 103 hospitalisations and 1 infant death per year. The US schedule, as recommended
by Advisory Committee on Immunization Practices, is to give DTaP at the ages of 2, 4 and 6 months with a 1 month time window for each dose beginning at age 60, 120 and 180 days. Based on the 2010 National Immunization Survey data of around 17,000 subjects, the observed mean age of vaccination was 76 days, 147 days and 224 days for the first, second and third doses respectively – corresponding to delays of 16, 27 and 44 days (excluding unvaccinated infants). 59

A small US-based study found that under-vaccination with DTaP was strongly associated with the risk of laboratory-confirmed pertussis in infants and children aged 3-36 months. The odds ratio of children having laboratory-confirmed pertussis having missed or delayed DTaP doses (1, 2, 3 or 4 doses) was 4.36 (2.23-8.55; p<0.001) when compared with children who had received age-appropriate vaccination (at 2, 4, 6 and 15-18 months). The attributable risk for the entire population was 36.39% (95% CI 19.65-49.66%), hence more than one-third of all cases were likely to be attributed to under-vaccination. The study population included 72 pertussis cases and 288 controls matched for age, managed-care organisation and sex, of which 34 cases and 64 controls were under-vaccinated for DTaP. Represented in Table 3.2

Table 3: Estimate of the risk of laboratory-confirmed pertussis, a comparison between under-vaccination age-appropriate vaccinations (adapted from Glanz, 2013)

<table>
<thead>
<tr>
<th>Number of under-vaccinated DTaP doses</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs 0</td>
<td>2.25 (0.97-5.24)</td>
<td>0.06</td>
</tr>
<tr>
<td>2 vs 0</td>
<td>3.41 (0.89-13.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>3 vs 0</td>
<td>18.56 (4.92-69.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 vs 0</td>
<td>28.38 (3.19-252.63)</td>
<td>0.002</td>
</tr>
<tr>
<td>1, 2, 3 or 4 vs 0</td>
<td>4.36 (2.23-8.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Significantly more reported cases of pertussis were seen in infants over 2 months of age in Israel in those who were unvaccinated or had delayed vaccination. The routine schedule was given at age 2, 4, 6 and 12 months with DTaP-IPV-Hib; wP was replaced with aP in 2002. Israel had a pertussis epidemic that peaked in 2011. A case-controlled retrospective study of reported pertussis during 1998-2011 found that VE increased with the number of vaccines doses received. In a study population of 1268 infants aged <1 year (mean age 3.95 ± 3 months, median 2.9 months), there were 317 pertussis cases and 951 age-matched controls. Of the cases, 106 (33.4%) were aged <2 months. Overall VE for the first, second and third doses of a pertussis-containing vaccine was 72.9%, 76.1% and 84.4%, respectively. A larger proportion of cases had delayed vaccination, 78.9% of cases were fully vaccinated at 18 months compared with 99% of controls. In infants aged 2-4 months, one dose of pertussis vaccine gave 75.6% (95% CI 58.1-85.7) protection against overall pertussis and 75.2% (95% CI 45.0-88.8) protection against hospitalisation. No significant difference in VE was shown between three time periods – wP period (1998-2001), aP period (2002-2010) and epidemic year 2011. Other independent risk factors that were identified were low birth weight <2.5Kg and high birth order (4th or above). Starting infant immunisations at 6 weeks of age has been approved in Israel and guidelines have been issued to recommend vaccination of pregnant women. 60

Before some states in Australia changed from first dose at age 2 months to 6 weeks, it was estimated that an annual reduction of 8% (12% when based on epidemic year in 2001) in
pertussis notifications would follow, with a 9% reduction in hospitalisations and with decreased length of hospital stay.61

**Conclusions**

The timeliness of infant doses of vaccine appears to have significant impact on disease. However, there is no consensus as to what is the optimum schedule, since there is wide variability between the ages and intervals at which DTaP is given. Despite this, incomplete or delayed vaccination according to schedule age does affect disease control in infants.

### 4.5 Duration of protection

Since older siblings, adolescents and adults are likely reservoirs for disease in infants, the duration of protection is an important consideration for pertussis immunisation. Young adults, rather than preschool and school-aged children, were identified as the most likely source of infection for infants to due to waning immunity and mild illness.47, 62

A meta-analysis conducted by McGirr et al (2015), investigated the probability of vaccine failure in relation to time since last dose of DTaP. No significant difference was found between the annual odds of pertussis for three infant doses versus five-dose DTaP regimens (three infant doses, one dose in second year of life and a preschool booster). A meta-regression model suggested that the odds of pertussis increased 1.33 times (95% CI 1.23-1.43) for every additional year after the last dose of DTaP. The average duration of protection of DTaP was predicted to be around 3 years, assuming 85% vaccine efficacy. Based on this, it was estimated that only 10% of children vaccinated with DTaP would be immune to pertussis 8.5 years after their last dose. The participants in the five-dose studies were older on average than those in the three-dose studies, and highlighted an increased risk of pertussis in older age groups. Where a preschool booster was offered at age 4-6 years, a booster is likely to be required for adolescents from the age of 10 years, i.e. earlier than that given at 14-16 years in Canada, but in line with the 11 year-old booster given in NZ.18

A study conducted in Australia found that children with comorbidities associated with prematurity, cardiorespiratory disorders or immune compromise were particularly vulnerable to pertussis without receipt of a booster dose of pertussis vaccine in the second year of life. Despite 94% of hospitalised pertussis cases aged ≥12 months having received at least three doses of vaccine, children aged ≥12 months with significant comorbidity accounted for 54% of pertussis hospitalisations, which increased to 67% in those aged ≥4 years as compared with 17% of cases aged ≤12 months. The study recommended the reintroduction of the 18-month booster dose to protect those children with comorbidities.14 As of June 2017, the 18 month DTaP booster is included on the Australian schedules.

A nested-case control NZ study found no waning in protection between the third primary dose and preschool booster in infants primed at 6 weeks, 3 and 5 months. Vaccine effectiveness against non-hospitalised pertussis was 86% (95% CI 80-90) in infants aged 5-11 months following 3 doses of DTaP and 84% (80-88) among 3 year-old children. Following a preschool booster dose at age of 4 years, VE increased to 93%.12

**Conclusions**

The duration of protection of DTaP is relatively short and booster doses are required. A preschool booster is necessary and again in early adolescence. The requirement for a booster in the second year of life in the NZ setting is unclear, however, children with comorbidities are at increased risk of pertussis and may benefit from an earlier booster.
4.6 Summary of pertussis

Maternal immunisation provides highly effective passive protection to young infants and demonstrates a role for antibody in preventing pertussis infection. Although, maternal antibody interference that can alter the immune response to DTaP when given in the primary series.

A Th2 cell bias is established from the first dose of aP in young infants for life. This immunity is less able to prevent transmission of disease and protection wanes more rapidly than when a Th1 biased response is induced, as seen following priming with wP vaccines or after wild-type disease. To prime the response to induce Th1 bias, DTwP may be required as the first dose in mixed DTwP/DTaP schedule. Alternatively, development of next generation aP vaccines that contain adjuvants to overcome the Th2 bias to induce a more Th1 type response is suggested. There appears to a significant role for Th17 cells in pertussis immunity, but it is not as yet understood.

Literature reviewing the long term effectiveness when comparing the wide variety of infant schedule and information around the age and timing of the primary immunisation is lacking. For aP vaccination schedules, the literature generally supports booster vaccination in the second year of life, preschool boosters, boosters in early adolescence and maternal vaccination. Timeliness of primary series vaccinations is potentially important for disease control, although there is no consensus as to what spacing is optimum. Recommendations to start at 6 weeks of age may help to reduce any delay in the first dose to before 2 months of age.

NZ data to date has not supported the need for a booster in the second year of life, although, children with some comorbidities appear to be at increased risk of pertussis and may require additional boosters. It is important to monitor the effect of improving maternal immunisation uptake, in case of more rapid waning of pertussis immunity.

Due to rapidly waning immunity within 5-8 years after previous dose, frequent boosters are needed, especially in adolescents aged 10-12 years, if there is an intention to prevent disease in these older age groups and to reduce transmission to infants.

5 Haemophilus influenzae type B

5.1 Background

Since the introduction of Hib conjugate vaccines to childhood immunisation schedules, there have been dramatic declines in invasive disease rates in a variety of settings. In immunised people, Hib vaccination prevents new nasopharyngeal colonisation, thereby reducing transmission, and where immunisation coverage is adequate, provides community / herd immunity. Even in areas with moderate coverage (60-75%) or where vaccine supply has been intermittently interrupted, invasive Hib disease has virtually disappeared.

In some communities, including of indigenous Australian Aboriginal, Navajo and White Mountain Apache peoples and certain metropolitan areas of the UK, there have been small increases in invasive non-type b H. influenzae disease rates, but these have been very small compared to the decline in invasive Hib since the introduction of the vaccine.

Following the introduction of Hib vaccine in the US, there was a 98% decline in Hib disease in Alaskan Native children under 5 years of age. However, despite high coverage rates for Hib vaccination, these children continued to have rates of Hib around five-times higher than
for non-Native Alaskan or other children in the US. As reported in 2006, continued presence of Hib colonisation of unimmunised adults and older children suggests that transmission from older community members increases the risk of disease for young children. The poor living conditions, such as overcrowding, poverty and lack of indoor plumbing, are more prevalent among rural than urban Alaskans, and these are likely to contribute to disease transmission. Poverty and overcrowded living conditions are also seen in at-risk communities in New Zealand, particularly for some Māori and Pacific Islanders, and continued surveillance is essential.

Most countries administer the primary series of Hib vaccine as a combination vaccine with the pertussis schedule. There is variability in the timing of the booster doses in the second year of life and concurrent vaccines. Australia administer a Hib booster at 12 months with MMR and separate MMRV and DTaP boosters at 18 months. The UK give a single dose of Hib-MenC dose at 12 months together with MMR, PCV and MenB vaccines.

### 5.2 Hib vaccination

Three doses of Hib vaccine are provided as part of the NZ Schedule in a combination vaccine given together with pneumococcal conjugate vaccine (PCV) starting at 6 weeks of age, and a second year of life booster is given at 15 months of age concurrently with MMR, PCV and, more recently, varicella vaccine.

### 5.3 Immunogenicity of Hib vaccines

It is unknown whether high anti-polyribosylribitol phosphate (PRP) antibody titres can be correlated with protection against Hib disease, since certain individuals with apparently adequate antibody levels have had breakthrough illness events. However, based on population-level studies, antibody concentration of more than 0.15 μg/ml provides protection against invasive Hib for the short-term. For long-term protection, a concentration >1.0 μg/ml is necessary. The persistence of the antibody response following immunisation is age-dependent. Antibody levels were shown to decline rapidly within a few months of immunisation in children younger than 2 years, such that by 3.5 years post-vaccination GMTs fell to around 0.5 μg/ml in children who were immunised at age 18-35 months.

Although it was initially thought that anti-PRP memory induced by Hib conjugate vaccines was maintained after circulating antibody had waned, an increase in Hib cases were reported in 2003 in children with waning antibody levels. This reduction in antibody was observed amongst children receiving Hib vaccine in combination with DTaP, notably with tetanus conjugated Hib vaccine. To maintain protective antibody levels, booster doses were introduced.

#### 5.3.1 Priming and booster schedules

A systematic review and meta-analysis of RCTs was conducted by Low et al (2013) to compare Hib vaccine schedules and to evaluate the need for booster vaccinations. Few relevant differences were found in immunogenicity outcomes from 20 trials. These trials compared PRP conjugate vaccines (conjugated with either tetanus toxoid, diphtheria carrier protein variant, CRM197, or meningococcal outer membrane protein complex [OMP]) given as two or three primary doses with or without boosters (2+0, 2+1, 3+0 or 3+1 schedules). In some cases, the vaccine was given in combination with wP or aP containing vaccines.

Although there was much heterogeneity between three studies that compared 3+0 and 2+0 schedules, the overall the analysis found no differences in seropositivity (anti-PRP IgG ≥1 μg/ml) by 6 months after last primary dose. One study, which compared antibody responses
at 13 months of age (7 months after last primary dose and 1 month after booster) following the 3+0 and 2+1 schedules, favoured the 2+1 schedule. Two trials found that the proportion of seropositivity 1 month after booster vaccinations was high and similar between 2+1 or 3+1 schedules. Higher seropositivity was seen at 13 months of age in two trials in which infants were immunised with 3+1 than those given 3+0 schedules.\textsuperscript{22}

Only small differences in seropositivity were found between schedules and heterogeneity was low when both the age at the start of the primary schedule and intervals between doses were compared.

When comparing 2 months or 1 month intervals between doses, the results were heterogeneous and neither was favoured for the 1μg/ml seropositivity threshold. Little difference was found in seven trials comparing long and short intervals between primary and booster schedules. There was no evidence that the interval between primary series and booster doses or the age at which the booster dose is given affected seropositivity levels. The review did not consider the long term effects of each schedule. No clear evidence of a difference in protection against Hib between different Hib vaccination schedules was found from vaccine trials. In light of a lack of further data, the choice of Hib vaccination schedules is determined on an individual setting basis by disease epidemiology and programmatic conditions.\textsuperscript{22}

\textbf{Conclusions}

The age at the start of the primary series and the intervals between doses do not influence anti-Hib antibody responses significantly. However, schedules that include a booster dose (3+1 or 2+1) in the second year of life provide better seroprotection than 3+0 or 2+0 schedules.

\subsection*{5.3.2 Duration of antibody protection}

The persistence of antibodies was evaluated in 5 year-old children following three doses of at 3, 5, 11-12 months of age with DTaP-IPV-HepB/Hib or DTaP-IPV/Hib vaccine (Infanrix-hexa or Infanrix-IPV/Hib). Seroprotective antibody concentrations of Hib anti-PRP antibodies were detected in 10 out of 12 and 40 out of 45 children, respectively, at 5 years of age. The study concluded that anti-PRP antibody persistence at age 5 years was similar to that seen in a previous study giving four prior doses (at 3, 4, 5 or 2, 3, 4 and 12-23 months). The previous study also found that protective anti-PRP antibody persisted up to 9 years of age in ≥98% of participants.\textsuperscript{53, 65}

In the UK, following routine immunisation with Hib-MenC-TT conjugate vaccine (primary series at 2, 3, 4 months) in children aged 6-12 years, a greater proportion of those who had received a booster fourth dose in the second year of life had anti-PRP IgG at baseline above short-term (>0.15 μg/ml) and long-term (1 μg/ml) thresholds compared with children who had not: 74/78 (95%) vs 117/166 (70%) and 62/78 (79%) vs 72/166 (43%), respectively. Young children (aged 6-7 years), more recently primed, had better persistence of anti-PRP IgG than older children (aged 8-11 years), and sustained Hib immunity was dependent on receipt of booster fourth dose. There was suggestion of ongoing natural boosting (via PRP or cross-reactive antigens) due to Hib nasopharyngeal carriage in school-age children who did not receive a booster dose. The study also found that, as well as maintaining serum antibody concentrations, booster doses support expansion of memory B cell-clones.\textsuperscript{66}

\textbf{Conclusions}

Similar seroprotective levels of anti-PRP antibodies were shown in children aged 5 years following a 2+1 and 3+1 schedules with Hib containing vaccines. Seroprotection was also shown in most children following 3+1 schedules up to 9 years of age. To provide long-term
protection from Hib, at least during primary school years, booster doses in the second year of life are necessary to maintain seroprotective antibody levels.

5.3.3 Influence of maternal antibodies

As described in section 4.3.4.3, the immunogenicity of the first dose of infant immunisation can depend on the presence of maternal antibody and the age at which the priming doses are given. An individual participant meta-analysis to investigate the influence that maternally-derived antibodies have on the infant vaccine responses found that pre-existing maternal antibody inhibited infant antibody responses to priming doses for 20 out of 21 antigens (although when pre-existing antibody was modelled as a binary variable there was no difference for anti-PRP). When infants were immunised at an older age, higher antibody responses to priming doses were seen for 18 out of 21 antigens after adjusting for maternal antibody effects. The largest effect was seen for PRP antibody for which antibody responses were 71% higher per month increase in age at first vaccination and for the booster dose, there was a 15% increase in antibody per month delay.8

Conclusions
The presence of maternal antibody has an inhibitory effect on the anti-PRP antibody levels following priming doses. Delay in the age at which the first priming vaccination and booster dose is given results in higher anti-PRP antibody responses, when adjusted for the presence of maternal antibody.

5.4 Effectiveness of Hib vaccines

A systematic review and meta-analysis was conducted to investigate the effectiveness of conjugate Hib vaccines administered in different immunisation schedules, as reported by 30 observational studies. Overall, the review found that two or three doses of Hib vaccine are highly effective against invasive Hib disease in case-control studies (VE one dose: 59% and three doses 97%) and against Hib meningitis (VE 55% one dose, 96% two doses and 96% three doses). The review did not find that VE was influenced by intervals of 1 or 2 months in intended dosing schedules for the primary series. Consistent with immunogenicity data, two cohort studies suggested that a booster dose of Hib vaccine after the full primary series enhances VE against invasive Hib, and may also compensate for incompletion of primary series immunisation. The review concluded that to achieve high effectiveness (>85%), at least two doses of Hib vaccine are required, particularly for vaccines other than PRP-OMP conjugates (as discussed in section 5.5).21

Another systematic review was conducted to investigate the effectiveness of Hib or pneumococcal conjugate vaccines on bacterial meningitis. Eighteen studies reported outcomes relevant to meningitis morbidity and mortality. Although few provided dose-specific effects, one meta-analysis of four case-control studies (including low income countries) examined the dose-specific effects of Hib vaccine on Hib meningitis morbidity. It found that the relative risk (RR) of Hib meningitis was significantly reduced following two and three doses of vaccine (one dose: RR=0.64 [95% CI 0.38-1.06]; two doses: RR=0.09 [0.03-0.27]; and three doses: RR=0.06 [0.02-0.22]). Findings indicated that approximately three-quarters of meningitis deaths are preventable by the existing Hib and PCV vaccines.67

Conclusion
A primary course of two or three doses of Hib vaccine is highly effective (>85%) in preventing invasive Hib disease. Booster doses enhance the vaccine effectiveness and may compensate for incomplete primary immunisation.
5.5 Effects of different conjugates

Two protein conjugates are used in Hib vaccines. The most frequently used is PRP-tetanus toxoid conjugate (PRP-TT; as contained in the ActHIB®, and Pentacel®, Hiberix® and Infanrix®-hexa vaccine brands). In other vaccines, Hib PRP is conjugated to the outer membrane protein complex of Neisseria meningitidis strain B11 (PRP-OMP; PedvaxHIB® and Comvax®). A Hib vaccine conjugated with non-toxic variant of diphtheria toxin (CRM197) was found to be less immunogenic in children aged <18 months and was discontinued.20, 68

Early pivotal trials of Hib conjugate vaccines were reviewed by Pichichero et al, as summarised in Table 4.64

Table 4: Summary of early pivotal trials for Hib conjugate vaccines (based on Pichichero, 2013)

<table>
<thead>
<tr>
<th>Vaccine conjugate</th>
<th>Immunogenicity</th>
<th>Age group in trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-CRM₁₉₇</td>
<td>Strong anti-PRP response, even after booster – PRP antibody &gt;1000 times pre vaccine levels.</td>
<td>Toddlers and adults Now discontinued</td>
</tr>
<tr>
<td>PRP-TT</td>
<td>Bactericidal antibodies, levels 1000 times greater than unconjugated PRP</td>
<td>Adults and infants</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>First dose higher than other conjugates and higher still after 2nd but not boosting with 3rd dose.</td>
<td>Infants and toddlers</td>
</tr>
</tbody>
</table>

5.5.1 Interactions of conjugate vaccines

The interactions of Hib conjugate vaccines were reviewed by Findlow et al (2016). Immune interference from the vaccine carrier proteins with co-administered vaccines can impair or enhance the immune response to vaccine antigens. When specific T cells to one vaccine have an increased response to the same antigen in another vaccine, immune enhancement occurs, thereby augmenting the effect of co-administered vaccines. For example, anti-Hib IgG responses were enhanced when DTaP-IPV/Hib-TT vaccine was coadministered with MenC-TT in the UK compared with coadministration with MenC-CRM₁₉₇ vaccine. This enhancement in Hib responses was also seen when PCV10 (Synflorix) was given with DTaP-HepB-IPV/Hib-TT (Infanrix-hexa) compared with PCV7 (Prevenar).24

Conversely, suppression can occur. Immunity to a polysaccharide antigen conjugated to a carrier protein may be suppressed by pre-existing immunity to that carrier protein; termed carrier-induced epitopic suppression (CIES). In which case, where there is a lower frequency of vaccine antigen-specific B cells than carrier-specific clones, an overload of carrier will be rapidly presented to the T cells by the dominant carrier-specific B cells. This results in an impaired antibody response to the polysaccharide, PRP. The decrease in polysaccharide response is proportional to the intensity of the immune response to the carrier. For example, coadministration of PCV-TT vaccine with Hib-TT and DTaP significantly impairs the Hib antibody response when compared with coadministration with PCV-CRM₁₉₇.24

A literature review that investigated data on carrier priming of conjugate vaccines identified a potential role for carrier priming to maximise the immunogenicity of conjugate vaccines and to reduce then number of doses in the primary schedule. However, these effects were
dose-dependent and hard to predict. It was identified that a low ratio of hapten (antigen of interest such as polysaccharide) to carrier protein results in CIES and carrier overload may suppress immunity in primed individuals.46

Conclusions

Although conjugate interactions are known, there appears to be no effect clinically on the population-wide effectiveness of these vaccines when conjugates are given simultaneously. In the majority of study cohorts, the antibody levels achieved were above protective thresholds.

5.5.2 Hib-OMP conjugate vaccine use in indigenous populations

Indigenous children, such as Alaskan Native, American Indian, Australian and Canadian Aboriginal and NZ Māori populations, living in isolated, low socioeconomical situations with suboptimal living conditions are at highest risk of Hib. There is an increased force of infection and carriage in these populations and robust vaccine-induced immunity is required to prevent disease, but indigenous children in remote rural areas with significantly worse overall health status respond less well to booster doses of Hib vaccine than urban non-indigenous children.23

In the US, PRP-OMP vaccines are used among indigenous people with high incidence of early onset invasive Hib disease, whereas in Canada PRP-TT vaccines are used. Between 1996 and 2001, the US switched from PRP-OMP vaccines to PRP-CRM197, and observed an increase in invasive Hib in rural Alaskan Natives in children aged <5 years from 19.8 to 91.1 cases per 100,000 per year. During 2001-2004, following a return to the use of PRP-OMP vaccine the incidence of Hib decreased to 5.4/100,000 and 0 per year in Alaskan Native and non-Native children, respectively.63

Australia switched from PRP-OMP to PRP-TT vaccines during 2005-2009. To examine whether there had been a change in incidence of Hib disease within the indigenous Australian population following the switch, Menzies et al conducted an analytical descriptive study of 20 years of invasive Hib disease surveillance data (from 1993-2013) for children aged <10 years. During the time period, 579 cases of Hib were reported, 78 (13%) were indigenous children and 47 (60%) lived in regions with high incidence prevaccination. Following the introduction of PRP-OMP vaccination (1993-1996), Hib incidence was 18.1 per 100,000 (95% CI 10.4-29.4), which fell to 6.2/100,000 (4.0-9.2) during the later PRP-OMP (1996-2009) period and to 4.7/100,000 (1.7-10.3) following the switch to PRP-TT (2009-2013). The incidence rate ratio (IRR) between indigenous and non-indigenous children was more than ten-fold higher than seen in lesser-incidence regions of Australia (later PRP-OMP period: IRR=43 [16-145]; PRP-TT period: IRR=58 [7-2660]). The study concluded that there was no change in Hib incidence in the first 4 years following the change to PRP-TT containing combination vaccines among indigenous children living in high-incidence regions of Australia.23

Conclusions

Both PRP-TT and PRP-OMP vaccines provide protection against Hib for indigenous children living in areas of increased risk. Earlier studies found an increased incidence in Alaskan Native children when the vaccines were switched to PRP-CRM197 from PRP-OMP vaccines; PRP-CRM197 vaccine has since been discontinued due to low immunogenicity in children younger than 18 months.
**5.6 Summary of Hib vaccination**

There is no evidence of significant differences in immunogenicity following different primary and booster schedules in infants with 2 or 3 primary doses, age of commencement of schedule or spacing of 1 or 2 month intervals between doses.

Seroprotection against Hib persisted to at least 5 years of age in children who received three or four doses of DTaP-IPV-HepB/Hib or DTaP-IPV/Hib in infancy.

Recent data have shown that when the presence of maternal antibodies was considered the age of commencement of the schedule and of booster doses influenced the infant antibody response to Hib vaccination. However, it seems unlikely that this has a significant effect clinically.

Hib vaccine is highly effective (>85%) in preventing invasive Hib disease when at least two doses are administered. Booster doses in the second year of life enhance the vaccine effectiveness and can also compensate for incomplete immunisation.

Various conjugate proteins have been used in Hib vaccines. Hib antibody levels can be suppressed or enhanced when different conjugate vaccines are used in combination and with routine immunisation. These differences appear not to have an effect clinically and most children achieve seroprotection regardless of the conjugate used.

No change was observed in the incidence of invasive Hib in Australian indigenous children living in rural, high-incidence regions when the vaccine was switched from PRP-OMP to PRP-TT.

Continued surveillance is important, particularly in populations at higher risk from earlier Hib disease, to ensure that the current immunisation schedule, increased coverage with maternal immunisation with TT containing vaccine, and changes to the vaccines given do not reduce effectiveness of the Hib immunisation.

**6 Hepatitis B**

There are two main objectives for hepatitis B immunisation programmes. Firstly, since the risk of developing chronic hepatitis B infection is greatest when the infection is acquired at a young age, immunisation of infants is aimed at preventing chronic infection. Young children are likely to be asymptomatic, but later in life, chronic infection can lead to liver damage and liver cancer. The risk of chronic infection is highest in children under the age of 5 years. Also, children are highly like to transmit the infection to others through minor injuries and exposure to blood and faecal matter. Secondly, in adolescents, immunisation programmes are designed to reduce the peak in infection seen in young adults. These older age groups are less likely to develop chronic infection, but are more likely to spread the virus through sexual activity. A key question is whether infant immunisation can achieve both outcomes and if the protection provided by the vaccine is sufficiently long-lived into adulthood.

The WHO recommends that all infants to be given a first dose of hepatitis B (HepB) vaccine within 24 hours of birth, followed by two or three doses to complete the primary series. Options for three doses include monovalent birth dose and second or third doses to be given at same time as first and third DTaP vaccination; or four doses given as monovalent vaccine at birth plus three doses with other routine vaccinations. Infants who were vaccinated at birth to infected mothers were 3.5 times less likely to become infected with HepB than those who did not receive HepB vaccine. In NZ, a birth dose is only offered to infants of hepatitis B carrier mothers.
6.1 Hepatitis B vaccination

Three doses of hepatitis B-containing vaccine is delivered as combined vaccine as part of the primary series on the NZ Schedule, concurrently with PCV and oral rotavirus vaccine. Only infants born to mothers who are hepatitis B surface antigen (HBsAg) positive, or with status unknown, receive a dose of single antigen hepatitis B vaccine at birth followed by the routine primary series doses.

6.2 Duration of immune memory

A recent study conducted in Canada assessed whether hepatitis B (HepB) vaccination given at 2, 4, 6 months of age would provide protection for at least 10-16 years into adolescence and adulthood. Although little antibody was detected in some, most booster recipients responded to challenge and confirming the presence of immune memory. However, the anamnestic response was weaker or lost in more 15-16 year olds than 10-12 year olds. All participants with low baseline antibodies were offered challenge vaccinations with a standard paediatric HepB vaccine dose (10μg). A month following challenge, 97.2% of 10-11 year-olds versus 91.1% of 15-16 year-olds produced anti-HepB titres ≥12 mIU/ml (p=0.06), and most had robust responses to the challenge (≥100 mIU/ml in 91.4% younger and 79.7% of older participants, p=0.01). A loss of immune memory was thought to have occurred for three (2.2%) of the younger children and 12 (5.6%) of the older children, who were non-responsive to this first vaccine challenge and whose antibody levels remained low. All of these younger recipients and 9/12 of the older children were subsequently able to respond to a second challenge, but with a less robust response suggesting new primary responses. Of the 137 participants aged 10-11 years, 78% had low anti-HepB antibody levels (<12 mIU/ml) at baseline compared with 64% of the 213 participants aged 15-16 years (p=0.006). This puzzled the investigators, who had expected a higher proportion of the older participants to have lower antibody levels than the younger ones. After the commencement of the study, an unknown proportion of the participants aged 15-16 years were discovered to have received full adult doses rather than half adult doses of recombinant HepB vaccine due to a shortage of paediatric dosage vaccine at the time of their primary immunisations, and this may have accounted for the fewer than expected 15-16 year olds with low antibody levels at baseline. The study concluded that the British Columbian HepB vaccination programme provides satisfactory protection into mid-adolescence, but questioned whether infant vaccination can protect into adulthood. A booster vaccination given in adolescence may reinforce and extend protection for those immunised as infants.

A systematic review and meta-analysis was conducted by Schönberger et al (2013) on 46 studies reporting on anti-HepB antibodies in children and adolescents 5 to 20 years after primary vaccination. The case definitions for this review were the proportion of children/adolescents with anti-HepB antibody titre ≥10 mIU/ml and proportion of participants with a booster response that increased from below to over 10 mIU/ml. The analysis identified 55 subpopulations in 28,329 individuals across all the studies with full information on potential confounders. At the respective time measurement, 15,994 (56.3%) individuals had seroprotective antibody levels of ≥10 mIU/ml. Within 13 of the study subpopulations, consisting of 982 individuals, fewer than 25% of individuals aged 5 – 17.7 years had persistent antibody titres above 10mIU/ml. When primary immunisation responder status was excluded, most of these subpopulations shared three characteristics: 1) the gap between last and preceding dose of primary immunisation series was <6 months; 2) the first dose of vaccine was given at birth, 3) vaccine dose was
less than current recommendations [dosages not given]. When mutually adjusted, only a gap time of <6 months between last and preceding vaccinations and lower vaccine dosage were found to be related to lower proportions of seroprotective antibody titres.25

For subpopulations in which the proportion of those with antibody titres ≥10 mIU/ml was >90% until the age of 13 years or >60% older than 13 years, the characteristics were: 1) normal or higher doses of vaccine were given in the primary series, and 2) the gap time between the last and preceding dose was >6 months, and included those with carrier mothers. Univariate analysis of the data determined that significant associations were observed with: 1) maternal carrier status; 2) vaccine dosage - low compared with normal/high dose: odds ratio (OR) 0.06 (95% CI 0.03-0.15); 3) number of doses - four doses versus three: OR 3.79 (1.68-8.55); and 4) gap time of <6 months as compared with a gap of between 6 to 8 months, OR 0.27 (0.12-0.59). Natural boosting is thought to occur in infants in contact with carrier mothers.25

In a further adjusted analysis, a low antibody response (<10 mIU/ml) to booster vaccination given 5 to 17.7 years after primary vaccination was significantly associated with primary immunisation with lower doses of vaccine (adjusted OR 0.2 [0.1-0.38]). The review concluded that the timing between the second and third dose and the dosage given determines the proportion of adolescents with adequate protection into adolescence, as illustrated in Table 5.25

Table 5: Proportions of off-spring of non-carrier mothers likely to be protected against hepatitis B after primary vaccination in infancy (reproduced with permission, Schönberger, 2013)

<table>
<thead>
<tr>
<th>Hepatitis B Vaccination in Infancy</th>
<th>Proportion of Individuals Protected After Vaccination by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 5 yr (95% CI)</td>
</tr>
<tr>
<td>Estimation irrespective of dose and vaccination schedule</td>
<td>0.99 [0.97; 1.01]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Vaccination Schedule</th>
<th>At 5 yr (95% CI)</th>
<th>At 10 yr (95% CI)</th>
<th>At 15 yr (95% CI)</th>
<th>At 17 yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>Gap time &lt;6</td>
<td>0.98 [0.95; 1.01]</td>
<td>0.95 [0.89; 1.01]</td>
<td>0.89 [0.76; 1.02]</td>
<td>0.87 [0.72; 1.03]</td>
</tr>
<tr>
<td>Adequate</td>
<td>Gap time 6-8</td>
<td>0.99 [0.97; 1.00]</td>
<td>0.97 [0.92; 1.01]</td>
<td>0.92 [0.82; 1.02]</td>
<td>0.90 [0.77; 1.02]</td>
</tr>
<tr>
<td>Lower</td>
<td>Gap time &lt;6</td>
<td>0.82 [0.74; 0.89]</td>
<td>0.71 [0.60; 0.83]</td>
<td>0.59 [0.46; 0.73]</td>
<td>0.54 [0.40; 0.68]</td>
</tr>
<tr>
<td>Lower</td>
<td>Gap time 6-8</td>
<td>0.85 [0.71; 1.00]</td>
<td>0.74 [0.62; 0.86]</td>
<td>0.61 [0.52; 0.73]</td>
<td>0.55 [0.47; 0.64]</td>
</tr>
</tbody>
</table>

CI indicates confidence interval of the prediction.

A US based study investigated the duration of HepB immunity in 420 participants aged 16-19 years who had received three doses of HepB vaccine as infants, either given dose 1 within 7 days of birth (group 1) or at ≥4 weeks of age (group 2). The final third dose was given by the age of 12 months and within 10 months of dose 1. The participants received either 10µg or 20µg challenge doses at visit one. Baseline and post challenge (13-15 days after challenge dose) antibody titres were assessed to be seroprotective at ≥10 mIU/ml. At baseline most participants (76%) had anti-HepB surface antigen (anti-HBsAg) IgG titres <10 mIU/ml, and a significantly higher proportion were in group 1 than group 2. Following a challenge dose, 92% achieved seroprotection with no difference between group 1 and group 2 and booster doses. GMT in response to challenge doses were significantly higher in group 2 than group 1 and for those who received 20µg challenge dose. As of 2014, a higher dose of vaccine is given in immunisation schedule birth doses than received by these participants (5µg or 10µg per dose versus 2.5µg), and has been shown to produce 100% seroprotection rates in following primary series.71

The immune memory and ability to mount a challenge response to hepatitis B was investigated in German children aged 7-8 years who were routinely immunised with four doses of DTaP-IPV-HepB/Hib vaccine in infancy, at 2, 3 and 4 months with a booster before
18 months of age. The study found that 223/284 (78.5%) of 7-8 year olds had anti-HepBs antibody levels ≥6.2 mIU/ml (seropositive) and 205/284 (72.2%) had anti-HepBs levels ≥10 mIU/ml (seroprotected). One month after challenge dose, 259/262 (98.9%) of children had anti-HepB levels ≥10 mIU/ml and 251/262 (95.8%) had levels ≥100 mIU/ml – an anamnestic response (>4-fold increase from seropositive baseline or ≥10 mIU/ml from seronegative at baseline) was observed in 253/262 (96.6%) of participants overall. The study concluded that, even when detectable levels of circulating antibody are lost, protection from HepB is retained through immune memory in those who respond to primary immunisation.72

A Cochrane systematic review conducted in 2016 was unable to find RCT based evidence to support or reject the need for booster doses of HepB vaccine in individuals with normal immune status who had been primed with three or four doses of HepB vaccine.73

**Conclusion**

The duration of protection of HepB immunity depends on the size of the dose given in infancy and the timing of the final doses in the primary series. Where the spacing between the final two doses of the primary series are 6 months or less or the dose given during the primary series is low, seroprotection is not as well maintained into adolescence as when the spacing is >6 months and the dose is adequate. For most immunised adolescents with low antibody levels, challenge doses produce an anamnestic response demonstrating immune memory. However, when the primary series does not adequately prime immune memory, booster doses given in adolescence are insufficient to achieve seroprotective antibody levels.

### 6.3 Summary of hepatitis B vaccination

Doses of hepatitis B vaccine given at 6 weeks, 3, 5 months of age may not provide long term protection – spacing of at least 6 months is immunologically preferable between last two doses to generate long lived seroprotection.

A three-dose primary course plus a booster in the second year of life shows a good anamnestic memory in mid-childhood. Around three-quarters of children (aged 7-8 years) also had seroprotective antibody levels.

Most adolescents (92%), immunised before the age of 12 months, were able to produce a seroprotective anamnestic antibody response following challenge demonstrating that immunological memory was retained. However, more individuals had lost the anamnestic response at age 15-16 years than those aged 10-12 years.

Where cellular memory exists, whether the presence of circulating seroprotective antibodies provides any greater protection from hepatitis B infection is unclear.
Tetanus and diphtheria

7.1 Background

The scheduling of tetanus and diphtheria containing vaccines as part of the primary series sits alongside the schedule for pertussis, as they are often combined into one vaccine, such as DTaP, or in combination boosters including reduced doses of diphtheria and pertussis antigens (Td or Tdap). Three-dose primary schedules are predominant, but there are variations around the age of delivery of the first dose and subsequent intervals between doses. Two-dose primary series are mainly used in Nordic countries at 2 and 4 or 3 and 5 months of age. There is also variability in the use of booster doses in childhood, in the timing and the formulation of vaccine, and in some countries low dose diphtheria vaccine (Td or Tdap) is given from 3 years of age.

For tetanus, there is no established definitive correlate of protection and seroprotective levels depend on the type of assay used. For example, concentrations >0.01 IU/ml are considered protective for neutralising tests and modified ELISA assays, whereas, in standard ELISA define antibody concentrations of ≥0.1-0.2 IU/ml are considered as protective. However, higher antibody levels are not guaranteed to provide immunity.

Defined correlates of protection have been established for serum antibodies to diphtheria toxin (antitoxin). Antitoxin levels above 0.01 IU/ml provide some level of protection and over 0.1 IU/ml indicate full protection, however, antitoxin levels of ≥1.0 IU/ml provide long-term protection. Antitoxin levels required for complete protection can vary between individuals.

7.1.1 World Health Organization position on tetanus

The WHO released a tetanus vaccine position paper in February 2017, which particularly focussed on providing guidance around the use of booster doses to provide life-long protection against tetanus. Tetanus infection continues to occur but is rare in developed countries. Neonatal tetanus still occurs in some low income countries, despite targeted programmes for children and pregnant women.

The recommendation is for high coverage of six doses of tetanus-containing vaccines, i.e. three primary doses and three booster doses prior to adolescence, starting from 6 weeks of age. The minimal interval between the primary doses is 4 weeks, preferably, with dose 3 given by 6 months of age. Boosters are recommended in the second year of life, preschool and early adolescence (age 11-15 years). There should be at least 4 years between booster doses.

For catch-up in unimmunised adolescents, only five doses of Td are required for life-long protection against tetanus.

7.1.2 World Health Organization position on diphtheria

Diphtheria remains a significant health problem in countries without adequate routine vaccination with case fatality rates of around 10% in endemic areas.

In April 2017, the Strategic Advisory Group of Experts on Immunization (SAGE) reviewed the evidence for decennial diphtheria booster to adults in light of revised recommendations on the use of tetanus and pertussis containing vaccines and a supply shortage of diphtheria antitoxin. There has been a lack of progress in decreasing diphtheria incidence worldwide and investigation of outbreaks in 33 countries indicated that a failure to vaccinate, rather than waning immunity, was a key factor. It was noted that a significant proportion of
countries were failing to submit reports on diphtheria, that the number of cases were likely to be much higher and that it was a forgotten disease in large parts of the world. However, in non-endemic regions and based on a systematic review of the duration of protection, data do not support a need for decennial booster doses.74

The WHO states that all children worldwide need to be immunised against diphtheria and to sustain high levels of immunisation coverage. A primary series of three doses is recommended – first dose at 6 weeks of age with a minimum of 4-8 weeks between doses to be completed by 6 months of age. Three booster doses are recommended at 12-23 months, 4-7 years and 9-15 years, ideally, with at least 4 years between boosters.30

7.2 Tetanus and diphtheria vaccination

There are currently no single antigen tetanus or diphtheria vaccines available; all vaccines contain these antigens in combination. On the Schedule, tetanus-diphtheria toxoid-containing combination vaccines are administered as part of the routine primary series, with a booster at 4 years of age (DTaP), at 11-12 years of age (Tdap) and in adults during pregnancy (Tdap). Boosters are funded at 45 and 65 years (Td), as well as for those with tetanus-prone injuries without up-to-date immunisation.

The current National Immunisation Schedule in NZ does not contain a tetanus booster during the second year of life. This is in contrast with the WHO evaluation of evidence concluded that such a booster in the second year of life provide better protection from tetanus until school entry than no booster.74 However, cases of tetanus are rare in NZ and occur mostly in elderly adults with unknown immunisation history or in unvaccinated children (4 cases aged <10 years out of 32 total cases notified during 1997-2015).28

7.3 Immunogenicity

7.3.1 Immunogenicity of primary course and toddler booster

During licensure clinical trials in five RCTs, when given as part of two or three-dose primary vaccinations (between ages 2-6 months), combined DTaP-IPV-HepB-Hib (Infanrix®-hexa) vaccine was highly immunogenic for diphtheria and tetanus. Seroprotective antibody levels were achieved in 95-100% of infants, regardless of immunisation schedule. In most infants, the level of protection against diphtheria and tetanus was maintained until the age of 11-19 months; 57.9-86.4% of infants had seroprotective anti-diphtheria titres and 89.9-98.1% had seroprotective anti-tetanus titres. A booster vaccination given in the second year of life elicited a strong immune response to both antigens and 99.3%-100% of infants had seroprotective antibody levels. Post-booster GMT in primed infants were 16-36 fold and 11-27 fold higher than pre-booster levels for diphtheria and tetanus antibodies, respectively.52

As reviewed by the WHO, two primary doses of diphtheria-containing vaccine resulted in substantially lower antitoxin titres than three primary doses, but no difference in clinical protection was evident. This difference did not persist during the second year of life or after boosting. When compared with a more widely spaced schedule, with around 6 months between the second and third doses, accelerated schedules (2-3-4, 2-4-6 or 2-3-5 months) resulted in lower antibody titres. In the absence of natural boosting, booster doses are required following the primary series to maintain protection.30
Conclusion

From these pivotal clinical trial data, it appears that some infants may not be fully protected by primary immunisations for diphtheria, in particular, or possibly for tetanus in the second year of life. A booster dose successfully induces a good immune response and almost all of the infants are then protected. As incidence of both of these diseases are very rare in NZ, the importance of a second year of life booster is unclear.

Although accelerated primary series DTaP schedules induced lower antibody titres against diphtheria than more widely spaced second and third doses, these schedules provide more timely and complete protection against pertussis, which is a greater threat than diphtheria infection in NZ.

7.3.2 Influence of maternal antibodies on immunogenicity

As described previously (refer to section 4.3.4.3), the immunogenicity of the first dose of infant immunisation can depend on the presence of maternal antibody and the age at which the priming doses are given. An individual participant meta-analysis examined antigen-specific antibody concentrations prior to and at one month after priming doses and at one month after booster vaccinations. Where there were two-fold higher maternal antibody concentrations against tetanus and diphtheria, antibodies in the infants were estimated to be 13% and 24% lower, respectively. The concentration of maternal antibody at the time of the first priming dose also influenced responses to booster doses of diphtheria at 12-24 months of age. The age at first vaccination had a persistent positive effect on post-booster antibodies levels, for diphtheria, a 28% increase in antibody response was seen for each month of age the vaccination was delayed by. For tetanus and diphtheria, the time delay estimated to offset a 2- to 5-fold increase in maternal levels of antibodies were 2.6 to 5.9 and 1.7 to 3.9 weeks, respectively. Clinical protection was not evaluated in this study.

7.3.3 Duration of immunity

7.3.3.1 Reduced diphtheria antigen doses following preschool booster

A follow-up study was conducted in France to investigate the duration of immunity to diphtheria, tetanus and poliovirus in 274 adolescents (aged 11-13 years) who had received DT-IPV priming doses (at age 2, 3, and 4 months) and either standard dose DT-IPV or a lower diphtheria dose with Td-IPV at 6 years of age in an earlier study. The mean interval between the previous vaccination at 6 years of age and the baseline blood sample for this study was 4.9 years (range 4.3-5.3) and 4.9 years (range 4.4-5.3) for DT-IPV and Td-IPV groups, respectively. Anti-diphtheria antibody levels were lower in the Td-IPV group at 0.24 IU/ml (95% CI 0.18-0.33) compared with 0.62 IU/ml (95% CI 0.48-0.8) for the DT-IPV group. Antibody persistence, as defined as participants with anti-diphtheria IgG ≥0.01 IU/ml (providing clinical immunity), was shown in 98.4% of the DT-IPV group and 99.3% of the Td-IPV. A month following a booster dose of Td-IPV, the GMC rise for anti-diphtheria antibodies was greater than the DT-IPV group resulting in comparable post-booster antibody concentrations ≥1.0 IU/ml for both groups. The study concluded that Td-IPV, given as a preschool booster, confers long-term immunity. As of 2013, the schedule in France is two-dose primary series at 2 and 4 months with booster doses of DTaP-IPV at 11 months and at 6 years, and a third booster with Tdap-IPV at 11-13 years. Low-dose diphtheria-containing vaccines (Tdap) were shown to provide comparable protection to the standard dose vaccine (DTaP) in preschool age children (age range 3.5-5.1 years) for at least 5 years in a UK-based study.
Conclusions

Vaccines containing low-dose diphtheria toxoid provided adequate booster responses when administered to preschool age children to confer immunity at least until early adolescence.

7.3.3.2 Duration of diphtheria protection in adults

A US-based study investigated the magnitude and duration of immunity to tetanus and diphtheria vaccination in 546 adults (mean age 49 years, range 19-87; recruited during 2002-2008). No details were provided about diphtheria vaccination experience of the participants. Approximately 99% of subjects aged <60 years (97% for overall population) had seroprotective antibody levels >0.01 IU/ml. Diphtheria-specific seroprotective immunity declined with a mean estimated half-life of 27 years (95% CI 18-51). It was predicted that 95% of the population would maintain seroprotection for 42 years without requiring further booster doses. A model of booster vaccination every 30 years predicted that protective immunity would remain at ≥95% and that ten yearly boosters are not indicated. 29

Recommendations for diphtheria vaccination varied widely in the last century and access to vaccine was limited during and soon after World War II in Europe. A study conducted in Austria found that the antibody levels varied substantially in elderly patients and that 65% of 257 participants (mean age 66 years [range 59-91 years]) did not have seroprotective antibody levels to diphtheria, Only half of the participants knew if they had ever been vaccinated against diphtheria and a third had received diphtheria vaccination within the last 10 years. The findings of this study suggested that some older adults in this population may never have received diphtheria immunisation, and in these individuals, booster doses were insufficient for priming. 77

Conclusions

Immunity of adults to diphtheria is maintained for around 42 years without the requirement of further boosters and that childhood immunisation is long lasting. However, in populations where older adults may not have received priming immunisations, low immunity to diphtheria results in an insufficient or short-lived immune response when given low antigen booster doses (Td).

7.3.3.3 Duration of tetanus protection in adults

Although tetanus vaccine has been available since the 1920s, and the majority of older adults were vaccinated during childhood, it has been shown that the number of vaccines doses received during a life time decreases with age. The study in Austria (mentioned in 7.3.3.2) found that although 12% of participants did not have seroprotective antibody levels to tetanus (above 0.1 IU/ml), all participants produced a protective anamnestic response 4 weeks after a booster dose of Tdap-IPV. Antibody concentrations fell below protective levels in 10% of participants over 5 years prior to a second booster. Vaccination against tetanus had been received by 64% of the participants during the previous 10 years. 77

The US study, mentioned in section 7.3.3.2, found that, in general, tetanus-specific antibody levels were high (averaging 3.6 IU/ml), and as for diphtheria, 99% of subjects aged ≤60 years (97% for overall population) had protective immunity above 0.01 IU/ml. No details were provided about tetanus vaccination experience of the subjects. The half-life of tetanus-specific antibody was estimated to be 14 years (95% CI 11-17) overall as a function of time since last vaccination. A model predicted that 95% of the adult population would continue to be seroprotected against tetanus for up to 72 years without additional booster vaccinations. The recommendation in the US is to vaccinate adults over 60 years because it is the age group within the majority of unprotected individuals occur and who may not have received a full primary series. 29
Conclusion

Immunity to tetanus is very long lasting when fully immunised. However, for some older adults (over 60 years) who may not have received sufficient priming doses, and a single booster dose does not provide long-lived seroprotection; further boosters may be required.

7.4 Effect of conjugate vaccines on tetanus and diphtheria immunity

As mentioned in section 5.5.1, tetanus toxoid is used in some polysaccharide conjugate vaccines as a carrier protein. There is evidence that vaccine conjugates can enhance the immune response to tetanus. However, they also may have suppressive effect on the immune response to the polysaccharide, if tetanus vaccine is given prior to the use of a TT conjugate vaccine. It is therefore recommended by the WHO that Hib (PRP-TT) and meningococcal conjugate (PsA-TT) vaccines are given concurrently or before a tetanus-containing vaccine.

A meningococcal A capsular polysaccharide vaccine conjugated with TT (PsA-TT) has been successfully used in Sub-Saharan Africa to reduce the high incidence of meningococcal A disease. It has also been shown to significantly boost tetanus antibody levels in previously immunised recipients aged 12 month to 35 years, and may be helping to reduce the incidence of neonatal tetanus in these countries.27

Maternally-derived tetanus antibodies in infants of Tdap immunised mothers, resulted in enhanced immune response to TT and TT-conjugated vaccines (Hib-TT, MenC-TT) after primary immunisation. However, conversely, antibody responses to diphtheria and CRM-conjugated vaccines (PCV13, MenC-CRM) were reduced in these infants, although the antibody levels induced remained seroprotective.27

A systematic review conducted by the WHO concluded that coadministration of the priming doses of DT with other childhood vaccines do not interfere with the primary or booster responses to these other antigens, such as IPV, PCV, MMR, human papillomavirus and rotavirus vaccines. Preferably, diphtheria-containing vaccines should be administered with or before DT or CRM conjugated vaccines (Hib, PCV, MenCV).30

Conjugate vaccines available in NZ that contain tetanus or diphtheria antigens include:

- PCV10 (Synflorix®)
- PCV13 (Prevenar® 13)
- Hib-TT (Hiberix® / ACT-Hib)
- Meningococcal ACYW-135 (Menactra®)
- Meningococcal ACYW-135(Nimenrix®)
- Meningococcal C (NeisVAC-C®)

7.5 Summary of tetanus and diphtheria

A primary course of tetanus vaccination induces long-term memory, however, the protection against diphtheria may not be as adequate as for tetanus. Fortunately, in NZ diphtheria is extremely rare, but remains in circulation elsewhere in the world and there is a risk of importation of the disease through international travel, particularly from South-East Asia.

The current National Immunisation Schedule in NZ does not contain a tetanus booster during the second year of life. This is in contrast with the WHO evaluation of evidence that concluded that such a booster in the second year of life provides better protection from tetanus until school entry than no booster.74 However, cases of tetanus are rare in NZ and
occur mostly in elderly adults with unknown immunisation history or in unvaccinated children (4 cases aged <10 years out of 32 total cases notified during 1997-2015). A second year of life DT booster dose is recommended as some children do not achieve adequate antibody levels following primary immunisation to maintain seroprotection against diphtheria, and in some cases against tetanus, through to the second year of life. Immunity induced by this booster provides protection for at least 5 years. A preschool dose of either DTaP or Tdap further boosts immunity. A booster in early adolescence induces long lasting immunity to at least 60 years of age.

Adults who have not been fully primed in childhood are at higher risk of losing seroprotection against diphtheria and tetanus over the age of 60 years.

Priming with TT conjugate vaccines or maternally-derive tetanus antibodies may enhance response to tetanus vaccines given in infancy. However, it may depend on the age the first dose of primary vaccination occurs and cannot substitute for timely vaccine doses.

8 Pneumococcal conjugate vaccines

8.1 Background

The introduction of pneumococcal conjugate vaccines (PCVs) to national immunisation schedules have resulted in significant declines in invasive pneumococcal disease (IPD) and pneumonia in infants. Recent data are also demonstrating declines in acute otitis media. Herd immunity is being observed in older age groups due to reductions in nasopharyngeal carriage (NPC) of vaccine-type strains *Streptococcus pneumoniae*.

The use of pneumococcal polysaccharide vaccine (PPV-23) is not considered in this review. Antigen literature reviews were conducted in 2016 specifically investigating the use of pneumococcal vaccines in high-risk groups and the effectiveness of 10-valent PCV (PCV10), hence consideration is only given in this review to the routine childhood schedule.

In most countries, the scheduling of PCVs coincide with DTaP doses. However, in some countries, reduced schedules (e.g. a primary course of two doses in the UK) have been introduced to minimize the number of injections given per immunisation visit. Three systematic reviews were conducted in 2014 to review the effect of different schedules on pneumococcal disease and NPC.

In a position paper in 2012, the WHO recommended three doses of PCV to be administered in infancy. Three doses may be given as a primary series at 6, 10 and 14 weeks or 2, 4, 6 months (3+0), or alternatively, as a 2+1 schedule starting from 6 weeks of age with 8 weeks between doses until 7 months of age or 4-8 weeks if older than 7 months with a booster at 9-15 months of age.

8.2 Pneumococcal vaccination

Priming doses of pneumococcal conjugate vaccines are given concurrently with DTaP vaccines as part of the primary series in NZ, with a booster dose at 15 months. PCV10 is used universally and PCV13 is given to high risk groups (as of 1 July 2017).
8.3 Immunogenicity

Knoll et al conducted a systematic review in 2014 to evaluate the effect of PCV dosing schedules on immunogenicity. The review found that, in general, a three-dose primary series induced higher antibody levels than a two-dose series, which were increased by booster doses. Although a higher antibody response was induced when the third dose was given in the second year of life (2+1) than when a three-dose primary series was given before 6 months of age (3+0), infants may be less well protected to certain serotypes during the interval between the second and third doses. Similar pre and post booster antibody levels were generally observed following two- or three-dose primary series (2+1 or 3+1 schedules). The advantage of higher antibody levels is that there is likely to be a longer duration of protection and potentially more rapid induction of herd effects by reducing carriage in toddlers.31

Conclusion

Depending on when the peak age of disease incidence is, a 3+0 schedule may provide better individual protection than 2+1 for certain serotypes for earlier infancy disease, in the absence of herd immunity. For longer duration of protection or increased effectiveness against some serotypes, a 2+1 schedule induces higher antibody levels.

8.4 Effectiveness and efficacy

8.4.1 Invasive pneumococcal disease

A systematic review (conducted by Conklin et al in 2014) identified one study that directly compared the effect of schedules, with or without booster doses, on vaccine-type IPD. This found that a booster dose confers slightly higher protection against IPD. No studies were identified that specifically compared two-dose and three-dose primary series, only studies which compared children partially vaccinated with two doses with fully vaccinated children who had received three doses. The review noted that a three-dose primary series potentially provides better protection in the first year of life, where the risk of infection is high, but a two-dose primary with a booster in the second year of life may provide longer lasting protection. Note that this review was conducted when there was limited data on PCV10 and PCV13.82

The Finnish Invasive Pneumococcal disease (FinIP) study investigated the use of PCV10 in two or three-dose infant series plus toddler booster (2+1 or 3+1, respectively in infants younger than 7 months). Infants enrolled before 7 months of age, received three-dose (at a minimum of 4 week intervals) or two-dose (minimum interval of 8 weeks) primary vaccinations and a booster dose at least 4 months after last primary dose and not before 11 months of age. Control groups received hepatitis B vaccine. Study vaccines were given concomitantly with national immunisation programme vaccines at scheduled visits. VE against culture-confirmed vaccine-serotype IPD was shown to be 100% (95% CI 83-100) following the 3+1 schedule and 92% (95% CI 58-100) for the 2+1 schedule.32, 83

8.4.2 Pneumonia

A systematic review conducted by Loo et al 2014 examined the effect of PCV dosing schedules on the prevention of pneumonia. It found reductions in pneumonia incidence (radiologically and clinically confirmed) for all schedules assessed (2+1, 3+0 and 3+1) using
PCV7 and PCV10. The authors concluded that the data support the WHO 2012 recommendations for three dose schedules (2+1 or 3+0).84

8.4.3 Nasopharyngeal carriage

Fleming-Dutra et al also conducted a systematic review in 2014 to assess the effect of PCV dosing schedules on the reduction of NPC of vaccine-type S. pneumoniae. All schedules reviewed reduced NPC compared with no vaccination. Carriage was reduced more following three rather than two primary doses at 1-7 months and in a 2+1 schedule more than a 2+0 schedule at 18 months (not 24 months); all of these schedules reduced vaccine-type NPC. Note that no studies in this review included PCV10 or PCV13, only PCV7 (and PPV-23).34

A study conducted in South Africa examined vaccine-serotype NPC in 252 black-African children immunised with PCV7, either as 3+1 (historical cohort, 6, 10, 14 and 64-76 weeks) or 2+1 (at 6, 14 and 40 weeks) schedules. There was a high rate of overall colonization up to the booster dose in 2+1 recipients, following which there was a steady decline from 29% to 16% by 2 years of age. No difference in temporal acquisition of vaccine or non-vaccine-type pneumococci was detected between the two cohorts.85

Conclusions

As recommended by the WHO in 2012, three dose schedules are effective in preventing pneumococcal disease and in reducing nasopharyngeal carriage of vaccine-type pneumococci. These can be either a 3+0 or a 2+1 regime. However, there may be advantages in a full primary course of three doses to reduce carriage and earlier disease transmission.

8.5 Summary

Immunisation with PCV vaccines are effective in preventing IPD, pneumonia and reducing NPC. Three doses are more effective than two doses. Booster doses induce better immunity than without booster doses, however, assessment of disease prevalence is required when choosing between giving three priming doses or two priming doses plus a booster at 12 months of age since the gap between priming doses and booster could leave infants unprotected until after their booster dose.

New Zealand has observed a significant decline in pneumococcal disease since PCV vaccines were introduced, therefore a 2+1 schedule may be most cost-effective and appropriate to provide longer lived protection in an already well protected population.
9 Measles, mumps, rubella and varicella vaccines

9.1 Background

In 2012, the WHO Global Vaccine Action Plan set an objective to eliminate measles in five out of six WHO regions by 2020, and in September 2016, measles was declared eliminated in the Region of the Americas. To interrupt transmission of measles, a high level of population immunity is required with a herd immunity threshold of 89-94%. The Western Pacific Region was estimated to have 96% coverage for the first dose of measles vaccine in 2015, but only 85% for dose two. In New Zealand, 88% of 5-year old children are fully immunised and have received the second MMR dose.

Following natural infection, long lasting, possibly life-long memory is induced, including continued production of virus-specific antibodies and circulating virus-specific CD4 and CD8 T cells. The live-attenuate measles vaccine induces similar humoral and cellular responses to the wild disease, although IgG antibody levels are lower. Passive protection through IgG antibodies is provided to infants through the placenta. Neutralising antibodies against H and F viral proteins of >120 mIU/ml, as measured by plaque reduction neutralisation assay, are considered the most reliable correlates of protection.

The WHO recommend that, in countries with low levels of measles transmission, the first dose can be administered from 12 months of age rather than at a younger age. Measles-containing vaccines, most commonly, the combined measles-mumps-rubella (MMR) vaccine, are given as two doses: The first dose (MMR1) at 12-15 months, and a second dose (MMR2) is given at least 4 weeks following the first, often after a few years. The purpose of the second dose is to protect children in whom the first dose does not induce sufficiently protective immunity. The timing of the second dose of MMR varies between countries, some schedules administer it at preschool age and others in early adolescence. Australia have introduced the second dose at 18 months of age, 6 months after the first.

9.2 Immunogenicity of MMR and MMRV

The measles vaccine is less immunogenic and effective when given before 12 months of age due to immaturity of the infant’s immune system and ability to generate high antibody avidity, therefore, the risk of infection needs to be balanced with the risk of vaccine failure. Approximately 95% of children who do not respond to the first dose will develop protective immunity following the second dose. Primary vaccine failure is around 5% in those who are administered the first dose in the second year of life, as in NZ.

In Belgium, a second dose of MMR was administered at 10-13 years of age as a catch-up dose for those who did not received a first dose or to cover primary vaccine failures. MMR replaced the rubella vaccination formerly given to adolescent girls. Blood samples were collected from 144 children aged 5 years who were immunised with MMR1 at 12-14 months (and who had been part of a study from birth investigating maternal measles antibodies). The mean interval between MMR and blood sampling was 1445 days (range 1089-1679). Of all the children, 70.8% had positive measles IgG titres (16% were equivocal) and 94.4% were seropositive for rubella antibodies. For mumps, only 32% were seropositive and 44% were seronegative for mumps IgG ELISA, but when retested by seroneutralisation test, 88% were seropositive. The study concluded that children could be vulnerable to measles and
mumps at 5 years of age if they receive a MMR dose at 12-14 months of age only. However, it was unable to conclude whether a long or short interval between doses would provide benefit when immunisation coverage was high. Further follow-up of these children in preadolescence is planned.44

9.2.1 Measles

A review of literature concluded that, in a population immunised with two MMR doses, serum antibody levels against measles depend on the MMR immunisation schedule, the time elapsed since the last dose and the area-specific epidemiology status. A cohort study was conducted in Portugal, involving three cohorts, to measure the association between these determinants and serum anti-measles IgG: Cohort 1 were born in 2001-2003 and received MMR2 at 5-6 years (n=41, mean age 11.4 years [range 10.3-13.1]); cohort 2, born between 1990-1993, had received MMR2 at age 10-13 years (n=66, mean age 20.4 years [18.9-22.8]); and cohort 3, born between 1994-1995, had received MMR2 at age 5-6 years (n=60, mean age 18.9 [18.0-20.6]). All had received MMR1 at 15-16 months of age (range 12-22; 62% received MMR1 at age of 16 months and 80% were vaccinated between age of 15 and 17 months). Measles IgG levels was shown to decrease with time since MMR2: in 60/124 (48.4%) participants, IgG levels had dropped to below the 150 mIU/ml threshold when time since MMR2 was ≥7.5 years. When considering the time since MMR2 dose, significant differences were seen in the proportions of children with seronegative measles IgG between the 2001-03 and 1994-95 birth cohorts (2.4% vs 58.3%, respectively, p<0.001). When time between doses was removed from analysis instead of age of second dose, being vaccinated at 5-6 years or 10-13 years did not seem to influence the long-term antibody levels. It is unknown whether waning antibody levels and presence of CMI memory affect clinical protection against measles.86

9.2.2 Mumps

A longitudinal study was conducted in Brazil to examine the immunogenicity of MMR in 150 children aged 12-15 months. The seroconversion rate was 89.5% for mumps and 100% for measles and rubella in samples collected 42 days after vaccination (range 30-60 days). Revaccination achieved high antibody titres and seroconversion rates. The study concluded that two MMR doses provided optimal immune responses for all three antigens. This study demonstrated lower immunogenicity following one dose of MMR against mumps than rubella or measles, and that two doses of MMR are necessary to ensure a high level of immune protection against mumps.36

9.2.3 Rubella

A study in the West Midlands of England found an increase in the susceptibility of pregnant women to rubella (antibody levels <10 IU/ml). The proportion of non-immune women rose from 1.4% in 2004 to 6.9% in 2011, including 17.8% of those born between 1987 and 1996. The latter group were given one dose of MMR in the second year of life, however, coverage during the late 1990s was low.87

9.2.4 MMRV

A systematic review and meta-analysis was conducted to assess the immunogenicity of combination MMR and varicella (MMRV) vaccine in children aged 9-24 months compared with concurrent immunisation with separate MMR and varicella vaccines (MMR and MMR+V). Pooled analysis from 14 MMRV vs MMR+V and 6 MMRV vs MMR RCTs found that seroconversion rates for measles and mumps were not significantly different between MMRV and MMR or MMR+V groups. Measles seroconversion rates were 93.2%, 88-98.9% and 87.5-100%, respectively. For mumps, seroconversion rates ranged from 84.7-100% and
91.5-100% in the MMRV and MMR+V groups, respectively, and when comparing MMRV with MMR rates were 71.3-97.2% and 72.8-98.6%, respectively. For rubella, no significant difference in seroconversion rate was observed between MMRV (>95.1 to >97.2%) and MMR (>93.2%) and MMR+V (>92.8%). For varicella, across all groups seroconversion rates were >91% and a sensitivity analysis found no significant difference in GMT between MMRV and MMR+V groups. The review concluded that rigorous evidence showed comparable immunogenicity between MMRV and MMR administered with or without varicella vaccine.42

An open-label RCT compared the immunogenicity of MMRV (Priorix-Tetra®) vaccine with MMR+V (Priorix® plus Varilrix®) in 458 Korean children aged 11-24 months. Based on seroconversion rates MMRV was found to be non-inferior to MMR+V for measles (98.0% vs 99.4%), rubella (99.7% vs 100%) and varicella (98.9% vs 100%, respectively), but not mumps (88.8% vs 94.2%), based on a lower 95% CI group difference of greater than -10%. However, the anti-mumps GMTs were comparable between the two vaccines groups and post hoc assay analysis showed non-inferiority.88

Conclusions

Two doses of MMR given after 12 months of age are immunogenic and induce long lasting antibody. Serum anti-measles IgG wanes with time since immunisation, independently of the age at which the second dose is given. Seropositivity may be lost in almost half of vaccine recipients within 7.5 years, however, immune memory to measles is likely to be longer lasting.

Good immunity against rubella is provided by just one dose of MMR.

It is uncertain whether a MMR2 dose given at the age of 4-6 years or 10-13 years provides the best protection against measles and mumps. Two doses of MMR are required to ensure a high rate of seroprotection against mumps.

9.3 Effectiveness of MMR vaccine

MMR has historically been shown to be highly effective. However, declines in coverage have resulted in outbreaks in inadequately immunised populations.

Despite high levels of immunisation coverage, imported cases of measles have caused outbreaks in NZ and elsewhere, particularly in those aged 0-2 years (too young to be immunised) and ages 5-17 years. Inadequate coverage and potential failures in cold chain, particularly prior to 2005, has resulted in a population of potentially vulnerable adolescents and young adults. It has therefore been difficult to fully assess the effectiveness and duration of protection provided by childhood MMR immunisation against measles, mumps and rubella.89, 90

9.3.1 Measles

During a measles outbreak with 1435 notifications in Wales, UK, buccal swabs were collected from notified cases; 1211 of these notifications were within a defined outbreak area. The outbreak predominantly affected children aged 10-18 years. Of the 847 notified cases who returned samples, 474 (56%) were laboratory confirmed. Within the 53 cases with prior history of MMR immunisation, measles RNA was detected but viral loads were lower than in the unimmunised cases. The average age of these vaccinated cases was 18 years. Based on semi-quantitative data using viral RNA loads post rash and immunisation history, VE was calculated to be 96% for MMR1 and 99% for MMR2. Six cases were deemed to have resulted from primary vaccine failure.91
9.3.2 Mumps

The risk factors and VE were assessed during a mumps outbreak in Orthodox Jewish community in New York City during 2009-2010, including 311 households (median age 13 years). Of the 7-17 year olds, 86.7% had received ≥1 dose of MMR and 76% had received 2 doses. Out of 2176 residents, 462 (21.2%) met the study mumps case definition. Adolescents aged 10-14 years or 15-19 years were at highest risk of mumps (OR= 2.4 [CI 1.3-4.7]) and 2.5 [1.3-5.0], respectively). Two dose MMR VE for secondary contacts age ≥5 years was found to be 86.3% (and consistent with other published VE estimates). Suboptimal coverage was also believed to have contributed to disease transmission and the outbreak.92

9.3.3 MMRV

The effectiveness of varicella vaccination was assessed in Puglia, Italy during 2006-2012. Universal varicella vaccination began in 2006 in this region; MMRV replaced MMR + V in 2009 given at 13 months of age and a second dose of MMRV or MMR+V was given at 5-6 or 11-12 years of age. Coverage of one dose of varicella vaccine by the age of 24 months increased from 49% in 2006 birth cohort (given at 15 months of age) to 91% in the 2010 cohort (given as MMRV at 13 months of age). Two-dose coverage was 64.8% in the 2005 birth cohort. The study found that the VE of one dose of varicella vaccine against all varicella disease was 98.8% and against severe hospitalised disease was 99%. The number of reported varicella cases decreased from 7330 in 2004 to 234 in 2012, and varicella hospitalisations fell from 216 in 2004 to 22 in 2012. This decrease was most significant in the 1–4 year-old age group.93

Australia introduced a single dose of MMRV at 18 months of age, following a dose of MMR at 12 months of age. An Australian mathematical modelling study concluded that considerable reductions in severe varicella morbidity are obtainable using one-dose varicella vaccination if coverage of 95% is achieved, particularly in infancy, which would make a second dose less efficient and likely to be less cost-effective.94

9.3.4 Varicella

A population-based observational study in Germany compared the vaccine effectiveness (VE) of one or two doses of varicella vaccine. From 2004, one dose of varicella vaccine was recommended for all children aged 11-14 months, then from 2009, two doses were recommended for children aged 15-23 months with at least 4 weeks between doses. Individual catch-up of missed doses was recommended before the 18th birthday. By 2013, 82.7% of children aged 4-7 years had received one dose and 76.8% of children had received two doses. The study found that the overall estimated VE for one dose was 86.6% (95% CI 85.2-87.9) and the overall estimated VE for two doses was 97.3% (95% CI 97.0-97.6). The incremental increase in effectiveness of a two-dose schedule was calculated to be 84.6% compared with a single dose. The authors conclude that a schedule whereby a second dose given early in life is as effective as a second dose given 3-5 years after the first.37

Conclusions

The vaccine effectiveness of two doses of MMR is high. This effectiveness is dependent on having adequate and high levels of coverage (>90%).

MMRV is as effective as MMR+V. One dose of varicella-containing vaccine given in the second year of life is effective at preventing all varicella and highly effective in preventing severe varicella disease (99%). Two doses provide additional protection, whether the second dose is given soon after the first dose or years later.
9.4 Duration of protection

Seroconversion following correctly administered measles vaccination provides life-long protection for most healthy individuals and antibodies can persist for decades, even where measles is no longer endemic.\textsuperscript{35}

9.4.1 Measles in adolescents

An observational study of the NZ population in January 2007 to June 2014 investigated the risk factors for measles in NZ. The majority of measles cases during this time period were in unvaccinated people (82.8%), 17% of cases had been vaccinated at least once; 12.6% of cases had received MMR1 (around three-quarters of vaccinated cases) and 4.7% had received MMR2 (around a quarter of vaccinated cases). Of the vaccinated cases, approximately 23% were vaccinated when younger than 15 months of age. The study found that age was a strong risk factor for measles, particularly for 12-17 year olds, and catch-up vaccination of older age groups may be necessary to prevent outbreaks. Overall population immunity to measles was suggested to be around 90% and lower in those born around 1982 to 2005.\textsuperscript{90}

Analysis of a measles outbreak in Auckland in 2014 also identified age to be a risk factor. Vaccine effectiveness of 15-24 years age cohort was 92% (95% CI 82-97). Out of 113 cases, 68 (60.1%) were aged 10-19 years, 38.9% were unimmunised and 31.8% had unknown immunisation status. The lowest level of seroprotection was observed in the 10-24 years age group. These findings also suggested that a catch-up immunisation programme could prevent further outbreaks of imported measles in NZ adolescents.\textsuperscript{89}

An investigation of a measles outbreak in a high school in Quebec, Canada found two-dose MMR VE of 94%. A matched case-control study, which included 102 cases and 510 controls, reported that 89% of cases were aged 13-17 years. The risk of measles was six times higher when MMR1 was administered at 12 versus ≥15 months of age for participants outside of the school outbreak (95% CI 1.33-29.3). Age had no significant effect on the second dose.\textsuperscript{95}

Conclusions

The duration of protection from MMR is expected to be long lasting following two doses, although immunity may wane earlier for mumps. However, the main mechanism of control is via high coverage and maintaining herd immunity.

9.5 Summary of measles, mumps, rubella and varicella

The best protection is provided when MMR is given from 12 months of age. Younger infants have less mature immune responses and the presence of maternal antibodies can cause interference. Since in NZ, measles, mumps and rubella are not endemic, the risk of catching the infection younger than 12 months of age is low. Therefore giving the first dose at 15 months of age is adequate and expected to be protective. However, during outbreaks of imported disease, infants aged between 9 and 12 months may receive the vaccine, but it should not be considered as the first dose. The first dose will be required after 12 months of age.

Two-dose MMR vaccination is immunogenic and induces long-lived seroprotection. Serum anti-measles IgG wanes with time since immunisation, independently of the age at which the second dose is given. Seropositivity may be lost in almost half of vaccine recipients within 7.5 years, however, immune memory to measles is likely to be longer lived.
Vaccine effectiveness and duration of protection following two doses of MMR is high and long lasting. The timing of the second MMR dose does not appear to make any difference to vaccine effectiveness whether given in the second year of life, at the age of 4-6 years or at 10-13 years. Two doses of MMR are required to ensure a high rate of sero protection against mumps, in particular. A preschool dose can provide better protection against disease spread in the case of a school-based outbreak. However, this effectiveness is dependent on attaining and maintaining high levels of coverage (>90%).

Good immunity against rubella is provided by just one dose of MMR. However, due to low coverage in the late 1990s, some young women may be susceptible to rubella in pregnancy.

One dose of varicella-containing vaccine given in the second year of life reduces the incidence of all varicella disease and is highly effective in preventing severe varicella disease. Two doses provide additional protection, whether given soon after the first dose or years later. MMRV is as effective as MMR+V in preventing varicella.

The current NZ schedule of MMR and varicella vaccination at 15 months of age with a second dose of MMR at preschool age is protective against these diseases. To ensure immunisation programme effectiveness, it is important to achieve and maintain high coverage levels, and to establish herd immunity to prevent disease spread. Two doses provide added protection, whether given soon after the first dose or years later.

10 Meningococcal vaccines

10.1 Background

Currently, meningococcal vaccines are not included in the routine National Immunisation Schedule in NZ, except for use in certain high-risk groups, such as those who are immunocompromised or with asplenia and close contacts of meningococcal disease cases. Immunisation may also be implemented for the control of local outbreaks, if an appropriate vaccine is available. The incidence of meningococcal disease in NZ is predominantly caused by meningococcal serogroups B and C, although W and Y are also seen at times.

10.2 Meningococcal vaccines

Meningococcal conjugate vaccines are only available as part of the NZ Schedule for certain high-risk group to provide protection against serogroup C or combination of A, C, Y and W135. No meningococcal B vaccine is available in NZ, currently.

10.3 Control of meningococcal disease in the UK

Based on the experience of meningococcal disease immunisation in the UK, a review of meningococcal vaccination scheduling options was conducted by Findlow and Borrow in 2016. The UK introduced meningococcal C conjugate vaccination in 1999, with a primary series at 2, 3 and 4 months (3+0 schedule) alongside a catch-up campaign for children aged 1-18 years. In 2006, the schedule was changed from a 3-dose to a 2-dose priming schedule (at age 3 and 4 months) with a booster at 12 months (2+1), however, this schedule did not achieve long-term direct protection due to waning immunity.43

Circulating bactericidal antibodies were identified as being crucial for protection against invasive disease, immune memory alone was not adequate due to the rapid progression of
the infection. Seroprevalence data showed that infants immunised with single or multiple doses plus a booster in the second year of life did not have sufficient antibody levels to maintain protection into adolescence, which would affect direct protection and herd immunity in the older age-groups.

The schedule was further changed in 2013 to a single priming dose at 3 months of age, plus 12-month booster with combination Hib/MenC vaccine. A booster dose was also introduced in 2013 at age 13-14 years, and a university entrance ‘fresher’ booster was recommended for limited period for those aged <25 years as a catch-up for those who did not receive the earlier adolescent booster.43

Due to the success of UK MenC vaccination programme, cases of invasive group C disease are rare (1 case out of 116 meningococcal cases in infants aged <1 year during 2015-2016).96 In 2015, MenC was replaced by a quadrivalent MenACYW conjugate vaccine for the adolescent and ‘fresher’ boosters in response to an increase in group W disease in the UK and elsewhere. Therefore, in July 2016, the infant dose at 3 months was discontinued and a single dose of Hib/MenC is given at 12 months of age, and MenACYW is given at 14 years of age (year 9 of school).43

Herd immunity was seen as being key in the control of meningococcal disease in the UK. Prior to the introduction of MenC vaccination in adolescents and young adults, these age-groups accounted for 25% of carriage rates. A 71% reduction in MenC carriage was seen a year after the vaccine introduction. After just 2 months since the introduction of the MenACYW adolescent/fresher boosters, recently published data from a small study have demonstrated a 39% decrease in MenY carriage and 36.2% decrease in combined CWY carriage in university students.43

**Conclusion**

To control meningococcal disease and meningococcal carriage, maintenance of bactericidal antibodies is required through booster doses in the second year of life and in adolescence. The best mechanism for control appears to be through herd immunity, achieved by controlling the carriage of disease in older age groups by conjugate vaccines.

**10.4 Meningococcal group B vaccines**

Meningococcal B disease has historically been difficult to control through vaccination due to the poor immunogenicity and cross-reactivity with human antigens of capsular polysaccharides and antigenic variability of the outer membrane vesicle proteins of the serogroup B bacterium.97 During 1991-2007, NZ experienced an epidemic of a particular serogroup B meningococcus, and a specifically designed strain-specific vaccine (known as MeNZB) was used to successfully control the outbreak from 2004-2008. However, outbreaks of group B disease continue to occur in NZ.

In 2013, a multi-component MenB vaccine was licensed in Europe and Australia, and has since been licensed in US, Canada, Australia, Chile, Argentina and Brazil.98 The vaccine (4CMenB; Bexero®, GSK acquired from Novartis) consists of four recombinant Neisseria meningitidis group B fusion proteins and detoxified outer membrane vesicles (OMV; included in MeNZB vaccine specific to the former NZ epidemic strain). The vaccine is predicted to protect against 73-88% of group B strains. The UK was the first country to introduce this vaccine to its national infant immunisation programme in September 2015. The primary series consisted of a two-dose schedule at 2 and 4 months, with a booster at 12 months.99

Another MenB vaccine received accelerated approval in the US in 2014, and is under review in Europe, for use in adolescents and adults aged 10-25 years. MenB-FHbp (Trumemba®;
Pfizer) contains two purified recombinant lipidated factor H binding protein antigens. The vaccine is given as a three-dose series at 2 and 6 months after the first dose. Due to an increased risk of fever, it is not approved for children under 10 years of age.\textsuperscript{100} This vaccine is not reviewed here as it is not suitable for infant schedules.

10.4.1 Immunogenicity of 4CMenB vaccine in infants

A pre-licensure immunogenicity study was conducted in the UK to examine the presence of bactericidal antibodies in 4CMenB primed infants (at 2, 4, 6 and 12 months) before and after the pre-school booster at age 40-44 month. Participants also received routine doses of DTaP-IPV vaccine and MMR at the final study visit. A decline in the proportions of infants with bactericidal antibody was observed from 13 months of age (from 100%, 93%, 96% to 65%, 76% and 41% for the strains fHbp, NadA and NZ98/254 [PorA], respectively). However, it is not clear whether these differences between strains reflects persistence of efficacy or different susceptibilities of the strains to the bactericidal assay. Of the participants who were primed and boosted with 4CMenB, 86-100% achieved bactericidal antibody titres of $\geq 1:4$ for all except one strain.\textsuperscript{101}

The immunogenicity of 4CMenB was assessed for a primary infant course with catch-up schedules in an open label phase IIIb clinical trial. Infants ($n=754$) were randomised to receive the vaccine in 2+1 schedule at 3.5, 5 and 11 months or 6, 8 and 11 months, or as a 3+1 schedule at 2.5, 3.5, 5 and 11 months. Two catch-up doses were given 2 months apart to children aged 2-10 years who did not receive primary series ($n=404$). Across all groups post primary vaccination, 98-100% of infants developed seroprotective serum bactericidal activity (hSBA) titres ($\geq 4$) for fHbp, NadA and PorA, and 48-77% had antibody titres $\geq 4$ for NHBA reference strain. In the catch-up group, 95-99% of children developed hSBA titres $\geq 4$ for all four vaccine components. It was concluded that reduced infant schedules (2 primary doses) and catch-ups are immunogenic and potentially would provide adequate seroprotection.\textsuperscript{102}

**Conclusions**

Use of 4CMenB in 2+1 schedules in infants are immunogenic. Preschool booster doses are required to maintain seroprotective levels of bactericidal antibodies.

10.4.2 Effectiveness of 4CMenB in infants

There are few papers reporting the effectiveness of 4CMenB vaccine in preventing invasive MenB disease in infants, since the vaccine has only recently been introduced to routine schedules.

Two-dose vaccine effectiveness was found to be 82.9\% (CI 24.1-95.2) against all MenB cases in the UK between Sept 2015 and June 2016 in infants eligible for routine vaccination. The priming schedule consisted of two doses at 2 and 4 months, with opportunistic catch-up for 3 and 4 month olds. A 50\% IRR reduction was observed in vaccine-eligible cohort (37 vs average 74 cases; IRR 0.50 [CI 0.36-0.71]; $p=0.0001$) in the first 10 months of the programme, compared with the pre-vaccine period, irrespective of infant vaccination status or predicted MenB strain coverage.\textsuperscript{45}

Although this recombinant subunit vaccine may behave differently to conjugate vaccines, according to modelling data, this type of MenB vaccine may have a similar magnitude of effect as the conjugate vaccines, even if only vaccinating in the adolescent carrier population.\textsuperscript{96} However, currently, there is insufficient post-licensure data to assess the herd immunity effect.
10.5 Summary of meningococcal vaccines

Meningococcal conjugate vaccines are effective against invasive meningococcal disease and oropharyngeal carriage for A, C, Y and W135 serotypes. Maintenance of circulatory bactericidal antibodies are necessary for long-term protection and, as antibodies wane after 3-5 years, to achieve this booster doses are required. Herd immunity targeting the particular age group where carriage rates are highest (such as older teenagers) is probably the most effective strategy.

The age and number of priming doses necessary in NZ may depend on the age at which meningococcal disease is most prevalent and whether NZ chooses to adopt a catch-up programme at the start to gain herd immunity control. The UK gradually reduced the number of priming doses in infancy for MenC vaccine to just one at 3 months of age, but this was only effective due to the establishment of herd immunity and low carriage rate. Due to the success of the programme, cases of invasive MenC in infants are very rare in the UK, and hence, the infant dose was subsequently discontinued in 2016 and a dose of Hib-MenC vaccine is given at 15 months of age.

The multicomponent 4CMenB vaccine can provide good protection against the predicted most common MenB strains following two dose priming in infants. Booster doses are required to maintain seroprotective antibody levels. It is too early to know the longer term impact on serogroup B disease and herd immunity, which would require large studies with high immunisation coverage.
11 Literature search methodology

11.1 Strategy

Ovid MEDLINE® search terms and strategy

Immunisation schedule and pertussis

1. Keyword - Focussed MeSH term: immunization schedule = 234 [10500 expanded MeSH term]
   Limits 2013-current, English, human = 458 [expanded 1227]

2. Keyword MeSH term pertussis vaccine OR subheadings admin/dosage, immunology, prevention & control, therapeutic use = 2606
   Limits 2013-current, English, human = 342
   COMBINED #1 and 2 = 11 Selected 6

3. Title acellular pertussis vaccine = 403
   Limits 2013-current, English, human = 43
   Selected 18 (removed duplicates)

4. Title infant vaccination = 91
   Limits 2013-current, English, human = 32
   Selected 9 (removed duplicates)
   COMBINED 2 and 4 = 8 – none selected (duplicates)

5. Title DTwP = 33
   Limits 2013-current, English, human = 11

6. Title DTaP = 128
   Limits 2013-current, English, human = 23 (selected 7, kept 2 after removing duplicates)
   Combined DTwP AND DTaP = 2 (1 selected)

PubMed.gov search

MeSH term: immunization schedule
Limits 2013-current, English, human = 893
OR immunization program AND pertussis vaccine = 239
Selected 96
NOT cost
NOT low income countries (MeSH: developing countries)
DTwP and DTaP = 55
Limits 2013-current = 14 (5 selected after duplicates removed)
"T cell response and pertussis"
Limit 2013-current = 42, 8 selected

Hepatitis B

1. Keyword – hepatitis B vaccine, focus, include all subheadings 5229
   Limits English, 2013-current, human 669

2. Keyword ‘infant immunization’ – subheadings haemophilus vaccines/or pneumococcal vaccines/or *infant/ or *immunization /or hepatitis B vaccines or *vaccination/ (*focussed) 68213
   Limits English 2013-current human 7286
3. Multi-field search hepatitis B vaccine NOT adult (all fields) 5447

4. 1 & 3 = 152

5. Selected 80 by title – excluding developing countries, adults immunisation, developmental vaccines
   Removed duplicates 75

Further searches

Ovid MEDLINE®

“hepatitis B vaccine” 3984
Limits English, 2013-current, human = 319

1. “Dosing schedule” 11972
2. Limits English, 2013-current, human = 1527
3. 1+2 = 4
4. Selected 1

**Haemophilus influenzae type B**

Ovid MEDLINE®

1. Keyword: Haemophilus influenzae type b
2. MeSH – haemophilus vaccines – focus – subheadings administration and dosage OR immunology OR therapeutic use 1192
3. Limits – English 2013-current humans 160
4. Selected (by title) 23 after removing duplicates 15

PubMed

Phrase “Hib vaccine effectiveness” = 98
Limit human, 01/01/2013 - current, English = 16
Manually selected – to remove low income countries = 4

“Haemophilus influenzae type B conjugate vaccine”
Limit human, 01/01/2013-current, English = 29
Selected 4 after removing underdeveloped countries
Removed duplicates – 1

**Diphtheria and tetanus**

Ovid MEDLINE®

MeSH heading: diphtheria-tetanus vaccine – focus = 164
limit English language and humans and year 2013 -Current = 20
Selected 5

**Pneumococcal**

Conducted search of Pneumococcal antigen literature review 2016 library79, 80 – total library 977, Selected 32

Ovid MEDLINE®

MeSH term: “Pneumococcal vaccines AND conjugate”
Limit to Humans, English, 2013 – November 2016, removed duplicates = 781

Cochrane Library search terms and strategy
Search term: title, abstract, keywords “Pneumococcal vaccine”
Limit to Cochrane Reviews, Other Reviews, 2013- November 2016 = 6

**MMR and Varicella**

1. *Measles-Mumps-Rubella Vaccine/ad, im, tu [Administration & Dosage, Immunology, Therapeutic Use] = 629
2. limit 1 to (English language and humans and yr="2013 - 2017") = 193
3. *Chickenpox vaccine/ 1209
4. limit 3 to (English language and humans and yr="2013 - 2017") = 199
5. 2 & 4 = 30
6. 2 & keyword ‘Schedule.mp’ = 49 = selected 25 – 3 duplicates
7. 6 & keyword ‘Schedule.mp’ = 34 = selected 8

**Meningococcal B**

PubMed.gov

Meningococcal B vaccine effectiveness – limit 2013-01-01 to 2017-05-31 = 76
Selected 24
Bexero effectiveness, limit 5 years, 35 selected 9
Removed duplicates = 29

11.1.1 Grey literature

One unpublished report was used to inform this literature review.

11.1.2 Additional searches

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

11.1.3 Final Endnote Library 400 Articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

**11.2 Participants/populations**

The main aim of this review is to consider literature around the effectiveness and immunogenicity of childhood immunisation schedules, and is focussed on primary series and boosters given for children up to 5 years of age. However, where appropriate consideration is given to immunisation status and the scheduling of boosters give to older children and young adults age 10-19 years. The effect of priming doses given in infancy into adulthood is considered for diphtheria and tetanus, in particular.

11.2.1 Study designs

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


72. Van Der Meeren O, Bleckmann G, Crasta PD. Immune memory to hepatitis B persists in children aged 7-8 years, who were vaccinated in infancy with 4 doses of hexavalent DTPa-HBV-IPV/Hib (InfanrixTM hexa) vaccine. Human vaccines & Immunotherapeutics. 2014;10(6):1682-7.


75. Gajdos V, Vidor E, Richard P, et al. Diphtheria, tetanus and poliovirus antibody persistence 5 years after vaccination of pre-schoolers with two different diphtheria, tetanus and inactivated poliomyelitis vaccines (Td-IPV or DT-IPV) and immune responses to a booster dose of DTaP-IPV. Vaccine. 2015;33(32):3988-96.


