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

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Prepared by a scientific team incorporating the Immunisation Advisory Centre, The University of Auckland Institute of Environmental Science and Research Ltd.

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Executive summary

As a result of the introduction of vaccines against diphtheria, the disease is now rare in developed countries. Evidence suggests that the Diphtheria, Tetanus, acellular Pertussis vaccine (DTaP) is safe and well tolerated in infants, toddlers, adolescents and adults. The adult reduced antigen concentration tetanus-diphtheria (Td) is not associated with any safety concerns in 10-64 year olds or in 65+ year olds. Administration of tetanus, diphtheria, acellular pertussis vaccine (Tdap) to pregnant women is not associated with any unexpected safety patterns in maternal, infant, or fetal outcomes.

DTaP vaccines have been proven to be highly immunogenic as primary and booster vaccinations. When the primary series is given during the first few years of life, the antibody levels decrease over time with a booster dose being recommended around pre-school/early school and adolescence age. Adults who have received a primary course also require a booster dose at some time during their adulthood. For people who have never had a primary series of diphtheria vaccines as a child, three doses of the adult formulation vaccine has been found to induce an adequate immune response. The reduced-antigen-content Tdap-IPV vaccine has been found to be non-inferior to full-strength DTaP-IPV vaccine with respect to immunogenicity when administered to preschool children. The duration of protection from an adult booster dose of diphtheria containing vaccine is unknown as data is limited.

Co-administration studies suggest that Tdap vaccine could be co-administered, without compromise to either the reactogenicity or immunogenicity profiles, with pneumococcal conjugate vaccine containing antigens from 7 pneumococcal serotypes (PVC7), pneumococcal conjugate vaccine containing antigens from 10 pneumococcal serotypes (PCV10), pneumococcal conjugate vaccine containing antigens from 13 pneumococcal serotypes (PCV13), HPV16/18, MenACWY and influenza vaccines.

New multivalent combination DTaP vaccines are being developed, including two fully liquid hexavalent vaccines combining diphtheria (D), tetanus (T), acellular pertussis (aP), inactivated polio (IPV), hepatitis B virus (HBV) and Haemophilus influenzae type b (Hib) vaccines; and hexavalent and heptavalent vaccines based around three component aP. Early trials with transcutaneous vaccination patches also appear promising.

In developed countries, the primary series of immunisations usually consists of three doses of DTaP vaccine, given at intervals of four or more weeks, beginning at two or three months of age, and reinforced by a fourth dose sometime in the second year of life. The policy of using booster doses of vaccines containing diphtheria toxoid varies considerably. Diphtheria vaccines are well embedded in the immunisation schedule for children and adolescents around the world. Adult booster doses are generally recommended, but not always funded, and awareness of adult booster vaccines may be low amongst the adult population. Travellers may not be aware of the recommendations for them to have a booster vaccine before travelling to regions where diphtheria is endemic. With respect to diphtheria, the NZ immunisation schedule is in line with international policy and practice.
2012 Antigen Review
for the
New Zealand National
Immunisation Schedule:
Diphtheria

Prepared as part of a Ministry of Health contract
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This review is one of a series of 18 antigen reviews presented in 15 individual reports.
February 2013 (edited December 2014)
## Contents

**Executive summary** ............................................................... iii  

**Contents**  

Figures ................................................................................... vii  
Tables .................................................................................... vii  
Abbreviations.......................................................................... viii  

1. Background ........................................................................ 1  

2. Methodology for review .................................................. 2  
   2.1 Objectives ......................................................................... 2  
   2.2 New Zealand Epidemiology ............................................. 2  
   2.3 Literature search strategy ................................................. 2  
      2.3.1 Medline search terms and strategy .............................. 2  
      2.3.2 Cochrane Library search terms and strategy ............... 3  
      2.3.3 Scopus search terms and strategy ............................... 3  
      2.3.4 Grey literature .......................................................... 3  
      2.3.5 Additional searches .................................................. 3  
      2.3.6 Final library ............................................................... 3  

3. Recent epidemiology ........................................................ 4  
   3.1 Global epidemiology ...................................................... 4  
      3.1.1 Recent published examples of outbreaks in developed countries ........................................ 4  
      3.1.2 Serological memory .................................................. 5  
   3.2 NZ epidemiology .......................................................... 5  
   3.3 Summary of epidemiology ............................................ 5  

4. Safety ............................................................................... 6  
   4.1 Objective .......................................................................... 6  
   4.2 Outcomes ......................................................................... 6  
   4.3 Review ............................................................................ 6  
      4.3.1 Overview .................................................................. 6  
      4.3.2 Review articles and meta-analyses .............................. 6  
      4.3.3 Review of vaccine data bases ................................... 7  
      4.3.4 Pregnancy ............................................................... 7  
      4.3.5 Healthcare workers ................................................ 7  
      4.3.6 Recent studies ........................................................ 8  
   4.4 Summary vaccine safety ................................................ 8
Antigen Review–2012: Diphtheria

5. Immunogenicity, efficacy, effectiveness and vaccine impact ................................................. 9

5.1 Objective ................................................................................................................................................ 9
5.2 Outcomes ................................................................................................................................................ 9
5.3 Review ................................................................................................................................................... 9
5.3.1 Overview ................................................................................................................................... 9
5.4 Children ................................................................................................................................................ 10
5.4.1 Immunogenicity of Infanrix®–hexa ....................................................................................... 10
5.4.2 Concomitant administration with hepatitis B vaccine ..................................................... 10
5.4.3 Concomitant administration with MMR vaccine ............................................................... 10
5.4.4 Combination versus separate administration .................................................................... 10
5.4.5 DTaP-IPV//PRP-T (Pentaxim®) as a booster ......................................................................... 11
5.4.6 D or d as booster dose ......................................................................................................... 11
5.4.7 Single dose of tetanus-diphtheria vaccine among non/partially immune .................... 11
5.5 Adolescents ............................................................................................................................................. 12
5.5.1 Immunogenicity of diphtheria-tetanus vaccine ................................................................. 12
5.5.2 Second dose of Tdap ............................................................................................................. 12
5.6 Adults and special groups .................................................................................................................... 12
5.6.1 Immunogenicity of Tdap (Boostrix®) in adults 19-64 years of age.................................... 12
5.6.2 Vaccination of adults with unknown vaccination history ................................................. 12
5.6.3 Duration of antibodies in adults after Tdap ....................................................................... 12
5.6.4 Decennial boosters ............................................................................................................... 13
5.6.5 Immunogenicity and safety of diphtheria-tetanus vaccine in adults............................... 13
5.6.6 Immunogenicity in patients with chronic and recurrent rhinosinusitis ......................... 13
5.6.7 Pregnancy ................................................................................................................................ 13
5.6.8 Immunocompromised ............................................................................................................ 14
5.7 Co-administration of diphtheria antigen with other vaccines ......................................................... 15
5.7.1 Co-administration in children ............................................................................................ 15
5.7.2 Concomitant administration in adults ............................................................................. 15
5.8 Summary of effectiveness .................................................................................................................... 16

6. Age-specific issues – duration of immunity and booster doses ................................................. 17

6.1 Objective ................................................................................................................................................ 17
6.2 Review .................................................................................................................................................. 17

7. Vaccine options ....................................................................................................................................... 18

7.1 Objective ................................................................................................................................................ 18
7.2 Currently available vaccines ................................................................................................................. 18
7.3 Vaccines on the horizon ....................................................................................................................... 19
7.4 Summary for vaccine options ............................................................................................................ 19
8. Options for scheduling ........................................................................................................... 20
  8.1 Objective ............................................................................................................................. 20
  8.2 Outcomes ............................................................................................................................ 20
  8.3 Review ................................................................................................................................ 20
  8.4 Recent changes to vaccine recommendations ....................................................................... 23
  8.5 Summary of schedule options .......................................................................................... 23

9. Implementation issues ........................................................................................................... 24
  9.1 Objective ............................................................................................................................. 24
  9.2 Review ................................................................................................................................ 24
  9.3 Summary for implementation issues ................................................................................... 24

10. International policy and practice ..................................................................................... 25
  10.1 Objective ............................................................................................................................ 25
  10.2 Review ................................................................................................................................ 25
  10.3 Summary of international policy and practice ................................................................... 25

References .................................................................................................................................. 26

Figures
Figure 1. Flow of selection of articles for review ........................................................................ 3

Tables
Table 1. Countries with endemic diphtheria in 2012 (US CDC) (9) ...................................................... 4
Table 2. Seroconversion rates pre and post-booster vaccination, adapted from (42) ....................... 11
Table 3. Seroconversion rates at 1 month post-primary, pre and post-booster vaccination, adapted from (43) ........................................................................................................... 11
Table 4. Seroconversion rate against Diphtheria for 10 years after vaccination and 1 month after receipt of a booster dose of dTap vaccine, with permission (54) ......................... 13
Table 5. Newborn antibody levels stratified whether mothers received Tdap (59) ......................... 14
Table 6. List of diphtheria-containing vaccines licensed for immunisation and distribution in the US (US FDA) ........................................................................................................... 18
Table 7. Immunisation schedules for Europe, USA, Australia and Canada as of 2012 .................. 20
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunisation Practices</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
</tr>
<tr>
<td>C. diphtheriae</td>
<td>Corynebacterium diphtheriae</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>DTaP</td>
<td>Diphtheria, Tetanus, acellular Pertussis vaccine</td>
</tr>
<tr>
<td>dTap (or Tdap)</td>
<td>Diphtheria, Tetanus, acellular Pertussis vaccine. The lower case “d” and “p”, the concentration of diphtheria and pertussis toxoids has been reduced</td>
</tr>
<tr>
<td>DTwP</td>
<td>Diphtheria, Tetanus, whole cell Pertussis vaccine</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Program on Immunization (WHO)</td>
</tr>
<tr>
<td>ESR</td>
<td>Institute of Environmental Science and Research</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenza type b</td>
</tr>
<tr>
<td>HSCT</td>
<td>Haematopoietic stem cell transplant</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>PCV13</td>
<td>Pneumococcal conjugate vaccine containing antigens from 13 pneumococcal serotypes</td>
</tr>
<tr>
<td>PCV7</td>
<td>Pneumococcal conjugate vaccine containing antigens from 7 pneumococcal serotypes</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Tdap (or dTap)</td>
<td>Diphtheria, Tetanus, acellular Pertussis vaccine. The lower case “d” and “p”, the concentration of diphtheria and pertussis toxoids has been reduced</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US / USA</td>
<td>United States</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Events Reporting System</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

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1. Background

Diphtheria is a serious acute infectious disease caused by the bacteria Corynebacterium diphtheriae. Diphtheria spreads by respiratory tract droplets through close contact with a case or a carrier, by physical contact with skin lesions or by contact with contaminated objects or foods.

Most commonly, the infection is in the respiratory tract, but it can also infect the skin. Infection of the throat causes a grey to black, tough, fibre-like covering, which can block the airways and can cause respiratory obstruction. Cutaneous infection can cause a painful scaling rash and blisters.

When infected with a bacteriophage, the bacillus produces an exotoxin as it integrates the toxin-encoding genetic elements into the bacteria. This is known as the ‘toxigenic’ strain. Other strains are non-toxigenic, but they can become toxigenic if infected with the bacteriophage containing the diphtheria toxin gene. The toxin can affect the myocardium, leading to myocarditis and heart failure, the peripheral nervous system and cause demyelination and paralysis, and the kidneys, resulting in necrosis. The exotoxin may also cause severe swelling in the neck, “bull neck”. It is the toxigenic disease that is most serious. Mortality can be between 2-10%, even with treatment.

The first vaccination, which included a preparation of toxin and antitoxin, was widely used in the US from around 1914, offering approximately 85% protection. Treatment of the diphtheria toxin with formalin in the 1920s led to the replacement of the earlier preparation in favour of the toxoid vaccine. By the mid-1940s, diphtheria toxoid was combined with tetanus toxoid and whole cell pertussis to give the DTP vaccine. The widespread and routine childhood DTP immunisations, has led to the decline of these diseases; diphtheria is now rare in many parts of the world, although small outbreaks can occur (1).

Risk factors include crowded environments, such as military barracks and prisons, poor hygiene and low levels of no immunisation.
2. Methodology for review

2.1 Objectives

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

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options

2.2 New Zealand Epidemiology

The NZ Epidemiology has been sourced from the 2011 and 2012 Disease Surveillance Reports prepared by ESR. At the time of this report the 2012 annual data was not available.

2.3 Literature search strategy

The points below have formed the focus of the literature search:

- Safety
  - Effectiveness in disease control
  - Effect on
    i Indirect effects/herd immunity
    ii Duration of protection
  - Immunogenicity
  - Implementation issues (practicality of and possible impact on uptake)
  - Differences that need to be considered for each age group, and groups with particular needs
    - Age
      - High-risk groups — definition of which groups most likely to benefit and which vaccine/s
  - Different options for placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparison between the options
  - Current international research and evidence around use of vaccines

2.3.1 Medline search terms and strategy

MeSH term: Diphtheria AND Vaccin*

6965

Limit to Humans, English, 2009 - current

722

NOT Cost*, Attitud*

659

NOT Survey, Interview, Qualitative, Parents, Physician, Self-reported

569

199 Remove duplicates

184 (keep and view)
2.3.2 Cochrane Library search terms and strategy
Search term Diphtheria Vaccin*
Limit to Cochrane Reviews, Other Reviews, Trials 2009-present
2 results (keep and view)

2.3.3 Scopus search terms and strategy
Diphtheria Vaccin* Published 2011 – present
1225
Limit to: Medicine, humans, English
892
Exclude Letter, Short survey, editorial and erratum
804
Reject Veterinary, Arts and Humanities, Social Science articles. Delete duplicates
600 (keep and view)
Final Endnote Library 198 Articles

2.3.4 Grey literature
Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012. No abstracts or posters were accessed. Four reports and two data sheets were accessed.

2.3.5 Additional searches
Where questions arose, additional searches were undertaken to ensure there was no further available data.

2.3.6 Final library
The final library includes 204 references. Where systematic reviews and/or meta-analysis were available, the preceding literature has been excluded from the review.

Figure 1. Flow of selection of articles for review
3. Recent epidemiology

3.1 Global epidemiology

Four biotypes of *C. diphtheriae* are recognised; gravis, belfanti, intermedius and mitis. All strains produce an identical toxin, but the virulence and severity of disease they cause in humans can be explained by their different generation times and the rate and quantity of the toxin they produce. However, the severity of disease caused by different biotypes has not been found to be consistently different (1). Different strains may explain the cyclical nature of epidemics prior to the introduction of diphtheria containing vaccines. Humans appear to be the only host for *C. diphtheriae*.

Before the widespread introduction of diphtheria toxoid for childhood vaccination beginning in the 1930s and 1940s, diphtheria was a highly endemic childhood disease found in temperate climates. Immunisation programmes led to a rapid reduction in diphtheria incidence in the United States, Canada and many countries in Western Europe.

Since the introduction of vaccination programmes, outbreaks have occurred in some countries, but these have generally been small and controlled. The Soviet Union experienced an outbreak in the 1990s. Factors contributing to the epidemic included a large population of susceptible adults, decreased childhood immunisation, suboptimal socioeconomic conditions and high population movement (2).

### 3.1.1 Recent published examples of outbreaks in developed countries

In 2008, Norway had three laboratory confirmed cases of diphtheria (usually caused by toxigenic strains of *C. diphtheriae*), the first since 1962. The three cases were all members of the same family, which started with an unvaccinated five year old boy who had recently travelled to Latvia; his sister developed symptoms and their mother was also diagnosed with *C. diphtheriae*. The father, who was vaccinated as a child, was found to be an asymptomatic carrier. Another 41 samples were taken from contacts, but none were positive (3).

An isolated case occurred in France in 2011 in a 40 year old male with no history of travelling to an endemic area. After testing 53 contacts, only his asymptomatic partner proved positive. Testing 13 contacts of the partner also showed negative results. These two cases of toxigenic *C. diphtheria* were the first since 1989 (4).

Between 1986 and 2008, 102 patients with infections caused by toxigenic corynebacteria reported in the UK (an average of four per year). There were five fatalities, all in unvaccinated individuals (7).

A case of a toxigenic strain of *C. diphtheriae* gravis was recently diagnosed in a partially vaccinated teenager born in the UK with no recent history of travel or known contact with a case of diphtheria or a carrier (8).

Table 1 shows the US Center for Disease Control and Protection (CDC)’s list of the countries still with endemic diphtheria as of 2012.

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Algeria, Angola, Egypt, Eritrea, Ethiopia, Guinea, Niger, Nigeria, Sudan, Zamb, and other sub-Saharan countries</td>
</tr>
<tr>
<td>Americas</td>
<td>Bolivia, Brazil, Colombia, Dominican Republic, Ecuador, Haiti, and Paraguay</td>
</tr>
<tr>
<td>Asia/South Pacific</td>
<td>Bangladesh, Bhutan, Burma (Myanmar), Cambodia, China, India, Indonesia, Laos, Malaysia, Mongolia, Nepal, Pakistan, Papua New Guinea, Philippines, Thailand, and Vietnam</td>
</tr>
<tr>
<td>Middle East</td>
<td>Afghanistan, Iran, Iraq, Saudi Arabia, Syria, Turkey, and Yemen</td>
</tr>
<tr>
<td>Europe</td>
<td>Albania, Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan</td>
</tr>
</tbody>
</table>
3.1.2 Serological memory

Serological surveys for diphtheria in six European countries (Czech Republic, Hungary, Ireland, Latvia, Luxembourg, Slovakia) and Israel showed that increasing age is related to a gradual increase in seronegative subjects (<0·01 IU/ml of diphtheria antitoxin antibodies), with some variances being related to the different vaccination schedules used in the participating countries. Differences in seronegativity were also observed between males and females in Hungary, Ireland and Luxembourg, with more unprotected females. Booster doses given at the time of military service could explain the higher seropositive rates in males in Luxembourg and in both males and females in young adults in Israel (10).

3.2 NZ epidemiology

Whilst diphtheria is caused by toxin-producing strains of *C. diphtheriae*, diphtheria-like illness may also result from infection with toxigenic *Corynebacterium ulcerans*, although this is rare. In NZ, all isolates of *C. diphtheriae* and *C. ulcerans* are notifiable until toxigenicity is determined, including cutaneous isolates (11).

The laboratory based surveillance of diphtheria in NZ is conducted by the Institute of Environmental Science and Research (ESR), and the toxin testing and biotyping is performed by the Special Bacteriology Laboratory.

The NZ Public Health Surveillance Report covering Oct-Dec 2008 reports the last reported cases of *C. diphtheriae*. Four isolates of *C. diphtheriae* were received for toxigenicity testing, typing and surveillance purposes; all isolates were from cutaneous sources and were gravis strains; all the patients were from Auckland, and all the isolates were determined to be non-toxigenic by PCR examination for the toxin gene. One isolate of *C. ulcerans* was received from cutaneous source in a 46 year old male in Auckland - it was determined by PCR testing to be harbouring the diphtheria toxin gene (12).

In 2012, a case was reported of an adult male who developed a cutaneous infection after being tattooed in Samoa and a secondary case of toxigenic cutaneous diphtheria subsequently identified in a fully immunised 11-year-old household contact (13).

3.3 Summary of epidemiology

Diphtheria continues to circulate in some countries and cases are imported into countries who have eradicated endemic diphtheria. There was a case imported to NZ in 2012 which resulted in a secondary case in a fully immunised contact.
4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licenced diphtheria-containing vaccines.

4.2 Outcomes

Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE). Reactogenicity (injection site reactions and minor systemic reactions) have not been included as these have been thoroughly considered in the pivotal licensure studies. The safety of the diphtheria vaccines has been reviewed according to the following:

- Review articles, meta-analyses
- Vaccine safety databases
- Recent studies
- Pregnancy
- Healthcare workers
- Case reports

4.3 Review

4.3.1 Overview

The diphtheria-containing combination vaccines have been used in immunisation programmes throughout the world for decades. Combination vaccines of the DTP (diphtheria, tetanus and pertussis) core antigens plus additional other antigens, including polio, hepatitis B and/or Haemophilus influenza (Hib), are now in widespread use throughout the developed and developing world. This review focuses on the most recent reviews and also present recent individual case reports published during 2009-2012.

4.3.2 Review articles and meta-analyses

4.3.2.1 Combination vaccines: DTaP-IPV (Kinrix®) and DTaP-IPV/Hib (Pentacel®)

A 2010 review of articles from 1966 to 2009 compared the immunogenicity and safety of DTaP-IPV (Kinrix®) and DTaP-IPV/Hib (Pentacel®) vaccines to separate component vaccines. It concluded that combination vaccines were immunogenic and safe in infants and children. When co-administered with PCV-7 or hepatitis B vaccine, immunogenicity was unaffected (14).

4.3.2.2 DTPa-HBV-IPV/Hib Vaccine (Infanrix-hexa®)

In 2010, a spotlight review of 10 years of clinical data on Infanrix-hexa® (diphtheria, tetanus, acellular pertussis, hepatitis B (HBV), inactivated poliomyelitis and Hib conjugate vaccine) was published. The combination vaccine was considered “safe and well tolerated in infants under two years of age” with the incidences of local and general symptoms in Infanrix-hexa® recipients being similar to infants receiving comparator vaccines (DTPa-IPV/Hib plus HBV) (15).

4.3.2.3 Tdap (Boostrix®) a review of its properties and use as a single-dose booster immunisation

Tdap (Boostrix®, GlaxoSmithKline) was developed as a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine designed to avoid the increased reactogenicity observed with the fourth and fifth doses of the infant formulation. It is indicated from the age of four years in Europe and 10 years in the USA and New Zealand, and can be used as a booster dose for children, adolescents and adults. A recent review of its properties as a single dose booster immunisation described this Tdap vaccine as being safe, highly immunogenic with low reactogenicity in all age groups. The trials confirm that a single booster dose of Tdap induces seroprotective levels of antibodies to diphtheria and tetanus toxoids in virtually all children and adolescents, and in a high proportion of adults and elderly individuals at approximately one month post-vaccination irrespective of their vaccination history (16).
4.3.3 Review of vaccine data bases

4.3.3.1 US Vaccine Safety Datalink

A large retrospective cohort study, conducted over six years, assessed records for adolescents and young adults in the Vaccine Safety Datalink database from seven managed care organisations in the US from 1999 to 2004. Of the 436,828 persons aged 9-25 years receiving Td vaccines, the overall estimated risk of a medically attended local reaction was 3.6 events per 10,000 Td vaccinations. The 11-15 year old age group showed the lowest risk with 2.8 events per 10,000 vaccinations. The risk of a local reaction was significantly higher in persons who had received another tetanus and diphtheria toxoid containing vaccine in the previous five years (incidence rate ratio, 2.9; 95% CI, 1.2 to 7.2) (17).

4.3.3.2 Safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine

The safety of approximately 660,000 Tdap vaccines, administered to subjects aged 10-64 years during 2005-2008, was assessed using active surveillance for adverse events from the Vaccine Safety Datalink in the US. The data indicated that Tdap is similar in safety profile to Td regarding the outcomes studied and supports the viability of sequential analysis for post-licensure vaccine safety monitoring (18).

4.3.3.3 Safety of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine administered to adults 65 years of age and older

The Vaccine Adverse Event Reporting System (VAERS) was searched for adverse events (AE) in individuals aged ≥65 years who had received Tdap vaccine from 2005-2010. Of the 243 reports received for this ‘off-label’ use of Tdap vaccine, only the term ‘Cough’ was associated with disproportionately higher reporting after Tdap compared with Td, but most of these events were mild. No unusual or unexpected clusters of adverse events were identified. This review of the ‘off-label’ use of Tdap vaccine in adults ≥65 years did not find any safety concerns that warrant further study (19).

4.3.3.4 Tdap and Guillain-Barré syndrome

Since the Vaccine Safety Datalink (VSD) has accumulated data on over two million doses of Tdap, there is about 80% power to detect a relative risk of 2–3 and a risk difference of 3–6 per million doses for any outcome. Cases of Guillain-Barré syndrome (GBS) occurring in patients aged 10-64 years, up to 42 days after receiving Tdap vaccine were reviewed. The rate ratio of GBS in the exposed compared to the unexposed was 1.21 (95% CI: 0.82, 1.79). This indicates that Tdap is not associated with an increased risk of GBS within 6 weeks of vaccination (20).

4.3.4 Pregnancy

A search of reports to the Vaccine Adverse Event Reporting System (VAERS) identified 132 pregnant women who had received Tdap vaccine. The review of these reports did not identify any concerning patterns in maternal, infant or fetal outcomes (21).

The effect on neurodevelopment of infants exposed to thiomersal in tetanus-diphtheria (Td) vaccines during pregnancy was studied in Brazil. Pregnant mothers aged 15 - 45 years participated through their attendance at prenatal hospital clinics. Hair samples were taken from infants who were exclusive breastfed infants at six months and from their mothers. The mothers had received 0, 1, 2 or 3 doses of Td vaccine containing thiomersal during pregnancy. Regression analysis showed measures of neurodevelopment of the infants at six months was significantly associated with total mercury concentration of neonate’s hair, but was not sensitive to the number of vaccines taken by the mother. Other factors such as maternal fish consumption were considered important contributing factors (22).

4.3.5 Healthcare workers

An adverse event survey was completed by 207 healthcare workers after receiving an adult booster dose of Tdap vaccine. One-hundred and sixty-seven people reported at least one event (81%). Females were three times more likely than males to experience local reactions following the administration of Tdap vaccine. Also, those who had received the Tdap less than five years after their previous Td were more likely to report local reactions than those with a time interval of 10 years or greater since their previous Td (odds ratio 3.06; 95% CI 1.25–7.52). Participants aged 30 years or less were significantly associated with higher rates of systemic events (odds ratio 4.15; 95% CI 1.94–8.86) (23).
4.3.6 Recent studies

4.3.6.1 Concomitant administration with MMR vaccines

Local reactions were assessed in 1,250 healthy nine year old children who received MMR and Td-IPV vaccination as per the schedule in the Netherlands. Parental reports indicated that local reactions occurred in 86.5% of the children within seven days after vaccination, more often at the Td-IPV (83.4%) than at the MMR site (32.7%). All symptoms were transient (24).

4.3.6.2 Risk of febrile seizures and epilepsy after DTaP-IPV-Hib

A population-based study of 378,834 children in Denmark who had received DTaP-IPV-Hib vaccination given at three, five and 12 months was conducted to evaluate the risk of febrile seizures and epilepsy. Nine children were diagnosed with febrile seizures on the day of the first dose of vaccine (5.5 per 100 000 person-days), 12 children after the second (5.7 per 100 000 person-days), and 27 children after the third (13.1 per 100 000 person-days). A higher risk of febrile seizures was found on the day of the first and second doses (hazard ratio [HR] 6.02; 95% CI 2.86-12.65 and HR 3.94; 95% CI 2.18-7.10, respectively), but not on the day of the third vaccination (HR 1.07; 95% CI 0.73-1.57) when compared with the reference cohort. With respect to epilepsy, children had a lower risk of epilepsy between 3 and 15 months (HR 0.63; 95% CI 0.50-0.79) and a similar risk for epilepsy later in life (HR 1.01; 95% CI, 0.66-1.56) versus unvaccinated children. DTaP-IPV-Hib vaccination was associated with an increased risk of febrile seizures on the day of the first two vaccinations given at three and five months, although the absolute risk was small. Vaccination with DTaP-IPV-Hib was not associated with an increased risk of epilepsy (25).

4.3.6.3 Post-marketing safety in adolescents

A prospective, observational study was carried out in Kaiser Permanente, a US Health Maintenance Organization, to estimate the incidence of medically attended neurologic events during the 30 days following vaccination with Tdap (Boostrix®, GlaxoSmithKline). The study population was 13,427 adolescents aged 10 – 18 years. No increased risk for medically-attended neurologic, medically-attended haematological events nor allergic reactions was observed following Tdap vaccination (26).

4.3.6.4 Safety of Tdap-IPV given one month after Td-IPV

A randomised, double-blind, multicentre study assessed the safety of Tdap-IPV administered one month after vaccination Td-IPV in healthy adults vaccinated according to the French vaccination calendar (seven tetanus-diphtheria vaccinations by age 18 years). Participants received either Td-IPV (n = 249) or placebo (n = 251) followed by Tdap-IPV one month later. At seven days, 85.1% versus 93.4% participants reported at least one reaction at the injection site, mainly pain (82.6% versus 92.1%); 40.5% versus 45.0% reported at least one systemic AE (mainly headache: 26.4% versus 26.0%); fever concerned 1.7% of both groups. No serious vaccine-related AE were reported. Both safety profiles corresponded to documented product characteristics. No problems were identified with administering Tdap-IPV one month after Td-IPV (27).

4.3.6.5 Safety of Tdap in six to seven year-old children

Adverse events were evaluated in 243 healthy six and seven year-old children who were immunized with Tdap vaccine and were found to be mild and resolved within seven days (28).

4.4 Summary vaccine safety

There have been several publications relating to multivalent combination vaccines that contain DTaP, all of which have concluded that the vaccines are safe and well tolerated in infants, toddlers, adolescents and adults. The adult reduced concentration Td has also been found to have no safety concerns in adolescents and adults aged 10-64 years and in the elderly aged over 65 years.

Administration of Tdap to pregnant women did not identify any concerning patterns in maternal, infant or fetal outcomes.

In healthcare workers, Tdap given less than five years after their previous Td were more likely to report local adverse events than those with a time interval of 10 years or greater since their previous Td.
5. Immunogenicity, efficacy, effectiveness and vaccine impact

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

5.2 Outcomes
The outcomes considered for this review are:

- Children
- Adolescents
- Adults
- Pregnant women
- Healthcare workers
- Immunocompromised
- Co-administration

5.3 Review

5.3.1 Overview
Immunity against diphtheria is an antibody-mediated response to the diphtheria toxin and is primarily of the IgG type. Antitoxin antibodies can pass through the placenta to provide passive immunity to the newborn.

Before the widespread use of vaccination, newborn babies would have acquired passive immunity from maternal antitoxin offering protection for the first six-12 months of life. Throughout childhood, they would have been exposed to the diphtheria organism and have developed antibodies. By the age of about 15-20, most people would have developed acquired immunity to diphtheria.

Antitoxin levels decline over time in children after they have received a primary series of vaccines and a booster dose is given. In countries where diphtheria immunisation is common practice and high coverage rates are achieved, there will be no natural boosting from circulating disease and antitoxin levels declining with increasing age may result in a susceptible adult population (29).

Individuals with circulating antitoxin levels <0.01 IU/ml are generally considered susceptible, with less severe symptoms being associated with levels above this. The protective level is generally considered to be 0.1 IU/ml and an antitoxin level of >1.0 IU/ml is associated with long-term protection.

Vaccines combining pertussis antigens with diphtheria and tetanus toxoids have been gradually introduced into immunisation schedules throughout the world. An expert review of 16 years’ experience with the DTaP–IPV/PRP-T Hib combined vaccine, marketed as Pentaxim®/Pentavac® (Sanofi Pasteur) was published in 2011. First licensed in 1997 in Sweden, the experience with Pentaxim® now stretches to over 100 countries where over 87 million doses have been distributed. The findings of this review of clinical trials in many countries concluded that good diphtheria immunogenicity has been demonstrated after primary vaccination with Pentaxim®, regardless of the population ethnicity and primary vaccination schedule. A booster vaccination in the second year of life also results in high levels of immunogenicity for each antigen (30).

There are a number of different vaccine manufacturers producing vaccines with the core diphtheria, tetanus and pertussis components. Clinical data in a study of 97 Korean children indicates that the interchangeability of DTaP vaccines results in a non-inferior response in the primary series (31). However, a prospective phase III randomised multicentre trial of 253 infants in Canada concluded that, for the primary series, it was better to complete the primary infant three-dose vaccine series with the same vaccine. Immunogenicity and reactogenicity were different for mixed two, four, six-month pentavalent infant vaccine schedules. The percentage of children with PRP antibody ≥0.15 g/mL after completion of the 3-dose infant immunization schedule was higher in the Infanrix™, Pediacel, Pediacel (IPP) group than in the Pediacel, Pediacel, Infanrix™ (PPI). The anti-diphtheria toxin response was not assessed in this study, although Infanrix contains more diphtheria toxin than Pediacel (25Lf, 15Lf, respectively) (32).
5.4 Children

5.4.1 Immunogenicity of Infanrix®–hexa

The 2010 ADIS review of 10 years clinician data on Infanrix®-hexa found it to be highly immunogenic, as primary and booster vaccination, for all its component toxoids/antigens in infants aged <2 years, regardless of vaccination schedules. In large clinical studies, Infanrix®-hexa was found to elicit a strong immune response against vaccine toxoids/antigens which persisted for up to a mean of approximately 6 years after booster vaccination (15, 33, 34).

A review article from Germany reviewed published clinical trials and post-marketing surveillance data in relation to immunogenicity, efficacy and safety profile of Infanrix®-hexa. The data supported the immunogenicity of this across a range of different primary and booster vaccination schedules, as well as when administered concomitantly with other licensed vaccines (35).

The immunogenicity of two DTaP-HBV-IPV/Hib vaccines administered at 3, 5 and 11-12 months of age (Infanrix®-hexa and Hexavac) was studied in 494 infants enrolled in 10 centres throughout Finland, Italy and Sweden. The anti-diphtheria concentrations after three doses were similar in the two dose primary series but the three-dose primary series of Infanrix®-hexa induced higher anti-diphtheria concentrations than Hexavac™ (36).

5.4.1.1 Immunogenicity with different primary schedules

Most immunisation schedules in Europe use a three-dose primary schedules (2, 3, 4 months or 2, 4, 6 months), each with a booster dose in the second year of life. Denmark, Iceland, Sweden, Finland, Italy, Norway and Austria have implemented a two-dose primary schedule at three and five months of age, with booster at 11-12 months. A pooled analysis of data from four European studies, in which Infanrix®-hexa was administered to 702 healthy infants at three, five and 11-12 months of age, found that 96.3% and 100% of infants had seroprotective antibodies against diphtheria, tetanus and pertussis. Antibodies levels against diphtheria, tetanus and pertussis were dependent on the interval since last vaccination while HBs-antibodies were not. The seroprotective rates for diphtheria and pertussis at this age indicate that a booster dose at the age of about six - eight years is required, preferably with a vaccine containing the higher dose of diphtheria toxoid (39).

5.4.2 Concomitant administration with hepatitis B vaccine

The immunogenicity of Infanrix®-IPV/Hib co-administered with hepatitis B vaccine was assessed in an open-labelled randomised study of 62 healthy Taiwanese infants. The DTPa-IPV/Hib was given at 1.5, 3.5, 6 and 15–18 months, and hepatitis B vaccine at birth, 1.5, 6 and 15–18 months of age. One month after the three-dose primary series, 100% of infants had seroprotective levels of antibodies for diphtheria. The DTPa-IPV/Hib primary and booster vaccination were immunogenic, and well tolerated, when co-administered with HBV vaccine (38).

5.4.3 Concomitant administration with MMR vaccine

Immunity to diphtheria and tetanus was analysed in 338 Austrian children aged four - eight years. Most of the children (323) had received the schedules four doses of DTPa-IPV/Hib (according to the schedule of 2, 3, 4 months and a booster in the second year of life) and 15 children had received three doses as well as 1 or 2 doses of MMR. When measured between the ages of 4-8 years, 81% of children were seroprotected for diphtheria. Antibodies levels against diphtheria, tetanus and pertussis were dependent on the interval since last vaccination while HBs-antibodies were not. The seroprotective rates for diphtheria and pertussis at this age indicate that a booster dose at the age of about six - eight years is required, preferably with a vaccine containing the higher dose of diphtheria toxoid (39).

5.4.4 Combination versus separate administration

A randomised, parallel controlled, single centre clinical trial was conducted in China in 720 infants, aged 3, 4 and 5 months old and 18 months old for both primary and booster immunisation, to compare the administration of DTaP/Hib combination vaccine developed by a Chinese manufacturer with the administration of separate DTaP and Hib vaccines. The immunogenicity profile of the DTaP/Hib combination vaccine was equivalent to that of separately administered China-licensed DTaP vaccine and Hib conjugate vaccine (40).
5.4.5 DTaP-IPV//PRP-T (Pentaxim®) as a booster

The immunogenicity and safety of a pentavalent combination DTaP-IPV//PRP-T (Pentaxim®) as a booster at 18-19 months of age was assessed in 480 Thai infants who received doses of the same vaccine at two, four and six months of age. Anti-diphtheria antibody titres > 0.01 IU/ml were observed in the majority of children pre-booster. One month after the booster, seroprotection rates were 95% for diphtheria (> 0.10 IU/ml) (41).

An almost identical study of 123 Thai children also found that vaccination at two, four, six months and a booster at 18-19 months of age with the DTaP-IPV//PRP-T vaccine induced antibody persistence at four-six years of age. A second booster with DTaP-IPV induced a strong immune response with seroprotection rates increasing from pre-booster rate 60.2 % to 100 % for diphtheria (> 0.10 IU/ml) (42). See Table 3.

Table 2. Seroprotection and seroconversion rates pre and post-booster vaccination, adapted from (42)

<table>
<thead>
<tr>
<th></th>
<th>Pre-booster % (95%CI)</th>
<th>Post-booster % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Diphtheria ≥0.01 IU/ml</td>
<td>92.7 (86.6-96.6)</td>
<td>100.00 (97.0-100)</td>
</tr>
<tr>
<td>Anti-Diphtheria ≥0.1 IU/ml</td>
<td>60.2 (50.9-68.9)</td>
<td>100.00 (97.0-100)</td>
</tr>
</tbody>
</table>

A similar study in 207 healthy children in Delhi, India also concluded that the DTaP-IPV//PRP-T vaccine booster at 18-19 months of age induced strong antibody responses 98% > 0.10 IU/ml. As shown in Table 4 (43).

Table 3 Seroprotection and seroconversion rates at 1 month post-primary, pre and post-booster vaccination, adapted from (43)

<table>
<thead>
<tr>
<th></th>
<th>Post-Primary % (95%CI)</th>
<th>Pre-booster % (95%CI)</th>
<th>Post-booster % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Diphtheria ≥0.01 IU/ml</td>
<td>99.0 (96.5-99.9)</td>
<td>82.3 (76.3-87.4)</td>
<td>100.00 (98.2-100)</td>
</tr>
<tr>
<td>Anti-Diphtheria ≥0.1 IU/ml</td>
<td>18.3 (13.2-24.4)</td>
<td>14.1 (9.6-19.8)</td>
<td>98.00 (95.0-99.5)</td>
</tr>
</tbody>
</table>

5.4.6 D or d as booster dose

Booster doses or diphtheria are generally given as either standard (≥30 IU) or low (≥2 IU). To ascertain if the seroprotection generated after a dose of low-dose diphtheria vaccine was non-inferior to that induced following a high-dose vaccine given as a booster in children six years of age, 760 children were randomised to receive one of two vaccines. The seroprotective threshold of 0.1 IU/mL was reached by 98.6% and 99.3% of children for diphtheria [as measured by sero-neutralisation (SN)]. The confidence intervals overlapped for immunogenicity, but rates were slightly higher in the high-dose group. This supports the use low-dose diphtheria as a booster in children who have previously received a primary course of diphtheria (44).

Booster vaccination for pre-school children has been recommended in Italy since 1999. The immunogenicity of a booster dose of reduced-antigen content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine (Tdap-IPV; GSK Biologicals Boostrix™-Polio; 3-component pertussis) was compared with full-strength DTPa-IPV vaccine (sanofi-pasteur-MSD Tetravac; 2-component pertussis) in 303 pre-school Italian children. One month post-booster, all subjects were seropositive for anti-diphtheria antibodies. The reduced-antigen-content Tdap-IPV vaccine was found to be non-inferior to full-strength DTPa-IPV vaccine with respect to immunogenicity (45).

5.4.7 Single dose of tetanus-diphtheria vaccine among non/partially immune

A single dose booster vaccine has been demonstrated to boost previously acquired immunity in Hyderabad, India where diphtheria is common among children aged five-19 years. A single dose of (Td) vaccine was given to 483 school children aged seven-17 years who were susceptible/partially immune to diphtheria and/or tetanus. Serological testing, six weeks after vaccination, indicated that the vaccine was highly immunogenic with >96% seroprotected against both antigens (46).
5.5 Adolescents

5.5.1 Immunogenicity of diphtheria-tetanus vaccine

A multicentre, non-randomised, open label phase IV study was conducted in South Korea to compare the immunogenicity and safety of Td vaccine in 132 pre-adolescents aged 11–12 years with 145 adolescents aged 13–18 years. Immunogenicity was demonstrated in both the 11-12 year and 13-18 year age groups. Prior to vaccination, 11 (8.3%) of the pre-adolescent and 6 (4.1%) of the adolescents had anti-D antibody concentrations of <0.1 IU/mL. A month after vaccination, 100% in both groups achieved anti-D antibody levels of ≥0.1 IU/mL, indicative of seroprotection (47).

5.5.2 Second dose of Tdap

The immunogenicity of a second dose of an adult formulation Tdap was evaluated in 545 Canadian adolescents and adults aged 15 - 69 years, five years after a first dose. Post-vaccination, 100% of participants had a tetanus antibody level ≥0.1 IU/mL. A second dose of Tdap vaccine, five years after the initial dose, was well tolerated and immunogenic in adolescents and adults (48).

The immunogenicity of a booster dose of Tdap-IPV was evaluated in 415 German adolescents aged 9-13 years, who had previously received Tdap-IPV or Tdap +IPV at four to eight years of age. One month after the Tdap-IPV booster dose, 100% of subjects had antibody concentrations/titres associated with seroprotection against diphtheria, as compared with 98.2% before the booster dose (49).

5.6 Adults and special groups

5.6.1 Immunogenicity of Tdap (Boostrix®) in adults 19-64 years of age

A randomised study was conducted in the US to assess the immunogenicity of Boostrix® (Tdap3) in adults 19–64 years of age. A total of 2284 healthy adults received either Adacel® (Tdap5) or Boostrix®. Seroprotective levels of antibodies to diphtheria and tetanus toxoids (≥0.1 IU/mL) were observed in >98% of subjects. Boostrix® was shown to be comparable to Adacel® vaccine in providing seroprotection against diphtheria and tetanus, and produced immune responses to pertussis antigens consistent with protection against disease (50).

5.6.2 Vaccination of adults with unknown vaccination history

A study in 18-50 year old adults with unknown vaccination history reported that one dose of Repevax® Tdap-IPV administered one month after one dose of Revaxis® Td-IPV induced a high humoral response (51).

5.6.3 Duration of antibodies in adults after Tdap

An open-labelled, controlled, serological follow-up study was conducted in 36 centres in the US. Antibodies to Tdap antigens were measured three years after vaccination in 1386 adults aged 19–64 years. At three years post-vaccination, the antibody levels were lower than at one year post vaccination, but remained higher than pre-vaccination levels. Seroprotection rates for diphtheria were 96.9% for Boostrix® (GlaxoSmithKline Biologicals) and 97.8% for Adacel® (Sanofi Pasteur) (52).

The long-term persistence of antibodies among adults was assessed in New South Wales, Australia. Participants were vaccinated with Tdap vaccine or Td +monovalent acellular pertussis (pa) vaccines, At 60 months post-vaccination, 94.4% of Tdap vaccinees had anti-diphtheria antibody concentrations consistent with seroprotection, compared with 93.7% of Td recipients (53).

In Finland, a follow-up study was conducted in young adults, 10 years post-vaccination with single dose of Tdap vaccine at the age of 10-14 years, to assess the immunogenicity and safety of a second booster dose of dTap vaccine. At ten years, of the 74 participants, 82.4% had anti-diphtheria antibody concentrations prior to the dTap booster dose and 98.6% had seroprotective antibody levels against diphtheria one month after the booster, as shown in Table 5 (54).
Table 4. Seroprotection rate against Diphtheria for 10 years after vaccination and 1 month after receipt of a booster dose of dTap vaccine, with permission (54)

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. of subjects</th>
<th>Seroprotection rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria (ELISA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before initial dTpa vaccination 10 years ago</td>
<td>74</td>
<td>70.3 (58.5–80.3)</td>
</tr>
<tr>
<td>Month 1</td>
<td>75</td>
<td>100 (95.2–100)</td>
</tr>
<tr>
<td>Year 3</td>
<td>46</td>
<td>93.5 (82.1–98.6)</td>
</tr>
<tr>
<td>Year 5</td>
<td>52</td>
<td>90.4 (79.0–96.8)</td>
</tr>
<tr>
<td>Year 10 prebooster</td>
<td>74</td>
<td>82.4 (71.8–90.3)</td>
</tr>
<tr>
<td>Year 10 postbooster ELISA and Vero</td>
<td>74</td>
<td>98.6 (92.7–100)</td>
</tr>
<tr>
<td>Year 10 postbooster</td>
<td>73</td>
<td>100 (95.1–100)</td>
</tr>
</tbody>
</table>

5.6.4 Decennial boosters

Booster doses of Tdap vaccines are recommended every 10 years in many countries. A recent study evaluated the immunogenicity of a second dose of Tdap (Boostrix®) in 164 adults vaccinated with Tdap 10 years previously. Before the decennial booster, 89.4% were seroprotected (antibodies ≥0.1 IU/mL) for diphtheria. One month post-booster, all participants were seropositive against all vaccine antigens (55).

A Canadian study compared the immunogenicity of a first dose of Tdap with a repeat dose in adults who had received Tdap 10 years earlier. A total of 769 adults aged 20-72 years were enrolled. Post-vaccination antibody levels ≥0.1 IU/mL were achieved by 96.1% of the naïve group and 98.5% of the repeat-dose group for diphtheria (56).

5.6.5 Immunogenicity and safety of diphtheria-tetanus vaccine in adults

The immunogenicity and safety of three doses of diphtheria-tetanus (Td) vaccine was studied in Korea, in 242 adults over 40 years old who had never received a diphtheria-tetanus-pertussis containing vaccination. Before vaccination, 33.9% participants showed antibody levels of diphtheria below protective level (<0.1 U/mL). Following the first dose of Td vaccine, 92.6% of subjects achieved protective antibody concentrations (≥0.1 U/mL) for diphtheria, which increased to 99.6% after the third dose (57).

5.6.6 Immunogenicity in patients with chronic and recurrent rhinosinusitis

Responses to diphtheria and tetanus vaccine were measured in 25 adult patients (mean age 46 years) with chronic or recurrent sinusitis and in 30 healthy individuals (mean age 43 years). On average, the 25 patients with recurrent sinusitis had a 4.08-fold lower responses to diphtheria toxoid (and 2.2-fold lower responses to tetanus) than the controls. Nearly half (14 of the 25 patients) had antibody levels that did not reach the 95% normal distribution range of healthy controls after either diphtheria or tetanus vaccination. A significant proportion of patients with persisting symptoms of rhinosinusitis may have impaired responses to protein vaccines (58).

5.6.7 Pregnancy

A study in the US matched 52 pregnant women attending the University of Louisville Obstetrical Clinic, who were given Tdap vaccine (Sanofi Pasteur), with 52 pregnant women not given the vaccine. The study demonstrated that pregnant women who receive Tdap during pregnancy had significantly higher antibody levels in their serum at delivery to all six antigens in the vaccine than the women who were not vaccinated during pregnancy, as seen in Table 2 (59).
5.6.8 Immunocompromised

5.6.8.1 Chemotherapy

A Korean study measured diphtheria, tetanus and pertussis antibody titres after ‘antineoplastic’ treatment in 146 children aged one to 17 years with haematological conditions (leukaemias and lymphomas). All the children had been fully immunised for age prior to treatment. Protective serum antibody titres for diphtheria were decreased by 31.5% compared to age-matched healthy populations. The study found no significant correlation for levels of serum antibody titres with the severity of the illness, treatment or age of the patient. The re-immunised group displayed significantly higher protective immunity for diphtheria (72.9%) than those who were not re-immunised (46%, p = 0.001). The authors stressed the importance of re-immunisation after completion of treatment (60).

A Hong Kong based study assessed 56 children, aged one-18 years old who were treated successfully for paediatric haematological malignancy and solid tumours, for evaluation of humoral immunity against vaccine-preventable diseases (hepatitis B, diphtheria, tetanus, pertussis, measles, mumps, and rubella) and their responses to booster DTP vaccine. At baseline (six months after stopping chemotherapy treatment), 83.6% children had protective antibody levels against diphtheria. After three doses of DTP, all vaccinees demonstrated an increase in antibody titre which was significantly greater than the placebo group. The authors concluded that post-chemotherapy booster vaccinations produced a strong and sustained effect in humoral immunity against vaccine-preventable infectious diseases (61).

5.6.8.2 Post-transplant

Persistence of humoral immunity was evaluated in 82 haematopoietic stem cell transplant (HSCT) recipients up to 12.5 years after post-transplant immunization against tetanus and diphtheria. Full post-transplant revaccination resulted in long-term persistence of humoral immunity against tetanus and diphtheria in HSCT recipients, for an average of 8.6 and 9.0 years, respectively (63).

5.6.8.3 Haemodialysis

In an Iranian cross-sectional study, consisting of 52 patients who were on haemodialysis and 52 age- and sex-matched healthy individuals, the duration of haemodialysis was found to have a significant effect on anti-diphtheria immunity (64).
5.7 Co-administration of diphtheria antigen with other vaccines

5.7.1 Co-administration in children

In the US, 487 children aged four-six years were randomised to receive DTaP-IPV vaccine (Kinrix®, GlaxoSmithKline) + MMR+V on day 0 or Kinrix + MMR on day 0, followed by varicella vaccine after one month. One month post-vaccination, immune responses in the group receiving DTaP-IPV+MMR+V on the same day were non-inferior to the group receiving V one month after DTaP-IPV+MMR for responses to DTaP-IPV antigens (65).

A study compared the safety and immunogenicity of DTaP5-IPV-Hib vaccine (followed by monovalent hepatitis B vaccine [HBV]) with DTaP3-HBV-IPV/Hib vaccine, both co-administered with PCV7, as a fourth-dose booster in toddlers aged 11-18 months who had a hexavalent vaccine primary series. Results showed that DTaP5-IPV-Hib induced a marked immune response, and had a similar safety and immunogenicity profile compared with DTaP3-HBV-IPV/Hib (66).

DTaP-IPV/Hib co-administered with PCV-7 was assessed in a phase III trial. A group of 586 children were administered DTaP5-IPV/Hib and PCV-7 at the same visits at 2, 4, and 6 months of age (Stage I) and a booster vaccination at 15–16 months of age (Stage II). In a staggered group, 581 children received DTaP5-IPV/Hib on an identical schedule, but PVC7 was administered to participants ≥15 days after DTaP 5-IPV/Hib, at approximately 3, 5, 7, and 16–17 months of age. Seroprotection rates to diphtheria and tetanus toxoids were high in both groups (>99.7%), and thus noninferiority was demonstrated. In a descriptive, non-hypothesis-driven comparison, anti-diphtheria GMT were higher in participants who received the staggered immunisation schedule (7.4 IU/mL compared with 4.1 IU/mL) (67).

The immunogenicity of 10-valent PHiD-CV vaccine co-administered with DTPa-HBV-IPV/Hib vaccine was assessed in 229 Taiwanese children. Infants were given three doses of the vaccines within the first six months of life. One month after the third vaccine dose, all participants were seroprotected against the diphtheria and the other antigens contained in the co-administered DTPa-HBV-IPV/Hib vaccine. Strong immune responses were also observed against all 10 of the vaccine serotypes in PHiD-CV (69).

German (n=605) and Spanish (n=619) phase III trials, compared the administration of Infanrix™-hexa with PCV7 versus PCV13. Each participant received one dose of either PCV13 or PCV7 and a dose of Infanrix™-hexa at 2, 3, and 4 months (infant series) and 11–12 months of age (toddler dose) in the German study and at 2, 4, 6, months (infant series) and 15 months (toddler dose of Infanrix®-IPV + Hib) in the Spanish study. There was no impact on the immune responses to concomitantly administered antigens in the Infanrix™-hexa or Infanrix™-IPV + Hib combination vaccines (70).

Tdap-IPV has been evaluated for co-administration with ASO4-adjuvanted human papillomavirus (HPV) vaccine in an open-label, randomised, multicentre study in Spain among healthy females aged 10–18 years randomised to three parallel groups: HPV x 3, Tdap-IPV x 1 or HPV x 3 plus Tdap-IPV co-administered with the first dose. Seroprotection rates for anti-D were 100% in the Tdap-IPV group and 99.2% in the HPV + Tdap-IPV group (71).

5.7.2 Concomitant administration in adults

The immunogenicity of Tdap co-administered with influenza vaccine was assessed in an open-label, randomised, controlled study conducted in 12 centres in the United States with 1409 adults aged 19-64 years. Participants were randomised to receive Tdap (Boostrix®) and trivalent inactivated influenza vaccine (TIV), administered either concomitantly or one month apart (TIV followed by Tdap). Seroprotection rates for diphtheria antigen were over 94.1% for both vaccine regimens, and immune responses to these antigens in the concomitant group were non-inferior to those observed in the sequential group (72).

Similar results were reported in a study of 1104 healthy adults >65 years old, who received single doses of Tdap and seasonal influenza vaccine either co-administered or given one month apart. The authors concluded that Tdap was found to be immunogenic in participants aged ≥65 years, with a safety profile comparable to US-licensed Td vaccine, and that
Tdap and influenza vaccine may be co-administered without compromise to either the reactogenicity or immunogenicity profiles of the two vaccines (73).

Co-administration of MenACWY-CRM with Tdap was assessed in a phase III, observer-blind, multicentre, randomised, controlled study conducted in the US. The trial randomised 1054 adolescents and adults, aged 11-25 years, to three study groups: receiving either MenACWY-CRM + Tdap; MenACWY-CRM + saline placebo; or Tdap + saline placebo. The proportion of subjects with seroprotective anti-diphtheria antibody concentrations (1.0 IU/ml) at one month post-vaccination was significantly higher when Tdap was administered concomitantly with MenACWY-CRM than when Tdap was administered with saline placebo (94% versus 85%; LL of 95% CI >0%) and was associated with higher geometric mean concentrations (GMC) of anti-diphtheria antibodies (74).

5.8 Summary of effectiveness

DTaP vaccines have been proven to be highly immunogenic, as primary and when used with lower diphtheria antigen doses in booster vaccinations. When the primary series is given during the first few years of life, the antibody levels decrease over time leading to a booster dose being required around the ages of pre-school/early school and adolescence. Adults who have received a primary course also require a booster dose at some time in their adulthood. For people who have never had a primary series of vaccines as a child, three doses of the adult formulation vaccine have been found to induce an adequate immune response. The reduced-antigen-content Tdap-IPV vaccine has been found to be non-inferior to full-strength DTPa-IPV vaccine with respect to immunogenicity when administered to pre-school children.

Immunocompromised patients receiving chemotherapy have been found to have decreased antibodies to diphtheria but that these are restored with diphtheria vaccination post chemotherapy.

Co-administration studies suggest that Tdap vaccine is co-administered without compromise of either the reactogenicity or immunogenicity profiles with PCV7, PCV10, PCV13, HPV16/18, MenACWY and influenza vaccines.
6. Age-specific issues – duration of immunity and booster doses

6.1 Objective
The objective of this section is to consider the evidence for offering the diphtheria vaccine to different age groups, in particular older age groups.

6.2 Review
Evidence from recent publications suggests that the currently accepted international vaccine schedules of a primary series of diphtheria containing vaccines for infants followed by a booster around preschool/early school and adolescent ages seems to confer sufficient immunity to protect young persons.

As reported in previous sections, antibodies are known to decrease with increasing age and, in the absence of circulating diphtheria disease, a booster dose in adulthood is recommended.

There were no recent publications on vaccine uptake in adults, coverage or factors affecting uptake.

The duration of protection from an adult booster dose of diphtheria containing vaccine is unknown as data is limited.
7. Vaccine options

7.1 Objective

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

7.2 Currently available vaccines

No diphtheria-only vaccine is available. The diphtheria vaccine is available as:

- DTaP (Diphtheria, Tetanus, acellular Pertussis vaccine)
- DTaP in combination with *Haemophilus influenzae* type b (Hib) vaccine
- DTaP in combination with hepatitis B and inactivated polio vaccines
- DTaP in combination with Hib, hepatitis B and inactivated polio vaccines
- DT or Td (in combination with tetanus vaccine)
- Tdap (Tetanus, reduced diphtheria, acellular Pertussis)

Vaccines containing the whole cell pertussis component (DTwP) are no longer recommended for use in New Zealand and so are not listed here.

Table 6 List of diphtheria-containing vaccines licensed for immunisation and distribution in the US (US FDA)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Trade Name</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids Adsorbed</td>
<td>No Trade Name</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids Adsorbed</td>
<td>No Trade Name</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids &amp; Acellular Pertussis Vaccine Adsorbed</td>
<td>Tripedia</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids &amp; Acellular Pertussis Vaccine Adsorbed</td>
<td>Infanrix</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids &amp; Acellular Pertussis Vaccine Adsorbed</td>
<td>Daptacel</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus Toxoids &amp; Acellular Pertussis Vaccine Adsorbed</td>
<td>Pediarix</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine Combined</td>
<td>KINRIX</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>Tetanus &amp; Diphtheria Toxoids Adsorbed for Adult Use</td>
<td>No Trade Name</td>
<td>MassBioligics</td>
</tr>
<tr>
<td>Tetanus &amp; Diphtheria Toxoids Adsorbed for Adult Use</td>
<td>DECAVAC</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>Tetanus &amp; Diphtheria Toxoids Adsorbed for Adult Use</td>
<td>TENIVAC</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>Tetanus Toxoid</td>
<td>No Trade Name</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>Tetanus Toxoid Adsorbed</td>
<td>No Trade Name</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed</td>
<td>Adacel</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed</td>
<td>Boostrix</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
</tbody>
</table>
7.3 Vaccines on the horizon

A web search of major pharmaceutical companies (as of Nov 2010) has been reported in an 11-page review. A summary of diphtheria-containing vaccines is below.

- Two fully liquid hexavalent vaccines combining diphtheria (D), tetanus (T), acellular pertussis (aP), inactivated polio (IPV), hepatitis B virus (HBV) and Haemophilus influenzae type b (Hib) vaccines, in development.

- Hexavalent and heptavalent vaccines based around three component aP, in phase II development. These combine DTaP, IPV, Hib and meningococcal group C tetanus-conjugate vaccines, with or without HBV vaccine.

- A broad variety of DTP combinations of varying complexity produced by developing country manufacturers are also in development (75).

Novartis has developed a mercury-free formulation of the monovalent diphtheria toxoid vaccine (76).

A new diphtheria–tetanus toxoid (Td) vaccine, GC1107, has been developed by Green Cross Corporation, Korea. In an active comparator-controlled study, GC1107 has been reported to be non-inferior and well tolerated in Korean males aged >20 years (77).

Early trials with transcutaneous vaccination patches, using a hydrogel, for tetanus and diphtheria has been shown to induce an immune response without severe adverse reactions in humans (78).

7.4 Summary for vaccine options

Multivalent combination DTaP vaccines are now available for up to six different antigens (combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Poliovirus and Haemophilus influenzae type b vaccine). As of early 2013, the Hib component is a powder which requires reconstitution prior to injection.

Two fully liquid hexavalent vaccines combining diphtheria (D), tetanus (T), acellular pertussis (aP), inactivated polio (IPV), hepatitis B virus (HBV) and Haemophilus influenzae type b (Hib) vaccines are in development, as are hexavalent and heptavalent vaccines based around three component aP.

Results from early trials with transcutaneous vaccination patches are positive.
8. Options for scheduling

8.1 Objective
This section reviews the evidence for different options for placement of diphtheria vaccine on the childhood immunisation schedule and for special groups.

8.2 Outcomes
A summary of diphtheria-containing immunisation schedules for the US, UK, Australia, NZ and European countries are summarised.

8.3 Review

Table 7. Immunisation schedules for Europe, USA, Australia and Canada as of 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>D antigen – Primary series &amp; pre-school booster doses</th>
<th>Lower concentration (d) antigen – adolescent &amp; adult booster doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Union</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>DTaP at 2 months, 4 months, 6 months and 12 - 14 months as DTaP-Hib-IPV-HepB</td>
<td>Td-IPV at 6 - 9 years Tdap at 13 - 16 years</td>
</tr>
<tr>
<td>Belgium</td>
<td>DTaP at 8 weeks, 12 weeks, 16 weeks and 15 months recommended as the combined DTaP-HBV-IPV-Hib hexavalent vaccine, plus DTaP at 5 - 7 years recommended as the combined DTaP-IPV quadrivalent vaccine</td>
<td>Tdap at 14 - 16 years</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>DTaP at 2 months, 3 months, 4 months, 16 months and 6 years</td>
<td>Td at 12 years Td vaccination recommended at 25 years of age and every 10 years thereafter</td>
</tr>
<tr>
<td>Croatia</td>
<td>DTaP at 2 months, 4 months, 6 months, 12-18 months as a pentavalent DTaP-IPV-Hib combination vaccine and DTaP at 3 years</td>
<td>Td at 7 years, 14 years and 18 years</td>
</tr>
<tr>
<td>Cyprus</td>
<td>DTaP at 2 months, 4 months, 6 months 15-18 months and 4-6 years</td>
<td>Td at 14-16 years and Td, adult type-booster dose is then given every 10 years.</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>First dose of DTaP-Hib-HepB-IPV given as hexavalent vaccine at 13 weeks of age, Second dose of DTaP-Hib-HepB-IPV given as hexavalent vaccine at least one month after the first dose within the first year of life, Third dose of DTaP-Hib-HepB-IPV given as hexavalent vaccine at least one month after the second dose within the first year of life, Fourth dose of DTaP-Hib-HepB-IPV given as hexavalent vaccine 6 months after the third dose and by the end of 18 months of age, 5th dose at 5 years of age.</td>
<td>No d booster on schedule</td>
</tr>
<tr>
<td>Denmark</td>
<td>DTaP and IPV are given with Hib in one injection at 3 months, 5 months and 12 months</td>
<td>Tdap at 5 years (Tdap and IPV are given in one injection)</td>
</tr>
<tr>
<td>Estonia</td>
<td>DTaP at 3 months, 4½ months, 6 months, 2 years and 6-7 years</td>
<td>Td at 15-16 years. A seventh vaccine dose against diphtheria and tetanus is recommended to children at the age 17 years to children born in the period 1990-1995 and previously vaccinated at age 12 years with sixth vaccine dose. A Td booster dose is recommended every 10 years starting from the age of 25 years</td>
</tr>
<tr>
<td>Finland</td>
<td>DTaP at 3 months, 5 months, 12 months and 4 years. DTaP, IPV and Hib are given as a single pentavalent vaccine. DTaP and IPV are given as a single tetravalent vaccine.</td>
<td>Tdap at 14-15 years.</td>
</tr>
<tr>
<td>Country</td>
<td>D antigen – Primary series &amp; pre-school booster doses</td>
<td>Lower concentration (d) antigen – adolescent &amp; adult booster doses</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>France</td>
<td>DT at 2 months, 3 months, 4 months, 16-18 months, 6 years, 11-13 years. DTaP and IPV are given as a single tetravalent vaccine. Booster doses are mandatory before 18 months for diphtheria.</td>
<td>Td A booster dose of Td is recommended at 16-18 years of age, and later on, every 10 years, together with IPV either as Td-Polio or as Tdap-Polio for the booster at 26-28 years of age for those who had not received a pertussis booster in the previous 10 years</td>
</tr>
<tr>
<td>Germany</td>
<td>DTaP at 2 months, 3 months, 4 months and 11-14 months.</td>
<td>Tdap at 5-6 years and 9-17 years</td>
</tr>
<tr>
<td>Greece</td>
<td>DTaP at 2 months, 4 months, 6 months, 15-18 months and 4-6 years</td>
<td>Td at 11-18 years and &gt;18 years. Recommended after the age of 11-12 years if at least 5 years have passed since the last dose of DTaP/DTP. Thereafter, recommended every 10 years until the age of 65 years.</td>
</tr>
<tr>
<td>Hungary</td>
<td>DTaP at 2 months, 3 months, 4 months and 18 months (DTaP, IPV and Hib are given as a combined vaccine) and 6 years (DTaP and IPV are given as a combined vaccine)</td>
<td>Tdap at 11 years</td>
</tr>
<tr>
<td>Iceland</td>
<td>DTaP at 3 months, 5 months and 18 months. DTaP, IPV and Hib are given as a single pentavalent vaccine</td>
<td>Tdap at 4 years and 14 years. Tdap and IPV are given as a single vaccine</td>
</tr>
<tr>
<td>Ireland</td>
<td>DTaP at 2 months, 4 months and 6 months. (DTaP, Hib, IPV and HepB are given as a single hexavalent vaccine) and 4-5 years</td>
<td>Td at 11-14 years</td>
</tr>
<tr>
<td>Italy</td>
<td>DTaP at 2-3 months, 4-5 months, 10-12 months and 5-6 years</td>
<td>Tdap at 11-15 years and Td vaccination is recommended every 10 years thereafter</td>
</tr>
<tr>
<td>Latvia</td>
<td>DTaP at 2 months, 4 months, 6 months, 12-15 months (given as a combined DTaP-Hib-IPV-HepB vaccination) and 7 years (given as a combined DTaP-IPV vaccination).</td>
<td>Td at 14 years (Given as a combined Td-IPV vaccination)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>DTaP at 2 months, 4 months, 6 months, 18 months (Given as a combined DTaP-Hib-IPV vaccination) and 6-7 years</td>
<td>Td at 15-16 years</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>DTaP at 2 months, 3 months, 4 months, 12 months (Given as a combined hexavalent vaccine) and 5-6 years</td>
<td>Tdap at 16 years. Tdap and IPV recommended every 10 years after the age of 16 years</td>
</tr>
<tr>
<td>Malta</td>
<td>DTaP at 6 weeks, 3 months, 4 months. 18 months (Given in as a combined DTaP-IPV-Hib)</td>
<td>Td at 16 years (Given as a combined Td-IPV)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>DTaP at 2 months, 3 months, 4 months, 11 months (DTaP, IPV and Hib are given in a combined vaccine) and 4 years (DTaP and IPV are given in a combined vaccine)</td>
<td>Td at 9 years (IPV and Td are given in a combined vaccine)</td>
</tr>
<tr>
<td>Norway</td>
<td>DTaP at 3 months, 5 months and 12 months, plus at 7 years for children born in 1998 or later</td>
<td>Td at 11-12 years (For children born before 1998) or 15-16 years (For children born in 1998 or later)</td>
</tr>
<tr>
<td>Poland</td>
<td>DTaP at 6-8 weeks, 3-4 months, 5-6 months and 16-18 months</td>
<td>Td at 14 years and recommended at the age of 19 years or the last year of education at school</td>
</tr>
<tr>
<td>Portugal</td>
<td>DTaP at 2 months, 4 months, 6 months (DTaP, IPV and Hib are given in one injection), 18 months (DTaP and Hib are given in one injection) and 5-6 years (DTaP and IPV are given in one injection)</td>
<td>Td at 10-13 years and Td is given every 10 years thereafter</td>
</tr>
<tr>
<td>Romania</td>
<td>DTaP at 2 months, 4 months, 6 months, 12 months and 4 years</td>
<td>Td at 14 years. Subsequent doses of Td are offered at 24 years of age and every 10 years thereafter</td>
</tr>
<tr>
<td>Country</td>
<td>D antigen – Primary series &amp; pre-school booster doses</td>
<td>Lower concentration (d) antigen – adolescent &amp; adult booster doses</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Slovakia</td>
<td>DTaP at 2 months, 4 months, 10 months (Given in a combined form as DTaP-IPV-Hib-HepB hexavalent vaccine), 5 years (Given in a combined form as DTaP-IPV) and 12 years (Given in a combined form as Td-IPV trivalent vaccine)</td>
<td>Td at 12 years Given to adults as a booster dose every 15 years after the previous vaccination</td>
</tr>
<tr>
<td>Slovenia</td>
<td>DTaP at 3 months, 4-5 months, 6 months and 12-24 months (Delivered as pentavalent vaccine DTaP-Hib-IPV)</td>
<td>Tdap at 8 years</td>
</tr>
<tr>
<td>Spain</td>
<td>DTaP at 2 months, 4 months, 6 months, 15-18 months and 4-6 years</td>
<td>Td at 14-16 years</td>
</tr>
<tr>
<td>Sweden</td>
<td>DTaP at 3 months, 5 months, 12 months (DTaP, IPV and Hib are given as a single pentavalent vaccine), 5-6 years (Recommended to children born in 2002 and later) and 10 years (Recommended to children born before 2002).</td>
<td>Tdap at 14-16 years Recommended to children born in 2002 and later</td>
</tr>
<tr>
<td>Switzerland</td>
<td>DTaP at 2 months, 4 months, 6 months, 15-24 months (DTaP, IPV and Hib are usually given as a single pentavalent vaccine) and 4-7 years</td>
<td>Td at 11-15 years</td>
</tr>
<tr>
<td>Turkey</td>
<td>DTaP at 2 months, 4 months, 6 months, 18-24 months and 6 years</td>
<td>Td at 13 years</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>DTaP at 2 months, 3 months, 4 months (DTaP, IPV and Hib are given as a combined vaccine) and 3 years 4 months – 5 years (DTaP or Tdap) and IPV are given as a combined vaccine)</td>
<td>Td at 13-18 years (Td and IPV are given as a combined vaccine)</td>
</tr>
<tr>
<td>Australia</td>
<td>DTaP-IPV-HepB-Hib at 2 months, 4 months, 6 months and 4 years</td>
<td>Tdap at 10-15 years</td>
</tr>
<tr>
<td>USA</td>
<td>DTaP at 2 months, 4 months, 6 months, 15-18 months and 4-6 years. (The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose)</td>
<td>Td is a tetanus-diphtheria vaccine given to adolescents and adults as a booster shot every 10 years</td>
</tr>
<tr>
<td>Canada</td>
<td>DTaP at 2 months, 4 months, 6 months, 18 months and 4-6 years</td>
<td>Td every 10 years; 1 dose should be given as Tdap if not previously given in adulthood</td>
</tr>
</tbody>
</table>
8.4 Recent changes to vaccine recommendations

Since 2005, the US Advisory Committee on Immunization Practices (ACIP) has recommended a Tdap vaccine booster dose for all adolescents aged 11-18 years (preferred at 11-12 years) and for those adults aged 19 through 64 years who have not yet received a dose. In October 2010, ACIP recommended that unvaccinated adults aged 65 years and older receive Tdap if in close contact with an infant. In July 2011, the Food and Drug Administration (FDA) approved expanding the age indication for Boostrix® (GlaxoSmithKline Biologicals) to aged 65 years and older. In February 2012, ACIP recommended Tdap for all adults aged 65 years and older (79).

The American Academy of Pediatrics and the Centres for Disease Control and Prevention reviewed the results from clinical trials and in 2011, the recommendation for caution regarding Tdap use within any interval after a tetanus- or diphtheria-containing toxoid product was removed. Tdap should be given when it is indicated and when no contraindication exists. A single dose of Tdap is recommended for children 7-10 years of age who were under-immunised with diphtheria-tetanus-acellular pertussis (DTaP) (80).

In the USA, the Society for Adolescent Medicine (SAM) supports the use of Tdap among all adolescents and young adults aged 10-25 years (81).

In 2011, the Centres for Disease Control and Prevention’s Advisory Committee on Immunization Practices approved recommendations for the use of Tdap vaccine for pregnant women (82).

In 2011, the Food and Drug Administration (FDA) approved an expanded age indication for the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap; Boostrix®, GlaxoSmithKline Biologicals) to include persons aged 65 years and older. Boostrix® was originally licensed in 2005 for 10-18 year olds, and in 2008, this was expanded to 19-64 year olds.

8.5 Summary of schedule options

In developed countries, the primary series of immunisations usually consists of three doses of DPT vaccine, given at intervals of four or more weeks, beginning at two or three months of age, and reinforced by a fourth dose sometime in the second year of life. The policy of using booster doses of vaccines containing diphtheria toxoid varies considerably.
9. Implementation issues

9.1 Objective
The objective of this section is to consider the issues around implementation.

9.2 Review
There were no specific publications which addressed implementation issues.

Due to widespread vaccination programmes, diphtheria is no longer present in many countries. Although no animal reservoir exists for *C. diptheriae*, an animal reservoir does exist for *C. ulcerans* and this organism may carry the corynebacteriophage that encodes diphtheria toxin. Therefore, continuing active immunisation with diphtheria toxoid is important in the on-going control of diphtheria worldwide.

9.3 Summary for implementation issues
Diphtheria vaccines are well embedded in immunisation schedules for children and adolescents around the world. Adult booster doses are generally recommended, but not always funded, and awareness of adult booster vaccines may be low amongst the adult population.

Travellers may not be aware of the recommendations for travellers to have a booster vaccine before travelling the regions where diphtheria is endemic.
10. International policy and practice

10.1 Objective
The objective to this section is to summarise international practice with regard to the use of diphtheria vaccines.

10.2 Review
Diphtheria containing vaccines are well established in the immunisation schedules of developed countries.
A summary of international practices around diphtheria immunisation is provided in Table 7.

10.3 Summary of international policy and practice
With respect to diphtheria, the NZ immunisation schedule is in line with international policy and practice.
References


