



# The Immunisation Advisory Centre

## **Review of evidence to inform the New Zealand National Immunisation Schedule, 2019: Diphtheria**

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## Abbreviations

CI	Confidence interval
CRM	Cross-reactive protein, diphtheria derived protein
DT	Diphtheria toxoid
DTaP DTaP-IPV-HepB/Hib	Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and <i>Haemophilus influenzae</i> type b vaccines.
EPI	Expanded Program on Immunization
ESR	Institute for Environmental and Scientific Research
GSK	GlaxoSmithKline Ltd
MenC	Meningococcal C
NZ	New Zealand
PCV 7 or 13	Pneumococcal conjugate vaccine (7 or 13 valent)
RCT	Randomised clinical trial
Td / Tdap	Tetanus, reduced diphtheria / and acellular pertussis vaccine
UK	United Kingdom
US	United States of America
VFR	Visiting friends and relatives
WHO	World Health Organization

# 1 Executive summary

Clinically severe diphtheria is caused by toxin-producing (toxigenic) strains of *Corynebacterium diphtheriae*. Infection with toxigenic diphtheria strains is extremely rare in New Zealand (NZ), but they continue to circulate elsewhere in the world, so there is a risk of importation through international travel particularly from South-East Asia.<sup>(1)</sup> No cases of toxigenic respiratory diphtheria (infection of upper respiratory tract) have been reported in NZ since 1998, but isolated cases of cutaneous toxigenic diphtheria have been reported and 61 isolates of *C. diphtheriae* were detected in 2017.<sup>(2, 3)</sup>

It is important to ensure that all preschool and school-age children are fully immunised, as these age groups are at highest risk of spreading respiratory diphtheria if an outbreak was to occur.

Globally, immunity in young children has dramatically improved through targeted immunisation programmes, and as a result, from 1998 to 2000 reported diphtheria cases decreased by more than 90% globally. However, diphtheria remains a substantial cause of morbidity and mortality in countries with incomplete or disrupted childhood immunisation programmes. Around 14% of children worldwide are not fully immunised against diphtheria and all countries have variable-sized pockets of unvaccinated children.<sup>(1)</sup>

In countries with endemic diphtheria, adults acquire immunity through exposure to circulating disease. Despite this, most reported cases are unvaccinated or incompletely vaccinated adults or adolescents (40% of cases were age over 15 years in high incidence countries and 66% in low incidence countries).<sup>(1)</sup> An epidemic across Russia and the former Soviet Republics in the 1990s, resulting from a breakdown of immunisation services during the collapse of the Soviet Union, was brought under control by immunisation of both children and adults as all age groups were at risk due to low immunisation coverage. Emergency vaccination programmes were implemented to control recent outbreaks of respiratory diphtheria in Indonesia and in Rohingya refugee camp in Cox's Bazar, Bangladesh as a result of low immunisation coverage and forced migration.<sup>(4, 5)</sup>

This is a review of literature published between January 2015 and July 2019 focussing on questions relevant to diphtheria immunisation in NZ. The evidence presented has not been formally graded as in a systematic review, and cost effectiveness of pneumococcal vaccines is not included.

## 1.1 Immunity and duration of protection

### Childhood immunity

Diphtheria toxoid (DT) vaccine has been used in NZ since 1926 and as part of the routine immunisation schedule since 1940. A previous review, conducted in 2017 to examine literature around the childhood immunisation schedule, identified that although a primary course of diphtheria and tetanus toxoid-containing vaccines induces long-term memory, the long-term protection against diphtheria is less robust than against tetanus.<sup>(6)</sup>

A second-year-of-life DT booster dose is recommended because some children do not achieve adequate antitoxin levels to maintain seroprotection against diphtheria following primary immunisation. The antitoxin induced by this booster provides protection for at least five years and a preschool dose of either DTaP (diphtheria, tetanus and acellular pertussis vaccine) or lower dose Tdap further boosts immunity. After a sixth dose in early adolescence given as Tdap, diphtheria immunity is estimated to last until at least 60 years of age.<sup>(6)</sup>

In the absence of a DTaP booster in the second year-of-life, as in NZ, antitoxin levels induced by the primary series (at 6 weeks, 3, and 5 months) will not reach or persist at levels believed to provide seroprotection until 4 years of age. In Australia, 59% of children were found to be susceptible to diphtheria at age 3 years following removal of the toddler booster dose.<sup>(5)</sup>

A booster dose, with either DTaP or Tdap, given to preschool children provides protection for at least five years.<sup>(7)</sup> Note that evidence is derived from children who had previously received a DTaP booster in the second year of life, which is not included in the current NZ schedule, so duration of protection post booster at age 4 years may differ without a toddler booster dose.

### Conclusions:

- Evidence suggests that six doses of diphtheria vaccine in childhood are likely to better prevent diphtheria in children than under the current five-dose schedule
- Six childhood doses are likely to provide longer lived immunity in adults.
- A gap of more than five years between booster doses achieves better diphtheria antitoxin levels in adolescents than shorter intervals.
- Changes to the primary series, such as a 2+1 schedule, will require a more detailed review of international immunogenicity data to assess the effect such changes would have on diphtheria immunity.

### Adult immunity

The World Health Organisation (WHO) identified that adults in countries with long-standing childhood immunisation programmes were likely to be susceptible without booster doses to overcome waning immunity due to lack of exposure to diphtheria. Waning immunity contributed to the high number of cases in adults observed during the outbreak in the former Soviet Union.<sup>(8)</sup>

Although generally well protected, some adults are vulnerable to diphtheria infection based on accepted antibody thresholds and persistence of diphtheria protection is shorter than for tetanus. Decisions around booster doses in adults need to consider risks to individual and community immunity against diphtheria alongside those for tetanus and pertussis, especially in relation to travel or participation in humanitarian relief where risk is higher.

Adults who have not been fully primed in childhood with five or six doses of DT-containing vaccine are at higher risk of losing seroprotection against diphtheria and tetanus beyond the age of 60 years.<sup>(9)</sup> Older adults were likely to have received fewer life-time doses than adults aged less than 30 years.<sup>(10)</sup> To maintain diphtheria seroprotection in older adults, more booster doses may be necessary than are required for tetanus.

Although recommended in the United States (US), evidence from the United Kingdom (UK) suggests that ten-yearly boosters are unnecessary in fully immunised adults (defined in the UK as having received at least five doses in childhood). The current NZ schedule for adults provides diphtheria vaccine as Td at 45 and 65 years of age, as well as during each pregnancy and for tetanus-prone wound care (Td is to be replaced by Tdap in July 2020).

Vaccination histories are likely to differ between men and women, due to tetanus prophylaxis or pregnancy, and need to be considered. Traditionally, men were more likely to receive Td booster doses than women for tetanus prophylaxis due to workplace accidents, such as in the farming and building sectors, or military service. However, women are also actively employed in those industries now-a-days and there is increasing uptake of Tdap in

pregnancy, therefore, the profile of immunity across the adult population is likely to be changing. Although booster doses are often poorly documented, an evaluation of the current immunity of NZ adults against diphtheria and tetanus could be insightful, such as through serosurveys.<sup>(11, 12)</sup> In NZ, only 46% of blood donors aged 45 years were seropositive for diphtheria in 2009.<sup>(12)</sup>

Decisions around booster doses in adults need to consider both individual protection against disease as well as relevance for community or “herd” immunity against diphtheria at a population level should an outbreak occur. These considerations are especially important for adults travelling to and from regions with either persisting endemic diphtheria infection or experiencing outbreaks. Some adults may have adequate antitoxin levels to prevent clinically evident disease, but not mild or subclinical infection with the potential to be transmitted within communities with low immunisation coverage or to vulnerable individuals, such as incompletely immunised children or the elderly. Caution may be required when considering removing the middle-life (at 45 years) Td booster if herd immunity is suboptimal. A booster at age 65 years is recommended.

In the UK, like NZ, being fully immunised is considered as having received five childhood doses of DT vaccine rather than six. However, although the UK does not advocate ten-yearly booster doses for tetanus protection, due to the risk of acquiring the disease elsewhere, anyone traveling to areas with endemic or outbreak diphtheria are recommended to receive a booster dose of Td or Tdap if it was 10 or more years since a previous dose.

#### **Conclusions:**

- Although generally well protected, some adults are vulnerable to diphtheria infection based on accepted antibody thresholds.
- Persistence of diphtheria protection is shorter than for tetanus.
- Decisions around booster doses in adults need to consider risks to individual and community immunity against diphtheria alongside those for tetanus and pertussis.

#### **At risk populations**

Due to historically low immunisation coverage, it can be assumed that level of community immunity against diphtheria in some groups is likely to be suboptimal should an outbreak arise from an imported case. Immunisation is typically undocumented in older adults, and younger adults may lack immunity due to belonging to a non-vaccinating family. Older immunised adults may not be seroprotected due to waning immunity, especially if they have not received Td booster doses at 65 years.

In the absence of endemic diphtheria in NZ, the risk of infection is associated with travel to endemic regions or regions with outbreaks. Transmission may occur in the absence of clinically evident disease due to mild or subclinical infection in partially immunised people. This is the presumed route of infection for two unimmunised young adults who recently died in Queensland, Australia. Although less likely, the potential for outbreaks within localised regions with very low immunisation coverage cannot be ruled out. Vulnerable groups, such as non-quota former refugees, the elderly or those with significant co-morbidities compromising immunity are at high individual risk.

To reduce the risk of importation of diphtheria, it is advised that all travellers to countries with active diphtheria outbreaks or endemic diphtheria, such as India, Indonesia and other countries in South-East Asia (common destinations for visiting family and relatives [VFR]) have their diphtheria immunisation status checked. This may mean a course of three vaccinations if no records exist or a booster dose of Tdap if it has been longer than 10 years

since their last booster. It is important to recognise that VFR travellers differ from recreational travellers and may not fully understand their risk. They are also much more likely to visit a GP from their language or ethnic group.<sup>(13, 14)</sup> This is an issue for immunisation more broadly and requires targeted communication.

**Conclusions:**

- Booster doses are highly recommended for those travelling to areas with high incidence of diphtheria, such as South-East Asia and India.

## 1.2 Interference of diphtheria immunogenicity following the primary series

Some interference is observed when DT-containing vaccines are given after other vaccines containing diphtheria proteins. No clinically relevant interference occurs when given concurrently or before; in this case, immunity against diphtheria may also be enhanced.<sup>(1)</sup>

The presence of maternal antibody, following Tdap vaccine in pregnancy, reduces infant antibody responses to diphtheria-containing vaccines and is likely to be more relevant with the first primary dose given at 6 weeks of age than when given later.<sup>(15, 16)</sup> It is not known whether there is any interference with clinical protection; although a second-year-of-life booster is justifiable to minimise waning protection against diphtheria.

**Conclusions:**

- Whether interference from other diphtheria containing vaccines or maternal antibody has a clinically relevant influence on diphtheria immunity is uncertain.
- Infants are at a much higher risk from pertussis than diphtheria in NZ and therefore, pertussis immunisation takes priority.
- WHO recommendations are to give conjugate vaccines concurrently or before DT containing vaccine, but not after where possible to avoid any reduction in protection against pneumococcal or meningococcal polysaccharides.

## 1.3 Summary of recommendations

- Diphtheria immunisation is closely linked to the pertussis schedule.
- Changes to the National Immunisation Schedule will require consideration of the effect on diphtheria immunity, particularly for young children, to maintain community immunity thresholds.
- Immunity against diphtheria is not as long lived as for tetanus but the risk of infection is very low for most people.
- A dose of DTaP given in the second year of life would help to overcome any potential interference from maternal antibody, strengthen protection against diphtheria before and after the booster at 4 years of age and provide optimal priming for the adolescent booster to provide protection well into adulthood.
- However, considerations about a toddler dose are closely linked to the pertussis schedule, and as such, diphtheria is not a primary consideration.
- Efforts to ensure that all travellers, particularly those visiting areas of high risk for diphtheria receive a booster dose of Tdap prior to departure if one has not been

received for 10-20 years previously are desirable but challenging to implement. Children travelling overseas should be up to date with their routine immunisations.

- The WHO recommend DT vaccines be given concurrently or before CRM-conjugated vaccines to avoid potential interference with immunity against certain pneumococcal or meningococcal polysaccharides.

## 1.4 Recommended updates for the Immunisation Handbook

As appropriate include WHO position statement recommendations in 2017<sup>(17)</sup>

For 2020 Handbook- check for all references to Td and where relevant replace with Tdap

**5.3.1 Global burden of disease** - update global epidemiology from WHO data – e.g. outbreaks in Indonesia, for example, due to failure of immunisation services to highlight the importance of maintaining community immunity.

**5.3.2 NZ epidemiology** – most up-to-date ESR data (no cases reported in 2018). High risk from imported cases and overseas travel.

**5.4.1 Available vaccines** – ADT booster removed from schedule and to be replaced by Tdap

**5.4.2 Duration of immunity** – update references – models suggest around 30-42 years (shorter than tetanus). These data are based on populations who received six doses in childhood and therefore duration of protection is likely to be shorter in NZ under the five-dose schedule. Consideration around duration of protection with the diphtheria schedule is also determined by pertussis duration of protection (see pertussis chapter). Fully immunised older adults are likely to have received fewer priming doses than those age under 30 years, and therefore, duration of protection following a booster dose is potentially shorter.

**5.5.3 Booster doses for adults** – it is important to consider older adults when recommending booster vaccinations. Link booster dose requirements for diphtheria to those for pertussis.

## 2 Diphtheria infection and vaccination

The most important virulence factor for diphtheria is diphtheria toxin, an exotoxin released by the bacterium *Corynebacterium diphtheriae*, which inhibits host cell protein synthesis. Cell wall antigens may also contribute to disease pathogenesis and in establishing infection.<sup>(18)</sup> Transmission of the bacteria is through droplets and close physical contact with infected mucus membranes. Poverty and over-crowding are associated with increased transmission. Cutaneous diphtheria, presenting as non-healing skin lesions, has been associated with transmission in tropical climates, particularly, with overcrowding and poor hygiene conditions. Respiratory diphtheria is an infection of the nasopharynx and larynx clinically manifested by a pseudo-membrane forming across the airway and marked enlargement of the cervical lymph nodes. Toxin produced by the organism can also cause specific effects on the heart, kidneys and peripheral nerves. Neurological complications occur in 15-20% of cases and can cause paralysis up to 2 months after disease onset.<sup>(18)</sup> Treatment must thus be multi-faceted, including diphtheria antitoxin, antibiotics and measures to maintain the airway. Even with appropriate medical care, 10% of cases die as a result of acute systemic toxicity.<sup>(1)</sup> Rarely, non-toxigenic strains can cause invasive disease, including bacteraemia, endocarditis and arthritis, but vaccine has no impact on these infections.<sup>(18)</sup> Also, very rarely, human cases of diphtheria have been caused by other toxigenic strains of *Corynebacteria*, *C. ulcerans* and *C. pseudotuberculosis*, which are transmitted from animals and are clinically indistinguishable from toxigenic diphtheria.<sup>(18-21)</sup> Non-toxigenic strains can convert to toxigenic strains by infection with *tox*-gene containing  $\beta$ -corynebacteriophage, and both can occur during outbreaks.<sup>(18)</sup>

Prior to the introduction of diphtheria vaccination in the early twentieth century, half of the children who contracted diphtheria died and it was a major cause of childhood mortality. Diphtheria toxoid (DT), inactivated toxin, was first used for immunisation during the First World War.<sup>(1)</sup> Diphtheria vaccine first became available in New Zealand in 1926 for use in selected schools and orphanages.<sup>(22)</sup> Epidemics involving around 1 million cases were reported during the Second World War prior to routine immunisation in the late 1940s in North America and Europe. During 1990-1998 more than 157,000 cases and 5000 deaths were reported, most of which were associated with outbreaks in Russia and former Soviet Republics following breakdown of immunisation delivery after the collapse of the former Soviet Union. Total cases reported globally decreased by more than 90% following global immunisation campaigns during 1998-2000.<sup>(1, 8)</sup>

In countries with poor immunisation coverage, diphtheria remains a significant health issue. Around 14% of children globally are not fully immunised against diphtheria and all countries have pockets of unvaccinated children.<sup>(1)</sup> In temperate climates, most cases of diphtheria occur in colder seasons, but transmission occurs throughout the year in warmer climates. The South-East Asia region was the reported source of most cases of diphtheria during 2011-2015 (India, Indonesia and Madagascar, in particular), but under-reporting has been shown for Africa and Eastern Mediterranean regions.

Most reported cases were unvaccinated or incompletely vaccinated adolescents and adults (40% of cases were age over 15 years in high incidence countries and 66% in low incidence countries). Incidence was higher in women, believed to reflect men receiving more doses of tetanus-diphtheria (Td) vaccine through military service and tetanus prophylaxis for injuries.

## 2.1 World Health Organization position statement on diphtheria

In 2017, the World Health Organisation released a position paper on diphtheria vaccine to provide global guidance around routine childhood immunisation against diphtheria and recommendations for boosters later in life as summarised in Table 1.<sup>(1, 17)</sup>

*Table 1: Summary of WHO recommendations for diphtheria vaccine, 2017*

Group	Recommendation or comment
Primary vaccination for infants	Three primary doses: as early as 6 weeks, with a minimum of 4 weeks between doses, completed by 6 months of age.
Booster doses for children	Three booster doses: given at 12-23 months, 4-7 years and 9-15 years with age appropriate formulations of vaccine.
Adult boosters	Immunity gaps in older age groups have been identified related to antibody decline with age, however, data is too limited for recommendations around booster doses.
Booster doses for immune compromise	A need for additional booster doses for those with HIV infection and congenital or acquired immunodeficiencies has not yet been established due to low incidence of cases.
Timing with conjugated vaccines	Cross-reactive material (CRM)-conjugate vaccines, such as certain pneumococcal and meningococcal conjugate vaccines, can be administered with or before, but preferably not immediately after, DT-containing vaccine in routine immunisation programmes.
Healthcare workers and travellers in endemic or outbreak settings	Should ensure they have received six lifetime diphtheria-containing vaccines prior to departure.
Maternal Tdap	The impact of maternal Td or Tdap vaccination on infant immune responses to conjugate vaccines had not been adequately studied. (As of 2017 position statement; more data are emerging as uptake increases.)

The scheduling of diphtheria vaccination in New Zealand is dependent on the pertussis and tetanus schedules since diphtheria vaccine is only available in combination with tetanus and pertussis vaccines (DTaP, Td and Tdap in New Zealand).<sup>(6)</sup> As of August 2019, the NZ schedule provides DTaP-IPV-HepB-Hib at 6 weeks, 3 months and 5 months and a DTaP-IPV booster at 4 years of age (no booster is given in the second year-of-life as recommended by WHO). Tdap is provided at 11 years of age, 45 and 65 years. Pregnant women are recommended one dose of Tdap in each pregnancy and Td is provided for tetanus-prone wound care (Tdap to replace Td in 2020).<sup>(22)</sup>

## 3 Diphtheria epidemiology

New Zealand remains at risk of diphtheria outbreaks from imported cases within under-immunised population groups. In the past few years, although isolated cases of toxigenic diphtheria have been reported in various high-income countries, including the Australia, Finland, Germany, Netherlands, Sweden, the UK and the US, almost all were imported from endemic countries.<sup>(23-26)</sup>

Two deaths due to respiratory diphtheria occurred in 2011 and 2018 in Queensland, Australia in young unimmunised adults.<sup>(11, 27)</sup> Imported cases of cutaneous diphtheria have been reported in the UK and NZ, including in a fully immunised 5-year-old.<sup>(2, 26, 28)</sup>

Although increasingly children receive diphtheria vaccination in developing countries through the EPI, adults remain at risk due to historically low coverage and a lack of booster doses to maintain protection in adolescents and adults. This vulnerability in adults was highlighted by a recent outbreak in Indonesia.<sup>(5, 29)</sup>

Diphtheria remains a public health problem in Latvia, India, Dominican Republic and Singapore, and particularly in countries with disrupted immunisation programmes and civil unrest, like Indonesia, Venezuela and Yemen.<sup>(30-35)</sup>

### 3.1 New Zealand epidemiology

No cases of diphtheria were notified in 2018 in NZ.<sup>(36)</sup> In 2017, of 61 *C. diphtheriae* isolates, five from the throat and 56 were cutaneous. One cutaneous isolate was a toxigenic strain from an adult aged 70 years.<sup>(3)</sup> The last NZ case of toxigenic respiratory diphtheria was reported in 1998.

Two presentations of cutaneous diphtheria were notified at the refugee resettlement centre in Auckland in 2015 and an asymptomatic carrier was also identified. All three cases were children from Afghani refugee families who had lived in Pakistan prior to coming to NZ in February 2015 and had uncertain immunisation status. The outbreak investigation identified a total of 164 high-risk and low-risk contacts.<sup>(2)</sup>

## 4 Immunity and duration of protection

In high income countries, since diphtheria is extremely rare, levels of population immunity against diphtheria are usually estimated by serological surveillance.

Defined correlates of protection have been established for serum antibodies to diphtheria toxin (antitoxin), but levels required for complete protection can vary between individuals. Short-term protection is defined as an antitoxin level above 0.01 IU/ml for any protection and over 0.1 IU/ml for full protection against toxin-mediated disease. Levels of at least 1.0 IU/ml are required for long-term protection.<sup>(1, 18)</sup>

This section will consider whether children and adults are likely to be sufficiently protected against diphtheria in the case of an imported outbreak in NZ or when travelling overseas.

### 4.1 Children

In areas where diphtheria is endemic, unvaccinated or inadequately vaccinated preschool and school-aged children are affected most often by respiratory diphtheria. The disease is rare in adults living in urban areas due to acquired immunity from subclinical disease.<sup>(18)</sup> Maternal antibody is believed to provide some protection against diphtheria to young infants under the age of 6 months.<sup>(18)</sup>

A serological survey conducted in Australia in 2007 found that following the removal of the toddler booster dose, 59% of children aged 3 years were susceptible to diphtheria based on a protective threshold 0.1 IU/ml.<sup>(11)</sup> No apparent boosting of diphtheria immunity was observed in the relevant age groups from diphtheria-derived CRM conjugated vaccines - meningococcal C conjugate vaccine and seven-valent pneumococcal vaccine (PCV7) in the schedule.<sup>(11)</sup> Adolescent booster doses improved immunity in that age group.<sup>(11)</sup> The toddler dose of DTaP was reinstated in Australia at 18 months of age to improve protection against pertussis primarily. Further booster doses are given at 4 years (DTaP-IPV) and 12-13 years of age (Tdap).

Assessment of immunity in Polish children highlighted a need to consider diphtheria immunity as well as tetanus immunity when designing immunisation schedules. The proportion of fully vaccinated-for-age Polish children (aged 18 to 180 months) protected against diphtheria was significantly lower than for tetanus (229 [70.5%] vs 306 [94.1%], respectively).<sup>(37)</sup> The Polish immunisation schedule included seven doses – three primary, one toddler dose in the second year-of-life and boosters at 6, 14 and 19 years - but with less than 5 years between booster doses. Although mean antibody and percentage with high antibody titres increased with age for tetanus, this was not seen for diphtheria antibodies. It was concluded that although seven doses were given in Poland, the schedule required longer intervals between booster doses (e.g. 10 years), to be achieved potentially by removing the booster 14 years.<sup>(37)</sup>

In New Zealand, children are scheduled DTaP-IPV vaccine before school entrance (at 4 years of age) and Tdap-IPV is not available until over the age of 7 years. However, a comparison of these vaccines did not find significant differences in immunity conferred against diphtheria. Vaccines containing low-dose diphtheria toxoid provided adequate booster responses when administered to preschool age children to confer immunity at least until early adolescence. The use of Td-IPV in children at 6 years of age, instead of DT-IPV, as a second booster dose (first booster given at age 16-18 months) was supported by antibody persistence at the age of 11-13 years (i.e. 5 years after the preschool booster). In a follow-

up clinical trial in France, 96.5% of adolescents had antitoxin levels over 0.01 IU/ml. As part of this Sanofi-sponsored clinical trial, all participants were given a second booster dose with DTaP-IPV at 11-13 years of age and all achieved antitoxin levels of over 0.1 IU/ml.<sup>(38)</sup>

During five pre-licensure RCTs, two or three primary doses (from ages 2 – 6 months) of Infanrix-hexa (DTaP-IPV-HepB/Hib) provided protection until 11-19 months in 57.9-86.4% of infants.<sup>(39)</sup> As reviewed by 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 and this difference disappeared after boosting in the second year of life. 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.<sup>(1)</sup>

Low-dose diphtheria-containing vaccines (Tdap) were shown to provide comparable protection to standard-dose vaccine (DTaP) in preschool-age children (age range 3.5-5.1 years) for at least 5 years in a UK-based Sanofi-sponsored study. At five years after the booster dose, 75% of children who received Tdap-IPV and 79% who received DTaP-IPV had antitoxin levels higher than 0.1 IU/ml.<sup>(7)</sup>

## Conclusions

In the absence of a DTaP booster in the second year-of-life in NZ, antitoxin levels induced by the primary series (at 6 weeks, 3, and 5 months) may not be adequately long-lived to protect until 4 years of age.

Booster doses given to preschool children provide protection for at least 5 years. However, note that the data presented are from children who had previously received a booster in the second year of life, which is not included in the current NZ schedule.

## 4.2 Adults

The WHO identified that adults in countries with long-standing childhood immunisation programmes were likely to be susceptible without booster doses to overcome waning immunity due to lack of exposure to diphtheria. Waning immunity contributed to the high number of cases in adults observed during the outbreak in the former Soviet Union.<sup>(8)</sup>

A US-based study, investigating the magnitude and duration of immunity to tetanus and diphtheria vaccination, predicted that 95% of the adult population would maintain seroprotection for at least 42 years without requiring further booster doses. No details were provided about diphtheria vaccination experience of the 546 participants (mean age 49 years, range 19-87), but 99% of subjects aged under 60 years (97% all subjects) had antibody levels higher than the seroprotective threshold of 0.01 IU/ml. Diphtheria-specific seroprotective immunity declined with a mean estimated half-life of 27 years (95% CI 18-51), thereby was likely to decline to the 0.01 IU/ml threshold in 30-42 years. A model of booster vaccination every 30 years predicted protective immunity in at least 95% of adults and that ten yearly boosters, as currently recommended, were not indicated.<sup>(40, 41)</sup> Note that many of these adults were likely to have received several booster doses in their life-time, since 10-yearly boosters have been recommended in the US for those aged over 6 years since 1966.<sup>(40)</sup>

A serosurvey conducted in 2009 in NZ found that seroprevalence was significantly higher in those aged 11-15 and 16-24 years than children aged 6-10 years. Immunity in adult aged 25-44 and 45+ years (sampled from blood donors) was significantly lower than in children

(sample from routine venepuncture). Of those age 11-15 years, 77.2% (95% CI 73.6-80.5) were seropositive for diphtheria; seroprevalence declined with age to 45.6 % (41.6-49.7) in adults 45 years or older.<sup>(12)</sup>

Similarly, an Australia serological survey conducted in 2007 found that 40% of adults aged at least 30 years were potentially susceptible to diphtheria based on a protective threshold of 0.1 IU/ml. Across all age groups from 3 years of age, 67.5% were seroprotected against diphtheria in 2007.<sup>(11)</sup> A Singapore sero-epidemiological study found that 92% of adults (aged 18-70 years) had short-term protection against diphtheria (0.01 IU/ml).<sup>(42)</sup>

After assessing the half-life of vaccine-induced anti-diphtheria IgG antibody in military personnel in Italy, antitoxin levels above protective levels (0.1IU/ml) were predicted to persist for around 20 years against diphtheria (compared with 65 years for tetanus). The difference was considered due to the lower diphtheria toxoid content in the adult formulation of Td, but lower responses were also noted in the subset of individuals with the *HLA-DRB1\*01* allele, suggesting genetic variation in immune response.<sup>(43)</sup>

In a US-based clinical trial, 95% of adolescents (from 11-17 years) and 80% of adults (up to 64 years) were found to have seroprotection against diphtheria (antitoxin threshold 0.1 IU/ml) at 5 and 10 years after Tdap or Td boosters.<sup>(44)</sup>

## Conclusions

Although generally well protected, some adults are vulnerable to diphtheria infection based on accepted antibody thresholds and persistence of diphtheria protection is shorter than for tetanus. Decisions around booster doses in adults need to consider risks to individual and community immunity against diphtheria alongside those for tetanus and pertussis.

## 4.3 At-risk populations

At-risk groups for diphtheria include those who are most likely to bring diphtheria to New Zealand as well as those who are at high risk of being infected if an outbreak were to occur. Here we describe the predicted levels of immunity and risks factors of such groups.

### 4.3.1 Former refugees and migrants

Middle Eastern refugees entering Europe were found not to have adequate immunity for herd protection against diphtheria. In six Germany refugee centres, 76.1% of refugees did not have antibody levels required for long-term protection against diphtheria (IgG titres more than 1.0 IU/ml), 2.1% were seronegative and 47.7% required immediate vaccination due to unprotective antitoxin levels (< 0.1 IU/ml). An age-dependent decline in immunity was observed: around one quarter of children and young adults aged less than 25 years were fully immune (28.1% and 26.0%); just under half of children, adolescents and young adults had undetectable antibody or titres less than 0.1 IU/ml (46.1% and 45.2%); declining in adults aged over 50 years with 14.7% fully immune and 61.7% with undetectable or very low antitoxin titres.<sup>(45)</sup>

Discrepancies in vaccination coverage and burden of vaccine-preventable diseases were observed in two cohort studies comparing NZ-born and foreign-born migrant children. NZ-born children of Pacific ethnicity and former refugee backgrounds had a higher burden of vaccine-preventable disease-associated hospitalisations than foreign-born and NZ-born non-migrant children.<sup>(46)</sup> When immunisation rates were examined, less than half (46%) of the foreign-born children aged up to 5 years of age had a National Immunisation Register record compared to 95% and 96% in migrant and non-migrant NZ born children. Foreign-born children had fewer recorded age-appropriate vaccinations for all the assessed vaccines,

which may be due to disruption of schedules while immigrating or being classified as delayed according to the NZ immunisation schedule due to a misalignment with country of origin schedules. Notably, immunisation coverage was high for “quota refugee” children who entered NZ through the refugee orientation programme, which includes health checks and immunisation within 6 weeks of arrival.<sup>(47)</sup>

#### 4.3.2 Older adults

In Europe, recommendations for diphtheria vaccination varied widely across Europe in the twentieth century, and access to vaccine was limited during and soon after the Second World War. Recent studies have reported on diphtheria seroprevalence in European countries.

In Austria, 65% of 257 elderly patients (mean age 66 years; range 59-91 years) did not have seroprotective diphtheria antitoxin levels and antibody levels varied substantially. Only half of the participants knew if they had ever been vaccinated against diphtheria and one third had received diphtheria vaccine within the last 10 years. The study suggested some older adults in Austria may never have received diphtheria vaccine, and in these individuals, booster doses were insufficient for priming.<sup>(9)</sup>

A national serosurvey in the Netherlands found that despite high national immunisation coverage with increases between 1995/1996 and 2005/2006, susceptible populations and geographically clustered areas of low coverage remained. In 2006-2007, although 91% of the national population had minimum seroprotective levels (0.1 IU/ml), 18% of adults born prior to the diphtheria vaccination programme (aged over 51 years) had antibody levels below 0.01 IU/ml.<sup>(48)</sup>

The MARK-AGE study found the European population was not fully protected against tetanus and diphtheria. Antibody levels against tetanus and diphtheria varied between countries, gender, age and country of origin. Of adults aged 35-74 years, from 28 to 63% were unprotected (0.1 IU/ml threshold) and levels of protection decreased with age. Fewer were protected against diphtheria than tetanus, but unlike tetanus, no gender differences were seen for diphtheria immunity. The authors concluded that regular booster doses are necessary to sustain protection into older age, particularly for older adults who were likely to have received fewer life-time doses than those aged less than 30 years.<sup>(10)</sup>

In Singapore, a serological study found older adults were at higher risk of diphtheria especially those travelling to areas where diphtheria is endemic or epidemic. Although 92% had antibody levels sufficient for short-term protection, these declined significantly with age and were lower in the 50-59 years age-group (as compared with 60-69 years against tetanus).<sup>(42)</sup>

#### 4.3.3 Geographically clustered low immunisation coverage

Pockets of unvaccinated individuals who actively decline vaccinations are found in most countries. Around 5% of parents actively decline one or more vaccines in NZ and certain regions of NZ have lower immunisation coverage due to clustering of such parents.<sup>(49)</sup> Lower immunisation coverage in some regions is also linked to Māori ethnicity and high levels of deprivation, and but is typically associated with incomplete or delayed immunisation rather than non-immunisation associated with decliners. The estimated level of coverage required for community (“herd”) protection against diphtheria is around 85% for each birth cohort, and in a population where most adults are immune, at least 70% of the childhood population needs to be immunised to prevent major community epidemics.<sup>(50, 51)</sup>

Within the orthodox Protestant community in the Netherlands, which has previously declined all vaccines for religious reasons, 54% lacked adequate diphtheria seroprotection. However, this level of protection improved since the 1995/1996 serosurvey suggesting greater vaccine acceptance.<sup>(48)</sup>

#### 4.3.4 Travellers

People travelling to regions with endemic or epidemic diphtheria are at risk of exposure and should be fully immunised prior to departure and a booster dose is advisable.

In Sweden, a single booster dose of Td is recommended within a 20 year-interval. Regardless of the interval between doses (<20 years or more prolonged), a single booster dose of Td achieved immunity in 40 travellers. Of the 40 participants, 10/13 were immune with booster within 20 years (median age 62 years) and 19/27 were immune with booster > 20 years (median age 51 years ); post Td, 13/13 and 26/27 were seroprotected.<sup>(52)</sup>

It was noted that low immunity against diphtheria in Australian adults is of primary concern for travellers to endemic regions, particularly within the Asia-Pacific. In 2011, a partially immunised young man recently returned from Papua New Guinea with localised *C. diphtheriae* pharyngitis, was linked to two secondary cases of typical diphtheria, one of whom, an unvaccinated 19-year-old woman, died.<sup>(11)</sup>

Those visiting friends and relatives overseas are less likely to seek travel medicine advice, but more are likely to visit more remote regions and not fully understand their risk from vaccine-preventable diseases that are common in those places.<sup>(13)</sup>

#### 4.3.5 Conclusions

- Immunised adults may not be seroprotected against diphtheria due to waning immunity or inadequate immunisation.
- Immunisation status is typically undocumented in older adults.
- Unimmunised younger adults often belong to a non-vaccinating family.
- Currently, with the absence of endemic disease, the risk of diphtheria infection in NZ is associated with travel to endemic regions or regions with outbreaks.
- In partially immunised individuals, transmission is possible due to mild or subclinical infection in the absence of clinically evident disease. Such transmission has the potential to cause outbreaks within regions/communities with low immunisation coverage or vulnerable groups, including former non-quota refugees, the elderly or those with significant co-morbidities compromising immunity.

## 5 Interference with diphtheria vaccine immunogenicity from other vaccinations

The importance of adequate priming against diphtheria has been highlighted as being necessary to provide long-lasting protection. This is particularly relevant within the NZ immunisation schedule context with no booster in the second year-of-life and immunity is therefore reliant on a long-lasting protection from the primary doses until 4 years of age when the first scheduled booster dose is given.

Here we examine potential sources of interference with the immunogenicity of primary immunisations. It is important to note, that these effects may not be clinically relevant, especially in the NZ setting with low risk of exposure to diphtheria.

### 5.1 Effect of conjugate vaccines on diphtheria vaccine immunogenicity

The presence of pre-existing immunity to a carrier protein, as used in conjugated vaccines, can have the potential to enhance or suppress subsequent immune responses to that antigen or have a bystander effect on other antigens.<sup>(53)</sup>

A systematic review conducted by the WHO concluded that coadministration of the priming doses of DT with other childhood vaccines does not interfere with the primary or booster responses to BCG, Hib, IPV, PCV or measles-mumps-rubella (MMR), human papillomavirus, meningococcal conjugate vaccines, rotavirus and varicella vaccines. Immune responses to diphtheria have been increased when given simultaneously with or following administration of CRM-conjugated vaccines.<sup>(1)</sup> However, in adults, Tdap vaccination given before PCV13 significantly reduced antibody responses to 7 out of 13 pneumococcal serotypes.<sup>(1)</sup>

WHO recommend that CRM-conjugated vaccines (PCV13 and certain meningococcal conjugate vaccines) can be administered with or before, but preferably not after, diphtheria toxoid-containing vaccines in routine vaccination programmes.<sup>(1)</sup>

Conjugate vaccines available in NZ that contain diphtheria antigens include:

- PCV13 (Prevenar® 13) – CRM<sub>197</sub> conjugated
- Meningococcal ACYW-135 (Menactra®) – diphtheria toxoid conjugated
- PCV10 (Synflorix) – serotype 19F conjugated with diphtheria toxoid carrier protein

### 5.2 Effect of maternal vaccination

In the presence of maternally-derived antibodies in infants of Tdap immunised mothers, antibody responses to diphtheria and CRM-conjugated vaccines (PCV13, MenC-CRM) were reduced in their infants, although the antibody levels induced remained seroprotective.<sup>(15)</sup>

The immunogenicity of the first dose of infant immunisation is related to both 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 in 7,630 infants from 32 immunogenicity studies of licensed and unlicensed vaccines across 17 countries. In the presence of two-fold higher maternal antibody concentrations against tetanus or diphtheria, antibodies in the infants were 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 antibody levels. For diphtheria, there was a 28% increase in IgG antibody for each month of age that the first vaccination was delayed, with the time delay to offset a two- to five-fold increase in maternal antibody estimated to be 1.7 to 3.9 weeks.<sup>(16)</sup> Clinical protection was not evaluated in this study and none of the mothers in this study had received Tdap during pregnancy.

Antibody responses to routine vaccinations in England were compared in infants of mothers who received Tdap-IPV in pregnancy with those not vaccinated in pregnancy. Antenatal pertussis vaccination resulted in high infant pre-immunisation antibody concentrations, but subsequent antibody responses to all three pertussis antigens, diphtheria and some CRM-conjugated antigens (PCV13 and some meningococcal C vaccines) were blunted, although still reaching presumptive threshold levels. Diphtheria antibody levels were 0.55-fold lower (0.46-0.66;  $p < 0.001$ ).<sup>(54)</sup>

### **Conclusions**

Some interference is observed against conjugated polysaccharides when CRM-conjugated vaccines are given after diphtheria toxoid-containing vaccines. No clinically relevant interference occurs when given these vaccines concurrently or before. In this case, immunity against diphtheria may also be enhanced.

Maternal antibody post Tdap vaccine in pregnancy reduces infant antibody responses to diphtheria-containing vaccines, more so with the first primary dose given at 6 weeks of age rather than later. It is not known whether this interferes with clinical protection; a second-year-of-life booster could be justifiable to minimise waning protection against diphtheria.

## 6 Appendix

### 6.1 Diphtheria toxoid-containing vaccines available in New Zealand

The contents of the currently licensed diphtheria toxoid-containing vaccines available in NZ are provided in Table 2.<sup>(55-59)</sup>

Table 2: Diphtheria-containing vaccines available in New Zealand, licensed by Medsafe

DTaP combinations
<p><b>Infanrix-hexa<sup>®</sup>, GSK</b></p> <p>Combined diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B and <i>Haemophilus influenzae</i> type B vaccine (DTaP-IPV-HepB/Hib), containing ≥30IU DT, ≥40IU TT, 25µg PT, 25µg FHA, 8µg PRN, as well as HepB surface antigen, IPV, Hib-PRP conjugated to TT.</p>
<p><b>Infanrix-IPV<sup>®</sup>, GSK</b></p> <p>Combined diphtheria-tetanus-acellular pertussis and inactivated poliovirus vaccine (DTaP-IPV), containing ≥30IU DT, ≥40IU TT, 25µg PT, 25µg FHA, 8µg PRN with IPV types 1, 2 and 3.</p>
Td and Tdap combinations
<p><b>ADT-Booster, SSI</b></p> <p>Tetanus toxoid and reduced dose diphtheria toxoid (Td) containing ≥20IU TT and ≥2IU DT, adsorbed with aluminium hydroxide and water for injections. Used routinely for adult booster and for tetanus-prone wound prophylaxis from age of 7 years. [This vaccine will be discontinued in July 2020]</p>
<p><b>Boostrix<sup>®</sup> and Boostrix<sup>®</sup>-IPV, GSK</b></p> <p>Combined tetanus, reduced antigen dose of diphtheria and three-component acellular pertussis vaccine (Tdap) containing ≥2IU DT, ≥20IU TT, 8µg PT, 8µg FHA and 2.5µg PRN adsorbed 0.5mg aluminium and suspended in isotonic sodium chloride. A formulation combined with IPV is also available for catch-up.</p>
<p><b>Adacel<sup>®</sup> and Adacel<sup>®</sup>-Polio, Sanofi-Pasteur</b></p> <p>Combined five-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids (Tdap) containing ≥20IU TT, ≥2IU DT, 2.5µg PT, 5µg FHA, 3µg PRN and 5µg FIM2/3 adsorbed with 0.5mg aluminium. Also available is a formulation combined with IPV types 1, 2 and 3.</p>
<p>Abbreviations: DT – diphtheria toxoid; FHA – filamentous haemagglutinin; FIM2/3 -fimbriae types 2 and 3; GSK – GlaxoSmithKline; HepB – hepatitis B, Hib – <i>Haemophilus influenzae</i> type B; IPV - inactivated poliovirus; PRN – pertactin, PRP - polysaccharide polyribosylribitol phosphate; PT – pertussis toxin; SSI - Statens Serum Institut</p>

## 6.2 International policy and practice

Since there are no diphtheria-only vaccines use globally, the international schedules for diphtheria immunisation are the same as for tetanus and pertussis. Post-childhood, the availability of booster doses is determined by the tetanus immunisation programmes.<sup>(60)</sup>

*Table 3: Summary of international immunisation recommendations for diphtheria vaccines, as of 2019*

Country	Age of vaccination	Number of doses in childhood	Special recommendations
USA	2, 4, 6, 15-18m 4-6y, 11-12y	6	Tdap age ≥ 7 years Pregnancy 27-36gw Td boosters every 10 years, Tdap first booster if not previously received
Canada	2, 4, 6m, 18m 4-6y, 13-16y	6	Tdap-IPV at 4-6 years One Tdap dose per adult lifetime Pregnancy from prior to 36 gw (ideally 27-32 weeks)
Australia	6w/2, 4, 6m, 18m 4y, 10-15y	6	Pregnancy third trimester (28-32gw ideal)
NZ	6w, 3, 5m 4y, 11y 45y, 65y	5	Tdap to replace Td for adults and tetanus prophylaxis Pregnancy 28-38gw Tdap
Denmark	3, 5, 12m 5y	5	
Germany	2, 3, 4, 11-13m 5-6y, 9-17y	6	Adult formulation from 5 years From 18y, first booster as Tdap, then Td 10-yearly
Portugal	2, 4, 6, 18 months 5, 10 years 25, 45 and 65 years	6	Adult formulation from 10 years Tdap in pregnancy 20-36 gw
UK	2, 3, 4m 3y 4m 13-14 years	5	DTaP-IPV or TdaP-IPV at age 3y 4m Tdap-IPV in pregnancy from week 16

Abbreviations: w – weeks; m – months; y – years; gw – gestation weeks; Tdap – tetanus-diphtheria-acellular pertussis vaccine; IPV – inactivated polio vaccine

## 6.3 Methodology for review

### 6.3.1 Literature search strategy

#### Medline search terms and strategy

MeSH terms: diphtheria toxoid/ or diphtheria or diphtheria-tetanus vaccine 7936

Limit English, human 2015- current (30 July 19) 190 Selected 47

diphtheria vaccine [title] 57

Limit English, human 2015- current (24 Jun 19) 4; selected 1

\*Diphtheria toxoid [MeSH term – focus, all subheadings] 1773

Limit English, human 2017-2019 [24 Jun 19] 16 – none selected

#### 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.

#### Final Endnote Library 65 Journal articles

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

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

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