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

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ESR

Immunisation Advisory Centre
ĀRAINGA MATE
UNIVERSITY OF AUCKLAND

Contact details:

Helen Petousis-Harris
Immunisation Advisory Centre
Tāmaki Innovation Campus
The University of Auckland

Private Bag 92019,
Auckland 1142, New Zealand

Phone: +64 9 923 2078
Fax: +64 9 373 7030
Mobile: +64 27 471 6749
Email: h.petousis-harris@auckland.ac.nz

Executive summary

Since 2009, there have been 11 cases of tetanus in New Zealand to 2011 and two cases in 2012. No cases occurred in persons who were known to have received a primary course of tetanus vaccine.

No safety concerns have been raised for the tetanus toxoid combination vaccines in any groups studied including premature infants. The frequency and severity of local reactions increases with age and additional doses of vaccine. DTaP combination vaccines have been demonstrated to be safe when co-administered with routine vaccines in infants, toddlers and children. Tdap has a safety profile similar to Td. Both vaccines are generally well tolerated and Tdap vaccine has been demonstrated to be safe when co-administered with trivalent inactivated influenza vaccine in adults.

Tetanus vaccines are extremely immunogenic and data continues to support the immunogenicity in many groups including premature and low birth weight infants and older adults. There is some evidence that co-administration with Td and tetanus immunoglobulin can reduce the early GMT to the vaccine, but this is unlikely to be clinically relevant. Co-administration of tetanus vaccines with other vaccines including MMRV has been demonstrated to be both safe and immunogenic.

Vaccine options for the prevention of tetanus disease in infants, children and adolescents in New Zealand include combination vaccines that include DTaP for children up to the age of seven years and the lower strength Td in combination with aP (Tdap) for those seven years and older, adults and the elderly. The tetanus toxoid appears to be immunogenic and safe in all internationally studies of combination vaccines.

Tdap has been demonstrated to be safe, immunogenic for the tetanus toxoid antigen and comparable to Td when administered to adults ≥65 years of age and is also expected to be comparable to Td in adolescents and adults ≤64 years of age.

DTaP combination vaccines can be administered as a priming course of three vaccinations in the first year of life or as a primary course of two vaccinations plus a booster vaccination in the first year of life. A reduced-antigen content Tdap vaccine can be offered to toddlers and children up to nine years of age as a fourth/booster vaccination.

A single Tdap vaccination can be used for the first catch-up vaccination for partially vaccinated or unvaccinated children aged seven – 10 years of age. Tdap can be administered to adults, including pregnant women and adults ≥65 years of age.

Tdap vaccine is an acceptable alternative to Td for the first tetanus toxoid catch-up vaccination and for tetanus prophylaxis when an individual has a tetanus-prone wound.

No minimum interval is required between administration of Tdap and a previous Td vaccination.

Australia is considering increasing the upper age limit for administration of full strength DTaP vaccines to the 10th birthday. The UK already recommends this upper age limit.

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

Prepared as part of a Ministry of Health contract

by

Dr Helen Petousis-Harris, Immunisation Advisory Centre (PI and lead author)

Karin Batty, Immunisation Advisory Centre (Lead Author)

Dr Nikki Turner, Immunisation Advisory Centre

Dr Mary Nowlan, Immunisation Advisory Centre (editor)

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

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Abbreviations

ACIP	Advisory Committee on Immunization Practices (US)
AEFI	Adverse event following immunisation
BSE	Bovine spongiform encephalopathy
CCID50	50% cell culture infectious dose
CI	Confidence interval
DTaP	Full strength diphtheria-tetanus-acellular pertussis vaccine
DTaP-IPV	Full strength diphtheria-tetanus-acellular pertussis-polio vaccine
DTaP-IPV-Hib	Full strength diphtheria-tetanus-acellular pertussis-polio-Haemophilus influenzae type b vaccine
DTaP-IPV-HepB/Hib	Full strength diphtheria-tetanus-acellular pertussis-polio-hepatitis B-Haemophilus influenzae type b vaccine
DagU	D-antigen unit, a unit of measure for antigen content
ELISA unit	Enzyme-linked immunosorbent assay unit, a unit of measure for antigen content
EpiSurv	The New Zealand national notifiable disease surveillance database, operated by ESR on behalf of the Ministry of Health
ESR	The Institute of Environmental Science and Research
GMC	Geometric mean concentrations
HepB	Hepatitis B
Hib	Haemophilus influenzae type b
HR	Hazard ratio
ICD10	International Classification of Diseases 10th revision
IPV	Inactivated polio vaccine
IU	International unit, a measure for antigen content
kg	Kilogram
MeSH	Medical subject headings
mg	Milligram
mL	Millilitre
MMR	Measles-mumps-rubella vaccine
MMRV	Measles-mumps-rubella-varicella vaccine
MoH	Ministry of Health
n	Number of study participants
NZ	New Zealand
PFU	Plaque forming units, a measure of virus particles per unit of volume
SAE	Serious adverse event
Td	Reduced-antigen tetanus-diphtheria vaccine
Td-IPV	Reduced-antigen tetanus-diphtheria-polio vaccine
Tdap	Reduced-antigen tetanus-diphtheria-acellular pertussis vaccine
Tdap-IPV	Reduced-antigen tetanus-diphtheria-acellular pertussis-polio vaccine
TIG	Tetanus immunoglobulin
TIV	Trivalent inactivated influenza vaccine
µg	Microgram
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System (US)
VSD	Vaccine Safety Datalink (US)

1. Background – tetanus disease and vaccination

Clostridium tetani is a gram-positive, spore-forming, motile, anaerobic bacillus widely found in the environment, particularly soil and the gastrointestinal tract of animals. Following introduction of the bacilli and/or spores into a wound providing an anaerobic and acidic environment, such as puncture wounds and those with necrotic or devitalised tissue, bacilli replicate and spores may germinate, releasing two exotoxins, tetanolysin and tetanospasmin (tetanus toxin). Tetanospasmin acts on the central nervous system blocking release of inhibitory neurotransmitters that control muscle relaxation, resulting in the signs of tetanus. Natural disease confers little, if any, immunity as only nanograms/kg of toxin are required to cause disease.

Tetanus is a non-communicable disease. Adequate wound cleansing and debridement of devitalised tissue is required to prevent infection, spore germination and toxin release. Vaccination provides 'individual immunity' through generation of antibodies against tetanus toxin. The serologic correlate of protection against tetanus is generally accepted as 0.01IU/mL.

Although the disease was described in humans and animals as early as 1550BC, its aetiology was unknown until 1884. During World War I, protection against disease was through passive immunisation using tetanus toxin antibodies in equine sera. In the early 1960s, human tetanus immunoglobulin (TIG) became available. The first human tetanus toxoid vaccine became available in the late 1930s (1).

The epidemiology of tetanus in New Zealand from 1997 to 2010 is described in the Immunisation Handbook 2011. No cases of tetanus were notified in 2011(2).

This review aims to evaluate the literature on vaccination and wound management to prevent tetanus published from 2009 to 2012, after the writing of the Immunisation Handbook 2011. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 New Zealand antigen review and the specific specifications for tetanus toxoid containing vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around tetanus toxoid containing 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 for example the variable severity of disease and the immunisation concerns that differ with age
  - Different options for placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options
  - Current international research and evidence around use of vaccines
- Specific service specifications for tetanus vaccines
  - Investigation of whether a pertussis booster combined with the vaccine used for tetanus control — for example Tdap (tetanus, diphtheria and pertussis) can be used for wound control (i.e. prevention of tetanus following injury), or if the Td (tetanus, diphtheria) vaccine is needed for this purpose.

2.2 New Zealand epidemiology

The New Zealand epidemiological information presented is based on national tetanus disease surveillance data recorded on EpiSurv as at 21 February 2012.

The Health Act 1956 requires health professionals and laboratories to inform their local Medical Officer of Health of suspected or diagnosed tetanus disease. Notification data is entered onto a computerised EpiSurv database. These notifications provide the basis for surveillance in New Zealand.

National data on patients admitted and discharged from publicly funded hospitals is collated by the Ministry of Health. Cases are assigned disease codes using the 10th revision of the International Classification of Diseases (ICD10) coding system. Anonymised data for tetanus disease was extracted from Ministry of Health databases and sent to ESR for analysis and comparison with data from other surveillance systems. Hospitalisation numbers and notifications may differ (2).

2.3 Literature search strategy

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

1. Safety.
2. Effectiveness in disease control.
3. Implementation issues (practicality of and possible impact on uptake).
4. Differences that need to be considered for each age-group, for example the variable severity of disease and immunisation concerns that differ with age.
5. Different options for placement on the schedule, based on international findings and best practice.
6. Different vaccine options for each disease and comparison between the options.
7. Current international research and evidence around use of vaccines (covered in 1 – 6).

Other areas of special interest

Investigation of whether a pertussis booster combined with the vaccine used for tetanus control — for example Tdap (tetanus, diphtheria, pertussis) can be used for wound control (i.e. prevention of tetanus following injury), or if the Td (tetanus, diphtheria) vaccine is needed for this purpose.

2.3.1 Medline search terms and strategy

MeSH term: Tetanus, focus, all subgroups

12103

Limit to Humans, English, 2009 – current

549

NOT Cost*

531

NOT Attitud*

512

Remove duplicates

490 (keep and view)

2.3.2 Cochrane Library search terms and strategy

Search term Tetanus Vaccin*

6 results (keep and view)

2.3.3 Scopus search terms and strategy

Tetanus Vaccin* Published 2011 – present

1405

Limit to: Medicine, humans, vaccination, vaccine, journals, English

1031

Exclude Letter, Short survey, editorial

932

Reject social science, Arts and Humanities, Veterinary articles.

704 (keep and view)

Delete duplicates

Endnote library 353

2.3.4 Grey literature

There were 25 articles from the grey literature used in review

2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 32 articles and 14 medicine data sheets were accessed (46 additional documents in total).

2.3.6 Final library

The final library includes 398 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

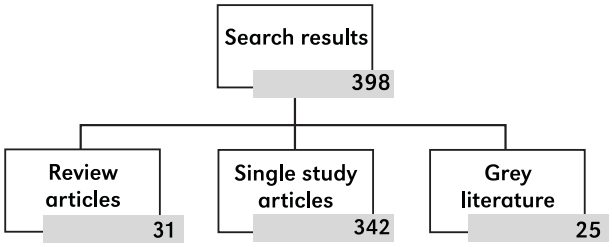


Figure 1. Flow of selection of articles for review

Articles referring to tetanus only in the context of a tetanus toxoid protein in a pneumococcal or meningococcal conjugate vaccine were also excluded. Literature assessing AEFI for whole-cell pertussis vaccines were excluded.

2.4 Participants/populations

The participants and populations include all age-groups.

2.5 Interventions

The interventions included are:

- Full strength tetanus toxoid combination vaccines for infants and children aged less than seven years as a primary series of vaccinations
- Reduced tetanus toxoid antigen vaccines for toddlers, children, adolescents and adults as a booster vaccination.

2.5.1 DTaP

Infanrix® (GlaxoSmithKline) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU) and *Bordetella pertussis* antigen (pertussis toxoid 25µg, filamentous haemagglutinin 25µg, pertactin 8µg). The diphtheria, tetanus and pertussis components of Infanrix® form the base for Infanrix®-IPV, Kinrix® and Infanrix®-hexa (GlaxoSmithKline). The vaccine contains aluminium adjuvant (<0.625mg by assay). Manufacture of the vaccine includes exposure to bovine materials sourced from countries without undue risk of bovine spongiform encephalopathy (BSE). The vaccine can be administered up to the seventh birthday (3).

2.5.2 DTaP-IPV

Infanrix®-IPV and Kinrix® (GlaxoSmithKline) are identical subunit vaccines. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), *B. pertussis* antigen (pertussis toxoid 25µg, filamentous haemagglutinin 25µg, pertactin 8µg) and inactivated poliovirus (type 1: Mahoney strain 40 DagU, type 2: MEF-1 strain 8 DagU, type 3: Saukette strain 32 DagU) (4, 5). The diphtheria, tetanus and pertussis components of Infanrix-IPV are the same as those in DTaP (Infanrix®). The vaccine contains aluminium adjuvant (<0.6mg by assay) and residuals of neomycin and polymyxin B. Manufacture of the vaccine includes exposure to bovine materials sourced from countries without undue risk of bovine spongiform encephalopathy (BSE). The vaccine can be administered up to the seventh birthday (5).

Tetravac™ (Sanofi) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), B. pertussis antigen (pertussis toxoid 25µg and filamentous haemagglutinin 25µg) and inactivated poliovirus (type 1: 40 DagU, type 2: 8 DagU, type 3: 32 DagU). The vaccine contains aluminium hydroxide adjuvant (0.3mg) and residuals of neomycin, streptomycin and polymyxin B (6). The vaccine can be administered up to the seventh birthday (5).

Quadracel® (Sanofi) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), *B. pertussis* antigen (pertussis toxoid 20µg, filamentous haemagglutinin 20µg, pertussis fimbriae types 2 and 3 5µg and pertactin 3µg) and inactivated poliovirus (type 1: Mahoney strain 40 DagU, type 2: MEF-1 strain 8 DagU, type 3: Saukette strain 32 DagU). The vaccine contains aluminium phosphate as an adjuvant (1.5mg) and residuals of neomycin and polymyxin B. The manufacture of this product includes exposure to bovine materials. However, there is no evidence that the human form of BSE has been caused by a vaccine (7).

2.5.3 DTaP-IPV-Hib

Ditekipol/Act-Hib® (Statens Seruminstitut [SSI]) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), B. pertussis antigen (pertussis toxoid 40µg), at least 60% of inactivated poliovirus (type 1: Brunhilde strain 40 DagU, type 2: MEF-1 strain 8 DagU, type 3: Saukette strain 32 DagU) and Hib polysaccharide (10µg) conjugated to tetanus toxoid as a carrier protein. The vaccine contains aluminium adjuvant (1mg) and neomycin residual (8). The vaccine is supplied as a suspension of DTaP-IPV and a vial of lyophilised Hib powder. The Hib powder must be added to the suspension before administration.

Pentacel® (Sanofi) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), B. pertussis antigen (pertussis toxoid 20µg, filamentous haemagglutinin 20µg, pertussis fimbriae types 2 and 3 5µg and pertactin 3µg), inactivated poliovirus (type 1: Mahoney strain 40 DagU, type 2: MEF-1 strain 8 DagU, type 3: Saukette strain 32 DagU) and Hib polysaccharide (10µg) conjugated to tetanus toxoid as a carrier protein. The vaccine contains aluminium adjuvant (0.33mg) and residuals of neomycin and polymyxin B. The manufacture of this product includes exposure to bovine materials (9). The vaccine is supplied as a suspension of DTaP-IPV and a vial of lyophilised Hib powder. The Hib powder must be added to the suspension before administration.

2.5.4 DTaP-IPV-HepB/Hib

Infanrix®-hexa (GlaxoSmithKline) is a subunit vaccine. Each dose contains diphtheria toxoid (≥30IU), tetanus toxoid (≥40IU), B. pertussis antigen (pertussis toxoid 25µg, filamentous haemagglutinin 25µg, pertactin 8µg), inactivated poliovirus (type 1: Mahoney strain 40 DagU, type 2: MEF-1 strain 8 DagU, type 3: Saukette strain 32 DagU), hepatitis B surface antigen (10µg) and Hib polysaccharide (10µg) conjugated to tetanus toxoid as a carrier protein. The diphtheria, tetanus, and pertussis components of Infanrix-hexa are the same as those in Infanrix®. The vaccine contains adjuvants of aluminium hydroxide, hydrated (0.5mg) and aluminium phosphate (0.32mg) and residuals of neomycin and polymyxin B (10). Manufacture of the vaccine includes exposure to bovine materials sourced from countries without undue risk of BSE. The vaccine can be administered up to the 7th birthday (3). The vaccine is supplied as a suspension of DTaP-IPV-HepB and a vial of lyophilised Hib powder. The Hib powder must be added to the suspension before administration.

2.5.5 Td

Decavac® (Sanofi) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (2IU) and tetanus toxoid (20IU). The vaccine contains aluminium adjuvant (<0.28mg by assay) and thimerosal residual. Manufacture of the vaccine includes exposure to bovine materials (11).

Td-pur® (SK Chemical) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (2IU) and tetanus toxoid (20IU). The vaccine contains aluminium hydroxide adjuvant (1.5mg) (12).

2.5.6 Td-IPV

Revaxis® (Sanofi) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (≥2IU), tetanus toxoid (≥20IU) and inactivated poliovirus (type 1: 40DagU, type 2: 8DagU, type 3: 32DagU). The vaccine contains aluminium hydroxide adjuvant (0.35mg) (13).

2.5.7 Tdap

Boostrix® (GlaxoSmithKline) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (≥2IU), tetanus toxoid (≥20IU) and B. pertussis antigen (pertussis toxoid 8µg, filamentous haemagglutinin 8µg, pertactin 2.5µg). The vaccine contains aluminium adjuvant (0.5mg) (14). Manufacture of the vaccine includes exposure to bovine materials sourced from countries without undue risk of BSE.

Adacel® (Sanofi) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (≥2IU), tetanus toxoid (≥20IU) and *B. pertussis* antigen (pertussis toxoid 2.5µg, filamentous haemagglutinin 5µg, pertussis fimbriae types 2 and 3 5µg and pertactin 3µg). The vaccine contains aluminium adjuvant (0.33mg). Manufacture of the vaccine includes exposure to bovine materials. However, there is no evidence that the human form of BSE has been caused by a vaccine (15).

2.5.8 Tdap-IPV

Adacel® **Polio and Repevax**® (Sanofi) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (not less than 2IU), tetanus toxoid (not less than 20IU), *B. pertussis* antigen (pertussis toxoid 2.5µg, filamentous haemagglutinin 5µg, pertussis fimbriae types 2 and 3 5µg and pertactin 3µg) and inactivated poliovirus (type 1: Mahoney strain 40DagU, type 2: MEF-1 strain 8DagU, type 3: Saukette strain 32DagU). The vaccine contains aluminium adjuvant (0.33mg) and residuals of neomycin, streptomycin and polymyxin B. Manufacture of the vaccine includes exposure to bovine materials. However, there is no evidence that the human form of BSE has been caused by a vaccine (16).

Boostrix®**-IPV** and **Boostrix**® **Polio** (GlaxoSmithKline) is a subunit vaccine. Each dose contains reduced diphtheria toxoid (≥2IU), tetanus toxoid (≥20IU), B. pertussis antigen (pertussis toxoid 8µg, filamentous haemagglutinin 8µg, pertactin 2.5µg) and inactivated poliovirus (type 1: Mahoney strain 40DagU, type 2: MEF-1 strain 8DagU, type 3: Saukette strain 32DagU). The vaccine contains adjuvants of aluminium hydroxide, hydrated (0.3mg) and aluminium phosphate (0.2mg). Manufacture of the vaccine includes exposure to bovine materials. However, there is no evidence that the human form of BSE has been caused by a vaccine (17).

2.5.9 Human anti-tetanus immunoglobulin

Hypertet (Green Cross) is a human-derived tetanus hyperimmune immune globulin product for intramuscular administration containing 250 IU/mL of tetanus toxin antibody (18).

2.6 Study designs

The studies included in this update are meta-analyses, systematic reviews, reviews, randomised controlled trials, observational studies using database matching and practice guidelines.

3. Recent New Zealand epidemiology

No cases of tetanus were notified in New Zealand in 2011. However, Ministry of Health hospitalisation data for 2011 recorded three hospitalisations with the primary reason for admission being tetanus. One case was recorded for each of the following age-groups: 20 – 29 years, 60 – 69 years and 70 years and over (2). No data on vaccination status or mortality outcome is currently available for these cases.

Seven cases of tetanus were notified in New Zealand in 2010. These were also identified in the 2010 hospitalisation data with the primary reason for admission being tetanus. The age and vaccination status of the cases were: one case aged one-four years (not vaccinated), one case aged 40 – 49 years (last vaccinated in 1995, full vaccination history unknown), one case aged 60 – 69 years (unknown vaccination status), four cases aged 70 years and over (two not vaccinated and two of unknown vaccination status). All seven cases were non-fatal (19).

One case of tetanus was notified in New Zealand in 2009 and also identified in the 2009 hospitalisation data with the primary reason for admission being tetanus. This case was in the 70 years and over age-group (unknown vaccination status) and non-fatal (20).

3.1 Summary of New Zealand epidemiology

Adults aged 70 years and over and the unvaccinated, or those with unknown vaccination status, had an increased risk of tetanus disease between 2009 and 2011 (Table 1) (2, 19, 20).

Table 1. Summary of tetanus cases, vaccination status and mortality data 2009 – 2011

Year	Age-group (years)	Notified	MoH hospital data	Vaccinated	Not vaccinated	Unknown vaccination status	Non-fatal	Fatal	Total cases
2009	70+	1	1			1	1		1
2010	1 – 4	1	1		1		1		7
	40 – 49	1	1	1[a]			1		
	60 – 69	1	1			1	1		
	70+	4	4		2	2	3	1	
2011	20 – 29	0	1	No data	No data	No data	No data	No data	3 possible
	60 – 69		1						
	70+		1						

a. This person had received their last tetanus vaccination 15 years earlier. However, their full vaccination history unknown.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed tetanus toxoid vaccines.

4.2 Outcomes

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

4.3 Review

4.3.1 DTaP combination vaccines

4.3.1.1 Preterm infants

The hexavalent combination DTaP-IPV-HepB/Hib (Infanrix®-hexa) is generally well tolerated in pre-term (24 – 36 weeks gestation) and/or low birth weight (820 – 2020 grams) infants (21, 22).

4.3.1.2 Infants, toddlers and children aged <7 years

A review of 11 safety studies of the hexavalent combination DTaP-IPV-HepB/Hib (Infanrix®-hexa) conducted over eight years identified the most commonly reported local reactions in all published studies have been mild and transient pain, redness and/or swelling at the injection site and fever, irritability and/or drowsiness (Table 2) (23).

Table 2. Most frequent adverse events for DTaP-IPV-HepB/Hib (Infanrix®-hexa) from launch up to 2008, spontaneously reported to the GlaxoSmithKline worldwide safety database (OCEANS)

AE	Number of AEs	Frequency per 100,000 doses
Pyrexia	1572	5.9
Injection-site erythema	570	2.1
Injection-site swelling	488	1.8
Crying	465	1.7
Injection-site reaction	294	1.1
Injection-site induration	256	1.0
Hypotonia	218	0.8
Urticaria	210	0.8
Pallor	200	0.8
Erythema	196	0.7

AE: Adverse event; DTaP-IPV-HepB/Hib: Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, hepatitis B/ *Haemophilus influenzae* type b vaccine; OCEANS: Operating Companies Event Accession and Notification System

Across five of these studies tolerability of Infanrix®-hexa was generally similar or superior to that of the control vaccines (two separate doses of DTaP-IPV-HepB + Hib or DTaP-IPV-Hib + HepB, or one dose of DTaP + HepB + OPV + Hib) (23).

Following primary vaccination doses, a low incidence (0 – 10% of doses administered) of solicited, clinically significant (preventing normal daily activities) AEFI have been reported in the first four to eight days post-vaccination. SAE were rare (2.6% in ≥2000 infants administered) most of which were common childhood disorders considered unrelated to vaccination, such as respiratory and urinary tract infections and gastrointestinal disorders (23).

4.3.1.2.1 Febrile events infants and toddlers less than 18 months of age

Fever is a common AEFI and a necessary cause of febrile seizures. A large six year study assessed the relative risk of febrile seizures in Danish children aged three – 18 months of age who received three doses of DTaP-IPV-Hib (Ditekipol/Act-Hib®) vaccine. The highest risk of febrile seizures during the first seven days post-vaccination was found to be on the day of the first vaccination and on the day of the second vaccination, but not on the day of the third vaccination (Table 3). The relative risk of febrile seizures was increased

on the day of the first two vaccinations although the absolute risk was <4 per 100,000 doses. Compared with the unvaccinated cohort, the risk of recurrent or subsequent febrile seizures was not increased nor was the vaccine associated with an increased risk of epilepsy (24).

Table 3. Risk of febrile seizures after DTaP-IPV-Hib vaccination (24)

Analysis method	Time after vaccination (days)			
	0	1 – 3	4 – 7	0 – 7
First vaccination				
No. of vaccinations	298,311	317,741	329,138	329,521
Children with febrile seizures	9	6	2	17
Adjusted HRa (CI 95%)	6.02 (2.86 – 12.65)	1.38 (0.58 – 3.31)	0.41 (0.10 – 1.81)	1.64 (0.93 – 2.88)
Second vaccination				
No. of vaccinations	339,276	339,252	339,196	339,288
Children with febrile seizures	12	14	6	32
Adjusted HRa (CI 95%)	3.94 (2.18 – 7.10)	1.57 (0.91 – 2.72)	0.52 (0.23 – 1.18)	1.36 (0.93 – 1.98)
Third vaccination				
No. of vaccinations	320,049	319,846	319,473	320,049
Children with febrile seizures	27	68	106	201
Adjusted HRa (CI 95%)	1.07 (0.73 – 1.57)	0.89 (0.70 – 1.14)	1.06 (0.86 – 1.28)	0.99 (0.86 – 1.15)

Abbreviations: DTaP-IPV-Hib - diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, H. influenzae type b vaccine; HR - Hazard ratios; a - Adjusted for gender, multiple birth, calendar year of birth (one year interval), seasons of birth, gestational age, birth weight, parity of mother, parental history of epilepsy, maternal education, and family income at time of birth.

4.3.1.2.2 Extensive site reactions

With all DTaP vaccines, the frequency and severity of swelling at the injection site increases with age and additional doses of vaccine. Higher incidences of local symptoms, including swelling >50mm at the injection site or extensive limb swelling, were observed after the administration of Infanrix®-hexa booster dose in the second year of life than were seen after the administration of primary doses (23).

As Infanrix®-hexa (DTaP-IPV-HepB/Hib) and Infanrix®-IPV (DTaP-IPV) contain the same tetanus, diphtheria and acellular pertussis components an increase in the incidence of injection site swelling following a booster vaccination/ fourth dose using Infanrix®-IPV at four years of age would be expected (3, 4, 10).

In a study of 76 healthy Canadian children aged four - five years, who had previously received four doses of DTaP-IPV-Hib (Pentacel®) with the last dose at 18 months of age, injection site redness ≥5mm following a booster vaccination with DTaP-IPV (Quadracel®) was twice as frequent in those who had pre-vaccination cell-mediated immunity against diphtheria and tetanus or pertussis fimbriae types 2 and 3 (mixed T_H1/T_H2 type by cytokine profile for all antigens) compared to children without. This suggested that a pre-existing immune memory is related to increased/extensive local reactions (25).

A small study of 53 Australian children who had previously experienced extensive swelling at the injection site after a fourth dose of DTaP (Infanrix®) vaccine showed an increased likelihood (85.2% recurrence rate) of an extensive site reaction after a fifth dose of DTaP, administered at four-six years of age, compared with 61.5% of children who received a reduced-antigen tetanus, diphtheria and acellular pertussis (Tdap; Boostrix®) vaccine (26).

4.3.2 Co-administration of DTaP combination vaccines

4.3.2.1 DTaP-IPV with measles, mumps, rubella and varicella vaccines

Safety and reactogenicity of co-administration of DTaP-IPV (Infanrix®-IPV) with MMR (measles, mumps, rubella; M-M-R® II) only (n=237) or MMR and a separate varicella (Varivax®) vaccines (n=239) in four – six year old children was assessed in a US study.

Reports of systemic and local reactogenicity at the DTaP-IPV injection site were similar between the two vaccine groups. Between 24.8% and 33.9% of participants reported any one symptom of drowsiness, loss of appetite or fever. Few participants (2.6%) reported systemic AEFI that prevented normal daily activities. Extensive swelling at the injection site was reported by 35 participants (34 at DTaP-IPV site and one at the MMR site). Extensive swelling extended to an adjacent joint, maximum recorded diameter 210mm, in one participant who received DTaP-IPV and MMR. One SAE was reported: croup after receipt of DTaP-IPV and MMR, which was not considered related to vaccination (27).

4.3.3 Tdap vaccines

4.3.3.1 Toddlers and children aged four to eight years

In a small Australian study (n=48, 16 in each of three groups) reactogenicity of DTaP (Infanrix®) and reduced-antigen Tdap (Boostrix®) booster vaccines were compared to a control hepatitis A vaccine (Havrix® Junior) in healthy toddlers 18 – 20 months of age who had completed primary vaccination with three doses of DTaP at two, four and six months of age (28). The small size of the study precluded conclusions with regards to reactogenicity of the study vaccines. However, the most commonly reported AEFI were redness and/or swelling at the injection site and irritability after the DTaP or Tdap vaccinations. Three participants, one received DTaP and two received Tdap, reported transient large local reactions of swelling >50mm at the injection site or extensive limb swelling, >30mm increase in limb circumference or diffuse swelling of the limb that affected or prevented normal daily activities. Cough and rhinorrhoea were reported in ≤31.3% of participants after DTaP and Tdap vaccinations. No serious adverse events occurred (28).

A study of 243 healthy Taiwanese six - seven year old children evaluated AEFI after booster vaccination with reduced-antigen diphtheria, tetanus and acellular pertussis vaccine, Tdap (Adacel®) on days one, two, four and seven post-vaccination. Observed AEFI were transient tenderness (53%), redness ≥10mm (19%) and/or induration (53%) at the injection site and fever (5%) (29).

The most common AEFI identified were pain (40 – 56%), redness (34 – 53%) and swelling (24 – 45%) at the injection site, according to unpublished data on AEFI in 703 children aged four - six year olds and 118 six - eight year old children following receipt of Tdap (Boostrix®) or Tdap-IPV (Boostrix®-IPV) and three published studies of Tdap (Boostrix® or Adacel®) or Tdap-IPV (Boostrix®-IPV) in four - six year olds (combined n=609) administered as a fifth dose of diphtheria, tetanus and acellular pertussis vaccine identified (30).

4.3.3.2 Adolescents and adults

Safety outcomes for 13,427 adolescents in the US aged 10 – 18 years who received a Tdap (Boostrix®) vaccination were evaluated for 59 days post-vaccination for neurological and haematological events and allergic reactions, and for six months post-vaccination for the onset of a new chronic illness. Outcomes were compared with historical, matched controls who had received a Td vaccine. No risk for medically-attended neurological or haematological events, allergic reactions or for the onset of a new chronic disease was identified in Tdap recipients. This study supports the known safety profile of the Tdap vaccine in adolescents (31).

A US study assessed outcomes of encephalopathy, encephalitis, meningitis, paralytic syndromes, seizures, cranial nerve disorders and Guillain-Barré Syndrome (GBS) following 660,245 Tdap vaccinations in adolescents and adults aged 10 – 64 years over the course of 145 weeks in 2005 – 2008 using the Vaccine Safety Datalink (VSD). Data for GBS, due to its rarity, was compared with overall background incidences. All other assessed outcomes were compared to historical data for Td vaccine. The statistical power enabled relative risks for GBS and the other outcomes to be detected. The study data indicated that Tdap is unlikely to increase the risk of GBS four-five times above the background risk. Tdap did not have a greater than two-fold increased risk of encephalopathy, encephalitis, meningitis, paralytic syndromes, seizure or cranial nerve disorders when compared with Td vaccine.

Safety data for these five pre-defined AEFI indicated that the risk after Tdap was not significantly higher than for Td and does not confer a risk of greater than about one excess case of any of these conditions per 100,000 doses of Tdap (32).

Reactogenicity of a Tdap (Boostrix® or Adacel®) vaccination was assessed in a US study of 2284 healthy adults (19 – 64 years of age). Observed AEFI of pain, redness and/or swelling at the injection site and fever of ≥37.5°C were more frequent following administration of Adacel® than Boostrix®. However, a small but significant number of adults reported fatigue preventing normal daily activities following Boostrix® (2.5%) compared to Adacel® (1.2%). Overall the safety profile of Boostrix® was comparable to Adacel® (33).

4.3.3.3 During pregnancy

Reports to the Vaccine Adverse Event Reporting System (VAERS), and available medical records of vaccination of a pregnant woman with Tdap (Boostrix® or Adacel®) between 1st January 2005 and 30 June 2010 (n=132), prior to approval and recommendation for this use, were reviewed. No maternal or infant deaths were reported and 55 (42%) women did not describe any AEFI. Spontaneous miscarriage, considered unlikely to be related to vaccination, was reported by 22 (16.7%) women following vaccination. Local reactions at the injection site were reported by 6 (4.5%) women. One infant was born with the congenital anomaly gastroschisis. Overall, there were no concerning patterns of adverse maternal, fetal or infant outcomes (34).

A US study of health care workers vaccinated with Tdap (Adacel®) within two years of a previous tetanus vaccination included 16 pregnant women in the first (n = 4), second (n = 8) and third (n = 4) trimesters at the time of vaccination. Two sets of survey results were included in the analysis of transient AEFI for four of the pregnant women. From 20 participant survey responses, severe swelling at the injection site was reported by one woman and two women reported feeling feverish, although fever was not documented. No adverse maternal, fetal or infant outcomes were reported (35).

Review of unpublished data from pharmaceutical company registers of pregnant women who received a Tdap (Boostrix® or Adacel®) vaccination did not identify more frequent or unusual patterns of adverse events in pregnant women. The reported SAE were considered unlikely to be related to vaccination (36).

4.3.3.4 Adults aged ≥65 years

In a large matched cohort study of almost 240,000 US adults ≥65 years of age, a small increase in the risk of a medically attended allergic or inflammatory event was observed following administration of either Tdap or Td vaccines during the first 1 – 6 days. This suggests that Tdap can be safely substituted for Td vaccination (37).

In another US study, safety and reactogenicity of Tdap (Boostrix®) vaccination was assessed in 864 adults ≥65 years of age. The most commonly reported AEFI were mild and transient pain, redness and/or swelling at the injection site (21.5%, 10.8% and 7.5%, respectively) and fatigue and/or headache. Thirty-seven participants (4.2%) reported SAE, none of which were considered related to vaccination (38).

Reports to the Vaccine Adverse Event Reporting System (VAERS) and medical records for reports of SAE following vaccination of adults aged ≥65 years of age with Tdap (Boostrix® or Adacel®, n=243) or Td (Decavac®, n=404) between 9 January 2005 and 9 August 2010 were reviewed. Most AEFI reported were local reactions at the injection site (41.2%). 'Cough' was reported disproportionately higher following administration of Tdap (5.8 times) than Td. Interestingly, 32.1% of reports related to vaccine administration errors. Clinical review of reported SAE did not identify any unusual patterns. Overall, no safety concerns associated with Tdap use in adults ≥65 years of age were identified (39).

Review of unpublished safety data from pharmaceutical companies for Tdap (Boostrix®, n=1,104) or (Adacel®, n=1,170) administered to adults ≥65 years of age identified the most frequent AEFI was local reactions at the injection site (37%). No increases in local or systemic AEFI were noted between administration of Tdap compared to Td and the AEFI profile in this age-group was similar to the profile in those aged <65 years. No SAE were considered related to vaccination (30).

4.3.4 Tdap vaccination following a previous Td vaccination

A study in France assessed safety and reactogenicity of a Tdap-IPV (Repevax®) when administered one month following Td-IPV (Revaxis®) or placebo in adults aged 18 – 40 years (n=242 in both groups). Most participants had received at least six doses of tetanus, diphtheria and polio vaccines prior to 18 years of age, and their last vaccination was more than five years, previously (98.0% - 99.2% had received six previous doses of a tetanus containing vaccine, a median of 6.8 - 7.1 years, previously).

Within 14 days of the first vaccination, the incidence of AEFI was lower following placebo injection, with at least one AEFI reported for 75.9% of Td-IPV recipients and 33.1% of placebo recipients. Local reaction at the injection site was reported by 69.9%, and 12%, respectively, and a systemic reaction was reported by 32.5% and 24.3% of participants, respectively.

After the second vaccination the percentage of participants who reported pain and swelling at the injection site was lower in those who received Tdap-IPV after Td-IPV than in those who received Tdap-IPV after placebo (85.1% vs 93.4%, respectively). The percentage of participants who reported redness at the injection site was similar in both groups. Participants, previously given Td-IPV, reported severe swelling at the injection site less frequently than those previously given placebo (1.2% vs. 7%, respectively). There were no reports of extensive swelling of the vaccinated limb or severe discomfort. Immediately after the second vaccination with Tdap-IPV, one participant who had received Td-IPV experienced vaccine-related malaise within 30 minutes of Tdap-IPV injection, which resolved the same day; and a case of neck rigidity that lasted eight days was assessed to be unlikely to be vaccine related. There were no immediate AEFI in participants who received Tdap-IPV after placebo. The percentage of participants who reported at least one systemic AEFI (related or unrelated to vaccine) was similar in both groups. No differences were observed for fever, headache or myalgia. Headache was the most frequently reported systemic AEFI in both groups (approximately one fifth of participants). Three SAE were reported, none of which were considered related to vaccination.

Overall, reporting of at least one AEFI was lower in the group who received Tdap-IPV after Td-IPV than after placebo (88.8% vs 94.6%). A limitation of this study is the small sample of subjects revaccinated one month after Td-IPV from which it would probably not be possible to detect any significant but rare (≤1/1000) AEFI (40).

A US survey of 250 healthcare workers documented AEFI responses over a two week period post-vaccination with Tdap (Adacel®), regardless of the interval since a previous tetanus vaccination. The frequency of reported AEFI was presented as a two results, the first representing responses from participants who completed the survey requiring more frequent AEFI recording (reported on days 3-7, "daily survey") and the second from surveys with less frequently documented responses (during 2 weeks after vaccination, survey completed on days 14-30; "2-week survey") (35).

In participants who had received a previous tetanus vaccination <2 years prior to Tdap, the most commonly reported AEFI were pain (82.5% and 67.9%, daily and 2-week surveys, respectively), redness (25.2% and 23.5%) or swelling (37.8% and 24.7%). Subjective fever was reported by 15.2% of participants, only 0.76% of these had documented fever >38°C (combined data from all survey responses). Moderate to severe local AEFI reports included moderate pain affecting normal daily activities (14% and 10.7%), redness (5.2% and 2.5%) or swelling ≥24.26mm to <48.52mm (5.9% and 6.2%), and severe pain preventing normal daily activities, (2.8% and 0%), redness (3% and 3.7%) or swelling ≥48.52mm (6.7% and 2.5%), for daily and 2-week surveys, respectively (35).

Three SAE were reported by non-pregnant participants, aged 18 – 64 years of age, who had received tetanus vaccination ≥2 years previously. One case of wheezing immediately following vaccination treated with adrenaline was considered related to vaccination. Eosinophilic nephritis in a participant who had a cadaveric renal transplant seven years before vaccination and a case of Guillain-Barré Syndrome were not considered related to vaccination.

Comparison of AEFI in participants, who had received a tetanus vaccination (Td or TT) <2 years previously with participants who were vaccinated ≥2 years previously, identified that the rates of any redness or swelling were higher after a <2 year interval versus ≥2 years. However, the rates of moderate to severe injection site reactions were not higher in the <2 year versus the ≥2 years group. The authors conclude that a short interval between immunisation with Td or TT and single dose of Tdap is considered safe in adults (35).

4.3.5 Tdap revaccination following a previous Tdap vaccination

Safety of revaccination with Tdap (Boostrix®) after vaccination with a Tdap (n=75) vaccine received 10 years previously was assessed in young Finnish adults 20 – 24 years of age. The most commonly reported AEFI were pain (93.8%), redness with swelling at the injection site (>50%) and fatigue (44.4%). One participant reported swelling ≥50mm at the injection site and one extensive swelling of the injected limb. One reported SAE, hyperventilation, was not considered related to vaccination. Local AEFI were reported more frequently compared with the Tdap vaccination 10 years previously. However, the overall safety and reactogenicity profile of the decennial booster vaccination was similar to the profiles of both vaccines used in the previous study (41).

Reactogenicity of revaccination with Tdap (Boostrix®) after vaccination with a Tdap vaccine given 10 years previously was assessed in 164 Australian adults 20 – 24 years of age. The most commonly reported AEFI were pain (70%), redness with swelling at the injection site (>50%), fatigue (23.2%) and headache (19.2%); however, approximately half of the systemic events were considered unrelated to vaccination. Two participants (1.2%), who had previously received Tdap, reported swelling ≥50mm at the injection site. No SAE occurred post-vaccination. The point estimate for the incidence of each local symptom of pain, redness and swelling after the decennial booster vaccination was higher compared to the Tdap vaccination 10 years previously. The point estimates for fever and headache were reduced after the decennial vaccination compared to the previous Tdap dose and the incidence of fatigue was the same. Overall, the decennial booster vaccination was well tolerated (42).

Safety and tolerability of revaccination with Tdap (Adacel®) was assessed in two studies, five years after previous Tdap vaccination of adolescents and adults in the US and Canada (aged 15 – 69 years, n=544) or after 10 years in Canadian adults (20 – 72 years, n=361) (43, 44).

Following revaccination after five years, 94.2% of participants reported at least one AEFI, including as pain (87.6%), redness (28.6%) or swelling (25.6%) at the injection site or systemic symptoms such as fever (6.5%), malaise (38.2%), headache (53.2%) or myalgia (61%). AEFI were reported slightly more frequently than after the previous dose five years earlier. Seven SAE were reported, none of which were considered related to vaccination: single cases of myocardial infarction with fatal malignant arrhythmia, carcinoid tumour of the appendix, malnutrition, intentional acetaminophen overdose, cellulitis, pyelonephritis and asthma episode. Generally, revaccination with Tdap after five years was well tolerated (43).

Following revaccination after 10 years, 92.7% of participants reported at least one AEFI, such as pain (90.3%), redness (25%) or swelling (23%) at the injection site or fever (4.2%), malaise (31.4%), headache (42.3%) or myalgia (62.4%). Three SAE were reported, none of which were considered related to vaccination: vaginal haematoma, animal bite and Arnold-Chiari malformation. Generally, revaccination with Tdap after 10 years was well tolerated (44).

4.3.6 Co-administration of Tdap vaccines

4.3.6.1 Boostrix® and influenza vaccine

In a US study, safety and reactogenicity of Tdap (Boostrix®) co-administered with trivalent inactivated influenza vaccine (Fluarix®) was assessed in 748 adults aged 19 – 64 years. The most commonly reported AEFI were pain (59.4%), redness (20.2%) and swelling (20.7%) at the injection site and muscle aches. In a small number of participants (3.9%) redness and swelling was ≥50mm at the injection site. Two SAE were reported, neither of which were considered related to vaccination: urosepsis plus renal failure and diabetic ketoacidosis. Tdap vaccine was shown to be well tolerated when co-administered with TIV vaccine (45, 46).

4.3.7 Comparability of Tdap and Td

Safety outcomes for 13,427 US adolescents aged 10 – 18 years who received a Tdap (Boostrix®) vaccination were evaluated for 59 days post-vaccination for neurologic and haematological events and allergic reactions, and for 6 months post-vaccination for the onset of a new chronic illness. Outcomes were compared with historical, matched controls who had received a Td vaccine. No risk for medically-attended neurologic or haematological events or allergic reactions or for the onset of a new chronic disease was identified in Tdap recipients. This study supports the known safety profile of the Tdap vaccine in adolescents (31).

In a large matched-cohort US based study, almost 240,000 adults ≥65 years of age received Tdap or Td. A small increase in the risk of a medically attended allergic or inflammatory event was observed following administration of both vaccines during the first 1 – 6 days, but no other significant adverse event was seen, which suggests that Tdap can be safely substituted for Td vaccination (37).

In another US based study, safety and reactogenicity of Tdap (Boostrix®, n=864) or Td (Decavac®, n=439) vaccination were assessed in adults ≥65 years of age. The most commonly reported AEFI were mild and transient pain, redness and/or swelling at the injection site (21.5%, 10.8% and 7.5% respectively) and fatigue and/or headache. Similar proportions of participants in both the Tdap and Td groups reported SAE, none of which were considered related to vaccination, (37/864 [4.2%] and 10/439 [2.2%], respectively). Tdap was found to have a comparable safety profile to Td in this age-group (38).

Review of unpublished safety data from pharmaceutical companies, for Tdap (Boostrix®, n=1,104) or (Adacel®, n=1,170) administered to adults ≥65 years of age, identified that the most frequent AEFI was local reactions at the injection site (37%). No increases in local or systemic AEFI were noted between administration of Tdap compared to Td, and the AEFI profile in this age-group was similar to the profile in those aged <65 years. No SAE were considered related to vaccination (30).

4.4 Summary vaccine safety

No safety concerns have been raised for the tetanus toxoid combination vaccines.

Various DTaP combination vaccines have been demonstrated to be safe and generally well tolerated in preterm infants born after 24 weeks and/or low birth weight infants born at/or greater than 820 grams, infants, toddlers and children up to seven years of age. The frequency and severity of local reactions increases with age and additional doses of vaccine.

DTaP combination vaccines have been demonstrated to be safe when co-administered with routine vaccines in infants, toddlers and children.

Tdap has a safety profile similar to Td; both vaccines are generally well tolerated.

Tdap vaccine has been demonstrated to be safe when co-administered with trivalent inactivated influenza vaccine in adults.

Overall, tetanus combination vaccines have demonstrated an excellent safety profile in all groups studied.

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 licensed tetanus toxoid vaccines. The focus is on DTaP-IPV-HepB/Hib, DTaP-IPV and Tdap. Consideration is given to relevant immunogenicity data that contribute to the current understanding of the development of seroprotective titres of tetanus toxoid antibody and evidence for the non-inferiority of alternative schedules.

5.2 Outcomes

The outcomes considered for this review are:

- Immunogenicity of DTaP combination vaccines in preterm and/or low birth weight infants.
- Immunogenicity of DTaP combination vaccines in infants, toddlers and children up to seven years of age.
- Immunogenicity of reduced-antigen content Tdap vaccines in toddlers and children to eight years of age, adolescents, adults, pregnant women and adults aged ≥65 years.
- Antibody persistence.
- Comparability of Tdap with Td.

5.3 Review

As all developed countries use tetanus vaccines, tetanus disease occurs rarely and, therefore, direct determination of vaccine efficacy and effectiveness with newer vaccines is not possible (47). Measurement of vaccine immunogenicity and comparison against the known correlates of protection against tetanus provides an indicator of vaccine efficacy. The generally accepted correlate of protection against tetanus is a tetanus toxoid antibody titre of ≥0.1 IU/mL (1). Data suggests partial protection is provided with an antibody titre of 0.01 – <0.1 IU/mL. The other accepted correlate of protection is a four-fold rise in antibody titre between pre and post-vaccination serology. However, the correlates of protection will not be an absolute figure for every vaccinated person, since a very small number of people with a protective antibody titre would still develop tetanus, if exposed (47, 48).

5.3.1 DTaP combination vaccines

5.3.1.1 Preterm and/or low birth weight infants

Greater than 98% of preterm and/or low birth weight infants, gestation less than 36 weeks or birth weight less than 2000 grams, developed seroprotective titres of tetanus toxoid antibody 1 – 2 months after receipt of three doses of a tetanus toxoid combination vaccine (Infanrix®-hexa) containing at least 40IU of toxoid (48).

5.3.1.2 Infants, toddlers and children aged <7 years

5.3.1.2.1 Immunogenicity

Seven large immunogenicity studies of DTaP-IPV-HepB/Hib (Infanrix®-hexa) vaccine have been conducted. Three studies assessed immunogenicity following dose schedules of three primary vaccinations in the first year of life and a booster vaccination in the second year of life and four studies investigated two primary vaccinations early in the first year and a booster vaccination at 11 – 12 months of age. Pooled data from four of these studies identified seroprotective titres ≥0.1 IU/mL of tetanus toxoid antibody in 94.7 – 100% of infants one month after completion of the primary series and 100% infants/toddlers one month after the booster vaccination. Vaccine immunogenicity was unaffected when a birth dose of hepatitis B vaccine had also been administered (21).

5.3.1.2.2 Antibody persistence

In a small Australian study, immunogenicity of DTaP (Infanrix®) and reduced-antigen Tdap booster (Boostrix®) vaccines were compared to a control hepatitis A vaccine (Havrix® Junior) in 48 healthy toddlers 18 – 20 months of age who had completed primary vaccination with three doses of DTaP at two, four and six months of age. Prior to vaccination, 75.0 – 87.5% of participants had seroprotective titres ≥0.1 IU/mL of tetanus toxoid antibody (28).

Tetanus antibody persistence was assessed in German children, aged four to six years (n=198) and seven to nine years (n=200), who had received three priming vaccinations followed by a booster vaccination between 12 – 18 months of age using DTaP-IPV-HepB/Hib (Infanrix®-hexa). All the children in the four - six years group and 51 children in the seven - nine

years group had not received a fifth DTaP booster vaccination at five to six years of age. The mean time elapsed between the fourth DTaP-IPV-HepB/Hib booster vaccination and serology was 3.63 (SD 0.48) in the four-six years group and 6.4 (SD 0.5) in the seven-nine years group. In the four-six years group, 148/198 (74.7%) of participants continued to have seroprotective tetanus toxoid antibody titres ≥0.1 IU/mL. Of the children in the seven-nine years group, 33/51 (64.7%) of those who had only received four doses of DTaP-IPV-HepB/Hib continued to have seroprotective titres, whilst 100% of children who had received a fifth dose of DTaP vaccine at five - six years of age had titres ≥ 0.1 IU/mL (49).

5.3.2 Co-administration of DTaP combination vaccines

5.3.2.1 DTaP-IPV-HepB/Hib with human rotavirus vaccine, pneumococcal or meningococcal conjugate vaccines, quadrivalent measles, mumps, rubella, varicella vaccine

Studies of co-administration of DTaP-IPV-HepB/Hib (Infanrix®-hexa) with the human rotavirus vaccine, pneumococcal or meningococcal conjugate vaccines, or a quadrivalent measles, mumps, rubella, varicella vaccine have shown nil or non-significant effects on the immunogenicity response of all antigens in the Infanrix®-hexa and the co-administered vaccine (21):

- Human rotavirus vaccine (Rotarix®) - co-administration of Infanrix®-hexa and Rotarix® did not affect immunogenicity of either vaccine.
- Pneumococcal conjugate vaccines (Synflorix® or Prevenar 13®) - high pneumococcal seroprotection rates and non-inferior immunogenicity of Infanrix®-hexa, similar to those observed after co-administration of Infanrix®-hexa and Prevenar® and after co-administration of Infanrix®-hexa and Synflorix® or Prevenar 13® as primary or booster vaccinations in healthy infants/toddlers <2 years of age.
- Meningococcal C conjugate vaccines (Meningitec® or NeisVac-C™) - immunogenicity of all antigens in Infanrix®-hexa were generally not affected by co-administration of Infanrix-hexa® and Meningitec® or NeisVac-C™ in healthy infants/toddlers aged <2 years.
- Quadrivalent measles, mumps, rubella, varicella vaccine (Priorix-Tetra®) - co-administration of an Infanrix®-hexa booster vaccination and Priorix-Tetra® did not affect the immunogenicity of either vaccine in healthy toddlers aged 12 – 23 months of age.

5.3.2.2 DTaP-IPV with measles, mumps, rubella and varicella vaccines

A US study showed that the immunogenicity of DTaP-IPV (Infanrix®-IPV) was not affected following co-administration with MMR only (measles, mumps, rubella, M-M-R® II; n=237) or MMR and varicella (Varivax®) vaccines (n=239) in four-six year old children. Immunogenicity of Varivax® was not measured (27). However, a previous study documented non-inferior immunogenicity of M-M-R® II when co-administered with Infanrix®-IPV (50).

5.3.3 Tdap vaccines

5.3.3.1 Toddlers and children aged four to eight years

In a small Australian study, immunogenicity of DTaP (Infanrix®) and reduced-antigen Tdap (Boostrix®) booster vaccines were compared to a control hepatitis A vaccine (Havrix® Junior) in 48 healthy toddlers 18 – 20 months of age, who had completed primary vaccination with three doses of DTaP at two, four and six months of age. Prior to booster vaccination, 75.0 – 87.5% of participants had seroprotective tetanus toxoid antibody titres ≥0.1 IU/mL. One month post-vaccination, robust increases in geometric mean concentrations (GMC) of tetanus antibody were observed and 100% of participants had seroprotective titres following DTaP or Tdap vaccination. Tetanus antibody GMC was higher in the DTaP group than the Tdap group, however, the 95% confidence intervals overlapped in all cases. Clinically significant differences in protection over time are considered to be unlikely to be affected by potential differences in the magnitude of the immune response (28).

Immunogenicity of Tdap (Boostrix®) compared with DTaP (Infanrix®) was assessed in a study of 53 Australian children aged four – six years who had previously experienced extensive swelling at the injection site after a fourth dose of DTaP (Infanrix®) vaccine. All participants had seroprotective tetanus toxoid antibody titres ≥0.1 IU/mL of post-vaccination, although higher tetanus antibody GMC were observed in the DTaP versus Tdap group (26).

Unpublished data of immunogenicity of Tdap (Boostrix®) or Tdap-IPV (Boostrix®-IPV) in four to six year olds (n=703) and six to eight year olds (n=118), and three published studies of Tdap (Boostrix® or Adacel®) or Tdap-IPV (Boostrix®-IPV) in four to six year olds (combined n=609) administered as a fifth dose of diphtheria, tetanus and acellular pertussis vaccine, found that the immunogenicity of the reduced-antigen vaccines to be comparable to that following DTaP or DTaP-IPV. Following receipt of Tdap-IPV (Boostrix®-IPV), 99.9% of four to eight year old children developed seroprotective tetanus toxoid antibody titres ≥0.1 IU/mL; and following receipt of Tdap (Boostrix® or Adacel®), all children aged four - six years developed seroprotective titres of tetanus toxoid antibody ≥0.1IU/mL (30).

5.3.3.2 Adults

5.3.3.2.1 Immunogenicity

Immunogenicity of a Tdap (Boostrix® or Adacel®) vaccination was assessed in a US study of 2284 healthy adults (19 – 64 years of age). Pre-vaccination, 95.9% (95% CI 94.8 – 96.9) in the Boostrix® group and 97.2% (95% CI 95.8 – 98.3) in the Adacel® group had seroprotective tetanus toxoid antibody titres ≥0.1IU/mL. One month post-vaccination, the immunogenicity of Boostrix® (n=1445) was shown to be comparable to Adacel® (n=728), with 99.6% (95% CI 99.1 – 99.8) and 100% (95% CI 99.5 – 100) of recipients, respectively, shown to have seroprotective tetanus toxoid antibody titres ≥0.1IU/mL (33).

Immunogenicity data from four trials assessing Tdap (Boostrix®) in adults aged 55 – 64 years (n=102) and ≥65 years (n=92) from Australia and Belgium were pooled, stratified by age and analysed. Pre-vaccination, 59.4% (95% CI 51.5 – 67.0) of participants aged 55 – 64 years and 45.7% (95% CI 36.8 – 54.7) aged ≥65 years had seroprotective tetanus toxoid antibody titres of ≥0.1 IU/mL. One month post-vaccination the number of participants with titres ≥0.1 IU/mL increased to 164/166 (98.8%; CI 95% 95.7 – 99.9) and 112/126 (88.9%; CI 95% 82.1 – 93.8), respectively. A significantly greater percentage of adults aged 55 – 64 years met the correlate of protection against tetanus one month post-vaccination than adults in the ≥65 year age-group (51).

5.3.3.2.2 Antibody persistence

Immunogenicity of a Tdap (Boostrix® or Adacel®) vaccination was assessed in a US study of 2284 healthy adults (19 – 64 years of age). One year post-vaccination, immunogenicity of Boostrix® (n=1015) was shown to be comparable to Adacel® (n=506). Although antibody titres had decreased relative to titres one month post-vaccination, they remained higher than pre-booster vaccination titres, with >98% of recipients shown to have seroprotective titres of tetanus toxoid antibody ≥0.1IU/mL (33).

An Australian study assessed immunogenicity of Tdap (Boostrix®) in adults aged 25 – 74 years four and five years post-vaccination (n = 240 and 239, respectively). The number of adults shown to have seroprotective titres of tetanus toxoid antibody ≥0.1IU/mL, four and five years post-vaccination, were 95.8% (95% CI 92.5 – 98.0) and 96.2% (95% CI 93.0 – 98.3), respectively, compared with 86.3% pre-vaccination (95% CI 81.2 – 90.3). Five years post-vaccination tetanus antibody geometric mean concentrations remained significantly higher than pre-vaccination levels (52).

The persistence of tetanus toxoid antibody was assessed three years post-vaccination with Tdap (Boostrix®, n=937 or Adacel®, n=449) in US adults aged 19 – 64 years. Geometric mean concentrations of tetanus antibody had decreased in both vaccine groups, relative to one month and one year post-vaccination, but remained higher than pre-vaccination levels. However, 919/937 (98.1%) of Boostrix® recipients and 447/449 (99.6%) of Adacel® recipients were shown to have seroprotective tetanus toxoid antibody titres of ≥0.1IU/mL (53).

5.3.3.3 During pregnancy

To assess immunogenicity in newborn infants, a small US study was conducted measuring tetanus antibody GMC in cord blood from infants born to mothers who had not been vaccinated with Tdap during pregnancy (n=52) and mothers who had received a Tdap (Adacel®) vaccination during the second trimester of pregnancy (n=52). The study identified significantly higher tetanus antibody concentrations when maternal vaccination had occurred (4.237 IU/mL vs. 9.015 IU/mL, p=0.004). Although the percentage of infants with seroprotective titres of tetanus toxoid antibody (≥0.1IU/mL) was higher when the mother had been vaccinated, this difference was not significant (100% vs. 96.2%, p=0.1533) (54).

5.3.3.4 Adults aged ≥65 years

In a US study, immunogenicity of Tdap (Boostrix®, n=864) or Td (Decavac®, n=439) vaccination was assessed in adults ≥65 years of age. Pre-vaccination tetanus antibody GMC were similar in both groups. One month post-vaccination a 6.7-fold rise and 11.8-fold rise in GMC were observed following Tdap and Td, respectively (38).

The percentage of participants with seroprotective tetanus toxoid antibody titres of ≥0.1IU/mL increased from 80.8% (CI 95% 78.0 – 83.4) to 96.8% (CI 95% 95.4 – 97.8) following Tdap and from 78.1% (CI 95% 74.0 – 81.9) to 97.5% (CI 95% 95.6 – 98.7) following Td. For tetanus antibody titres ≥1.0IU/mL, increases were observed from 48.6% (CI 95% 45.2 – 52.0) to 88.8% (CI 95% 86.5 – 90.8) following Tdap and 47.4% (CI 95% 42.6 – 52.2) to 90% (CI 95% 86.8 – 92.6) following Td. Immunogenicity of Tdap was non-inferior compared to Td and was found to be immunogenic in adults ≥65 years of age (38).

5.3.4 Tdap revaccination following a previous Tdap vaccination

5.3.4.1 Adolescents and Adults

Young Finnish adults aged 20 – 24 years, who had received a Tdap (Boostrix®, n=74) vaccination 10 years previously, were assessed for antibody persistence prior to revaccination with the Tdap (Boostrix®) vaccine. Although pre-revaccination tetanus antibody GMC had returned to levels close to those observed prior to the Tdap vaccination given 10 years earlier, 97.3% (CI 95%: 90.6 – 99.7) of participants still had seroprotective titres of tetanus toxoid antibody ≥0.1 IU/mL. One month post-revaccination, 100% (CI 95%: 95.1 – 100) of participants had seroprotective tetanus toxoid antibody titres of ≥0.1 IU/mL. Pre-revaccination geometric mean tetanus antibody concentrations 1.2 IU/mL (CI 95%: 1.0 – 1.6) increased substantially to 9.6 IU/mL (CI 95%: 8.0 – 11.5) one month post-revaccination (41).

Immunogenicity of revaccination with Tdap (Boostrix®) after vaccination with a Tdap vaccination given 10 years previously was assessed in 153 Australian adults aged 20 – 24 years. Prevaccination seroprotective tetanus toxoid antibody titres had returned to levels close to those observed prior to the Tdap vaccination, 10 years earlier. Of the participants who had previously received Tdap vaccine, 94.8% (CI 95% 90.0 – 97.7) had titres ≥0.1 IU/mL. One month post-vaccination, 100% (CI 95% 97.6 – 100) of participants had seroprotective titres of tetanus toxoid antibody ≥0.1 IU/mL. A robust increase in tetanus antibody GMC from pre-revaccination levels of 1.0 to 6.9 IU/mL (CI 95% 0.9 – 1.2; CI 95% 6.2 – 7.7, respectively) at one month post-revaccination indicated a booster response of similar magnitude to the first booster (42).

A study assessed the immunogenicity of revaccination with Tdap (Adacel®), five years after a previous Tdap vaccination in 451 Canadian and US adolescents and adults (aged 15 – 69 years). Prior to revaccination after five years, 427/451 (96.0%) of participants had seroprotective titres of tetanus toxoid antibody ≥0.1 IU/mL. Tetanus antibody GMC were high across all study participants (1.41 IU/mL; CI 95% 1.27 – 1.56) prior to revaccinations and increased to 9.62 (CI 95% 9.06 – 10.2) one month post-revaccination (43).

A second similar study assessed the immunogenicity of revaccination with Tdap (Adacel®) in 324 Canadian adults (aged 22 – 72 years), ten years after a previous Tdap vaccination. Prior to revaccination, 97.5% (95% CI 95.2 – 98.9) of participants had seroprotective titres of tetanus toxoid antibody ≥0.1 IU/mL. Geometric mean tetanus antibody concentrations across all study participants were relatively high (0.84 IU/mL; CI 95% 0.75 – 0.92) and increased substantially to 8.79 IU/mL (CI 95% 8.06 – 9.59) one month post-revaccination (44) .

5.3.5 Co-administration of Td and tetanus immunoglobulin (TIG)

Immunogenicity of the tetanus toxoid component of Td vaccine only (Td-pur®, n=126, 96 and 67 at respective follow up points) compared with Td co-administered with human anti-tetanus immunoglobulin (TIG, Hypertet, n=111, 89, 59 at respective follow up points) was assessed in healthy Korean adults ≥20 years of age. Participants were followed up at one, six and 12 months. The tetanus antibody titres were determined through enzyme-linked immunosorbent assay (ELISA) and reported in IU/mL with seroprotection being ≥0.1IU/mL.

Results of this study demonstrated that immunogenicity of the tetanus antigen in Td was affected by co-administration with TIG during the early period post-vaccination for adults aged 20 – 59 years and ≥60 years, and that the effect of TIG diminished by six and 12 months post-vaccination in the 20 – 59 years age-group, but not in the ≥60 years age-group. The authors comment that significant demographic differences of participants in the first four weeks of the study and of the adults ≥60 years may have affected the results (18).

Both groups had GMT above that considered protective and it is important to note that the immunisation history in this population is likely to be different to that of the New Zealand population as Korea has a different history of tetanus vaccine use and funding.

5.3.6 Co-administration of Tdap vaccines

5.3.6.1 Tdap and influenza vaccine

In a US based study, immunogenicity of Tdap (Boostrix®) co-administered with trivalent inactivated influenza vaccine (TIV, Fluarix®) was assessed in 714 adults aged 19 – 64 years (n=714). Post-vaccination geometric mean tetanus antibody titres increased markedly from pre-vaccination levels 1.5 to 6.5 IU/mL (95% CI 1.4 – 1.7 and 6.0 – 7.0, respectively) as did titres to all three influenza antigens (H1N1, 25.9 to 189.1 [95% CI 23.7 – 28.4 and 171.7 – 208.3, respectively]; H3N2, 27.1 to 368.7 [95% CI 24.4 – 30.0 and 337.9 – 402.3, respectively] and B, 29.6 to 210.1 [95% CI 27.1 – 32.3 and 194.4 – 227.0, respectively]) (45).

The percentage of participants with seroprotective tetanus toxoid antibody titres (≥0.1IU/mL) increased from 94.8% pre-vaccination to 98.2% (95% CI 92.9 – 96.3 and 96.9 – 99.0, respectively) as did the percentage with seroprotective influenza antibody titres ≥40 (H1N1, 41.2% to 94.1% [95% CI 37.6 – 44.9 and 92.1 – 95.7, respectively]; H3N2, 47.3% to 97.6% [95% CI 43.5 – 51.0 and 96.2 – 98.6, respectively] and B, 49.6% to 96.3% [95% CI 45.9 – 53.4 and 94.7 – 97.6, respectively]). Immunogenicity of Tdap for tetanus toxoid antigen and TIV vaccines were non-inferior when co-administered (45).

5.3.6.2 Tdap and quadrivalent measles, mumps, rubella, varicella vaccine

Non-inferiority of Tdap-IPV (Boostrix® Polio, n=139) immunogenicity compared with DTaP-IPV (Tetravac™, n=144) co-administered with quadrivalent measles, mumps, rubella, varicella (MMRV) vaccine (Priorix-Tetra®) was assessed in a study of healthy Italian children aged five - six years. Pre-vaccination, 86% of participants demonstrated seroprotective titres ≥0.1IU/mL of tetanus toxoid antibody and at least 90% were seropositive for measles, mumps and rubella antibodies and 71.9% for varicella. One month post-vaccination, 100% of participants in both tetanus vaccine groups demonstrated seroprotective titres of tetanus toxoid antibody. Following Tdap-IPV and DTaP-IPV, seropositivity was 100% in both groups for measles; 100% and 98.6%, respectively, for mumps; 100% and 99.3%, respectively, for rubella; and 97.1% and 95.9%, respectively for varicella. Immunogenicity of Tdap-IPV was shown to be non-inferior to DTaP-IPV, for tetanus toxoid antigen, when co-administered with Priorix-Tetra® (55).

5.3.7 Comparability of Tdap and Td

Immunogenicity of the tetanus toxoid antigen in Tdap has been shown to be non-inferior to tetanus toxoid antigen immunogenicity of Td in a US study comparing Tdap (Boostrix®, n=864) to Td (Decavac®, n=439) in adults ≥65 years of age (38).

Aging affects the magnitude and persistence of antibody responses to disease and vaccines with the process beginning from 20 years of age (56). Since the immunogenicity of tetanus toxoid antigen in Tdap was non-inferior to tetanus toxoid antigen in Td in adults ≥65 years of age, Tdap is also expected to be non-inferior to Td in adolescents and adults <64 years of age.

5.4 Summary of effectiveness

Full antigen strength DTaP combination vaccines have been shown to induce seroprotective tetanus antibody titres in pre-term and/or low birth weight infants, infants, toddlers and children <7 years of age.

Reduced-antigen content Tdap vaccines have been shown to induce seroprotective tetanus antibody titres in toddlers and children ≤8 years of age, who have been primed with three vaccinations of DTaP vaccine, adolescents, adults <64 years, including pregnant women and their infants, and adults ≥65 years of age.

Revaccination with Tdap five – ten years after a previous Tdap vaccination has been shown to effectively boost protection against tetanus disease.

In one study, it was observed that co-administration of Td with TIG was associated with reduced immunogenicity to tetanus toxoid antigen during the early post-vaccination period. This TIG effect diminished by six months post-vaccination in 20 – 59 years age-group, but persisted to 12 months in the ≥60 year age-group. All groups in this study had titres above seroprotective levels.

Co-administration of Tdap with TIV or MMRV does not diminish immunogenicity of tetanus toxoid antigen.

Immunogenicity of the tetanus toxoid antigen in Tdap is comparable to immunogenicity of tetanus toxoid antigen Td in adults ≥65 years of age and is expected to be comparable in adolescents and adults ≤64 years of age.

6. Age-specific issues

6.1 Objective

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

6.2 Review

6.2.1 Burden of disease by age

Adults aged 70 years and over and the unvaccinated, or those with unknown vaccination status, had the highest risk of tetanus disease between 2009 and 2011 in New Zealand.

6.2.2 Vaccine issues for different age-groups

Data supporting use of Tdap as an alternative to Td in adults is emerging. Use of Tdap in this age-group appears to have a good safety profile.

1.1.1.1 Infants and children aged <7 years

In infants and children <7 years of age, full strength DTaP combination vaccines are the only option for use. A variety of scheduling options are possible (refer to Options for scheduling).

6.2.2.1 Children aged 7 – 11 years

In New Zealand, full strength DTaP combination vaccines are not currently recommended for use in children ≥7 years. In children who have not completed the recommended vaccination schedule of three priming vaccinations and one booster vaccination prior to their seventh birthday, the reduced-antigen Td or Tdap vaccines are the only option for use for both priming and booster vaccinations. While there are not expected to be any safety or immunogenicity concerns, the Tdap vaccines are currently only licensed from 10 years of age.

6.2.2.2 Adolescents and adults aged <65 years

In adolescents and adults, reduced-antigen Td and Tdap vaccines are the only options for use for both priming and booster vaccinations. The reduced-antigen vaccines are not licensed for use in a priming course of vaccines as there is no data on their effectiveness as a primary course. However, there are no safety concerns, so they can be used for this purpose and are currently advised to be used if necessary in primary courses for unvaccinated adolescents and adults in New Zealand, the US, the UK and Australia.

Tdap safety and immunogenicity has been demonstrated as non-inferior to Td in adults ≥65 years of age. Based on the knowledge that advancing age reduces the magnitude and persistence of antibody responses, and Tdap has been demonstrated to be safe and immunogenic in the elderly, it is expected to be so for adults ≤64 years of age and can be used as an alternative to Td when administered as:

- The first dose of a tetanus toxoid catch-up vaccine.
- The adult booster vaccination at 45 years of age.
- Tetanus prophylaxis as part of wound management.

6.2.2.4 Adults aged ≥65 years

In adolescents and adults, reduced-antigen Td and Tdap vaccines are the only options for use for both priming and booster vaccinations. The reduced-antigen vaccines are not licensed for use in a priming course of vaccines, but are used for this purpose in New Zealand, the US, the UK and Australia.

Tdap is an alternative vaccine to Td for adults ≥65 years of age when administered as:

- The first dose of a tetanus toxoid catch-up vaccine
- The adult booster vaccination at 65 years of age.
- Tetanus prophylaxis as part of wound management.

6.3 Summary of age-specific issues

Tetanus disease is a particular risk for older adults and the unvaccinated, or those with unknown vaccination status.

Age-appropriate DTaP, Td and Tdap vaccines are available and currently on the National Immunisation Schedule to protect against tetanus disease in New Zealand.

7. Vaccine options

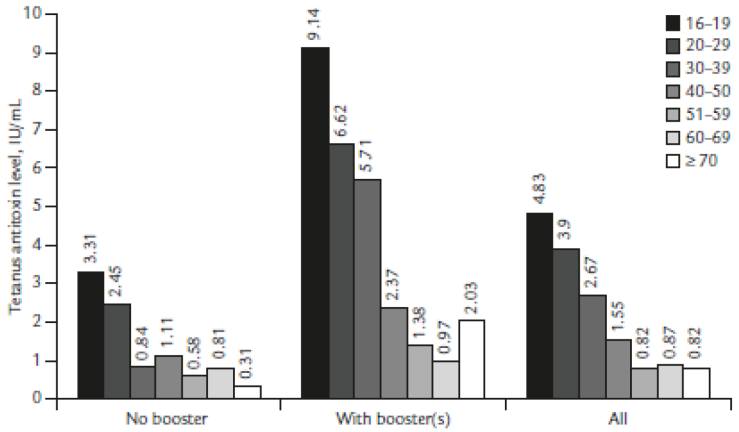
7.1 Objective

The objective for this section is to consider the different vaccine options available to New Zealand in terms of available vaccines and schedules. Consideration will be given to the roles of tetanus, diphtheria and acellular pertussis vaccines in the prevention of both tetanus and pertussis disease.

7.2 Review

Advancing age affects the magnitude and persistence of antibody responses to disease and vaccines, with the process beginning from 20 years of age (56). In a study of 326 Taiwanese adults aged ≥16 years of age, mean tetanus toxoid antibody titres declined with age from 4.83IU/mL in those aged 16 – 19 years to 0.82 – 0.87 IU/mL in those aged >51 years (Figure 2). Individuals with a history of a prior tetanus toxoid booster vaccination had higher titres compared with those who had not. However, the percentage of participants with seroprotective tetanus toxin antibody titres declined as the interval since the last booster vaccination increased. Bars represent mean values. Participants who had ever received a toxoid booster were associated with significantly higher antitoxin levels than those who had not, in all age-groups except 60 – 69 years ($p < 0.05$) (57).

Figure 2. Comparison of tetanus antitoxin levels between participants with or without toxoid booster(s) and among all participants (with permission Wu et al. 2009)



The correlates of protection against tetanus disease, tetanus toxoid antibody titre ≥0.1IU/mL or a four-fold rise in antibody titre between pre and post-vaccination serology will not be an absolute figure for every vaccinated person. A very small number of people with a protective antibody titre would still develop tetanus if exposed. Livorsi et al. (2010) published a case report of tetanus disease in a 44 year old man who was fully vaccinated and had had his previous tetanus vaccination nine years before the onset of disease and a tetanus toxoid antibody titre of 2.78IU/mL (47).

Current available options include a range of combination vaccines:

- For infants and children <7 years of age: Combinations of DTaP with other antigens - Hib, Hepatitis B and IPV.
- For children ≥7 years, adolescents and adults/elderly: Td as a two-antigen vaccine or in combination with other antigens - aP and IPV.

7.3 Summary for vaccine options

Vaccine options for the prevention of tetanus disease in infants, children, adolescents and adults/elderly in New Zealand include combination vaccines containing full strength DTaP for children <7 years and combination vaccines containing reduced-antigen Td for children ≥7 years, adolescents and adults/elderly. The tetanus toxoid appears to be immunogenic and safe in all international studies of combination vaccines.

Tdap has been demonstrated to be safe and immunogenic for the tetanus toxoid antigen and comparable to Td when administered to adults ≥65 years of age. Tdap is also expected to be comparable to Td in adolescents and adults ≤64 years of age.

8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of DTaP-IPV-HepB/Hib and Tdap on the National Immunisation Schedule.

8.2 Outcomes

The safety and immunogenicity of different administration schedules will be discussed for:

- DTaP vaccines in infants.
- Tdap vaccination in toddlers and children up to 10 years of age.
- Tdap vaccination and revaccination in adults, including adults ≥65 years of age.
- Infants whose mothers received Tdap during pregnancy.

8.3 Review

8.3.1 Schedules for DTaP-IPV-HepB/Hib

8.3.1.1 Preterm infants

Primary vaccination schedules administering combination vaccines containing not less than 40IU of tetanus toxoid, Infanrix®-hexa, at two, three and four months or two, four and six months of age, have been shown to be safe and immunogenic for the tetanus toxoid antigen in >98% of preterm and/or low birth weight infants, gestation less than 36 weeks or birth weight less than 2Kg (48).

8.3.1.2 Infants and toddlers

Primary vaccination schedules administering DTaP-IPV-HepB/Hib (Infanrix®-hexa) at three, four and five months; two, three and four months or two, four and six months have been shown to be safe and immunogenic (seroprotective antibody titres achieved) for diphtheria and tetanus toxoids, and poliovirus type 1, 2, and 3 antigens in the vaccine in 95.0 – 100% of infants one month post-vaccination (21).

A pooled analysis of four trials administering DTaP-IPV-HepB/Hib (Infanrix®-hexa) at three, five and 11 months of age (two priming and one boosting vaccination, n=702) identified that seroprotective antibody titres were achieved for diphtheria, tetanus, hepatitis B and poliovirus types 1, 2 and 3 antigens in 96.3 – 100% of participants, Hib in 91.7% of participants and for each pertussis antigen in ≥99.0% of participants, one month after the second primary vaccination. One month following the booster vaccination at 11 months of age, 98.9 – 100% of participants achieved seroprotective antibody titres for all antigens in the vaccine (58).

8.3.2 Schedules for booster vaccinations of Td or Tdap

8.3.2.1 Toddlers and children aged 18 months to eight years

The safety and immunogenicity of a fourth/booster Tdap vaccination has been shown to be non-inferior to DTaP in children aged 18 months through eight years who had previously received three priming vaccinations of DTaP (26, 28, 30).

8.3.2.2 Catch-up vaccinations for children aged seven – ten years

Partially vaccinated or unvaccinated children in the 7 - 10 year age-group can receive reduced-antigen tetanus, diphtheria and acellular pertussis (Tdap) vaccine in place of their first Td catch-up vaccination, followed by Td for the remaining catch-up vaccinations (59).

As Tdap is currently not licensed for multiple doses, when Tdap has been administered between 7 - 10 years of age, the Committee on Infectious Diseases, American Academy of Pediatrics, recommends a booster Td vaccination 10 years after the last Td-containing catch-up vaccination in place of a Tdap booster vaccination at 11 – 12 years of age (59).

8.3.3 Schedules for adults

The first Tdap vaccination in adults up to 64 years of age, adults ≥65 years of age and a decennial booster Tdap vaccination have been shown to be safe and immunogenic in adults 20 – 72 years of age (33, 38, 41, 42, 44, 51).

A Tdap vaccination during pregnancy has also been shown to be safe and immunogenic for the fetus/infant (54).

8.3.4 Timing of Tdap following a previous Td vaccination

A Tdap vaccination, as soon as one month after a previous Td vaccination, has been shown to be safe in adults (35, 40).

8.4 Summary of options for scheduling

DTaP combination vaccines can be administered to preterm and/or low birth weight infants following a three vaccination priming course in the first year of life.

DTaP combination vaccines can be administered as a priming course of three vaccinations in the first year of life or as a primary course of two vaccinations plus a booster vaccination in the first year of life.

A reduced-antigen content Tdap vaccine can be offered to toddlers and children <9 years of age as a fourth/booster vaccination.

A single Tdap vaccination can be used for the first catch-up vaccination for partially vaccinated or unvaccinated children aged 7 – 10 years of age.

Tdap can be administered to adults, including pregnant women and adults ≥65 years of age.

No minimum interval is required between administration of Tdap vaccine and a previous Td vaccination.

9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data for currently licensed tetanus toxoid combination vaccines with respect to potential implementation issues in the New Zealand context. This includes co-administration of the DTaP-IPV-HepB/Hib (Infanrix®-hexa), medically attended reactions at the injection site following booster vaccinations with DTaP combination vaccines or Tdap and tetanus prophylaxis as part of wound management.

As the childhood schedule already includes universal tetanus vaccination, other implementation issues such as workforce and increased service delivery are not covered in this review.

9.2 Review

9.2.1 Co-administration of DTaP combination vaccines

9.2.1.1 DTaP-IPV-HepB/Hib and measles, mumps, rubella, varicella vaccine (MMRV)

Studies of co-administration of DTaP-IPV-HepB/Hib (Infanrix®-hexa) with a quadrivalent measles, mumps, rubella, varicella vaccine (MMRV; Priorix® Tetra) have shown nil or non-significant effects on the immunogenicity of Infanrix®-hexa and the co-administered vaccine (21). However, the Centers for Disease Control and Prevention recommend that separate MMR and varicella vaccines are administered for the first vaccinations in the 12 – 47 months age-group unless a parent specifically requests MMRV. Administration of the first dose of quadrivalent vaccine is associated with an approximately two-fold increase in risk of fever and febrile convulsions, compared with co-administration of separate MMR and varicella vaccinations, during the biological window of vulnerability of febrile convulsions in children (60).

9.2.2 Medically attended Td and Tdap site reactions

The frequency and severity of swelling at the injection site increase with age and additional doses of tetanus, diphtheria (Td) and diphtheria, tetanus and acellular pertussis (DTaP and Tdap) combination vaccines (23, 25, 26).

In a study of medically attended reactions at the injection site within six days of a Td vaccination in children aged nine – 11 years, adolescents and young adults to 25 years of age, an estimated 159/463,828 vaccinations (estimated event risk 3.6, CI 95% 2.8 – 4.7) resulted in review by a health professional.

From these estimated 159 medically attended reactions at the injection site, 103 local reactions were validated by review of medical records. Twenty-five individuals had attended an emergency department or urgent care facility and 78 had attended an outpatient clinic.

Between days one to six, post-vaccination local oedema, redness or swelling was recorded for 97/103. For 59/97, the size of the local reaction was recorded <10cm (83%), 10 – 15cm (10%) and ≥15cm (7%). Of the 103, pain was recorded for 39 patients 2 had ulcerated skin lesions, 11 had lymphadenopathy and 5 had fever ≥37.8°C.

Twenty-three individuals were given a clinical diagnosis of cellulitis, of these four people were treated with parenteral antibiotics and 16 were prescribed oral antibiotics. Of 80 validated local reactions without a diagnosis of cellulitis, two were treated with parenteral antibiotics and seven were prescribed oral antibiotics (11% received antibiotic treatment in the absence of a diagnosis of cellulitis).

Overall, 28% of individuals aged 9 – 25 years with a medically attended local reaction were treated with antibiotics. This proportion is similar to a previous study of children receiving the fourth or fifth vaccination with DTaP, where 21% of children who sought medical attention for a reaction at the injection site (61).

9.2.3 Tetanus prophylaxis as part of wound management

9.2.3.1 Recognition of tetanus risk and adult recall of prior tetanus vaccination

Chronic wounds (e.g. varicose ulcers and diabetic foot ulcers) have been identified as entry portals for *Clostridium tetani*. In the UK, varicose ulcers, dermatosis and necrosed tumours have been estimated to be the entry portal for spores in 11 – 14% of tetanus cases, and in the US, diabetic foot ulcer has been identified as the entry portal for 25% of cases. A survey of patients attending wound healing clinics

was conducted at two hospitals in the UK over five days in 2010. The tetanus status of 100 patients was retrospectively analysed. Participants were aged 22 – 91 years with a median age of 70 years. The majority of patients presented with venous leg ulcers (n=36), venous and arterial leg ulcers (n=6) and arterial leg ulcers (n=8). Of the 48 patients with diabetes, 22 had diabetic foot ulcers, 10 had venous leg ulcers, 5 had arterial ulcers and 11 were wounds relating to surgery or trauma (62).

The majority of patients, 48/100 (48%), were unaware of their tetanus immunisation status, 30/100 (30%) thought they were not protected against tetanus (i.e. they had not received a booster vaccination in the preceding 10 years), this was considered to cover individuals who had not received a primary tetanus vaccine course, and 22/100 (22%) thought they were up to date with immunisation. After review of GP records, 43/100 (43%) were not protected against tetanus, 33/100 (33%) were up to date with immunisation, 13/100 (13%) had no immunisation records with their current GP and no GP details could be located for one respondent (62).

Around half the patients with chronic wounds were unaware of their tetanus status and only about one third of patients were actually up to date with tetanus immunisation (62).

For inclusion in a study of Td (Td-pur®) immunogenicity, Korean adults aged ≥40 years were required to have no prior vaccination with a tetanus containing vaccine (n=242). However, pre-vaccination 241/242 (99.6%) of participants had tetanus antibody titres 0.01 – 0.09 IU/mL and 160/242 (66.1%) had seroprotective titres ≥0.1IU/mL of tetanus toxoid antibody (63). As development of immunity against tetanus requires vaccination, because the small amount of tetanus toxin required to cause disease is generally not enough to induce an immune response, the results of this study suggest that at least two thirds of participants who had no recall of tetanus vaccination were likely to have been vaccinated.

9.2.3.2 Management of tetanus risk

In a survey of 64 medical directors in Korean hospital emergency departments, 41/64 (64.1%) of respondents reported applying tetanus prophylaxis guidelines to 80% of people presenting with wounds. However, only 35/64 (54.7%) reported prescribing or administering a Td booster vaccination to people with a tetanus-prone wound. The most common age-group for trauma patients, presenting to the emergency departments managed by respondents, was 26 – 40 years (47/65 [73.4%]) followed by the 41 – 54 year age-group (37.5%). A previous study cited showed that tetanus immunity is decreased in Korean adults over 20 years of age and by 40 years of age only 10% of Koreans have seroprotective titres ≥0.1IU/mL of tetanus antibody (64).

The most frequent, non-cost related reason for not considering Td vaccination was the respondents' assumption that the person would have had adequate tetanus protection, as cited in 20/34 (58.8%) of responses (64).

Anecdotally, from the NZ Immunisation Advisory Centre national 0800 immunisation advice phone line, health professionals working in primary care and hospitals are not confident in implementing the tetanus prophylaxis guidelines. In particular, recognition of tetanus-prone wounds and knowing when to offer a tetanus booster vaccination and/or tetanus immunoglobulin (TIG).

9.3 Summary for implementation issues

Co-administration of DTaP-IPV-HepB/Hib with MMRV vaccine is safe and immunogenic. Timing of co-administration would usually be during the second year of life. However, the quadrivalent MMRV vaccine is not recommended for the first vaccination against measles, mumps, rubella and varicella due to the risk of fever and febrile convulsions.

Expected local reactions following DTaP, Td and Tdap vaccines may be diagnosed as infection without administration and/or prescription of unnecessary antibiotics.

Chronic wounds as well as traumatic wounds provide a portal for entry of *Clostridium tetani.*

Adult recall of tetanus vaccination history may be unreliable and leave them vulnerable to tetanus disease in the presence of a chronic or traumatic wound.

Not all health professionals are confident in implementing tetanus prophylaxis guidelines or may make assumptions about an individual's protection against the disease.

10. International policy and practice

10.1 Objective

The objective of this section is to summarise some of the international experience on the use of pneumococcal vaccines and position statements and policies from countries with comparable populations to New Zealand.

10.2 Review

10.2.1 United States

The Advisory Committee on Immunization Practices (ACIP) make the following recommendations for tetanus toxoid vaccination with consideration of prevention of pertussis through use of the tetanus, diphtheria, acellular pertussis combination (Tdap) vaccine.

10.2.1.1 Catch-up vaccinations

10.2.1.1.1 Children aged 7 – 10 years

Children who are not fully vaccinated* against pertussis should receive a single dose of Tdap. If additional doses of tetanus and diphtheria vaccines are needed, Td is used for the remaining doses (30, 59).

*Fully vaccinated is defined as five doses of DTaP or four doses of DTaP if the fourth dose was administered on or after the fourth birthday.

10.2.1.2 Booster vaccinations

10.2.1.2.1 Adolescents aged 11 – 18 years

A single dose of Tdap should be administered, preferably at 11 – 12 years of age, to those who have completed the recommended childhood priming doses of tetanus, diphtheria and pertussis vaccine (30, 59).

10.2.1.2.2 Adults aged 19 – 64 years

A single dose of Tdap should be administered (30, 59).

10.2.1.2.3 Pregnant women

A single dose of Tdap should be administered late in the second trimester, after 20 weeks gestation, or during the third trimester (36, 65). To maximise the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 – 36 weeks gestation (66).

Pregnant women with unknown or incomplete tetanus vaccination should receive a single dose of Tdap. If additional doses of tetanus and diphtheria vaccines are needed, Td is used for the remaining doses (36, 65).

Pregnant women should receive a single dose of Tdap during each pregnancy, irrespective of the individual's prior history of receiving Tdap (66).

Women who have not received Tdap during pregnancy should be vaccinated with Tdap immediately postpartum (66).

10.2.1.2.4 Adults aged ≥65 years

All adults who have or anticipate having close contact with an infant less than 12 months of age (e.g. grandparents, childcare workers and healthcare workers) should receive a single Tdap vaccination (30, 59, 65).

For other adults, ≥65 years of age, a single dose of Tdap vaccine may be given instead of Td vaccine in persons who have not previously received Tdap (30, 59, 65).

10.2.1.3 Tetanus prophylaxis in pregnant women

When a pregnant woman requires a tetanus toxoid booster vaccination as part of standard wound management care to prevent tetanus (at more than five years since the last tetanus toxoid vaccination), Tdap should replace Td, if Tdap has not already been administered during the current pregnancy (36, 65).

10.2.1.4 Timing of Tdap following a previous Td vaccination

No minimum interval is required between administration of Tdap and a previous Td vaccination. The potential benefits from vaccination against pertussis outweigh the possible risk of an increased reaction at the injection site (30, 59).

10.2.2 United Kingdom

The Department of Health recommends a minimum of five tetanus toxoid-containing vaccinations (67).

10.2.2.1 Catch-up vaccinations

10.2.2.1.1 Children aged <10 years

Use full strength DTaP combination vaccines (67).

10.2.2.1.2 Children aged ≥10 years, adolescents and adults

Use a reduced-antigen Td combination vaccine for priming and booster vaccinations (67).

10.2.2.2 Booster vaccinations

10.2.2.2.1 Children aged ≥10 years, adolescents and adults

Use reduced-antigen Td combination vaccine if the person has only had three previous vaccinations and it is at least five years since the previous vaccination (67).

All individuals should receive a second Td booster vaccination 10 years after the first Td booster vaccination, except when previous vaccinations have been delayed and the second booster is administered five years after the first booster vaccination (67).

10.2.2.3 Travellers

Travellers, who have a high risk of sustaining a tetanus-prone wound or may experience a delay in accessing healthcare services for a tetanus toxoid booster vaccination, should receive a Td booster vaccination if it is at least 10 years since the previous vaccination (67).

10.2.3 Australia

Recommendations of the Australian Technical Advisory Group on Immunisation have been sourced from the draft version of the 10th edition of the Australian Immunisation Handbook that was made available for public comment, with consideration as to where these possible recommendations differ to the current 9th edition of the Australian Immunisation Handbook.

10.2.3.1 Catch-up vaccinations

10.2.3.1.1 Children

Full strength DTaP combination vaccines were previously recommended for children under eight years of age (68). The updated recommendation is expected to increase this age limit to children <10 years of age (69).

10.2.3.1.2 Children, adolescents and adults

Reduced-antigen tetanus toxoid combination vaccines were previously recommended for children aged eight years or older, adolescents and adults (68). The updated recommendation is expected to increase this age limit to children ≥10 years of age (69).

Use a reduced-antigen Td combination vaccine for priming and booster vaccinations (68). This recommendation is not expected to change in the 10th edition.

Tdap should replace the first Td catch-up vaccination (68). This recommendation is not expected to change in the 10th edition.

10.2.3.2 Booster vaccinations

10.2.3.2.1 Children, adolescents and adults

All adults who reach 50 years of age without receiving a Td vaccination in the previous 10 years should receive a Tdap vaccination (68, 69). This recommendation is not expected to change in the 10th edition.

10.2.3.3 Tetanus prophylaxis

10.2.3.3.1 Children

DTaP combination vaccines were previously recommended for children <8 years of age and Td/Tdap vaccines for children ≥8 years of age (68). The updated recommendation is expected to change the age limit for DTaP combination vaccines to children <10 years of age and for Td/Tdap vaccines to ≥10 years (69).

10.2.3.3.2 Adults

Tdap was previously recommended as an alternative vaccine to Td, if Td was unavailable or if the individual had not previously received a Tdap vaccination (68). This recommendation is not expected to change in the 10th edition.

10.2.3.4 Travellers

Travellers, who have a high risk of sustaining a tetanus-prone wound or may experience a delay in accessing healthcare services for a tetanus toxoid booster vaccination, should receive a Td booster vaccination if it is at least 10 years since the previous vaccination. Tdap can be administered if the individual has not previously received a Tdap vaccination (68, 69). This recommendation is not expected to change in the 10th edition.

10.2.3.5 Timing of Tdap following a previous Td vaccination

No minimum interval is required between administration of Tdap and a previous Td vaccination. The potential benefits from vaccination against pertussis outweigh the possible risk of an increased reaction at the injection site (66, 68). This recommendation is not expected to change in the 10th edition.

10.3 Summary of international policy and practice

Tdap vaccine is an acceptable alternative to Td for the first tetanus toxoid catch-up vaccination and for tetanus prophylaxis when an individual has a tetanus-prone wound.

In the US, children aged 7 – 10 years who are partially vaccinated or unvaccinated should receive a Tdap vaccination in place of the first Td catch-up vaccination.

Australia is considering increasing the upper age limit for administration of full strength DTaP vaccines to the 10th birthday. The UK already recommends this upper age limit.

In the US, adults from 19 – 64 and ≥65 years of age, who have or anticipate having close contact with an infant less than 12 months of age, should receive a single Tdap booster vaccination to decrease the risk of pertussis disease.

In the US, a single dose of Tdap is recommended for all pregnant women after 20 weeks gestation. Provisional recommendations have been published for pregnant women to receive a Tdap vaccination in every pregnancy regardless of previous Tdap doses. When catch-up tetanus toxoid vaccinations are required Tdap should be used for the first catch-up vaccination. When tetanus prophylaxis is required Tdap should be used if the individual has not received Tdap during the current pregnancy.

In the US, women who have not received Tdap during pregnancy should be vaccinated with Tdap immediately postpartum.

In the UK, individuals should receive a minimum of five tetanus toxoid vaccinations, typically a priming course of three vaccinations and two booster vaccinations, the first booster five years after the priming course and the second booster ten years after the first.

In the UK and Australia, travellers, who have a high risk of sustaining a tetanus-prone wound or may experience a delay in accessing healthcare services for a tetanus toxoid booster vaccination, should receive a tetanus toxoid booster vaccination if it is at least 10 years since the previous vaccination.

No minimum interval is required between administration of Tdap and a previous Td vaccination.

References

1. Roper MH, Wassilak SGF, Tiwari TSP, Orenstein WA. Tetanus toxoid. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines. 6th ed. London: W.B. Saunders; 2013. p. 746-72.
2. The Institute of Environmental Science and Research Ltd. Notifiable and other diseases in New Zealand: Annual report 2011. Internet. Porirua: The Institute of Environmental Science and Research Ltd.; 2012.
3. U.S. Food and Drug Administration. Package insert: Infanrix [Internet] [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2012. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM124514.pdf
4. Medsafe. Datasheet: Infanrix-IPV [Internet] [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/i/InfanrixIPVinj.pdf
5. U.S. Food and Drug Administration. Package insert: Kinrix [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2012. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241453.pdf
6. Irish Pharmaceutical Healthcare Association. Summary of product characteristics: Tetravac [Internet] Dublin: Irish Pharmaceutical Healthcare Association Ltd.; 2012. Available from: http://www.medicines.ie/medicine/3172/SPC/TETRAVAC/
7. Medsafe. Datasheet: Quadracel [Internet] Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2012. Available from: http://www.medsafe.govt.nz/profs/Datasheet/q/Quadracelinj.pdf
8. Decker MD, Edwards KM, Bogaerts HH. Combination vaccines. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines. 6th ed. London: W.B. Saunders; 2013. p. 981-1007.
9. U.S. Food and Drug Administration. Package insert: Pentacel [Internet] Silver Spring (MD): U.S. Food and Drug Administration; 2012. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109810.pdf
10. Medsafe. Datasheet: Infanrix-hexa [Internet] [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/I/Infanrixhexainj.pdf
11. U.S. Food and Drug Administration. Package insert: Decavac [Internet] Silver Spring (MD): U.S. Food and Drug Administration; 2011. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM246215.pdf
12. Bureau of Drug Control Thailand. Summary of product characteristics: Td-pur [Internet] Bangkok: Bureau of Drug Control Thailand; 2009. Available from: http://drug.fda.moph.go.th/zone_search/files/2C_9_48_Td%20pur.pdf
13. Datapharm. Summary of product characteristics: Revaxis [Internet] Surrey: Datapharm Communications Limited; 2008. Available from: http://www.medicines.org.uk/emc/document.aspx?documentid=15259
14. Medsafe. Datasheet: Boostrix [Internet] [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/b/Boostrixinj.pdf
15. Medsafe. Datasheet: Adacel [Internet] [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/b/Boostrixinj.pdf
16. Medsafe. Datasheet: Adacel Polio [Internet] [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2008. Available from: http://www.medsafe.govt.nz/profs/Datasheet/a/AdacelPolioinj.pdf
17. Medsafe. Datasheet: Boostrix-IPV [Internet] Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/b/Boostrix-IPVinj.pdf
18. Shin J, Kim J, Song K. Influences on formation of tetanus antibody after simultaneous injection of tetanus immunoglobulin with tetanus vaccine. J Korean Med Sci. 2012;27(8):934-8.
19. The Institute of Environmental Science and Research Ltd. Notifiable and other diseases in New Zealand: Annual report 2010. Porirua: The Institute of Environmental Science and Research Ltd.; 2011.

20. The Institute of Environmental Science and Research Ltd. Notifiable and other diseases in New Zealand: 2009 annual surveillance report. Porirua: The Institute of Environmental Science and Research Ltd.; 2010.

21. Lyseng-Williamson KA, Dhillon S. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa): a guide to its use in infants. Paediatr Drugs. 2012;14(5):337-43.

22. Omenaca F, Garcia-Sicilia J, Garcia-Corbeira P, Boceta R, Romero A, Lopez G, et al. Response of preterm newborns to immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio and Haemophilus influenzae type b vaccine: first experiences and solutions to a serious and sensitive issue. Pediatrics. 2005;116(6):1292-8.

23. Zepp F, Schmitt HJ, Cleerbout J, Verstraeten T, Schuerman L, Jacquet JM. Review of 8 years of experience with Infanrix hexa (DTPa-HBV-IPV/Hib hexavalent vaccine). Expert Rev Vaccines. 2009;8(6):663-78.

24. Sun Y, Christensen J, Hviid A, Li J, Vedsted P, Olsen J, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. JAMA. 2012;307(8):823-31.

25. Scheifele DW, Ochnio JJ, Halperin SA. Cellular immunity as a potential cause of local reactions to booster vaccination with diphtheria and tetanus toxoids and acellular pertussis antigens. Pediatr Infect Dis J. 2009;28(11):985-9.

26. Quinn P, Gold M, Royle J, Buttery J, Richmond P, McIntyre P, et al. Recurrence of extensive injection site reactions following DTPa or dTpa vaccine in children 4-6 years old. Vaccine. 2011;29(25):4230-7.

27. Klein NP, Weston WM, Kuriyakose S, Kolhe D, Howe B, Friedland LR, et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaP-IPV (Kinrix) co-administered with MMR vaccine with or without varicella vaccine in healthy pre-school age children. Vaccine. 2012;30(3):668-74.

28. Nolan T, Ruff TA, Lambert SB, Buttery J, O'Grady KA, Streeton C, et al. Booster vaccination of toddlers with reduced antigen content diphtheria -- tetanus -- acellular pertussis vaccine. Vaccine. 2009;27(18):2410-3.

29. Wei SH, Chao YN, Huang SE, Lee TF, Chang LY. Adverse effects of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine in 6- to 7-year-old children. Pediatr Neonatol. 2011;52(1):38-41.

30. Centers for Disease CaP. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR Morb Mortal Wkly Rep. 2011;60(1):13-5.

31. Klein NP, Hansen J, Lewis E, Lyon L, Nguyen B, Black S, et al. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. Pediatr Infect Dis J. 2010;29(7):613-7.

32. Yih WK, Nordin JD, Kulldorff M, Lewis E, Lieu TA, Shi P, et al. An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink. Vaccine. 2009;27(32):4257-62.

33. Blatter M, Friedland LR, Weston WM, Li P, Howe B. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19-64 years of age. Vaccine. 2009;27(5):765-72.

34. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012;207(1):59 e1-7.

35. Talbot EA, Brown KH, Kirkland KB, Baughman AL, Halperin SA, Broder KR. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine. 2010;28(50):8001-7.

36. Centers for Disease CaP. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months — Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(41):1424-6.

37. Tseng HF, Sy LS, Qian L, Marcy SM, Jackson LA, Glanz J, et al. Safety of a tetanus-diphtheria-acellular pertussis vaccine when used off-label in an elderly population. Clin Infect Dis. 2013;56(3):315-21.

38. Weston WM, Friedland LR, Wu X, Howe B. Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix((R))): results of two randomized trials. Vaccine. 2012;30(9):1721-8.

39. Moro PL, Yue X, Lewis P, Haber P, Broder K. Adverse events after tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine administered to adults 65 years of age and older reported to the Vaccine Adverse Event Reporting System (VAERS), 2005-2010. Vaccine. 2011;29(50):9404-8.

40. Beytout J, Launay O, Guiso N, Fiquet A, Baudin M, Richard P, et al. Safety of Tdap-IPV given one month after Td-IPV booster in healthy young adults: a placebo-controlled trial. Hum Vaccin. 2009;5(5):315-21.

41. Mertsola J, Van Der Meeren O, He Q, Linko-Parvinen A, Ramakrishnan G, Mannermaa L, et al. Decennial administration of a reduced antigen content diphtheria and tetanus toxoids and acellular pertussis vaccine in young adults. Clin Infect Dis. 2010;51(6):656-62.

42. Booy R, Van der Meeren O, Ng SP, Celzo F, Ramakrishnan G, Jacquet JM. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix) is immunogenic and well tolerated in adults. Vaccine. 2010;29(1):45-50.

43. Halperin SA, McNeil S, Langley J, Blatter M, Dionne M, Embree J, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011;29(46):8459-65.

44. Halperin SA, Scheifele D, De Serres G, Noya F, Meekison W, Zickler P, et al. Immune responses in adults to revaccination with a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. Vaccine. 2012;30(5):974-82.

45. Weston WM, Chandrashekar V, Friedland LR, Howe B. Safety and immunogenicity of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine when co-administered with influenza vaccine in adults. Hum Vaccin. 2009;5(12):858-66.

46. Plosker GL. Combined, reduced-antigen content tetanus, diphtheria, and acellular pertussis vaccine (Boostrix): a review of its use as a single-dose booster immunization in individuals aged 10-64 years in the US. BioDrugs. 2009;23(4):253-67.

47. Livorsi DJ, Eaton M, Glass J. Generalized tetanus despite prior vaccination and a protective level of anti-tetanus antibodies. Am J Med Sci. 2010;339(2):200-1.

48. Baxter D. Vaccine responsiveness in premature infants. Hum Vaccin. 2010;6(6):506-11.

49. Zinke M, Disselhoff J, a-HBV-IPV DTP, study g, Gartner B, Jacquet JM. Immunological persistence in 4-6 and 7-9 year olds previously vaccinated in infancy with hexavalent DTPa-HBV-IPV/Hib. Hum Vaccin. 2010;6(2):189-93.

50. Black S, Friedland LR, Schuind A, Howe B, GlaxoSmithKline D-IPVVSG. Immunogenicity and safety of a combined DTaP-IPV vaccine compared with separate DTaP and IPV vaccines when administered as pre-school booster doses with a second dose of MMR vaccine to healthy children aged 4-6 years. Vaccine. 2006;24(35-36):6163-71.

51. Van Damme P, McIntyre P, Grimprel E, Kuriyakose S, Jacquet JM, Hardt K, et al. Immunogenicity of the reduced-antigen-content dTpa vaccine (Boostrix((R))) in adults 55 years of age and over: a sub-analysis of four trials. Vaccine. 2011;29(35):5932-9.

52. McIntyre PB, Burgess MA, Egan A, Schuerman L, Hoet B. Booster vaccination of adults with reduced-antigen-content diphtheria, Tetanus and pertussis vaccine: immunogenicity 5 years post-vaccination. Vaccine. 2009;27(7):1062-6.

53. Weston W, Messier M, Friedland LR, Wu X, Howe B. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. Vaccine. 2011;29(47):8483-6.

54. Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol. 2011;204(4):334 e1-5.

55. Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. Hum Vaccin Immunother. 2012;8(3):355-62.

56. Siegrist C-A. Vaccine immunology. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines (Sixth Edition). 6th ed. London: W.B. Saunders; 2013. p. 14-32.

57. Wu CJ, Ko HC, Lee HC, Tsai WC, Li MG, Pao YZ, et al. Decline of tetanus antitoxin level with age in taiwan. J Formos Med Assoc. 2009;108(5):395-401.

58. Van Der Meeren O, Kuriyakose S, Kolhe D, Hardt K. Immunogenicity of Infanrix hexa administered at 3, 5 and 11 months of age. Vaccine. 2012;30(17):2710-4.

59. Centers for Disease CaP, American Academy of Pediatrics Committee on Infectious Diseases. Additional recommendations for use of tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis vaccine (Tdap). Pediatrics. 2011;128(4):809-12.

60. Centers for Disease Control and Prevention. Use of combination measles, mumps, rubella, and varicella vaccine. MMWR Recomm Rep. 2010;59(RR-03):1-12.

61. Jackson LA, Yu O, Belongia EA, Hambidge SJ, Nelson J, Baxter R, et al. Frequency of medically attended adverse events following tetanus and diphtheria toxoid vaccine in adolescents and young adults: a Vaccine Safety Datalink study. BMC Infect Dis. 2009;9:165.

62. Farnworth E, Roberts A, Rangaraj A, Minhas U, Holloway S, Harding K. Tetanus in patients with chronic wounds - are we aware? Int Wound J. 2012;9(1):93-9.

63. Choi JH, Choo EJ, Huh A, Choi SM, Eom JS, Lee JS, et al. Immunogenicity and safety of diphtheria-tetanus vaccine in adults. J Korean Med Sci. 2010;25(12):1727-32.

64. Yoon YH, Moon SW, Choi SH, Cho YD, Kim JY, Kwak YH. Clinician awareness of tetanus-diphtheria vaccination in trauma patients: a questionnaire study. Scand J Trauma Resusc Emerg Med. 2012;20:35.

65. Committee on Obstetric P. ACOG Committee Opinion No. 521: Update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination. Obstet Gynecol. 2012;119(3):690-1.

66. Advisory Committee on Immunization Practices. ACIP provisional updated recommendations on use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) for pregnant women. Atlanta: Centers for Disease Control and Prevention; 2012.

67. Department of Health. Tetanus. In: Salisbury DM, Ramsay M, Noakes K, editors. Immunisation Against Infectious Disease (the Green Book). London: Department of Health; 2009. p. 367-84.

68. Australian Technical Advisory Group on Immunisation. Tetanus. In: The Australian immunisation handbook. 9th ed. Canberra: Australian Government Department of Health and Ageing; 2008. p. 288-96.

69. Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. Draft for public consultation. 10th ed. Canberra: Australian Government Department of Health and Ageing; 2012.

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