The Immunisation Advisory Centre

Review of evidence to inform the New Zealand National Immunisation Schedule, 2019: Tetanus

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
CI	Confidence interval
DTaP	Combined diphtheria, tetanus, acellular pertussis vaccine
DTaP-IPV-HepB/Hib	Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines.
ELISA	Enzyme-linked immunosorbent assay
ESR	Institute for Environmental and Scientific Research
GMT	Geometric mean titre
GSK	GlaxoSmithKline Ltd
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
IPV or OPV	Inactivated polio virus vaccine or oral polio virus vaccine
IU/ml	International units per millilitre
MenACWY-TT	Tetanus toxoid-conjugated quadrivalent meningococcal vaccine
MenC	Meningococcal group C vaccine
NZ	New Zealand
RCT	Randomised controlled trial
SAE	Serious adverse events
Td	Combined tetanus toxoid and reduced antigen diphtheria toxoid vaccine
Tdap	Combined tetanus toxoid, reduced antigen diphtheria toxoid and acellular pertussis vaccine
TIG	Tetanus immunoglobulin
TT	Tetanus toxoid
UK	United Kingdom
US	United States of America
WHO	World Health Organization

1 Executive Summary

Tetanus toxoid vaccination has been part of the routine immunisation schedule in New Zealand (NZ) since 1958 and was funded from 1960. Prior to that time, tetanus toxoid (TT) had been used for voluntary vaccinations since the 1940s and 1950s, and was often delivered to those on military service. The number of doses provided by the National Immunisation Schedule (the Schedule) has increased over the decades from four childhood doses commencing in 1960.[1, 2]

As of January 2019 as part of the Schedule in New Zealand, children now receive five doses of tetanus vaccine from 6 weeks to 12 years of age. Tetanus vaccine is given as combination vaccines primarily with diphtheria toxoid and acellular pertussis antigens (DTaP or Tdap). Further doses of tetanus-diphtheria (Td) vaccine are funded at the ages of 45 and 65 years. Td is administered following tetanus-prone injury where more than 5 years has elapsed since a previous booster, and Tdap is provided as part of pertussis control during each pregnancy.

The World Health Organisation (WHO) recommends six doses of tetanus toxoid prior to adulthood to be fully primed and to provide long-lived booster protection: many countries' National Immunisation Schedules provide three priming doses and three booster doses, including a booster dose in the second year of life, preschool and for adolescents.[3] However, some countries follow a similar schedule to NZ by omitting the toddler dose, and others, particularly in parts of Europe, provide two primary doses and a toddler booster.

To help inform the New Zealand Immunisation Schedule, this review of evidence was conducted to investigate key questions:

1. Under the current Schedule in NZ, is tetanus protection adequate for the whole life?
2. How necessary are the currently funded tetanus vaccine booster doses at 45 years and 65 years of age?
3. Which groups are at highest risk of tetanus and can we improve the immunisation programme to provide greater protection for those most at risk?
4. For tetanus prophylaxis in wound management, is a booster dose needed for a tetanus-prone injury when it is more than 5 years since the last tetanus vaccine dose for those who have been fully immunised?
5. Does using tetanus toxoid as the carrier protein in conjugate vaccines, e.g. ten-valent pneumococcal and *Haemophilus influenzae* type B (Hib) conjugate vaccines, contribute to tetanus immunity?
6. Is there a need for further tetanus vaccine boosters in the context of other antigens, e.g. pertussis immunisation?

This review of evidence is not a systematic review and cost-benefit analyses are not considered. Evidence-based scientific literature, systematic reviews and review articles published during 2015-2018 are reviewed. Interpretations of the literature and conclusions are expressed solely by the author and do not form part of any official immunisation recommendations.

Whole-of-life protection

A need to review the immunisation status and booster requirements for older adults was highlighted in a previous evidence review to inform the New Zealand National Immunisation Schedule.[4]

The number of notified cases of tetanus is very low in NZ, with less than one case of tetanus is reported per year, on average. The most recently notified cases have all been in unvaccinated children or in adults over the age of 65 years unimmunised or with uncertain immunisation status. In the 10 years from 1997-2016, 33 cases were notified: 18 were unimmunised out of the 21 with known immunisation status - indicating that the current immunisation control methods appear to be effective overall.[2, 5] However, it is likely that milder cases of tetanus in partially immune adults are under-reported or undiagnosed.[6]

Currently, booster doses of tetanus-containing vaccine are recommended at 45 and 65 years of age in NZ. It remains unclear whether both booster doses are necessary. However, adults reaching 45 years of age may not have sufficient immunity to protect until 65 years.

Many adults, particularly those aged over 60 years, are at increased risk from tetanus due to waning immunity. Inadequate priming can lead to more rapid waning of immunity following booster doses.[7] Many adults, even if classified as fully immunised, are not likely to have received as many doses in childhood as are received by the age of 18 years today. Starting in 1960 in NZ, the childhood immunisation schedule included four doses of tetanus-containing vaccine; the adolescent dose was not introduced until 1980.[1, 2] Furthermore, more than a quarter of the current population in NZ were born overseas, and therefore, it cannot be guaranteed how many primary doses were administered for all adults.[8]

Although tetanus vaccine has been available for more than 65 years, immunisation coverage in NZ historically has been low, and with fewer vaccine doses given, it is likely that a fair proportion of New Zealand adults lack immunity to protect until 65 years of age without booster doses.

The requirement for the routine adult booster dose at 45 years is likely to decline with time as immunisation coverage in childhood improves and more adults reach 45 years of age who have received at least five childhood tetanus vaccine doses.

Additionally, many adults receive extra doses for wound management and, more recently, for women during pregnancy. Currently, the uptake of vaccination in pregnancy and at 45 years is inadequate in NZ to ensure most adults have long-lasting tetanus protection to at least 65 years of age.

A booster dose at 65 years will continue to be required in NZ due to age-related waning in humoral immunity, even for a fully-primed, fully immunised adult population who receive vaccination in pregnancy and/or booster doses at 45 years.

Using mathematical modelling, it was predicted that tetanus protection in fully-primed adults (antitoxin titre of at least 0.01 IU/ml) could be sustained for over 70 years for 95% of the adult population in the US without further booster doses. However, it is unknown if this antibody titre is adequately protective for all individuals and injuries (i.e. sufficient to neutralise tetanus toxin). Caution around contaminated wounds would be necessary – insufficient antitoxin may prevent death but not milder or non-fatal disease.[9] Other models have shown a shorter duration of protection.[10, 11]

It is generally agreed that routine decennial booster doses are not required throughout adulthood for those fully primed in childhood. Some countries recommend one dose in early adulthood, but this is primarily to enhance pertussis rather than tetanus immunity (since

Tdap is recommended in place of Td).[3] No safety concerns were found to suggest that booster doses given decennially increased the risk of adverse events, and injection site pain is the most commonly reported event.[12] It should be noted, however, that most of the recent data compared Tdap with Td, and therefore, assessed the addition of the pertussis component not tetanus and diphtheria.[13]

The protection afforded to immunised children by the current five-dose schedule appears to be adequate for tetanus control. Additionally, although it cannot be relied upon for tetanus protection, routine use of TT-conjugated vaccines, such as Hib-TT (as used in Infanrix-hexa®) and some serotypes in the ten-valent pneumococcal vaccine (PCV-10, Synflorix®), provide further boosting of tetanus immunity[3, 14] Hence, in NZ at least, it appears unnecessary to provide six doses of tetanus-containing vaccines in childhood, as recommended by the WHO. However, data remains limited to confirm or refute this.

Wound management

Mild cases of tetanus have been observed in partially immunised individuals. Minor injuries and abrasions, which may not be recognised as 'tetanus-prone' wounds can lead to tetanus in poorly immune or immunocompromised individuals[3] Delays in seeking treatment for such wounds can increase the risk of tetanus in those with insufficient tetanus immunity.[15]

Tetanus cases appear to have been significantly under-diagnosed and unreported.[16] A discrepancy was observed in Australia between reported tetanus morbidity and serological tetanus immunity - adults aged over 65 years were shown to have inadequate tetanus immunity and hence were at risk of tetanus.[16]

Debridement and wound cleaning play an important role in protecting against tetanus by removing the source of contamination of a wound and limiting the quantity of tetanus toxin released.

Protection provided by five doses in childhood appears to be long lasting and there are no concerns that fully immunised people are fully protected for several decades. However, this protection is reinforced by the current recommendation to provide prophylaxic tetanus booster vaccinations if five or more years have elapsed since the last dose for those presenting with a tetanus-prone wound. It is unclear whether tetanus control would be maintained into older age in the absence of this recommendation.

The literature suggests that the time interval between prophylaxic doses may be further extended to up to 10 years for fully immunised individuals, but since there is no agreed serological level of antitoxin protection many studies are cautious. Therefore, changing the current strategy is not suggested at present. The current evidence is unable to confirm whether this time period may be extended to 10 years by providing a sixth dose in childhood as recommended by the WHO for long-lasting immunity.

Summary and conclusions

1. **Under the current Schedule in NZ, is tetanus protection adequate for the whole-of-life?**
    - Tetanus vaccination is highly effective at preventing tetanus. Protection provided by the current NZ Schedule (childhood immunisation, plus boosters at 45 and 65 years) appears to be adequate in those who have been fully vaccinated, based on notified cases.
    - Data is limited to confirm whether the five-dose childhood tetanus immunisation schedule is adequate in general for long-lived protection, i.e. several decades, or whether six-doses would provide better protection.

2. **How necessary are currently funded tetanus vaccine booster doses at 45 years and 65 years of age?**
    - The current NZ recommendations for booster doses at 45 and 65 years provide sufficient protection against tetanus in adults who have been fully primed.
    - Although unclear, it seems that both booster doses are likely to be required currently.
    - The requirement for the 45-year-old adult booster dose is likely to decline with time as immunisation coverage in childhood improves and more adults reaching 45 years of age have received five or more childhood doses.
    - There are no safety concerns around giving adult booster doses as currently recommended.
3. **Which groups are at highest risk of tetanus and can we improve the immunisation programme to provide greater protection for those most at risk?**
    - For whole-of-life protection, particular attention is likely to be needed for adults at risk of injury through agricultural, animal husbandry or construction industry occupations, and who may not have been sufficiently primed to induce long-lasting responses to tetanus vaccine booster doses.
    - Older adults with waning immunity and poor circulation are at risk of tetanus from minor injuries or lesions that may not be identified as being tetanus-prone.
    - At least one booster at 65 years of age and older is recommended to provide greater protection for the older age groups, in whom humoral immunity wanes more rapidly, particularly for those who may not have been sufficiently primed.
4. **For tetanus prophylaxis in wound management, is a booster dose needed for a tetanus-prone injury when it is more than 5 years since the last tetanus vaccine dose for those who have been fully immunised?**
    - There is no evidence to date to recommend changing current wound management strategies (i.e. administering prophylaxic tetanus vaccine to fully immunised individuals presenting with dirty or deep wounds, five or more years distant from a previous tetanus vaccine dose)
    - This strategy should be reviewed periodically with improvements in the proportion of younger adults being fully-primed (i.e. having received at least five childhood-doses).
    - Evidence suggests that it is important to assess the vaccination history of all individuals presenting with wounds, even minor ones, particularly for those with delays in seeking medical attention.
    - Even in fully immunised adults, levels of neutralising antitoxin may be inadequate to prevent tetanus in the case of a contaminated wound.
    - No safety concerns have been identified around giving repeat doses of tetanus-containing vaccines at least 5 years apart. The data is limited around adverse events in multi-parous pregnant women who have received more than one Tdap booster in a short time-frame.

5. **Does using tetanus toxoid as the carrier protein in conjugate vaccines contribute to tetanus immunity?**
    - Although it cannot be relied upon for tetanus protection, routine use of TT-conjugated vaccines, such as Hib-TT (as used in Infanrix-hexa®) and some serotypes in the 10-valent pneumococcal vaccine (PCV-10, Synflorix®), provides further boosting of tetanus immunity.
6. **Is there a need for further tetanus boosters in the context of other antigens, e.g. pertussis immunisation?**
    - Protection against tetanus is adequate in general within the current schedule.
    - Further doses of tetanus vaccine are given with other vaccine antigens, such a pertussis.
    - Pertussis vaccination with Tdap is recommended in pregnancy. However, uptake is too low to insure that tetanus immunity is being boosted widely in women up to the age of 45 years.
    - Therefore, for the time-being, tetanus vaccine booster doses are likely to be required at both 45 and 65 years to extend protective tetanus immunity in all adults.

Immunisation Handbook update recommendations

19.3.1 Global burden of disease – review most recent WHO data. Add voluntary circumcision as part of HIV control as risk factor, as well as maternal-neonatal tetanus. Include WHO position paper on tetanus 2017 in references.

19.3.2 New Zealand epidemiology – update for most recently available data

19.4.2, subsection Duration of protection – include references around half-life (Hammarland et al 2016). In older adults, who were likely to be less well primed, seroprotection from booster doses may not be as long lived as in fully-primed individuals (Weinberger 2013)

2 Background – tetanus infection and vaccination

Tetanus is caused by a neurotoxin (tetanospasmin, also known as tetanus toxin) that has a severe effect on the nervous control of muscles. Tetanus toxin is released by an anaerobic spore-forming bacterium, *Clostridium tetani*, which usually enters the body through contaminated wounds. It is an environmental pathogen found widely in soil and animal faeces, and is not transmitted between individuals.[9]

For protection, each individual needs to be immunised. Inactivated tetanus toxin, termed tetanus toxoid (TT), is used in tetanus-containing vaccines to induce toxin-neutralising antibodies (antitoxin). To maintain sufficient antitoxin titres to prevent disease, booster doses are administered following priming in infancy.

Tetanus toxoid has been used for immunisation in New Zealand since the 1940s and a triple antigen tetanus-diphtheria-pertussis vaccine became routinely funded as part of the National Immunisation Schedule in 1960. Over the decades, the number of doses given in childhood has increased. However, it is unknown how well protected the NZ population is as a whole. Based on reported incidence, tetanus control is excellent and disease cases are predominantly seen in unimmunised young children and unvaccinated or partially immunised older adults.[1, 2] Table 1 demonstrates the historical changes to the primary and boosting vaccinations on the NZ National Immunisation Schedule.

Historically, immunisation coverage in NZ has been low, and has only in the last decade increased to over 85%-90% in children up to the age of 5 years, still falling short of the 95% coverage target.[17] Therefore, it is likely that a significant proportion of the adult population is under-immunised for tetanus and some adults may have missed out entirely, especially those aged over 65 years.

As in many countries, tetanus toxoid vaccines are only available in combination with diphtheria toxoid vaccine in NZ. They are also combined with other antigens (e.g. pertussis, inactivate poliovirus). Details of the vaccines available in NZ and their contents are presented in the Appendix in Table 2.

The scheduling of tetanus-containing vaccines, as part of the primary immunisation series, sits alongside the schedule for pertussis and diphtheria and is provided in combination vaccines - combinations with DTaP for infants and young children, and as booster doses containing TT and reduced doses of diphtheria toxoid and pertussis antigens (Tdap).

Internationally in high income countries, three-dose primary schedules with DTaP are predominant but vary around the age of delivery of the first dose and subsequent intervals between doses, as illustrated in Table 4. Two-dose primary series are mainly used in Nordic countries at 2 and 4 or 3 and 5 months of age. There is also variability in the use of booster doses given in childhood, in the timing and the formulation of vaccine, and in some countries tetanus toxoid combined with a low dose diphtheria vaccine (Td or Tdap) is given from age 3 years rather than age 10 years, as in NZ.[3]

This literature review has been conducted to assess scientific evidence about tetanus vaccinations, with the aim of helping to inform decisions about the New Zealand National Immunisation Schedule (the Schedule) around the use of tetanus-containing vaccines for immunisation against tetanus. The focus of this review is on the whole-of-life immunisation

programme and recent literature on wound management. Evidence-based, scientific literature published between January 2015 and January 2019 is considered. It is not a systematic review and cost-benefit analyses are not examined. The literature search methodology and a summary of the studies reviewed provided in Table 4 are given in the Appendix. Interpretation of data and opinions are made solely by the author and do not represent official recommendations around tetanus vaccination.

2.1 World Health Organization position on tetanus

The World Health Organization (WHO) released a tetanus vaccine position paper in February 2017, which particularly focussed on providing guidance around the use of booster doses to provide life-long protection against tetanus.[3]

Tetanus infection continues to occur globally, but is rare in developed countries. Despite targeted programmes for children and pregnant women, the majority of cases are neonatal and maternal in some low income countries, occurring as a result of poor hygiene practices during and following delivery among under-immunised women.[3] Tetanus in males in some sub-Saharan countries has been associated with voluntary circumcision aimed at reducing the risk of HIV infection.[18]

The WHO immunisation recommendation is for high coverage of six doses of tetanus-containing vaccines, i.e. three primary doses and three booster doses prior to adulthood, starting from 6 weeks of age. The minimal interval between the primary doses is 4 weeks, preferably with dose three given by 6 months of age. Boosters are recommended in the second year of life, preschool and early adolescence (age 9-15 years), with at least 4 years between booster doses.[3]

For catch-up in unimmunised adolescents, only five doses of Td are required for life-long protection against tetanus.[3]

WHO position paper key points:[3]

1. All children worldwide should be immunised against tetanus.
2. The aims of tetanus immunisation are:
    a. to achieve global elimination of maternal-neonatal tetanus, and
    b. to ensure life-long protection against tetanus.
3. Every country should seek to achieve early vaccination and timely infant doses (i.e. from 6 weeks of age, third dose given by 6 months of age ideally).
4. To maintain high coverage of a complete three-dose primary series plus a three-dose booster series by adolescence.
5. In order to provide life-long protection, WHO recommends three booster doses with at least 4 years between doses, i.e. given at 12-23 months, 4-7 years and 9-15 years of age.
6. WHO continues to support the use of Td for maternal immunisation in pregnancy (focussing on preventing maternal/neonatal tetanus).
7. In the case of injury, although adequate vaccination should provide sufficient protection against tetanus, physicians may give a dose of Td in addition to other preventative measures if the injury is severe or the patient's previous immunisation history is unreliable. TIG may be needed in addition for prophylaxis in the case of dirty wounds and for incompletely immunised patients.

3 Tetanus epidemiology

Although many unprimed adults may have had opportunities to receive booster doses of tetanus vaccine during their lifetime (through occupational health, previous recommendations for 10-yearly boosters or tetanus-wound prophylaxis), the protection from these doses may wane more rapidly than for individuals who were primed in childhood, increasing their risk of tetanus in older age.

An evaluation of tetanus epidemiology and immunity in Australia found that the burden of tetanus was significant in the elderly: 82/106 (77%) of notifications with recorded date of birth were born before 1939. Of the 70 cases aged over 65 years with sex recorded, 43 were female (incidence rate 1.53 per 100,000 females and 1.19 per 100,000 in males). Immunity in those aged <60 years was high and the overall tetanus incidence declined over 20 years (1993-2010), although there appeared to be under-reporting of hospitalised and fatal cases. Tetanus vaccination was first introduced in Australia to members of the armed forces in 1939 and infants were routinely vaccinated with DTP from 1953 (although booster doses were not introduced until after 1975). In agreement with disease incidence, one in five adults aged over 50 years, particularly females, did not have sufficiently protective levels of antitoxin. The majority of these were born pre-1950 and only one-third of the age groups not targeted by the childhood immunisation programme had received three or more doses of tetanus vaccine.[16] One explanation given for the difference in elderly male and female immunity is that, historically, fewer women were vaccinated during military service or through wound management for occupational accident or life-style-related wounds.

Similarly in the UK, during 2001-2014, all the tetanus-associated deaths occurred in incompletely immunised adults aged over 45 years. Of all the cases with known vaccination history, 8.8% were appropriately immunised for age, 50.0% were partially immunised and 41.2% were unimmunised.[6] A cluster of seven cases in 2003/2004 in the UK was linked to the injection of a contaminated batch of illicit drugs, and ‘people who inject drugs’ are officially identified as a group at increased risk from tetanus.[19]

Milder cases of tetanus were observed in the UK in partially vaccinated individuals. Therefore, as also observed in Australia, the number of cases or deaths due to tetanus may be underestimated if tetanus was not considered as part of the differential diagnosis for hospitalisation due to its rarity. The estimated level of under-notification of tetanus in Australia was 83% during 1998-2006.[6, 16]

The rates of refugees without secure tetanus immunity, entering Germany and other European countries from the Middle East, ranged from 25% in under-18-year-olds, 28.8% in young adults and 64.7% in those aged over 50 years.[20] A proportion of refugees to NZ are immunised through the refugee resettlement programme, however, some entering as asylum seekers may not be fully immunised.[21] Therefore, an awareness around the potential incomplete tetanus immunisation in these groups is important for wound management and catch-up immunisation.

3.1 New Zealand epidemiology

According to the most recently published data from the Institute of Environmental Science and Research (ESR), during 2018 no cases of tetanus were notified.[22] In 2016, one case was notified in a female aged between 60-69 years, and a ‘European or other’ female case aged over 70 years was notified in 2015. The immunisation status of these cases was not published. Between 1997 and 2016, there were a total of 33 cases, including four

unvaccinated children aged younger than 10 years. Two females aged 70 years or older died - one was unvaccinated and the other's vaccination status was unknown.[5] The Immunisation Handbook 2017 reports that of the 32 cases notified between 1997 and 2005, 21 had recorded immunisation status, four were unvaccinated children, 14 unvaccinated adults and three were vaccinated but time since vaccination was unknown.[2] No further details were given about the remaining cases.

4 Safety

Tetanus toxoid, the active component of tetanus vaccines, has been used since the 1930s and its safety is well characterised. The most recent changes to the tetanus vaccine is its use in combination with acellular pertussis, which has been used routinely for immunisation since 2000.

Virtually all the recent literature found evaluated the safety of Tdap combination vaccines in comparison with Td when given as booster doses, or the safety of Tdap for pertussis control when given in pregnancy.

As studies comparing Tdap to Td can only demonstrate the safety of the pertussis component, they have limited relevance to consideration of the safety of tetanus alone. Briefly, no increased risk of potential adverse events (AE) were observed in the US through the Vaccine Safety Datalink database of 61,394 non-pregnant adults and adolescents (aged 11-65 years) who received repeat Tdap doses compared with 7,521 people who received Td after an initial Tdap dose.[12] Similarly, in a US-based phase III clinical trial, the incidence of AEs was similar in young adults (aged 19-30 years) who received a Tdap booster dose 10 years after a dose with either Td or Tdap given in adolescence (AE incidence: Td group 80.6% vs Tdap 85.6%). No serious AE were reported.[13]

Further information on the safety studies is presented in the Appendix in Table 4.

4.1 Booster doses in pregnancy

As the safety of Tdap given in pregnancy was presented in detail in a previous review on pertussis, this section highlights the most recent findings.[23]

4.1.1 Response in pregnancy

Three studies, conducted in the US and NZ, found Tdap to be equally and generally well-tolerated in pregnant and non-pregnant women.[24-26] No serious adverse events (SAE) were reported. As expected, local injection site reactions were common and a small number (<3%) experienced systemic responses such as mild fever, general aches and headache. Pregnant women more commonly reported moderate to severe injection-site pain, although none sought medical attention. One study found that prior Tdap receipt did not increase moderate to severe local or systemic reactions in pregnant women.[24, 25]

Generally, the patients tolerated the vaccination; however, in one US-based study, a small proportion of pregnant women (3%) stated that they would not receive Tdap in subsequent pregnancies due to the response in the current pregnancy.[26] This study did not assess receipt of prior Tdap vaccination within 2-5 years of the study.

Co-administration with either quadrivalent or trivalent influenza vaccine did not appear to increase the risk of local or systemic reactions ($p=0.62$).[25]

Of the 31 SAE reported in the NZ study, none were clinically assessed to be vaccine related.[27]

4.1.2 Pregnancy outcomes

No biologically plausible adverse maternal outcomes were detected following Tdap immunisation in pregnancy given during weeks 28-38 gestation in New Zealand and Tdap vaccination was not associated with unexpected safety risks. A national retrospective observation study, Pertussis Immunisation in Pregnancy Study (PIPS), used linked administrative datasets for a cohort of 68,550 vaccine-eligible women during 2013, of which 8,178 (11%) were vaccinated. A protective effect was observed on pre-eclampsia with severe features, preterm labour, preterm delivery and antenatal bleeding.[25]

4.1.3 Infant outcomes

No safety concerns related to infant outcomes were identified in infants of women who were vaccinated in pregnancy in NZ studies, including PIPS and a small prospective observational study in the Canterbury region of NZ.[25, 28] In the latter study, infants were followed for between 6-12 months after birth and no cases of pertussis occurred in this cohort despite high rates of disease in the community at the time.[28] No significant differences in birth weight, gestational age at birth, congenital abnormalities or infant groups were detected in infants of mothers who received Tdap in pregnancy when compared with the baseline population.[28]

Conclusion

Tdap vaccination in pregnancy is generally well tolerated and has a similar safety profile to that observed in non-pregnant individuals, although a small proportion (3%) of pregnant women who experienced moderate AE stated that they would not consider repeat vaccinations in subsequent pregnancies.

There are no safety concerns around the safety of the mother, the unborn baby or long term effects on the infant.

4.2 Booster doses in children

Benign, transient and usually painless extensive limb swelling (swelling >100mm diameter) has been observed in some children after a fourth school-entry dose of aP-containing vaccine (TdaP or DTaP). A study in the UK found that swelling was more prevalent in children receiving DTaP vaccines than TdaP (>50mm 7.0% TdaP-IPV vs 13.3-17.7% of DTaP-IPV recipients). Local swelling or redness was not associated with a history of atopy.[29] It was concluded that parents need be informed of the possible occurrence of swelling, but be reassured that it is transient. (Note that the TdaP vaccine used in this study contained the same dose of pertussis antigens as the DTaP vaccine, and a higher dose than that used in Tdap in NZ; tetanus content is comparable.)

4.3 Summary of vaccine safety

Booster doses of tetanus vaccine are generally well tolerated when given as Td or Tdap.

Repeat doses of Tdap administered after 10 years do not appear to increase the risk of adverse events. However, the most recent data compared Td with Tdap vaccines and was therefore unable to inform any differences in safety for the tetanus component.

There is limited data around repeat doses given to pregnant women for subsequent pregnancies less than 5-10 years apart. For a few women (less than 3%), adverse events experienced following vaccination in pregnancy may deter them from receiving further doses in future pregnancies.

There are no safety concerns when Tdap is given during pregnancy for the mother, pregnancy outcomes, or for the baby before or after birth.

Extensive limb swelling was seen occasionally in children (in less than of 18% of recipients) following a fourth dose of acellular pertussis-containing immunisation. The swelling was benign, transient and usually painless.

5 Tetanus immunity and vaccine immunogenicity

A definitive correlate of protection has not been established for tetanus since seroprotective titres depend on the type of assay used to assess antitoxin levels. For example, concentrations >0.01 IU/ml are considered protective for toxin neutralising tests and modified ELISA (enzyme-linked immunosorbent assay), whereas for standard ELISAs, antitoxin concentrations of ≥0.1-0.2 IU/ml are considered as protective.[9]

High antibody levels are not guaranteed to provide immunity, since sufficient levels of neutralising antitoxin are required for protection to inactivate the tetanus toxin effectively, especially in necrotic wounds where large quantities of toxin are released. In this situation, in addition to immunisation, wound-care and sterile surgical practices play an important role in the prevention of tetanus.[9]

The presence of antitoxin can protect against death, but mild or non-fatal disease may result from insufficient immunity to neutralise all the toxin. Exposure to the natural pathogen does not generate sufficient immunity - if at all - to be protective.[9]

5.1 Immunogenicity in children

5.1.1 Primary series

A systematic review observed that tetanus antibody levels were substantially lower after two versus three priming doses in infancy. Schedules with longer than 6 months between the second and third doses (e.g. 2+1) provided high antibody titres in the second year of life, and booster doses after three primary doses substantially increased antibody levels (e.g. 3+1 or 3+0 plus preschool booster as in NZ).[3]

Alterations to the DTaP timing in the primary series are likely to depend upon the requirements for pertussis control in infants and the influence of maternal Tdap vaccination of pertussis control; therefore, finding a balance between effective pertussis protection and optimum tetanus protection is necessary. One question that has been raised in terms of pertussis control is whether a booster dose is required in the second year of life in NZ.[23] If this is found to be required, it would provide an extra dose of DTaP and, therefore, six doses of tetanus vaccine in childhood.

5.1.2 Preschool booster dose

A post-hoc analysis of data from a five-year follow-up study investigating pertussis immunity in the UK estimated that 82%, 86% and 69% of children (aged 3.5 years to 5th birthday at time of vaccination) would have seroprotective antitoxin levels 9 years after receiving a booster with Tdap-IPV, Tdap-OPV and DTaP-IPV, respectively. The observed rate of decline in antitoxin levels was the same for each group, although those in the DTaP-IPV group had lower tetanus antibody levels 3 and 5 years after the booster. Regardless of the treatment group, it was predicted that the children would maintain good protection against tetanus up to the time of an adolescent booster.[30]

5.2 Conjugated vaccine carrier protein effects

Certain vaccines contain carrier proteins conjugated to bacterial capsular polysaccharides to enhance immunogenicity and to generate immune memory. Tetanus toxoid is used as the carrier protein for some components of conjugate vaccines. Since these carrier proteins are antigenic, they can influence immunity to these antigens – positively and negatively.[4]

A quadrivalent meningococcal conjugate vaccine with a TT-carrier (ACWY-TT) was shown to induce a robust TT-specific T-helper cell response in middle-aged adults (aged 50-65 years), decades after previous tetanus vaccinations.[14]

Associated with group A meningococcal vaccination campaigns in Sub-Saharan Africa, which used a meningococcal vaccine conjugated to TT in individuals aged 1-29 years, the cases of neonatal tetanus declined by 25%, consistent with the hypothesis that TT-conjugated vaccines have an impact on tetanus immunity.[31]

The administration of the TT-conjugated vaccines available in NZ, such as PCV-10 (Synflorix®), Hib (Act-Hib®) or MenC (NeisVac-C®) or MenACWY (Nimenrix®), may also enhance tetanus immunity. However, these vaccines are generally given in infancy so there is unlikely to be long-lasting enhancement of immunity into adulthood and it may depend on the age at which the first dose was given.[3]

5.3 Duration of immunity in adults and requirement for booster doses

Serological studies to date have suggested that the three-dose primary series of a TT-containing vaccine given in infancy plus a booster during the second year of life, provide 3-5 years of protection against tetanus. A further booster given in early childhood provides protection into adolescence and then a further booster in adolescence induces tetanus immunity that lasts for much of adulthood.[3]

After six doses of TT-containing vaccine, antibody levels (GMT 0.44 IU/ml) were shown to persist for at least 20 years (as measured in adults aged 30-34 years) and protective levels (0.22 IU/ml) have been predicted by regression analysis to persist until 90 years of age.[3]

However, tetanus antibody levels decline and titres may not persist to provide sufficient protection into older age after five doses, as compared to receiving six doses.[3] Although some countries, including the UK, consider five doses to be sufficient to protect throughout the life course, it is argued that this decision is based on the vaccination history of tetanus cases and does not identify fully the number of susceptible individuals within a population, particularly when the sample size of cases is very small. The WHO recommends at least one booster dose to be given in adulthood.[3]

5.3.1 Decennial booster doses

In NZ, adults are no longer recommended to have tetanus booster vaccinations every 10 years. For most individuals this was considered to be unnecessary and resulted in over immunisation.

Certain groups, particularly those in healthcare, will continue to receive 10-yearly booster doses of Tdap to protect their patients (infants and high-risk individuals) and themselves from pertussis, rather than tetanus. Other individuals may receive tetanus doses frequently if at increased risk of tetanus-prone injuries and exposure to tetanus – such as veterinary, animal husbandry, construction and farm workers.

A question remains as to whether tetanus immunity is sufficiently long-lived in individuals who may not have been adequately primed (due to low immunisation coverage or changes to the Schedule) and whether decennial boosters are necessary to maintain protective antitoxin levels. Recent studies have demonstrated that 10-yearly tetanus vaccine booster doses are unlikely to be necessary up to the age of 60 years. Generally, within adult populations the immunity to tetanus is adequate.

A study in the US found that antitoxin levels averaged 3.6 IU/ml and over 96% of participants younger than 60 years have antitoxin levels above 0.15 IU/ml.[11] However, as reported elsewhere, this study observed that older adults (aged >50 years) were more likely to lack protective tetanus immunity.

The half-life of tetanus-specific antibody was estimated to be 14 years (95% CI 11-17) overall, as a function of time since last vaccination and not statistically different for those older or younger than 50 years. A mathematical model using duration of protection and rate of antitoxin titre decline parameters, predicted that 95% of the adult population would continue to be serologically protected against tetanus for 64 to 72 years after their last vaccination without additional booster vaccinations.[11]

Following the completion of five-dose or more primary series, decennial boosters are unnecessary for up to 20 years. However, testing for tetanus immunity may be necessary prior to tetanus wound prophylaxis since the proportion of unprotected individuals increased from 5.8% to 16.1% after 15 years.[10, 32]At 10 years since the last dose of tetanus vaccines, most participants (95.0%) in an Italian serological study had protective tetanus antibody levels (≥0.1 IU/ml) and half (49.1%) had long-term protective titres (>1.0 IU/ml). Titres depended significantly on number of prior doses and time since last dose ($p<0.0001$). Five vaccine doses and an interval of at least 10 years since the last dose were predictive of a long-term protective titre in the absence of a booster.[10, 32]

In a letter in response to this study, caution was urged in the case of tetanus-prone wounds since over 16% of individuals were unprotected after 15 years. The letter cited a case of tetanus in a fully-immunised 50 year old man who was wounded 17 years after his previous tetanus dose.[33]

Conclusions

In fully-primed individuals, tetanus immunisation provides long-lasting immunity. The level of antitoxin is significantly dependent on the number of prior doses and the time since the previous dose.

Caution is required when estimating vaccine effectiveness based on serology. It has been shown in fully-primed individuals that a long-lasting, amnestic response is induced by booster doses of tetanus-containing vaccine, even when antibody levels have waned below purported seroprotection, demonstrating immunity - but not necessarily protection from the effects of the toxin.

Decennial booster doses are not necessary in fully-primed adults. However, immunity cannot be assumed for those 10 – 15 years since last dose when treating tetanus-prone wounds. Some wounds are more heavily contaminated or there may have been longer delays in seeking medical attention, thus requiring a greater level of antitoxin to neutralise the large quantities of tetanus toxin that may have been released.

5.4 Tetanus immunity in the elderly

A need to review the immunisation status and booster requirements for older adults was highlighted in a previous literature review to inform the New Zealand National Immunisation Schedule.[4]

The US-based study mentioned above also recommended tetanus vaccination for adults aged over 60 years, because this age-group has the majority of unprotected individuals and those who may not have received a full primary series.[11]

As well as rare cases of tetanus in unvaccinated children, adults born prior to the implementation of wide-spread childhood immunisation programmes in the 1950s and 60s are expected to be at higher risk of tetanus, particularly women. Older people have increased risk of contaminated, anaerobic wounds due to slower healing times, amplified by conditions such as poor circulation due to diabetes and cardiovascular disease. According to the US Centers for Disease Control and Prevention (CDC), the risk of dying from tetanus is five-times greater in patients older than 65 years.[3]

Although tetanus vaccine has been available since the 1920s, and the majority of adults were vaccinated during childhood, the number of vaccines doses given as part of the Schedule decreases with age. A review of literature identified that older people are likely to have had fewer tetanus doses in their lifetime than those aged <30 years, and documentation for booster doses is often incomplete.[34]

Clinical trials conducted in Austria found that for some adults who may not have received sufficient priming doses, a single tetanus vaccine booster dose may not provide long-lived tetanus seroprotection. All participants aged ≥60 years produced a protective anamnestic response 4 weeks after a booster dose of Tdap-IPV. Vaccination against tetanus had been received by 64% of the participants during the previous 10 years, however, antibody concentrations fell below protective levels in 10% of participants prior to a second booster dose given after 5 years.[35]

A serum survey in Europe found that between 2-31% of adults of various ages had anti-toxin concentrations lower than 0.1 IU/ml protective levels and these levels decreased with age. Tetanus-specific antibodies were generally higher in males than females, thought likely due to military service vaccinations or booster doses given following injury, although no gender differences were observed for anti-diphtheria antibodies.[36]

Following a review of tetanus immunity in Ireland, it was concluded that the use of tetanus booster doses be explicitly advocated, especially for the elderly and those who travel between countries, outside of the normal vaccination programme. Tetanus immunity significantly reduced with increasing age, and the mean age of non-immune adults was 20 years older than immune adults (66 versus 46 years). As age increased by 10 years, there was an associated 50% reduction in immunity.[37]

5.5 Summary

The NZ Schedule provides five doses to adolescents and no further doses are provided, unless given as Tdap in pregnancy or as part of wound management, until the age of 45 years and then at 65 years.

It is likely many adults, particularly those aged over 60 years, are at higher risk from tetanus due to waning immunity and, even if classified as fully immunised, are not likely to have received as many doses as part of their primary series as children receive now. In NZ, the primary series from 1960 contained four doses. The adolescent dose was not introduced

until 1980 for 15-year-olds (described in Table 1). Additionally, at least one quarter of the current adult population in NZ were born overseas and therefore, it cannot be guaranteed how many primary doses were administered for all adults.

In adults who were primed in childhood according to previous schedules with fewer than five childhood doses, the current recommendation for booster doses to be given at 45 years and 65 years appears necessary. The need for a booster dose at 45 years is likely to be less important than the 65-year old dose, and is expected to lessen further with time as more 45-year-olds receive five or more doses in childhood and vaccine uptake in pregnancy increases.

In fully-primed individuals, tetanus immunity is likely to remain for several decades. However, it is unclear whether there would be sufficient antitoxin levels to provide adequate toxin neutralisation in the case of injury. Treatment and management of wounds remains important in the control of tetanus, as well as routine tetanus vaccination.

6 Wound management

In this section, recent literature around wound management and tetanus post-exposure prophylaxis is considered. The incidence of tetanus is highest in older adults in NZ, which likely reflects lower tetanus immunity, fewer tetanus vaccine doses included in earlier immunisation schedules, and historically low immunisation coverage. This indicates a need for greater awareness and assessment of tetanus prophylaxis requirements for all wounds in these older age groups.

Tetanus booster vaccination is recommended for fully immunised individuals with dirty wounds (or wounds older than 6 hours) sustained more than 5 years after previous tetanus vaccination or with clean wounds (within 6 hours of injury) sustained more than 10 years after previous tetanus vaccination. A full schedule should be completed for those who have not received all the recommended doses of the primary schedule in order to provide long-term protection. In most adults, a third dose given 6-12 months after the first two doses induces high-levels of long lasting tetanus-specific antibodies.[3]

The prophylaxis required to prevent tetanus developing from wounds depends on the nature of the injury and the patient's immunisation history. In NZ, the standard practice is to clean and debride a dirty wound. In incompletely immunised patients, passive immunisation with tetanus immunoglobulin (TIG) is recommended followed by tetanus vaccination.

Although tetanus definition in adults requires a history of injury or wound, tetanus may occur in individuals with no recall of a specific wound.[3]

Health providers are recommended to assess the vaccination status of patients with wounds (even minor wounds or abrasions), in particular those at increased risk of tetanus, including older adults, injection-drug users, patients with diabetes and those with chronic wounds. A Californian Public Health Department study identified 21 patients (aged 21-89 years) hospitalised with tetanus and only 16 had knowledge of a prior acute injury. Nine sought medical attention and only two received appropriate post-exposure prophylaxis. Of those for whom tetanus vaccine history was recorded, nine (75%) recalled receiving at least one tetanus vaccine dose, six had received their last doses 10-50 years before illness, and the remaining three could not recall when they received the last dose.[38]

Unimmunised children are also at risk from tetanus. A retrospective chart review study in NZ recommended early wound debridement to be emphasised to prevent further toxin release and for physicians to be alert to this disease in unimmunised children. Four unimmunised

children aged 16 months to 9 years were admitted for tetanus to Starship Children's Hospital during 2000 to 2013. All four required ventilator support in the paediatric intensive care unit (PICU) with a length of stay of 2.5 to 7 weeks. Unfortunately, three of the four remained partially or completely unimmunised despite the severity of illness.[39]

Tetanus is rare in urban environments, however, natural disasters increase the risk of tetanus-prone injuries due to compounding factors that include types of injuries, lack of medical services and supplies, and treatment delays. During such events, those injured may be unable to provide reliable evidence of vaccination history. An investigation of literature around wound care guidelines, prophylaxis and treatment of tetanus was conducted that identified low immunisation rates increase the incidence of disease, and have a higher mortality rate during large-scale natural disasters. The authors concluded that it is important for urban doctors, caring for trauma and critical patients, to be familiar with protocols and treatment of patients with tetanus-prone wounds, particularly in the settings of major natural disasters. They recommended that when resources are limited, for TIG to be reserved for those least likely to have good immunity.[15]

6.1 Summary for wound management

There is a general consensus in the literature that the management of tetanus-prone wounds requires debridement and cleaning of the wound to reduce the level of contamination to prevent the release of tetanus toxin.

In some situations, individuals are at increased risk of tetanus due to delays in treatment, being under-immunised, or being immune deficient. Older adults are at highest risk of tetanus even from minor wounds that would not ordinarily be classified as tetanus-prone, due to poor tissue circulation and oxygenation, and waning immunity.

In the case of infected wounds in older adults, booster doses of vaccine are likely to be more necessary than perhaps for younger individuals with adequate immunisation history.

Mild cases of tetanus are likely to be undiagnosed and under-reported through passive surveillance. Therefore, the risk of tetanus morbidity may be higher in those with tetanus-specific immune memory, but low serum antibody titres.

Evidence suggests that it is important to assess the vaccination history of all individuals presenting with wounds, even minor ones, particularly those with delays in seeking medical attention.

No literature was found that presented evidence for changes to current wound management policies or frequency of booster doses in the case of tetanus-prone injury.

7 International policy and practice

WHO recommendations are for six doses of a tetanus toxoid containing vaccine in childhood – three primary doses and three booster doses (second year of life, preschool and adolescence). The scheduling of tetanus vaccinations are mainly related to pertussis immunisation since all developed countries provide combination vaccines containing diphtheria, tetanus and pertussis antigens. This section presents the Schedules for tetanus immunisation and wound management recommendations of the US, Canada, Australia and the UK, and summarises the immunisation schedules for selected European countries.

An overview of the international recommendations is presented in Appendix Table 3

7.1 United States

The Advisory Committee on Immunization Practices (ACIP) in the US recommends three primary doses of DTaP starting at 2 months of age, and DTaP boosters at 15 months and 4-6 years and a Tdap booster at age 11-12 years.[40] In adults, the first tetanus dose is recommended to be Tdap for those who had not previously received Tdap as an adult or child (at 11-12 years) followed by Td boosters given every 10 years. Tdap is recommended in each pregnancy, preferably during the early part of 27-36 weeks gestation. Tdap or Td are also provided as part of wound management for tetanus prophylaxis more than 5 years after the last vaccine dose.[41]

ACIP recommendations for wound management are in line with those in NZ.[42] TIG is recommended for individuals with contaminated wounds who are HIV positive or have severe immunodeficiency regardless of their tetanus immunity.

7.2 Canada

The Canadian schedule varies by province, but generally, doses of DTaP-containing vaccine are recommended at 2, 4, 6 and 18 months of age; a preschool dose of Tdap-IPV is recommended at age 4-6 years; and a Tdap booster is given between ages 11 to 16 years at school.[43-45]

In Canada, TIG is recommended for individuals with wounds, other than clean minor wounds, who are known to have a humoral immune deficiency state.[45]

7.3 Australia

The Australian Government provide three doses of DTaP-IPV-HepB/Hib from 6 weeks, 4 and 6 months of age; booster doses at 18 months and 4 years of DTaP-IPV; and Tdap as part of a school-based programme from 10-15 years. Tdap is also recommended in pregnancy between 28-32 weeks gestation (currently under consultation to commence from 20 weeks for pertussis protection). Booster doses are recommended at the age of 50 years or older for anyone who has not received a tetanus dose in the past 10 years (and has completed a three-dose primary course). Booster doses are also given for tetanus-prone wounds acquired 5 or more years since the last dose.[46, 47]

7.4 United Kingdom (UK)

The primary schedule (recommended up to 10 years of age) is DTaP-IPV-HepB/Hib at 8, 12 and 16 weeks, and DTaP-IPV at the age of 3 years and 4 months. A booster dose of Tdap-IPV is give at 14 years of age. In pregnancy, Tdap-IPV is available from 16 weeks gestation (ideally 20 weeks for pertussis control).[19]

Since people who inject illicit drugs are at increased risk from tetanus, it is recommended that every opportunity is taken to ensure they are fully protected and booster doses should be given if there is any question of the immunisation status.[19]

Public Health England recommends that anyone with uncertain immunisation history and/or born before the introduction of routine immunisation (1961) who may not have received an adequate priming course, should receive both TIG and a booster dose of tetanus vaccine in the case of a tetanus-prone injury.[19]

8 Appendix

8.1 History of tetanus vaccination in New Zealand

Tetanus toxoid has been used for immunisation in New Zealand since the 1940s and the 'triple vaccine' containing diphtheria, tetanus and whole-cell pertussis became funded as part of the National Immunisation Schedule in 1960. Over the decades, the number of doses given in childhood has increased. However, it is unknown how well protected the NZ population is as a whole. Based on incidence, protection is high and disease cases are predominantly seen in unimmunised young children and unvaccinated or partially immunised older adults.[1, 2]

Table 1: Tetanus immunisation programmes and practices: history in New Zealand (adapted from 2017 and 2006 Immunisation Handbooks, Ministry of Health)

Year	Programmes	Target population
1940-1955	TT available as voluntary vaccination	Often used in military service
1958	DTwP – schedule commences	Childhood
1960	DTwP – funded by general practices	Routine childhood schedule 3, 4, 5 months, DT at 5 years
1964	DT (adsorbed) booster added	18 months (4-month dose removed, but reintroduced in 1980)
1980	Monovalent TT at 15 years replaced DT at 5 years	Adolescents
1994	Td replaced TT, 10-yearly boosters recommended DTaP-Hib introduced	Adolescents / Adults Infants
1996	Td booster changed from 15 years to 11 years	Adolescents
2000	DTaP replaced DTwP	Infants
2002	Adult boosters replaced 10-yearly boosters Childhood schedule	45 and 65 years 6 weeks, 3 and 5 months, 15 months, 4 years, 11 years.
2006	Tdap-IPV changed to Tdap only in 2008 DTaP dose discontinued at 15 months	Adolescents 11 years 6 weeks, 3 and 5 months, 4 years
2013	Tdap in pregnancy	Funded during 28-38 weeks pregnancy
2014	Td revaccination	Funded following immunosuppression
Abbreviations: TT – tetanus toxoid; DTaP - combined diphtheria, tetanus and acellular pertussis vaccine; DTwP – combined diphtheria, tetanus and whole-cell pertussis vaccine; Td – tetanus and reduced dose diphtheria vaccine; Tdap – tetanus, diphtheria and acellular pertussis; IPV – inactivated polio vaccine; Hib – *Haemophilus influenzae* type B		

8.2 Tetanus toxoid containing vaccines available in New Zealand

The contents of the currently licensed tetanus-containing vaccines available in NZ are provided in Table 2.[48-52]

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

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

8.3 Summary of international recommendations

Table 3: Summary of international immunisation recommendations for tetanus vaccines, as of 2018

Country	Age of vaccination	Total number of doses in childhood	Special recommendations
USA	2, 4, 6, 15-18m 4-6y, 11-12y	6	Pregnancy 27-36gw Td boosters every 10 years, Tdap first booster if not previously received
Canada	2, 4, 6m, 18m 4-6y, 13-16y	6	One aP dose per adult life-time Pregnancy from prior to 36 gw (ideally 27-32 weeks)
Australia	6w/2, 4, 6m, 18m 4y, 10-15y	6	Pregnancy third trimester (28-32gw ideal)
NZ	6w, 3, 5m 4y, 11y 45y, 65y	5	Pregnancy 28-38gw Tdap
Austria	2, 4, 11m 6y, 12y	5	Tdap-IPV every 10 years from age 18-60y, unfunded Tdap 12y, if received Td-IPV at 7-9y
Denmark	3, 5, 12m 5y	5	
France	8w or 2, 4, 11m 6y, 11-13y	5	Mandatory primary series Tdap-IPV booster at 25y if no pertussis-containing booster given in previous 5 years (until age 39y)
Germany	2, 3, 4, 11-13m 5-6y, 9-17y	6	From 18y, first booster as Tdap, then Td 10-yearly
Portugal	2, 4, 6, 18 months 5 , 10 years 25, 45 and 65 years	6	Tdap in pregnancy 20-36 gw
UK	2, 3, 4m 3y 4m 13-14 years	5	Tdap-IPV in pregnancy from week 16 (ideally from 20gw)
Abbreviations: w – weeks; m – months; y – years; gw – gestation weeks; Tdap – tetanus-diphtheria-acellular pertussis vaccine; IPV – inactivated polio vaccine			

8.4 Summary of evidence reviewed

Table 4: Summarised details of studies reviewed

Study type	Findings	Participants	Reference
SAFETY			
Vaccine Safety Datalink data analysis	No increased risk of adverse events from repeat doses of Tdap or Td following previous Tdap	68,195 aged 11-65 years, non-pregnant (US)	[12] Jackson, 2018
Phase III RCT	Similar incidence of AE following Tdap booster given 10 years after booster doses with either Td or Tdap in adolescence. Injection site pain most common.	165 adults aged 19-30 years (US)	[13] Kovac, 2018
Pregnancy			
Prospective observational	Tdap equally well tolerated in pregnant and non-pregnant women. Moderate to severe injection site pain reported more frequently by pregnant women. Injection site pain reported in more pregnant than non-pregnant women (17.0% vs 11.1%), but did not seek medical attention, 3% reported systemic or more severe local reactions.	374 pregnant and 225 non-pregnant women (US)	[24] Fortner, 2018
	67% reported at least one AE, 25% reported two or more (pain, swelling or redness at injection site and generalised aches, fever); 3% intended to decline Tdap in future pregnancies. Prior receipt of Tdap within 2-5 years not assessed.	737 pregnant women (Netherlands)	[26] Perry, 2017
	None of 31 SAE were related to vaccine. Following Tdap, 79% participants reported mild or moderate injection-site pain, 2.6% reported severe pain. Of the participants, 27.9% were given trivalent seasonal influenza vaccine concurrently. Other adverse events reported included swelling and redness at injection site (7.6% and 5.8%), fever (2.1%) and fewer than 4% reported headache, dizziness, nausea, myalgia or arthralgia, and 8.4% reported fatigue.	793 pregnant women (NZ)	[27] Petousis-Harris, 2016

Study type	Findings	Participants	Reference
Retrospective, cohort observational, Data-linking	No unexpected safety risks to mother associated with Tdap in pregnancy. Protective effect observed for preterm outcomes. No safety concerns identified for infant outcomes of mothers given Tdap in pregnancy.	Cohort 68,550, including 8,178 vaccinated (11%) and 60,732 unvaccinated pregnant women (NZ)	[25] Griffin, 2018
Prospective observational	No safety concerns identified for infant outcomes of mothers given Tdap in pregnancy.	403 infants of vaccinated mothers (NZ)	[28] Walls 2016
Children			
Prospective observational	Transient extensive limb swelling is a possible occurrence following fourth-dose vaccination with DTaP or TdaP in preschool children. Swelling>50mm reported in 7.0% TdaP-IPV group vs 13.3-17.7% of DTaP-IPV recipients. (Note: TdaP has a greater pertussis antigen content than Tdap)	973 children (UK)	[29] Southern, 2017
IMMUNOGENICITY AND IMMUNITY			
Children			
Systematic review	Antitoxin levels significantly lower following two primary doses than three. A third dose given 6 months after dose two provides high antibody titres in second year of life. A booster after three primary doses induces significantly higher antibody levels		[3] WHO, 2017
Post hoc analysis	Good antibody protection likely to be maintained to adolescence following preschool booster with Tdap-IPV or DTaP-IPV. Seroprotective antitoxin levels (≥0.1 IU/ml) predicted nine years after booster in 83% (74-90) of Tdap-IPV recipients and 69% (95% CI 58-79) of DTaP-IPV recipients.	Data from 5-year follow-up of RCT, from 300 children (aged 3.5-5 years) at time of original RCT with 53% loss-to-follow-up overall (UK).	[30] Voysey, 2016

Study type	Findings	Participants	Reference
Adults			
Cross-sectional analysis	10-yearly boosters unnecessary in adults, since more than 97% of immunised adult population were potentially seroprotected against tetanus; 99% ≤60 year-olds had antitoxin titres ≥0.01 IU/ml. (97% for overall population); 96% of population antitoxin titre was ≥0.15 IU/ml). Average antitoxin titre was 3.6 IU/ml. Half-life of tetanus antitoxin estimated to be 14 years (95% CI 11-17). Adults over 60 years were recommended tetanus vaccination. Mathematically modelling predicted duration of protection since last booster would be 64-72 years in 95% of adult population.	546 adults, age range 19-87 years, mean 49 years. (US), recruited during 2002-2008 (previous vaccine experience not given)	[11] Hammarlund,2016
Prospective observational	At 10 years since the last dose of tetanus vaccine, most participants (95.0%) had protective antibody levels (≥0.1 IU/ml) and had long-term protective titres (>1.0 IU/ml). Antitoxin titres depended significantly on number of prior doses and time since last dose ($p<0.0001$). Five previous doses of tetanus vaccine and at least 10 years since last dose were predictive of long-term protective antibody titre (1.99 IU/ml). Unprotected individuals were predicted to rise from 5.8% to 16.1% after 15 years. Following completion of primary series, booster doses were unnecessary for up to 20 years. Caution required around tetanus wound prophylaxis and recommended testing for tetanus immunity.	1,433 university staff and students (Italy)	[10] Borella-Venturini, 2017
Older adults			
Literature review	Older adults were likely to have received fewer doses of tetanus vaccine in their lifetime compared with adults aged less than 30 years, although booster documentation was often incomplete.		[34] Weinberger, 2017

Study type	Findings	Participants	Reference
Explorative clinical trial	Tdap-IPV boosters induced a protective anamnestic response in all participants, amongst whom 12% of participants aged ≥60 years did not have seroprotective antitoxin levels (<0.1 IU/ml) and 64% had received tetanus vaccination within 10 years. Antitoxin levels fell below protective levels in 10% of participants with over 5 years between Tdap-IPV booster doses. Insufficient priming may mean that single booster doses may not provide long-lived protection in older adults.	252 adults age ≥60 years (Austria)	[35] Weinberger 2013
Serum survey	2-31% of adults did not have protective antitoxin levels (<0.1 IU/ml), and these levels decreased with age. Antitoxin levels were generally higher in males than females.	2,100 samples (six European countries)	[36] Weinberger 2018
Serum survey	Immunity to tetanus significantly reduced with age ($p<0.001$). Proportion of immune adults decreased by 50% for each 10 year increase in age. Mean age of non-immune adults was 66 years compared with 46 years for immune adults. Advocate booster doses for the elderly. No significant difference between genders ($p=0.94$).	216 blood samples from patients in ED, unrelated to injury (Ireland)	[37] Moughty 2013
WOUND MANAGEMENT			
Retrospective chart review	Early wound debridement and being alert for tetanus are important to reduce the risk of tetanus in unimmunised children. All four cases required PICU care for ventilator support, mean length of stay 2.5 to 7 weeks.	Four hospitalised tetanus cases aged 16 months to 9 years. Chart review of those aged 0-15 years between 2000-2013 (NZ)	[39] Wen, 2016

Study type	Findings	Participants	Reference
Observational	Study identified 16 out of 21 tetanus cases had knowledge of a prior injury; only nine sought medical care, of which two received post-exposure prophylaxis. For those with recorded tetanus vaccine history, three (25%) did not recall having received tetanus vaccine; nine (75%) had ≥1 dose, of which six were 10-50 years since their last dose and three had no recall of when the last dose was given. Study recommended assessment of vaccination status of patients with all wounds (even minor), particularly older adults, injecting drug users, patients with diabetes and those with chronic wounds.	21 hospitalised tetanus cases, age range 21-89 years (US)	[38] Yen, 2015
Literature review	Large-scale natural disasters increase risk of tetanus, particularly in under-immunised populations and where there is a delay in obtaining treatment.		[15] Finkelstein, 2017

8.5 Methodology for review

8.5.1 Literature search strategy

The aim of the literature review was to find literature to answer certain questions around tetanus immunisation in the NZ context. It was not a systematic review. Literature searches were limited to recent data published since 2016 when a review was conducted on the childhood schedule. Wider searches were conducted as necessary related to specific questions or for literature cited in the articles found.

Medline search terms and strategy

Medline

1. *Tetanus / or diphtheria-tetanus-pertussis vaccine or *diphtheria-tetanus-acellular pertussis vaccines/ or*diphtheria-tetanus vaccine/ 10023
2. Limit English humans 2015-2018 - 505
3. Wound management keyword 2773
4. Limit English humans 2015-2018 - 364
5. #2 AND #4 = 3 discarded (pertussis focussed)

1. Tetanus/ and adult/ and vaccination/ 553
2. Limit English humans 2015-2018 70
3. Aged/ and Tetanus/ and Adolescent/ and Vaccination/ 72
4. Limit 2015-current English humans [5/12/18] 4 – discarded

1. Tetanus / pc [Prevention & Control] 1515
2. Limited 70

Discarded references on neonatal tetanus control in developing countries.

Cochrane Library search terms and strategy

Abstract – wound management
AND keywords tetanus toxoid; tetanus vaccine; or tetanus immunisation
Jan 2013 – Jan 2019 reviews – nothing found.

Additional searches

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

Final Endnote Library 119 Articles and reference sources

Where systematic reviews and/or meta-analyses were available the preceding literature was excluded from the review, unless the reviewed literature was accessed to provide further details. A total of 93 journal articles were included. The remainder were government guidelines, data sheets or official websites.

8.5.2 Study designs

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

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