New Zealand Veterinary Journal

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/tnzv20

Tetanus prophylaxis in horses: guidelines for New Zealand and Australia based on a critical appraisal of the evidence

AL Lovett, CB Riley, V Chapman, B Bell, B Bishop, A Grierson, LJ Johnstone & BW Sykes

To cite this article: AL Lovett, CB Riley, V Chapman, B Bell, B Bishop, A Grierson, LJ Johnstone & BW Sykes (2024) Tetanus prophylaxis in horses: guidelines for New Zealand and Australia based on a critical appraisal of the evidence, New Zealand Veterinary Journal, 72:5, 241-255, DOI: 10.1080/00480169.2024.2365283

To link to this article: https://doi.org/10.1080/00480169.2024.2365283

NEW ZEALAND VETERINARY JOURNAL
2024, VOL. 72, NO. 5, 241–255
https://doi.org/10.1080/00480169.2024.2365283

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Tetanus prophylaxis in horses: guidelines for New Zealand and Australia based on a critical appraisal of the evidence

AL Lovett [a], CB Riley [a,b], V Chapman[c], B Bell[d], B Bishop[e], A Grierson[f], LJ Johnstone [a] and BW Sykes [a]

[a]Tāwharau Ora – School of Veterinary Science, Massey University, Palmerston North, New Zealand; [b]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada; [c]Zoetis New Zealand Ltd., Auckland, New Zealand; [d]VetSouth Equine, Invercargill, New Zealand; [e]Canterbury Equine Surgical Consultancy Ltd., Prebbleton, New Zealand; [f]Auckland Veterinary Centre, Takanini, New Zealand

ABSTRACT

Horses are exquisitely sensitive to tetanus neurotoxin and are exposed to the risk of infection with *Clostridium tetani* throughout life. The vaccine against tetanus is highly effective at preventing disease, whereas tetanus in unvaccinated populations is associated with high mortality rates. Current guidelines in New Zealand and Australia for the available vaccine contain contradictions and limitations surrounding the optimal tetanus immunisation protocols for both adult horses and foals. This review critically evaluates the scientific literature on tetanus prophylaxis in horses within the context of equine practice and available products in New Zealand and Australia. The review was conducted by a panel of industry and specialist veterinarians to obtain agreement on nine equine tetanus prophylaxis guidelines for practising veterinarians. The primary protocol for tetanus toxoid (TT) immunisation consists of a three-dose series IM for all horses ≥ 6 months of age, and a four-dose series IM is proposed if commencing vaccination in foals between 3 and 6 months of age. Tetanus prophylaxis in foals < 3 months of age relies on passive immunity strategies. Following the completion of the primary protocol, a TT booster dose IM should be administered within 5 years, and every 5 years thereafter. When followed, these protocols should provide adequate protection against tetanus in horses. Additional tetanus prophylaxis guidelines are provided for veterinarians attending a horse experiencing a known "risk event" (e.g. wound, hoof abscess, surgery, umbilical infection). When a correctly vaccinated horse experiences a risk event, pre-existing immunity provides protection against tetanus. When an unvaccinated horse or one with unknown vaccination status, or a foal born to an unvaccinated dam, experiences a risk event, TT IM and tetanus antitoxin (TAT) 1,500 IU SC should be administered simultaneously at separate sites, and the TT primary immunisation protocol should subsequently be completed for the horse's respective age. In previously immunised pregnant broodmares, a TT booster dose administered 4–8 weeks prior to parturition optimises the transfer of passive immunity against tetanus to the newborn foal via colostrum; provided that post-natal IgG concentration in serum is > 800 mg/dL (8 g/L), such foals should be passively protected against tetanus up to 6 months of age. Survivors of clinical tetanus must still receive the primary protocol for vaccination against tetanus. In summary, all horses in New Zealand and Australia should be vaccinated against tetanus with protection maintained throughout life via TT booster doses, facilitated by accurate medical record keeping and client education.

Abbreviations: AAEP: American Association of Equine Practitioners; FTPI: Failure of transfer of passive immunity; Lf: Limes flocculation; TAT: Tetanus antitoxin; TT: Tetanus toxoid

ARTICLE HISTORY
Received 18 June 2023
Accepted 19 May 2024

KEYWORDS
Vaccine; toxoid; antitoxin; horse; foal; immunisation; *Clostridium tetani*

Introduction

Tetanus is caused by *Clostridium tetani*, a spore-forming, Gram-positive bacillus that is ubiquitous in the environment worldwide (Popoff 2020). As tetanus is not contagious, cases tend to be sporadic (Barquero *et al*. 2007). In equids, *C. tetani* typically gains access to the body via wounds, hoof abscesses, surgical incisions (e.g. castration) and infected umbilici in neonates (Van Galen *et al*. 2017; Ribeiro *et al*. 2018). *Clostridium tetani* can also be detected in the gastrointestinal tract of domestic animals, including horses (Wilkins *et al*. 1988; Basta *et al*. 2018). In many clinical cases, no "access point" is identified (Van Galen *et al*. 2017; de Melo and Ferreira 2022; Dennis *et al*. 2022). An anaerobic tissue environment is required for this obligate anaerobe to sporulate, proliferate and produce toxins, and horses are exquisitely sensitive to the principal tetanus neurotoxin, tetanospasmin (Popoff 2020). Once transported

CONTACT AL Lovett a.lovett@massey.ac.nz
Supplemental data for this article can be accessed online at https://doi.org/10.1080/00480169.2024.2365283.

to the spinal cord, tetanospasmin irreversibly blocks neurotransmitter release from inhibitory internuncial neurons (Lalli *et al*. 2003), resulting in tetany – an extremely painful state (Cook *et al*. 2001). Incorporation into an immune-privileged location and the irreversible mechanism of disease limits the efficacy of treatment (Duchen and Tonge 1973; Cook *et al*. 2001; Van Galen *et al*. 2017). Documented fatality rates in treated equine cases of tetanus range from 24% to 76.3% (Kay and Knottenbelt 2007; Reichmann *et al*. 2008; de Melo and Ferreira 2022), with higher fatality rates reported in unvaccinated horses (Reichmann *et al*. 2008; Ribeiro *et al*. 2018). Reducing the welfare impacts of tetanus on horses is dependent on the effective use of tetanus prophylaxis strategies.

In New Zealand and Australia, two tetanus prophylaxis products are licensed for use in horses: the vaccine tetanus toxoid (TT; Equivac T or Equivac 2in1), and the serum-product tetanus antitoxin (TAT; Equivac TAT) (both Zoetis New Zealand Ltd., Auckland, NZ; Zoetis Australia Pty Ltd., Rhodes, NSW, Australia). *Equine Vaccination Guidelines for New Zealand* was released by Zoetis New Zealand Ltd. in 2014 and a diagram *When Should I Vaccinate My Horses?* was released by Zoetis Australia Pty Ltd. in 2016; both items are based on the 2012 *Australian Equine Infectious Diseases Advisory Board Vaccination Guidelines* (Pfizer 2012). These documents contain guidelines that are inconsistent with Zoetis' manufacturer labels. The label on the TT product in both countries itemises a primary course of two doses, 4 weeks apart, then states that a subsequent booster given a year later will produce "long-lasting immunity," yet advises to booster "particularly in valuable animals" approximately every 5 years. The manufacturer's quinquennial booster recommendation was possibly extrapolated from original studies in the 1970s and 1980s (Löhrer and Radvila 1970; Liefman 1981). In contrast, schematics in the aforementioned New Zealand and Australian guidelines recommend a booster dose annually (Pfizer 2012; Zoetis 2014, 2016). Thus, there is a need to examine the evidence behind tetanus prophylaxis strategies in New Zealand and Australia.

The manufacturer labels and current equine vaccination guidelines for New Zealand and Australia produced by Zoetis (Zoetis 2014, 2016) lack details regarding vaccination of horses < 6 months old and do not consider the vaccinal status of the dam. The American Association of Equine Practitioners (AAEP) guidelines for North America (not peer-reviewed) describe differing TT protocols for foals born to vaccinated dams (start at 4–6 months of age) compared to those born to unvaccinated dams or dams of unknown vaccination history (start at 3–4 months of age) (AAEP 2021). These protocols conflict with the latest peer-reviewed guidelines on equine core vaccines in North America that emphasise starting no earlier than 6 months of age for foals born to a vaccinated dam but defer to the AAEP guidelines regarding foals born to unvaccinated dams or dams of unknown vaccination history (Desanti-Consoli *et al*. 2022). Neither provide recommendations for tetanus prophylaxis in foals < 3 months of age born to unvaccinated dams. Comprehensive guidelines that recognise the complexity of tetanus prophylaxis strategies in horses < 6 months of age are required.

The purpose of this review was to conduct a critical evaluation of the scientific literature on tetanus prophylaxis in horses within the context of equine practice and available products (TT and TAT) in New Zealand and Australia. From this review, the authors sought to develop a set of practical guidelines for equine tetanus prophylaxis aimed at assisting veterinarians in clinical practice in New Zealand and Australia.

Literature review and guidelines for equine tetanus prophylaxis in New Zealand and Australia

Approach to guideline development, disclaimers and definitions

A panel of industry and accredited specialist veterinarians (equine internists, equine surgeons) conducted and authored the present review to obtain a group consensus on the following equine tetanus prophylaxis guidelines (see Supplementary Information 1 for methods). The review is presented across seven numbered sections and includes nine guidelines. The guidelines are also summarised in Supplementary Tables 1 and 2 which include reference to the relevant numbered sections in the review. Additionally, Guidelines 1–3 are summarised in Supplementary Figure 1.

Although grounded in the evidence presented, the guidelines are the authors' opinion, and clinical decisions pertaining to equine tetanus prophylaxis are considered the responsibility of the attending veterinarian, taking into consideration the horse's health, the accuracy of medical records and the veterinarian's liability. Some recommendations are off-label but are allowed under the Veterinarians Act 2005 in New Zealand and the Veterinary Practice Act 2018 in Australia (Anonymous 2005, 2018). Additionally, considering tetanus cases have been reported in horses with an immunisation history (Green *et al*. 1994; de Melo and Ferreira 2022), it is prudent to inform clients that no vaccine is 100% effective and that vaccination against diseases is a matter of risk reduction, not elimination. Ideally, horses should be vaccinated when apparently healthy.

The following definitions are provided for clarity: the term tetanus prophylaxis is used to encompass active, passive, and combined active–passive immunity. Active immunity against tetanus is defined as

the humoral immune response to the TT antigen (vaccination). Passive immunity against tetanus is acquired by administering TAT, administration of plasma from a vaccinated donor, or colostrum-derived maternal antibody transfer from a vaccinated mare to her foal. A "risk event" refers to a known clinical scenario involving an anaerobic tissue environment that could potentially have been inoculated with *C. tetani* and therefore theoretically increases a horse's risk of tetanus. The following examples of risk events are common clinical scenarios for which attending veterinarians need to devise a tetanus prophylaxis plan: penetrating injuries, trauma or wound, hoof abscess, surgery or invasive dentistry, a neonate with umbilical infection, and mares with periparturient trauma or retained fetal membranes (Sole *et al*. 2015; Theoret *et al*. 2016; Van Galen *et al*. 2017). Aside from elective surgical procedures, these risk events cannot be predicted.

Section 1. Defining protection against tetanus

a. Experimental tetanus challenge studies

True immunity against tetanus is defined as disease resistance following *C. tetani* infection. In controlled experimental tetanus challenge studies in horses, sheep and guinea pigs (Sneath *et al*. 1937; Saxinger and Heinig 1951; Chodnik *et al*. 1959), and an uncontrolled challenge study in horses (Löhrer and Radvila 1970), TT-immunised animals survived exposure to lethal doses of tetanus toxin or spore suspensions, many with complete resistance to disease (no clinical signs).

b. Serological measurement of anti-tetanus antibodies

Anti-tetanus antibody activity is expressed as international units (IU) and the literature perpetuates the "protective" serological threshold in an individual as > 0.01 IU/mL (Wilson 2017; Basta *et al*. 2018; AAEP 2021). This threshold was developed in the 1940s when two scientists performed tetanus challenge studies, using themselves as subjects (Wolters and Dehmel 1942). Since that experiment, supported by earlier research in guinea pigs, 0.01 IU/mL of circulating anti-tetanus antibody has remained the universally accepted threshold, yet vaccinated individuals (including horses) have shown resistance to tetanus challenge when antibody concentrations were below this threshold (Sneath *et al*. 1937; Löhrer and Radvila 1970). When 24 horses were challenged with tetanus toxin 5–8 years after their last TT administration, all horses survived, including one with a titre < 0.01 IU/mL (Löhrer and Radvila 1970). Survival of this individual horse might reflect the role of immunological memory from prior immunisation and/or that protective serum concentration of anti-tetanus antibody in vaccinated horses might be < 0.01 IU/mL. As discussed in the most recent international guidelines on core vaccines in equids, the protective serological threshold from active immunisation in equids specifically is yet to be determined (Desanti-Consoli *et al*. 2022) Thus, 0.01 IU/mL remains the accepted standard for actively immunised horses (Wilson 2017). To the authors' knowledge, the required threshold of circulating anti-tetanus antibody for protection against tetanus from passive immunisation (e.g. TAT) has not been published. Recent publications from Europe and North America advocate for the clinical application of tetanus titre testing (Recknagel *et al*. 2015b; Desanti-Consoli *et al*. 2022). Although such testing could be offered by laboratories in New Zealand and Australia should there be demand, at the time of publication tetanus titre measurement is not commercially available for veterinary use (A Black,[1] E Crosser,[2] pers. comm.).

Section 2. Tetanus toxoid: development and duration of active immunisation in horses

a. Adjuvant-enhanced tetanus toxoid immunisation

Tetanus toxoid is formalin-inactivated tetanospasmin (Bergey and Etris 1936; Chodnik *et al*. 1959; Edsall 1964). With the addition of an adjuvant, TT is a highly efficacious vaccine in horses and other species (Saxinger and Heinig 1951; Levine *et al*. 1955; Chodnik *et al*. 1959). In horses, the use of oil-based adjuvants decreased in popularity with the development of aluminium-based-adjuvanted TT vaccines (Löhrer and Radvila 1970; Jansen and Knoetze 1979; Liefman 1981). More recently, immune-stimulating complex (ISCOM) adjuvanted TT vaccines have been developed for use in horses but are not available in New Zealand or Australia (Heldens *et al*. 2010; Kendall *et al*. 2016). At the time of publication, the only TT product for horses available in NZ and Australia contains an aluminium-based adjuvant and 20 Limes flocculation (Lf) of inactivated tetanus toxin per dose.

b. Serologic responses to aluminium-adjuvanted tetanus toxoid immunisation in horses > 6 months old

Despite the antigenic potency of TT, in all studied mammalian species a single TT dose will not confer long-lasting immunity as immunity slowly declines over time; thus, a primary series followed by booster doses are recommended for an anamnestic response to maintain life-long protection in horses (Chodnik *et al*. 1959; Jansen and Knoetze 1979; Liefman 1981).

[1]A. Black, Idexx Laboratories Pty. Ltd., NZ.
[2]E. Crosser, Idexx Laboratories Pty. Ltd., Australia.

A protective serological immune response (anti-tetanus antibody concentration > 0.01 IU/mL) develops by 12–14 days, but not within 7 days, following the first TT (aluminium-adjuvanted) dose in a previously unvaccinated horse (Saxinger and Heinig 1951; Liefman 1980). The duration of protective anti-tetanus antibody concentrations achieved by the first TT dose varies between individual horses, and some horses do not maintain adequate titres to afford protection to 12 months (Liefman 1981). When the first TT dose is followed by a second TT dose 4 weeks later, a much greater serological immune response is achieved (Chodnik *et al*. 1959); in a study by Liefman (1981), all horses maintained anti-tetanus antibodies > 0.01 IU/mL for at least 12 months after the second TT dose. The precise interval between the first and second TT dose does not appear to be critical but should be no less than 4 weeks, and ideally no more than 8–12 weeks (Löhrer and Radvila 1970; Liefman 1981).

From 12 months after the second TT dose, antibody titres steadily wane unless provided additional immunogenic stimulation (Liefman 1981). To achieve long-lasting immunity, a third TT dose within 12 months of the second TT dose is required in horses (Löhrer and Radvila 1970; Scarnell 1974; Liefman 1981). Most horses maintain anti-tetanus titres > 0.01 IU/mL for many years following an appropriate primary immunisation protocol (Saxinger and Heinig 1951; Löhrer and Radvila 1970; Scarnell 1974). Subsequent booster doses assist immunologic recall, but the required frequency of booster vaccination is debated. In a study where immunised horses received TT booster doses every 3–8 years, all horses maintained titres > 0.1 IU/mL, and when compared to a group of horses receiving a booster every 2 years, there was no statistical difference between the groups' titres (Recknagel *et al*. 2015a). In 24 appropriately immunised horses whose last aluminium-adjuvanted TT dose was 5–8 years prior, none developed clinical tetany when challenged with 3 times the minimum lethal dose of toxin, including one horse (7 years since its last TT booster) whose titre measured below 0.01 IU/mL (Löhrer and Radvila 1970). Although not included in the challenge component of that study, one of the horses had a tetanus titre of 0.01 IU/mL, despite not having had a TT booster for 9 years (Löhrer and Radvila 1970). These studies suggest TT booster doses at an inter-dose interval of up to 8 years are acceptable for maintaining long-lasting immunity against tetanus. While accepting the limitations of cross-species extrapolation, this inter-dose interval is shorter than that of guidelines for humans, another mammalian species that is highly susceptible to tetanospasmin (Basta *et al*. 2018). In humans a 10-year interval for TT boosters throughout life is established in some countries (e.g. USA, Germany, Austria, Australia), and in New Zealand TT boosters are recommended approximately every 20 years following the juvenile immunisation protocol (Nowlan 2019; Anonymous 2023).

As the rate of antibody titre decline is not uniform across individual horses (Recknagel *et al*. 2015a), and equine tetanus titre testing is not commercially available to practising veterinarians in New Zealand and Australia at present, it is the authors' opinion that an inter-dose interval of 5 years throughout a horse's life is prudent. Additionally, this is what the New Zealand and Australian TT product labels advise. In other countries, administering aluminium-adjuvanted TT boosters to horses at a shorter interval (i.e. annually) is standard practice (AAEP 2021). The manufacturer of the TT vaccine in New Zealand and Australia (Zoetis) reports that adverse drug events are very rare in equids (< 1 in 10,000 animals treated) (W Clough,[3] pers. comm.). However, hyperimmunisation-related adverse events to TT booster doses are reported in vaccinated humans (Korger *et al*. 1986). Administering TT booster doses more frequently than every 5 years is likely safe, but such practice does incur additional expense to clients, and vaccine cost was a concern to 20% of respondents in an Australian survey on tetanus prevention in horses (Dennis *et al*. 2022).

Guideline 1. Tetanus toxoid immunisation for unvaccinated horses > 6 months old

All horses in New Zealand and Australia should be vaccinated against tetanus. To achieve and maintain immunity against tetanus, an unvaccinated horse must receive the TT primary immunisation protocol consisting of a three-dose series administered via IM injection followed by TT booster doses, as follows:

- The first and second doses of TT should be administered IM 4–6 weeks apart.
- A protective immune response develops by 12–14 days following the first TT dose.
- A third dose of TT must be administered within 12 months of the second TT dose.
- A booster dose of TT is then recommended within 5 years of the third dose of the primary protocol and subsequent TT booster doses are recommended every 5 years throughout a horse's life.

Section 3. Tetanus antitoxin: indications, limitations and duration of passive immunisation in horses

a. Tetanus antitoxin indications and limitations

Tetanus antitoxin is a biological serum product harvested from hyperimmunised horses (Trinca 1979). When TAT is administered it leads to a temporary

[3]W. Clough, Zoetis NZ Ltd. Auckland, NZ.

increase in circulating anti-tetanus antibodies that neutralise unbound tetanospasmin (Ramon 1936; Liefman 1980). However, the superiority of active immunisation compared to passive immunisation for tetanus prophylaxis has long been acknowledged (Sneath *et al*. 1937; Chodnik *et al*. 1959; Trinca 1979). Unlike TT immunisation, tetanus prophylaxis via TAT is reactive and long-lasting immunity is not conferred (Cooke and Jones 1943; Liefman 1980). Equine challenge studies have not compared the efficacy of TT and TAT for preventing disease, but a guinea pig challenge study reported 21/55 passively immunised (1,500 IU TAT) guinea pigs died compared to 5/55 actively immunised (TT) guinea pigs (Sneath *et al*. 1937).

An additional consideration when administering biological products is horizontal transmission of disease. Theiler's disease has been linked to TAT administration and recent clinical and experimental studies support equine parvovirus-hepatitis virus as the likely aetiologic agent (Divers *et al*. 2018, 2022). PCR testing of commercial equine serum pools supports a world-wide distribution of equine parvovirus-hepatitis virus, including positive isolation from two New Zealand herds (Meister *et al*. 2019), as well as positive detection in 6/188 (3.2%) serum samples from Australian horses (Fortier *et al*. 2021). However, in an Australian survey, no cases of equine Theiler's disease associated with TAT were reported by 77 respondents (Dennis *et al*. 2022). Furthermore, no reports of equine Theiler's disease in New Zealand have been made to Zoetis New Zealand Ltd. (W Clough,[4] pers. comm.) or reported in peer-reviewed literature. Whether the risk for TAT-associated Theiler's disease is lower or absent in New Zealand and Australia compared to other countries remains speculative.

b. Serological duration of tetanus antitoxin in horses

As previously discussed, challenge studies determining the protective tetanus titre threshold for passively acquired immunity to tetanus are lacking and studies have assumed 0.01 IU/mL to be adequate. In three horses (mean body weight 340 kg), a TAT dose of 1,500 IU SC (as per New Zealand and Australian label instructions) provided passive immunity for up to 14 days but no more than 21 days (Liefman 1980). Furthermore, TAT at this dose did not interfere with the development of active immunity in response to concurrent TT administration (Liefman 1980).

Dose-dependent duration of protection by TAT in horses has been studied (non-peer-reviewed), where a higher dose provided an extended duration of passive immunity (Liefman 1977; Trinca 1979). Whether heavier horses achieve similar or lower serum antibody concentrations compared to smaller horses per dose of TAT has also been questioned (Desanti-Consoli *et al*. 2022). The label dose of the licensed TAT product for tetanus prophylaxis in New Zealand and Australia is "not less than 1,500 IU" for horses and foals and was used by 96% of equine veterinarians in a recent Australian survey (Dennis *et al*. 2022). Doses as high as 10,000 IU are included on label claims for tetanus prophylaxis in other countries (NOAH 2021), but the degree to which these higher TAT doses interfere with active immunity from concurrent TT administration in horses has not been published. In the Australian survey of veterinarians, three equine cases of tetanus post-castration were reported within 2 weeks of TAT administration per label direction (1,500 IU SC), including a miniature horse (Dennis *et al*. 2022). Although vulnerable to recall bias, these reports suggest a TAT dose (1,500 IU) provided inadequate passive immunity in the face of infection with *C. tetani*. Further research into combined active–passive protocols using TAT doses > 1,500 IU in horses is warranted to determine an optimal TAT dose for first-line prophylaxis in unvaccinated horses that simultaneously does not interfere with the active immune response to concurrent TT.

Section 4. Tetanus prophylaxis for horses > 6 months old experiencing a risk event

a. Tetanus prophylaxis in vaccinated horses experiencing a risk event

Many reports of equine tetanus do not have a known or observed risk event associated with them (Van Galen *et al*. 2017; de Melo and Ferreira 2022; Dennis *et al*. 2022), reinforcing the need to maintain active immunity against tetanus throughout a horse's life as described in Section 2. It is the authors' opinion that a 5-year booster interval will provide sufficient immunity for most horses that experience a risk event. However, owner recall and immunisation documentation can be unreliable, and individual horses can respond heterogeneously to TT immunisation (Jansen and Knoetze 1979; Liefman 1980; Recknagel *et al*. 2015a). The latest equine vaccination guidelines published for North America addressed these issues by recommending the administration of a TT booster when tetanus titre measurements are < 0.01 IU/mL (Desanti-Consoli *et al*. 2022). However, appropriately validated point-of-care tetanus titre testing is not available for horses in New Zealand and Australia. Considering that in a study by Liefman (1981), all horses' (n = 5) serum titres 12 months after the second aluminium-adjuvanted TT dose were > 0.01 IU/mL, administration of a TT booster to an appropriately vaccinated horse that experiences a risk event

[4]W. Clough, Zoetis NZ Ltd. Auckland, NZ.

within 12 months of the last TT booster dose is not justified, unless they are due for the third TT dose of the primary protocol (Guideline 1).

When a previously vaccinated horse is administered a TT booster, antibody titres far exceed 0.01 IU/mL within 4–7 days as a result of pre-existing immune memory (Liefman 1981). This was similarly demonstrated in eight horses following an oil-based-adjuvanted TT (Jansen and Knoetze 1979). Incubation time from initial infection to clinical signs varies; one study of 155 adult horses reported a median incubation time for tetanus of 8 (min 1, max 43) days (Van Galen *et al*. 2017). Thus, in the face of natural *C. tetani* infection, pre-existing active immunity against tetanus, in combination with TT booster vaccination, should prevent disease, whereby concurrent TAT administration is not indicated.

Guideline 2. Tetanus prophylaxis for vaccinated horses > 6 months old experiencing a risk event

When a correctly vaccinated horse (i.e. has completed the primary protocol per Guideline 1) experiences a risk event, in addition to appropriately managing the presenting risk event:

- Previously acquired active immunity should provide adequate protection against tetanus.
- Do not administer a TAT dose.
- If it has been ≤ 12 months since the last TT, do not administer a TT booster dose.
- If it has been ≥ 5 years since the last TT, administer a TT booster dose.
- If it has been > 12 months but < 5 years since last TT, administration of a TT booster dose is at the attending veterinarian's discretion.

b. Tetanus prophylaxis in unvaccinated horses experiencing a risk event

Unvaccinated horses do not have measurable antitetanus serological titres, and prior natural exposure is thought not to produce protective humoral immunity (Liefman 1981; Kay and Knottenbelt 2007; Popoff 2020). Therefore, when an unvaccinated horse experiences a risk event, combined use of passive (TAT) and active (TT) immunity is required to provide optimal protection against tetanus (Trinca 1979; Liefman 1980). As discussed in Section 2b, the first TT dose in horses provides antibody titres > 0.01 IU/mL by 12–14 days (Saxinger and Heinig 1951; Liefman 1980). While awaiting seroconversion to the first TT dose, protection of the horse relies on TAT for immunity against tetanus. As discussed in Section 3, although a 1,500 IU TAT dose does not appear to interfere with the serologic response to concurrent TT administration (Liefman 1980), in some horses experiencing a risk event, this dose of passive immunity might be inadequate (Dennis *et al*. 2022). Based on such reports, it is the authors' opinion that a repeat TAT dose at 7 days could be considered in high-risk cases (e.g. complicated wound healing, on-going anaerobic tissue environment) to maintain protective titres while awaiting the serological response that occurs 12–14 days following the first TT dose (Saxinger and Heinig 1951; Liefman 1980). Whether this second TAT dose given 7 days after attending a risk event might interfere with the immune response to the first TT dose is unknown, but the authors consider it a more prudent approach than administering an off-label higher TAT dose at the first visit.

Guideline 3. Tetanus prophylaxis for unvaccinated horses > 6 months old experiencing a risk event

When an unvaccinated horse or a horse with an unknown vaccine history experiences a risk event, in addition to appropriately managing the presenting risk event:

- A TT should be administered IM to commence the first TT dose of the primary protocol, and;
- A TAT (1,500 IU) should be administered SC at a separate site to the TT (e.g. contralateral side) to provide immediate passive immunity.
- If an on-going risk is deemed likely, a repeat TAT dose within 7 days of the first dose can be considered by the attending veterinarian.
- For long-lasting active immunity, it is imperative that the horse receives the second and third TT doses of the 3-dose series to complete the primary protocol as described in Guideline 1.

c. Tetanus prophylaxis for elective surgery in horses

Tetanus has been reported in horses following elective surgery (Van Galen *et al*. 2017; Ribeiro *et al*. 2018; Dennis *et al*. 2022). Because active immunity provides superior protection against tetanus compared to passive immunity (Section 3), active immunity should be achieved prior to an elective surgery whenever possible (Sneath *et al*. 1937; Van Galen *et al*. 2017; Dennis *et al*. 2022). Vaccinating horses against tetanus prior to an elective surgery is immunologically advantageous, and eliminates the reliance on concurrent TAT use – reducing the potential risk of serum hepatitis and the higher cost to clients of TAT.

Guideline 4. Tetanus prophylaxis for unvaccinated horses > 6 months old undergoing elective surgery

When an unvaccinated horse or a horse with an unknown vaccine history requires elective surgery, prior to undergoing surgery:

- The first TT dose of a primary immunisation protocol should be administered IM 4–6 weeks prior to undergoing surgery. Subsequently, the second TT dose can be given at the time of surgery provided this occurs 4–6 weeks following administration of the first TT dose.
- For long-lasting active immunity it is imperative that the horse receives the third TT dose of the 3-dose series to complete the primary protocol as described in Guideline 1.
- If this time frame cannot be afforded, then a TT and a TAT should be administered as described in Guideline 3 and the primary protocol completed per Guideline 1.

Section 5. Tetanus toxoid immunisation in broodmares

a. Achieving active immunity against tetanus in mares intended for breeding and pregnant mares

Vaccination of pregnant mares against tetanus is routinely practised to protect the mare during the periparturient period and provide adequate transfer of passive immunity against tetanus to the newborn foal via colostrum post-partum (Liu *et al*. 1982; Desanti-Consoli *et al*. 2022). It is generally accepted that TT is safe to use in pregnant animals as it has been shown to be safe and effective in pregnant women (Basta *et al*. 2018). However, the safety of TT administration to the pregnant mare and fetus has not been investigated. Eight previously vaccinated pregnant mares showed an acceptable anamnestic response to a booster TT dose when administered 6–8 weeks pre-partum (Liefman 1981). However, response to commencing active immunisation against tetanus in an unvaccinated mare during pregnancy has not been published. In humans, pregnancy is acknowledged within the "young, old, pregnant and immunocompromised" category as responding less well to immunisation (Zimmermann and Curtis 2019). Therefore, for reasons of safety and efficacy, unvaccinated mares intended for breeding should undergo TT immunisation prior to breeding. If the primary protocol of TT immunisation needs to be commenced during gestation in an unvaccinated mare, there is an opinion (although not specifically regarding horses) that the administration of vaccines should be avoided during the first 60 days of gestation during fetal organogenesis (Wilson *et al*. 2014).

b. Indications for administering a tetanus toxoid booster to vaccinated pregnant mares

Selective concentration of immune proteins by the mammary gland of pregnant horses occurs approximately 2 weeks prior to foaling (Jeffcott 1974). Therefore, a TT booster dose 4–8 weeks prior to expected parturition ensures maximal colostral anti-tetanus Ig concentrations are achieved (Liu *et al*. 1982). Results of one study inferred a positive correlation between mare and foal anti-tetanus titres (Jansen and Knoetze 1979). Furthermore, maternal anti-tetanus antibody concentrations persisted for 4 months in foals born to mares that had received a TT booster in late gestation compared to < 2–3 months in foals whose dams had received a TT booster 5 months to 2 years prior to parturition (Liu *et al*. 1982). In a different study, eight previously vaccinated pregnant mares had pre-booster serum anti-tetanus antibody titres that already comfortably exceeded 0.01 IU/mL (Liefman 1981). Therefore, in regularly bred, multiparous mares, pre-partum TT booster doses administered more frequently than every 5 years will likely result in tetanus titres in the mare exceeding those recommended for disease prevention (0.01 IU/mL). However, the possible advantage of this practice is longer lasting passive immunity against tetanus for the foal. A potential disadvantage of a pre-partum vaccine booster in pregnant broodmares is the theoretical phenomenon of immunotolerance (Desanti-Consoli *et al*. 2022). Immunotolerance was implicated in foals that lacked a detectable humoral immune response to equine influenza vaccination when the same vaccine was used in their dams pre-partum (Cullinane *et al*. 2001). However, in the absence of such evidence in the context of TT immunisation, the authors consider that administering a pre-partum TT booster to pregnant broodmares is the preferred method for ensuring foals are optimally protected against tetanus after birth.

Guideline 5. Tetanus toxoid immunisation for pregnant broodmares

The TT product available in New Zealand and Australia has no specified label instructions for use in pregnant mares. Ideally, all mares intended for breeding should receive a complete tetanus primary immunisation protocol as described in Guideline 1 prior to breeding.

When a previously vaccinated broodmare (per Guideline 1) is pregnant:

- A TT booster dose should be administered 4–8 weeks prior to parturition during every pregnancy.

When an unvaccinated broodmare is pregnant:

- A primary protocol for tetanus vaccination should be administered as described in Guideline 1, whereby the first and second doses of TT are given 4–6 weeks apart during gestation. If possible, the primary protocol should be commenced after the first 60 days of gestation but no later than 12 weeks prior to parturition (i.e. by 8 months of gestation).

- For long-lasting active immunity, it is imperative that the broodmare receives all three TT doses to complete the primary protocol as described in Guideline 1.

Section 6. Tetanus prophylaxis in foals ≤ 6 months old

a. Passive immunity against tetanus in foals

In a European case series of equine tetanus, 21/176 cases were foals < 6 months old, three of which were neonates with infected umbilici, all of which died (Van Galen *et al*. 2017). In another report of tetanus in foals, all six cases died (Muylle *et al*. 1975). As such, although a seemingly rare disease in foals, the likelihood of death in this cohort is high. These equine reports echo the poor prognosis documented for human cases of neonatal tetanus (Lambo and Anokye 2013), where the dominant risk factors are unhygienic birth and poor umbilical cord care (Schofield 1986). These factors might apply to foals, but risk factors for equine neonatal tetanus have not been studied. As with adult horses, strategies for tetanus prophylaxis in foals involve a combination of passive and active immunity. In addition to maternally derived anti-tetanus antibodies (Section 5), passive immunity against tetanus can also be granted to a foal via plasma transfusion from an appropriately vaccinated donor or via the administration of TAT. The combination of maternally derived passive immunity against tetanus followed by the commencement of TT immunisation at a later age (Section 6b) provides the greatest security for uninterrupted prophylaxis in foals (Corrado and Carta 1964; Liu *et al*. 1982; Davis *et al*. 2015).

Sufficient transfer of maternal anti-tetanus IgG from a mare to her foal relies on appropriate TT immunisation of the dam (Section 5), adequate colostrum production and, lastly, adequate ingestion and absorption of colostrum by the foal within 24 hours of birth (Thein *et al*. 2013). This is because the equine epitheliochorial placenta precludes transfer of maternal IgG to the fetus prior to parturition (Borghesi *et al*. 2014). Foals born to dams vaccinated prior to foaling with multivalent vaccines containing TT had detectable serum anti-tetanus antibody titres after the ingestion of colostrum, indicating that colostral transfer of passive immunity against tetanus is effective (Wilson *et al*. 2001; Davis *et al*. 2015). In lieu of tetanus titre testing in New Zealand and Australian equine clinical practice, serum IgG concentration > 800 mg/dL (8 g/L) at circa 24 hours old approximates sufficient passive immunity against tetanus in foals born to vaccinated mares, as per Guidelines 1 and 5 (Liepman *et al*. 2015). Following ingestion of colostrum, serum anti-tetanus antibody titres in foals decline over time (Corrado and Carta 1964; Liu *et al*. 1982). Although there was variation between individual foals' rate of decline, one study showed all foals' (n = 13) anti-tetanus antibodies remained detectable up to 6 months, indicating a prolonged duration of passive immunity against tetanus in foals born to mares receiving TT in their last trimester (Wilson *et al*. 2001). In contrast, maternal anti-tetanus antibodies waned below 0.01 IU/mL by 3 months in one study (the timing of dams' last TT was not stated) (Corrado and Carta 1964), and by 4 months (dams received their last TT dose in late gestation) and < 2–3 months (dams received their last TT dose 5 months to 2 years prior to parturition) in another study (Liu *et al*. 1982). According to Wilson *et al*. (2001), maternally derived anti-tetanus antibodies might protect foals up to 6 months, and the importance of administering a TT booster in the dam's last trimester is supported by the results of Liu *et al*. (1982). However, challenge studies in foals are lacking, and the protective threshold for passively derived anti-tetanus antibodies has not been determined. Some foals might have a faster decline in their maternally derived antibodies creating a susceptible "window" between waning antibodies and preactive immunisation against tetanus in foals 3–6 months old (Corrado and Carta 1964; Liu *et al*. 1982).

Foals with partial or complete failure of transfer of passive immunity (FTPI) are unprotected against tetanus, wholly or partially, until treated for FTPI (Jansen and Knoetze 1979). The diagnosis and treatment of FTPI in foals is based on measuring IgG concentrations in serum where an IgG concentration > 800 mg/dL (8 g/L) following treatment is indicative of adequate passive immunity (Sellon 2000; Liepman *et al*. 2015). In neonatal foals diagnosed with FTPI or a critical illness where plasma transfusion is indicated (Wilkins and Dewan-Mix 1994), the veterinarian should ensure the plasma donor has been correctly vaccinated against tetanus (this can be assumed with commercial hyperimmunised plasma products). According to one manufacturer's product information, antibodies contained in plasma have a half-life of 21 days in healthy foals, but as low as 8 days in sick foals (Equiplas 2023). In comparison, maternally derived anti-tetanus antibodies have been reported to have a half-life of 28.8 (SE 3.0), 34.8 (SE 5.1), and approximately 35 days for IgGa, IgGb, and IgG(T), respectively (Wilson *et al*. 2001). Although crude, it might be assumed that after five half-lives post-plasma transfusion (105 days) a foal is unlikely to be sufficiently protected against tetanus and therefore might benefit from commencement of active immunisation from 3 months old. The more rapid decline of serum IgG in critically ill foals is thought to relate to catabolism, equilibration between intra- and extra-vascular spaces and consumption in immune interactions (LeBlanc 1988; Wilkins and Dewan-Mix 1994). How

neonatal illness might influence the decline in anti-tetanus antibodies has not been studied. Further research regarding serum anti-tetanus antibody levels achieved after plasma transfusion in foals and their half-life is required to better guide tetanus prophylaxis strategies in FTPI foals.

TAT administration is common practice in some equine breeding operations to provide tetanus prophylaxis, particularly in foals born to dams of unknown or naïve vaccination status (Rogers *et al*. 2007). There does not appear to be a benefit from routine administration of TAT after birth for foals born to vaccinated dams that demonstrate post-partum serum IgG > 800 mg/L (8 g/L), as this cohort should already have adequate maternally derived passive immunity (Wilson *et al*. 2001; Davis *et al*. 2015). The influence of age and dose on the duration of protective titres from TAT in foals is uncertain but might extend beyond the 21 days reported in adult horses (Liefman 1980). In a study of 30 foals administered TAT (1,500 IU) IM at birth, at 1 month 83% had tetanus titres ≥ 0.01 IU/mL and by 4 months 17% still had titres ≥ 0.01 IU/mL (Liu *et al*. 1982). As with maternally derived antibodies, TAT appears to steadily decline over time and although TAT maintained titres ≥ 0.01 IU/mL in many of the studied foals, 5/35 foals failed to maintain supposed protective titres to 1 month (Liu *et al*. 1982). In one case example, neonatal tetanus was reported in a 6-day-old foal born to a dam of unknown vaccination status, despite receiving TAT (unknown dose) at birth (Van Galen *et al*. 2017). To the authors' knowledge, research directly comparing the half-life of serum anti-tetanus antibody concentration in foals receiving passive immunity against tetanus post-partum via colostrum *versus* plasma or TAT administration has not been conducted. Additionally, for neonatal foals born to unvaccinated dams, the benefits of plasma *vs*. TAT for tetanus prophylaxis with regard to the extent and duration of protection is unclear and requires further research (Liu *et al*. 1982).

b. Tetanus toxoid immunisation in foals ≤ 6 months old

As discussed in Section 6a, one study demonstrated prolonged duration of maternally derived passive immunity against tetanus up to 6 months in foals born to dams vaccinated during pregnancy with a multivalent vaccine containing TT (Wilson *et al*. 2001). As such, the latest peer-reviewed equine guidelines for vaccination against tetanus in North America suggest that TT immunisation of foals born to dams vaccinated against tetanus should commence no earlier than 6 months (Desanti-Consoli *et al*. 2022). However, other studies suggest a potential window of vulnerability prior to 6 months in this cohort that might be minimised by commencing vaccination prior to 6 months (Corrado and Carta 1964; Liu *et al*. 1982). Foals born to mares with unknown or naïve immune status against tetanus would theoretically also benefit from this approach. The equine immune system develops early during fetal life (Perryman *et al*. 1980), and several studies support innate and adaptive immune responses of the equine neonate (Flaminio *et al*. 2000; Sponseller *et al*. 2009; Wagner *et al*. 2010). However, investigations of neonatal foal immune responses to various *Rhodococcus equi* antigens suggest that their ability to respond to vaccination might be more nuanced (Ryan and Giguère 2010; Perkins and Wagner 2015). Studies indicate that neonatal foals can mount adequate humoral immune responses but that the nature and dose of the antigen and adjuvant heavily influence the magnitude and IgG subclass of the response (Lopez *et al*. 2003; Jacks and Giguère 2010).

Several studies show a positive correlation between age and immune response to vaccination in foals, but none is more relevant and clearer than Corrado and Carta (1964). This study compared serological responses to an aluminium-adjuvanted TT in foals born to vaccinated dams when two TT doses were administered 1 month apart to five different age groups of juvenile horses (1, 3, 6, 12 and 18 months of age; n = 6 for each group). One month following the two TT doses, titres remained the same in the 1-month group to pre-vaccine titres, whereas all the remaining groups (i.e. ≥ 3 months) showed an acceptable serological response (titres > 0.01 IU/mL) following vaccination (Corrado and Carta 1964). The reasons for this trend are difficult to tease apart but likely include age-related immunodeficiency and maternal antibody interference. When compared to foals with no passive immunity against tetanus, six foals < 8 weeks old had a complete absence of serological response to an 8-Lf, water-in-oil TT dose (Jansen and Knoetze 1979). Although this failure supports the theory of age-related immunodeficiency in foals < 3 months, the low TT dose and adjuvant type must be considered. Similar to Corrado and Carta's (1964) findings, Davis *et al*. (2015) also reported sufficient serologic responses following TT immunisation of 3-month-old foals born to vaccinated dams (TT-containing multivalent vaccine). However, Wilson *et al*. (2001) reported failure of seroconversion at 3 months, but sufficient response when TT immunisation was commenced at 6 months. The reason for the discrepancies between these studies is uncertain but the antigenicity, adjuvant or dose of the vaccine might influence the vaccine's ability to overcome the influence of age-related immune deficiencies and maternal immunity. Individual variation in the initial concentration of passively derived anti-tetanus antibody and its rate of decline might also influence individual foal responses to TT immunisation.

The potential for maternal immunity to interfere with the active immune response to TT vaccination in foals remains contentious (Mason and Schaafsma 1962). Wilson *et al*. (2001) evaluated foal serum tetanus titres in foals (n = 13) born to vaccinated mares (TT-containing multivalent vaccine) that had received a booster in the last 2 months of gestation, and proposed an inhibitory effect of maternal antibodies on the foals' responses to vaccination. In this study, foals that commenced the vaccination protocol at 3 months (n = 7) failed to seroconvert after two vaccine doses, whereas foals first vaccinated at 6 months (n = 6) had a qualitatively similar serological response to yearlings (Wilson *et al*. 2001). In contrast, Davis *et al*. (2015) demonstrated a strong humoral response to vaccination (TT-containing multivalent vaccine) of foals born to vaccinated dams at 3 months, including induction of a pronounced memory immune response with subsequent TT doses. When the response to vaccination included a control group, response to a two-dose primary injection of an experimental antigen at 4, 8 and 26 weeks of age were similar in foals born to naïve mares when compared to foals born to vaccinated mares administered doses 12 and 8 weeks prior to foaling (Sturgill and Horohov 2010). In a study that observed the response to a series of two IM injections of a killed adjuvanted cattle vaccine in healthy 3-day-old foals (n = 11), 3-month-old foals (n = 15) and adult horses (n = 6), age-related immune deficiency was demonstrated distinct from the influence of maternal antibody interference (Ryan and Giguère 2010). Although neonates showed a modest immune response, immune responses were greater in 3-month-old foals compared to neonates, but muted compared to adult responses (Ryan and Giguère 2010).

Although serologic responses to TT appear to increase with age, the goal of immunisation in foals is not necessarily to achieve the greatest response but rather to achieve a sufficient response. From the studies discussed, commencing vaccination in foals less than 3–6 months old might not substantially increase antibody concentration at the time (Corrado and Carta 1964; Wilson *et al*. 2001; Ryan and Giguère 2010), yet priming of the immune response to subsequent vaccination has been demonstrated (Corrado and Carta 1964; Wilson *et al*. 2001; Sturgill and Horohov 2010; Davis *et al*. 2015). Furthermore, all foals (n = 29) in Corrado and Carta's (1964) study showed a strong anamnestic response (titres ≥ 1.0 IU/mL) to a third TT dose administered within 12 months of the second dose, including the group whose TT immunisation commenced at 1 month old. When TT immunisation was commenced ≥ 3–6 months old, the serologic response was even greater (titres ≥ 5.0 IU/mL) (Corrado and Carta 1964).

Guideline 6. Tetanus toxoid immunisation of foals born to vaccinated dams with documentation of adequate transfer of passive immunity or foals administered plasma for treatment of FTPI

There are no specific label instructions for use in foals for the TT product available in New Zealand and Australia. In this cohort, passive immunity against tetanus is likely to be sufficient for up to 3 months and up to 6 months for foals receiving colostrum-derived passive immunity from vaccinated dams per Guideline 5. Adequate transfer of passive immunity should be documented clinically in all foals post-partum, i.e. serum IgG concentrations > 800 mg/dL (8 g/L).

When commencing the TT primary protocol for vaccination against tetanus in foals born to vaccinated dams (per Guideline 5):

- A four-dose series should be started between 3 and 6 months of age as follows:
  - The first, second and third doses of TT should be administered IM, each 4–6 weeks apart.
  - The timing of the third TT dose should be no earlier than 6 months.
  - The fourth TT dose should be administered within 12 months of the third TT dose.
- Alternatively, a three-dose series can be started at 6 months per Guideline 1.
- For long-lasting immunity, booster doses of TT should be administered as described in Guideline 1.

When commencing the TT primary protocol for vaccination against tetanus in foals that were administered plasma (from a TT-immunised donor) to treat FTPI in the neonatal period:

- A four-dose series (as above) should be started from 3 months.

Guideline 7. Tetanus toxoid immunisation of foals born to unvaccinated dams, foals with unknown history of colostral transfer of passive immunity, or foals born to dams with an unknown vaccine history

In this cohort TT immunisation could commence at any age, but attending veterinarians should recognise that foals < 3 months old might not develop a serological response to the initial doses; a more reliable response is likely from 3 months. Prior to 3 months, passive immunity (TAT or plasma from a TT-immunised donor) might be a more reliable means of protection against tetanus, recognising that the duration of protection from these forms of prophylaxis is variable between individual foals.

When commencing the TT primary protocol for vaccination against tetanus in this cohort:

- A four-dose series as described in Guideline 6 should be started from 3 months.
- Alternatively, if TT immunisation is commenced earlier than 3 months, TT should be administered IM every 4–6 weeks until 6 months inclusive. The final TT dose of the primary protocol should be administered within 12 months of the TT dose administered at 6 months.
- For long-lasting immunity, booster doses of TT should be administered as described in Guideline 1.
- The unvaccinated mare or mare with an unknown vaccine history should also be administered the primary protocol for vaccination against tetanus as described in Guideline 1. If the on-going use of the mare is for breeding, refer to Guideline 5.

Guideline 8. Tetanus prophylaxis for foals ≤ 6 months old experiencing a "risk event"

When a foal ≤ 6 months old born to a vaccinated dam (per Guidelines 1 and 5) that has documentation of the adequate transfer of passive immunity (IgG > 800 mg/dL) experiences a risk event, in addition to appropriately managing the presenting risk event:

- For foals < 3 months old, previously acquired passive immunity should provide adequate protection against tetanus. Administration of TAT should not be required.
- For foals 3–6 months old, the primary protocol for vaccination against tetanus can be commenced as a four-dose series as described in Guideline 6. Administration of TAT should not be required.
- For foals 6 months old, the primary protocol for vaccination against tetanus should be commenced as a three-dose series as described in Guideline 6. A TAT (1,500 IU SC) as described in Guideline 3 is optional depending on the attending veterinarian's perceived risk.

When a foal ≤ 6 months old that was administered plasma from a TT-immunised donor to treat FTPI in the neonatal period, with corresponding documentation of adequate transfer of passive immunity (IgG > 800 mg/dL), experiences a risk event, in addition to appropriately managing the presenting risk event:

- For foals < 3 months old, previously acquired passive immunity should provide adequate protection against tetanus. Administration of TAT could be considered if the foal suffered a critical illness early in life.
- For foals 3–6 months old inclusive, the primary protocol for vaccination against tetanus should be commenced as a four-dose series as described in Guideline 6. TAT (1,500 IU SC) should be administered as described in Guideline 3.

When a foal ≤ 6 months old born to an unvaccinated dam, with an unknown history of colostral transfer of passive immunity, or born to a dam with an unknown vaccine history, experiences a risk event, in addition to appropriately managing the presenting risk event:

- TAT (1,500 IU SC) should be administered as described in Guideline 3.
- The primary protocol for vaccination against tetanus should be commenced as described in Guideline 7.
- If an on-going risk is deemed likely (e.g. complicated wound healing, on-going anaerobic tissue environment), a repeat TAT dose within 7 days of the first dose can be considered by the attending veterinarian, as described in Guideline 3.
- The unvaccinated mare or mare with an unknown vaccine history should also be administered the primary protocol for vaccination against tetanus as described in Guideline 1. If the on-going use of the mare is for breeding, refer to Guideline 5.

Section 7. Remaining considerations on equine tetanus prophylaxis in New Zealand and Australia

a. Inadequate immune response following natural infection with C. tetani

There are no studies evaluating the serological response to natural infection with *C. tetani* in horses, only those in an experimental challenge setting (Saxinger and Heinig 1951; Löhrer and Radvila 1970). In humans, acquired protective immunity does not consistently develop following natural infection with tetanus, whereby a small amount of toxin can induce disease but is insufficient to generate a serological immune response (Basta *et al*. 2018). This is likely true in equids, being similarly susceptible to the tetanus neurotoxin, but there is little evidence to support this except for one recent case report of recurrent tetanus in a donkey (Kay *et al*. 2022). Until studies investigating tetanus titres in horses following natural infection with *C. tetani* are conducted, it should not be assumed that equine survivors of clinical tetanus have an immunologic advantage should they suffer re-infection.

Guideline 9. Tetanus toxoid immunisation in horses that have survived clinical tetanus

When a horse survives a case of clinical tetanus:

- A primary protocol for vaccination against tetanus and subsequent boosters should be administered as described in Guideline 1.
- This can be commenced at the time of tetanus diagnosis or during recovery.

b. Inadequate immune response to tetanus toxoid immunisation

Successful active immunisation and robust duration of protection via TT vaccination are dependent on several key factors: the individual horse's response to the antigenic stimulus (assuming the vaccine is delivered to an immunocompetent patient capable of an effective immune response), the product preparation (including product storage), and the method of intervention (the delivery of an optimal vaccination protocol). Immunocompetency regarding pregnant horses and young horses (foals) was discussed in Sections 5 and 6b, respectively. To the authors' knowledge, immunosenescence in the context of vaccinating geriatric horses has had limited investigation (DeNotta and McFarlane 2023), including potential implications of pituitary pars intermedia dysfunction on the immune response to TT vaccination.

The potential for poor compliance, inaccurate immunisation history or incorrect product storage are likely present in equine tetanus prophylaxis strategies in New Zealand and Australia. In New Zealand, equine TT can only be provided by a veterinarian. In Australia, TT and TAT are available through non-veterinary retailers (i.e. sold over-the-counter). Over-the-counter sales of TT and TAT in Australia might facilitate the availability of tetanus prophylaxis for horses. However, it might also increase the risk of suboptimal product handling and/or suboptimal methods of TT intervention (e.g. whether manufacturer instructions are followed or differences between the TAT and TT products are understood).

Of the current vaccines available for use in horses, TT is one of the most immunogenically reliable. However, vaccination against tetanus does not guarantee full protection. In the largest multi-centre retrospective study on equids with tetanus (155 adults and 21 foals between 2000 and 2014 in Europe), cases with a history of appropriate vaccination were rare (4/176) and the majority (3/4; 75%) survived (Van Galen *et al*. 2017). In a survey of Australian veterinarians, none of the reported cases of tetanus had a history of vaccination according to the manufacturer's recommendations (Dennis *et al*. 2022). A smaller North American retrospective study of 20 horses with tetanus during 1970–1990 documented a strong association between survival and prior vaccination (Green *et al*. 1994). In a small retrospective study of horses treated for tetanus in Brazil (2012–2021), 10/17 horses had a history of tetanus immunisation within 365 days of presentation (de Melo and Ferreira 2022). The reported fatality rate due to tetanus (24%) in this study was low, likely a testament to the high proportion of immunised horses (90% of immunised horses survived compared to 43% of unvaccinated treated horses) (de Melo and Ferreira 2022). Other than suggesting the individual variability in the immune response to TT as a reason for why supposedly immunised horses developed clinical tetanus in this population, discussion was lacking on the adequacy of the vaccine protocol (compliance), the possibility of recall bias (inaccurate owner reporting), and inappropriate vaccine storage (de Melo and Ferreira 2022).

c. Inadequate protection from tetanus antitoxin

Development of clinical tetanus despite prophylactic passive immunity via TAT is documented in equine practice. As discussed in Section 3, three cases of tetanus post-castration were reported in Australian horses receiving TAT at the time of surgery; two did not survive (Dennis *et al*. 2022). In 2/17 horses in the aforementioned Brazilian study, clinical tetanus manifested 30 days post-castration despite receiving TAT peri-operatively (10,000 IU IM) (de Melo and Ferreira 2022). Of 21 foals (< 6 months old) with tetanus in the largest multi-centre retrospective study on equine tetanus, the vaccination status of the dam was unknown in all cases, and one case of neonatal tetanus was in a 6-day-old foal that had received TAT at birth (dose not reported) (Van Galen *et al*. 2017). These examples, although few and subject to recall bias, highlight that overwhelming infection can overcome a prophylactic TAT dose. Lastly, administering TAT to an unvaccinated horse with an incubating subclinical infection might also lead to failure of this product (Trinca 1979).

Conclusion

This review presents nine comprehensive guidelines for tetanus prophylaxis in horses for veterinarians practising in New Zealand and Australia. Evidence from a review of the literature strongly favours disease prevention through routine TT immunisation. All horses, regardless of their use, should undergo the described primary protocol for TT immunisation relevant to their age group with subsequent maintenance of active immunity through TT booster doses. Additionally, improved immunisation rates and medical record-keeping within the New Zealand and Australian equine populations will reduce the reliance on TAT when attending a horse suffering a tetanus risk event; the advantages include less cost to the client, more effective tetanus prophylaxis through pre-existing active immunity, and elimination of the risk of TAT-associated Theiler's disease. Moreover, many cases of equine tetanus are not associated with a risk event, further emphasising the advantage of maintaining protection against tetanus through appropriate TT immunisation and client education.

The TT and TAT label instructions in New Zealand and Australia have significant deficits pertaining to tetanus prophylaxis in foals, broodmares and horses that have survived tetanus. The presented guidelines

attempt to address these deficits, acknowledging that off-label use is a decision of the attending veterinarian following a suitable risk-benefit assessment and obtaining client consent. Future research on equine tetanus prophylaxis is required to better determine the duration of active immunity, the advantages and disadvantages of vaccination during pregnancy, the persistence of antibodies of maternal, plasma and TAT origin in foals, and seroconversion patterns in actively immunised foals of different ages born to vaccinated and unvaccinated dams using the aluminium-adjuvanted TT product available in New Zealand and Australia.

Disclosure statement

V Chapman is an employee of Zoetis NZ Ltd. Zoetis did not have any direct input into the formulation of the manuscript. The guidelines and the opinions expressed are those of the authors alone. No other author has any relevant conflicts of interest to declare.

ORCID

AL Lovett http://orcid.org/0000-0001-5167-939X
CB Riley http://orcid.org/0000-0001-8679-7986
LJ Johnstone http://orcid.org/0000-0002-0668-3610
BW Sykes http://orcid.org/0000-0002-0505-6228

References

*__AAEP__. *Core Vaccination Guidelines: Tetanus*. https://aaep.org/guidelines/vaccination-guidelines/core-vaccination-guidelines/tetanus (accessed 1 May 2024). American Association of Equine Practitioners, Lexington, KY, USA, 2021

*__Anonymous__. *Veterinarians Act 2005*. New Zealand Government Printer, Wellington, NZ, 2005

*__Anonymous__. *Veterinary Practice Act 2018*. Parliamentary Counsel, Canberra, ACT, Australia, 2018

*__Anonymous__. *Australian Immunisation Handbook – Tetanus*. https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/tetanus#overview (accessed 5 March 2024). Australian Government Department of Health and Aged Care. Canberra, ACT, Australia, 2023

Barquero N, Gilkerson JR, Newton JR. Evidence-based immunization in horses. *Veterinary Clinics of North America: Equine Practice* 23, 481–508, 2007. https://doi.org/10.1016/j.cveq.2007.04.003

*__Basta NE, Borrow R, Miller E.__ *World Health Organization Immunological Basis for Immunization Series Module 3: Tetanus*. https://www.who.int/publications/i/item/9789241513616 (accessed 13 May 2024). World Health Organization, Geneva, Switzerland, 2018

Bergey D, Etris S. Active immunization against tetanus infection with refined tetanus toxoid. *The Journal of Immunology* 31, 363–71, 1936. https://doi.org/10.4049/jimmunol.31.5.363

Borghesi J, Mario LC, Rodrigues MN, Favaron PO, Miglino MA. Immunoglobulin transport during gestation in domestic animals and humans – a review. *Open Journal of Animal Sciences* 4, 323, 2014. https://doi.org/10.4236/ojas.2014.45041

Chodnik J, Watson A, Hepple J. Active immunisation of sheep and horses against tetanus with aluminium hydroxyde-adsorbed toxoid. *Veterinary Record* 71, 904–8, 1959

Cook T, Protheroe R, Handel J. Tetanus: a review of the literature. *British Journal of Anaesthesia* 87, 477–87, 2001. https://doi.org/10.1093/bja/87.3.477

Cooke JV, Jones F. The duration of passive tetanus immunity: and its effect on active immunization with tetanus toxoid. *Journal of the American Medical Association* 121, 1201–9, 1943. https://doi.org/10.1001/jama.1943.02840150015005

Corrado A, Carta L. Tetanus vaccination of foals having maternal antibodies. *La Nuova Veterinaria* 40, 240–5, 1964

Cullinane A, Weld J, Osborne M, Nelly M, McBride C, Walsh C. Field studies on equine influenza vaccination regimes in thoroughbred foals and yearlings. *The Veterinary Journal* 161, 174–85, 2001. https://doi.org/10.1053/tvjl.2000.0546

Davis EG, Bello N, Bryan A, Hankins K, Wilkerson M. Characterisation of immune responses in healthy foals when a multivalent vaccine protocol was initiated at age 90 or 180 days. *Equine Veterinary Journal* 47, 667–74, 2015. https://doi.org/10.1111/evj.12350

de Melo UP, Ferreira C. Clinical findings and response to treatment of 17 cases of tetanus in horses (2012–2021). *Brazilian Journal of Veterinary Medicine* 44, e005321, 2022. https://doi.org/10.29374/2527-2179.bjvm005321

Dennis S, El Hage C, Brookes V. A survey of veterinarians' practices, recommendations and perceptions associated with the prevention of tetanus in horses in Australia. *Australian Veterinary Journal* 100, 181–6, 2022. https://doi.org/10.1111/avj.13144

DeNotta S, McFarlane D. Immunosenescence and inflammaging in the aged horse. *Immunity & Ageing* 20, 2, 2023. https://doi.org/10.1186/s12979-022-00325-5

Desanti-Consoli H, Bouillon J, Chapuis RJ. Equids' core vaccines guidelines in North America: considerations and prospective. *Vaccines* 10, 398, 2022. https://doi.org/10.3390/vaccines10030398

Divers TJ, Tennant BC, Kumar A, McDonough S, Cullen J, Bhuva N, Jain K, Chauhan LS, Scheel TKH, Lipkin WI. New parvovirus associated with serum hepatitis in horses after inoculation of common biological product. *Emerging Infectious Diseases* 24, 303, 2018. https://doi.org/10.3201/eid2402.171031

Divers TJ, Tomlinson JE, Tennant BC. The history of Theiler's disease and the search for its aetiology. *The Veterinary Journal* 287, 105878, 2022. https://doi.org/10.1016/j.tvjl.2022.105878

Duchen LW, Tonge DA. The effects of tetanus toxin on neuromuscular transmission and on the morphology of motor end-plates in slow and fast skeletal muscle of the mouse. *Journal of Physiology* 228, 157–72, 1973. https://doi.org/10.1113/jphysiol.1973.sp010078

Edsall G. Current status of tetanus immunization. *Archives of Environmental Health: An International Journal* 8, 731–41, 1964. https://doi.org/10.1080/00039896.1964.10663744

*__Equiplas__. *Equiplas Product Information*. https://plasvacc.com/wp-content/uploads/2023/06/PV-USA-2023-Product-Sheet-Equine-Final-WEB.pdf (accessed 13 November 2023). Plasvacc USA Inc., Templeton, CA, USA, 2023

Flaminio MJB, Rush BR, Davis EG, Hennessy K, Shuman W, Wilkerson MJ. Characterization of peripheral blood and pulmonary leukocyte function in healthy foals. *Veterinary Immunology and Immunopathology* 73, 267–85, 2000. https://doi.org/10.1016/S0165-2427(00)00149-5

Fortier C, El-Hage C, Hue E, Sutton G, Marcillaud-Pitel C, Jeffers K, Bamford N, Oden E, Paillot R, Hartley C,

***et al*.** Hepatitis viruses: prevalence of equine parvovirus-hepatitis virus and equine hepacivirus in France and Australia. *Equine Veterinary Journal* 53, 68, 2021. https://doi.org/10.1111/evj.103_13495

Green SL, Little CB, Baird JD, Tremblay RR, Smith-Maxie LL. Tetanus in the horse: a review of 20 cases (1970 to 1990). *Journal of Veterinary Internal Medicine* 8, 128–32, 1994. https://doi.org/10.1111/j.1939-1676.1994.tb03210.x

Heldens J, Pouwels H, Derks C, Van de Zande S, Hoeijmakers M. Duration of immunity induced by an equine influenza and tetanus combination vaccine formulation adjuvanted with ISCOM-Matrix. *Vaccine* 28, 6989–96, 2010. https://doi.org/10.1016/j.vaccine.2010.08.043

Jacks S, Giguère S. Effects of inoculum size on cell-mediated and humoral immune responses of foals experimentally infected with *Rhodococcus equi*: a pilot study. *Veterinary Immunology and Immunopathology* 133, 282–6, 2010. https://doi.org/10.1016/j.vetimm.2009.08.004

Jansen B, Knoetze P. The immune response of horses to tetanus toxoid. *Onderstepoort Journal of Veterinary Research* 46, 211–6, 1979

Jeffcott L. Studies on passive immunity in the foal: I. γ-Globulin and antibody variations associated with the maternal transfer of immunity and the onset of active immunity. *Journal of Comparative Pathology* 84, 93–101, 1974. https://doi.org/10.1016/0021-9975(74)90031-0

Kay G, Knottenbelt D. Tetanus in equids: a report of 56 cases. *Equine Veterinary Education* 19, 107–12, 2007. https://doi.org/10.2746/095777307X181320

Kay G, Souhail M, Mazan M. Recurrent tetanus in a donkey. *Equine Veterinary Education* 34, e418–e421, 2022. https://doi.org/10.1111/eve.13580

Kendall A, Anagrius K, Gånheim A, Rosanowski S, Bergström K. Duration of tetanus immunoglobulin G titres following basic immunisation of horses. *Equine Veterinary Journal* 48, 710–3, 2016. https://doi.org/10.1111/evj.12502

Korger G, Quast U, Dechert G. Tetanusimpfung – Verträglichkeit und Vermeidung von Nebenreaktionen [Tetanus vaccination – tolerance and avoidance of side reactions]. *Journal of Molecular Medicine* 64, 767–75, 1986. https://doi.org/10.1007/BF01732184

Lalli G, Bohnert S, Deinhardt K, Verastegui C, Schiavo G. The journey of tetanus and botulinum neurotoxins in neurons. *Trends in Microbiology* 11, 431–7, 2003. https://doi.org/10.1016/S0966-842X(03)00210-5

Lambo JA, Anokye EA. Prognostic factors for mortality in neonatal tetanus: a systematic review and meta-analysis. *International Journal of Infectious Diseases* 17, e1100–e1110, 2013. https://doi.org/10.1016/j.ijid.2013.05.016

*__LeBlanc M.__ Responses to plasma transfusion in clinically healthy and clinically ill foals. *Proceedings of the 34th Annual Convention of the American Association of Equine Practitioners*, 1988

Levine L, Stone JL, Wyman L. Factors affecting the efficiency of the aluminum adjuvant in diphtheria and tetanus toxoids. *The Journal of Immunology* 75, 301–7, 1955. https://doi.org/10.4049/jimmunol.75.4.301

*__Liefman CE.__ Active and passive immunisation of the horse against tetanus. *PhD thesis*, University of Melbourne, Melbourne, Australia, 1977

Liefman C. Combined active-passive immunisation of horses against tetanus. *Australian Veterinary Journal* 56, 119–22, 1980. https://doi.org/10.1111/j.1751-0813.1980.tb05647.x

Liefman C. Active immunisation of horses against tetanus including the booster dose and its application. *Australian Veterinary Journal* 57, 57–60, 1981. https://doi.org/10.1111/j.1751-0813.1981.tb00444.x

Liepman R, Dembek K, Slovis N, Reed S, Toribio RE. Validation of IgG cut-off values and their association with survival in neonatal foals. *Equine Veterinary Journal* 47, 526–30, 2015. https://doi.org/10.1111/evj.12428

Liu I, Brown S, Kuo J, Neeley D, Feeley J. Duration of maternally derived immunity to tetanus and response in newborn foals given tetanus antitoxin. *American Journal of Veterinary Research* 43, 2019–22, 1982

Löhrer J, Radvila P. Active tetanus prophylaxis in the horse and the duration of immunity. *Schweizer Archiv für Tierheilkunde* 112, 307–14, 1970

Lopez AM, Hines MT, Palmer GH, Knowles DP, Alperin DC, Hines SA. Analysis of anamnestic immune responses in adult horses and priming in neonates induced by a DNA vaccine expressing the vapA gene of *Rhodococcus equi*. *Vaccine* 21, 3815–25, 2003. https://doi.org/10.1016/S0264-410X(03)00329-3

Mason J, Schaafsma A. The active immunization of the horse against tetanus. *Journal of the South African Veterinary Association* 33, 589–91, 1962

Meister TL, Tegtmeyer B, Brüggemann Y, Sieme H, Feige K, Todt D, Stang A, Cavalleri J-M, Steinmann E. Characterization of equine parvovirus in Thoroughbred breeding horses from Germany. *Viruses* 11, 965, 2019. https://doi.org/10.3390/v11100965

Muylle E, Oyaert W, Ooms L, Decraemere H. Treatment of tetanus in the horse by injections of tetanus antitoxin into the subarachnoid space. *Journal of the American Veterinary Medical Association* 167, 47–8, 1975

*__NOAH__. *Tetanus Antitoxin Behring IU*. https://www.noahcompendium.co.uk/?id=-456172&fromsearch=true#iosfirsthighlight (accessed 11 June 2023). National Office of Animal Health, Enfield, UK, 2021

*__Nowlan M.__ *Review of Evidence to Inform the New Zealand National Immunisation Schedule, 2019: Tetanus*. Immunisation Advisory Centre, Auckland, NZ, 2019

Perkins G, Wagner B. The development of equine immunity: current knowledge on immunology in the young horse. *Equine Veterinary Journal* 47, 267–74, 2015. https://doi.org/10.1111/evj.12387

Perryman L, McGuire T, Torbeck R. Ontogeny of lymphocyte function in the equine fetus. *American Journal of Veterinary Research* 41, 1197–200, 1980

*__Pfizer__. *Equine Infectious Diseases Advisory Board Vaccination Guidelines.* https://www.awha.com.au/Controls/ViewAttachment.aspx?ID=1986 (accessed 6 November 2023). Pfizer Animal Health, Sydney, NSW, Australia, 2012

Popoff MR. Tetanus in animals. *Journal of Veterinary Diagnostic Investigation* 32, 184–91, 2020. https://doi.org/10.1177/1040638720906814

Ramon G. L'anatoxine tétanique et la prophylaxie du tétanos chez l'homme et chez les animaux domestiques [Tetanus toxoid and tetanus prophylaxis in man and domestic animals]. *La Presse Médicale* 44, 1625–8, 1936

Recknagel S, Snyder A, Brueser B, Schusser GF. Immunization strategies and seroprotection against tetanus in horses in central Germany. *Pferdeheilkunde* 31, 469–76, 2015a. https://doi.org/10.21836/PEM20150506

Recknagel S, Snyder A, Blanke A, Uhlig A, Brüser B, Schusser GF. Evaluation of an immunochromatographic dipstick test for the assessment of tetanus immunity in horses. *Berliner und Munchener Tierärztliche Wochenschrift* 128, 376–83, 2015b

Reichmann P, Lisboa J, Araujo R. Tetanus in equids: a review of 76 cases. *Journal of Equine Veterinary Science* 28, 518–23, 2008. https://doi.org/10.1016/j.jevs.2008.07.019

Ribeiro MG, de Nardi Júnior G, Megid J, Franco MMJ, Guerra ST, Portilho FVR, Rodrigues SA, Paes AC. Tetanus in horses: an overview of 70 cases. *Pesquisa Veterinária Brasileira* 38, 285–93, 2018. https://doi.org/10.1590/1678-5150-pvb-5441

Rogers C, Gee E, Firth E. A cross-sectional survey of Thoroughbred stud farm management in the North Island of New Zealand. *New Zealand Veterinary Journal* 55, 302–7, 2007. https://doi.org/10.1080/00480169.2007.36785

Ryan C, Giguère S. Equine neonates have attenuated humoral and cell-mediated immune responses to a killed adjuvanted vaccine compared to adult horses. *Clinical and Vaccine Immunology* 17, 1896–902, 2010. https://doi.org/10.1128/CVI.00328-10

Saxinger G, Heinig A. Duration of immunity in horses and sheep after a single injection of tetanus toxoid aluminium hydroxide vaccine. *Monatshefte für Veterinärmedizin* 6, 434–7, 1951

Scarnell J. Recall of immunity in horses previously immunised with an aluminium based tetanus toxoid. *Veterinary Record* 95, 62–3, 1974. https://doi.org/10.1136/vr.95.3.62

Schofield F. Selective primary health care: strategies for control of disease in the developing world. XXII. Tetanus: a preventable problem. *Reviews of Infectious Diseases* 8, 144–56, 1986. https://doi.org/10.1093/clinids/8.1.144

Sellon DC. Secondary immunodeficiencies of horses. *Veterinary Clinics of North America: Equine Practice* 16, 117–30, 2000. https://doi.org/10.1016/S0749-0739(17)30122-0

Sneath P, Kerslake E, Scruby F. Tetanus immunity: the resistance of Guinea pigs to lethal spore doses induced by active and passive immunization. *American Journal of Hygiene* 25, 464–76, 1937. https://doi.org/10.1093/oxfordjournals.aje.a118318

Sole A, Bolwell C, Dart A, Riley C, Theoret C. Descriptive survey of wounds in horses presented to Australian veterinarians. *Australian Equine Veterinarian* 34, 68–74, 2015

Sponseller B, De Macedo M, Clark S, Gallup J, Jones D. Activation of peripheral blood monocytes results in more robust production of IL-10 in neonatal foals compared to adult horses. *Veterinary Immunology and Immunopathology* 127, 167–73, 2009. https://doi.org/10.1016/j.vetimm.2008.09.013

Sturgill TL, Horohov DW. Vaccination response of young foals to keyhole limpet hemocyanin: evidence of effective priming in the presence of maternal antibodies. *Journal of Equine Veterinary Science* 30, 359–64, 2010. https://doi.org/10.1016/j.jevs.2010.05.008

Thein P, Röhm A Jr, Voss J. Experimental investigations to the immune response of foals and adult horses to tetanus toxoid using the Fassisi TetaCheck. *Pferdeheilkunde* 29, 686–99, 2013. https://doi.org/10.21836/PEM20130601

Theoret C, Bolwell C, Riley C. A cross-sectional survey on wounds in horses in New Zealand. *New Zealand Veterinary Journal* 64, 90–4, 2016. https://doi.org/10.1080/00480169.2015.1091396

*__Trinca JC.__ *CSL Medical Handbook*. Fifth Edtn. Commonwealth Serum Laboratories, Melbourne, VIC, Australia, 1979

Van Galen G, Saegerman C, Rijckaert J, Amory H, Armengou L, Bezdekova B, Durie I, Findshøj Delany R, Fouché N, Haley L. Retrospective evaluation of 155 adult equids and 21 foals with tetanus in Western, Northern, and Central Europe (2000–2014). Part 1: description of history and clinical evolution. *Journal of Veterinary Emergency and Critical Care* 27, 684–96, 2017. https://doi.org/10.1111/vec.12668

Wagner B, Burton A, Ainsworth D. Interferon-gamma, interleukin-4 and interleukin-10 production by T helper cells reveals intact Th1 and regulatory TR1 cell activation and a delay of the Th2 cell response in equine neonates and foals. *Veterinary Research* 41, 47, 2010. https://doi.org/10.1051/vetres/2010019

Wilkins CA, Richter MB, Hobbs WB, Whitcomb M, Bergh N, Carstens J. Occurrence of *Clostridium tetani* in soil and horses. *South African Medical Journal* 73, 718–20, 1988

Wilkins PA, Dewan-Mix S. Efficacy of intravenous plasma to transfer passive immunity in clinically healthy and clinically ill equine neonates with failure of passive transfer. *The Cornell Veterinarian* 84, 7–14, 1994

Wilson W, Mihalyi J, Hussey S, Lunn D. Passive transfer of maternal immunoglobulin isotype antibodies against tetanus and influenza and their effect on the response of foals to vaccination. *Equine Veterinary Journal* 33, 644–50, 2001. https://doi.org/10.2746/042516401776249435

*__Wilson WD.__ Assessment of vaccination status and susceptibility to infection. In: Pusterla N, Higgins J (eds). *Interpretation of Equine Laboratory Diagnostics*. Pp 227–41. John Wiley & Sons Inc., Hoboken, NJ, USA, 2017. https://doi.org/10.1002/9781118922798.ch40

*__Wilson WD, Pusterla N, Long DC.__ Immunoprophylaxis. In: Long MT, Sellon DC (eds). *Equine Infectious Diseases*. Second Edtn. Pp 551–70. Elsevier, Amsterdam, The Netherlands, 2014. https://doi.org/10.1016/B978-1-4557-0891-8.00064-6

Wolters K, Dehmel H. Active immunization against tetanus. *Zeitschrift für Hygiene und Infektionskrankheiten* 124, 326–32, 1942. https://doi.org/10.1007/BF02178438

Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. *Clinical Microbiology Reviews* 32, 2019. https://doi.org/10.1128/CMR.00084-18

*__Zoetis__. *Equine Vaccination Guidelines for New Zealand*. https://www.zoetis.co.nz/tools/equine-vaccination-guidelines/equine-vaccination-guidelines.aspx (accessed 13 November 2023). Zoetis New Zealand Ltd., Auckland, NZ, 2014

*__Zoetis__. *When Should I Vaccinate My Horses?* https://www.health4horses.com.au/health-care/preventative-care/eidab-chart-v2.pdf (accessed 13 November 2023). Zoetis Australia Pty Ltd., Rhodes, NSW, Australia, 2016

*Non-peer-reviewed