Vaccination schedules used for preventing neonatal and/or maternal tetanus and duration of vaccine-induced protection

Review of published reviews

1. Introduction

Tetanus is caused by a neurotoxin produced by the gram-positive bacterium *Clostridum tetani* which forms spores. Tetanus begins when spores are introduced into damaged tissue. The toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus. The disease may affect any age group, and case-fatality rates are high even where modern intensive care is available. The overall tetanus case-fatality rate varies between 10% and 70%, depending on treatment, age and general health of the patient. Without hospitalization and intensive care, fatality is almost 100% among the oldest and the youngest patients. In settings with optimal care, it may be reduced to 10–20%. The overwhelming majority of tetanus cases are birth-associated and occur in developing countries among newborn babies or in mothers following unclean deliveries and poor postnatal hygiene. [1]

Neonatal tetanus (NT) is defined as a disease that occurs within the first 28 days of life, maternal tetanus is defined as a disease during pregnancy or within 6 weeks of the end of pregnancy (independent of pregnancy ending with birth, miscarriage or abortion).

Tetanus can be prevented through immunization with tetanus-toxoid (TT) (-containing) vaccine (TTCV) which is recommended by WHO as a part of routine immunization to children and women of reproductive age (WRA), particularly to those in high risk areas. [1] To obtain long-lasting immunity, after a primary series, booster doses are required. NT can be prevented by immunizing WRA with tetanus toxoid, either during pregnancy or outside of pregnancy. This protects the mother and - through a transfer of tetanus antibodies to the fetus - also her baby. Additionally, clean practices when a mother is delivering a child are also important to prevent neonatal and maternal tetanus.

Toxoid-specific antibodies, which neutralize the bacterial toxins upon infection, are well accepted as indicators of protection against tetanus. The concentration of antibodies decreases linearly with time and has been estimated to be 5–10% per year[2-4]. The value 0.01 IU/mL is often used as a cut off value indicating protection. Tetanus antitoxin concentrations between 0.01 and 0.1 IU/mL are conventionally considered as low positive, whereas antitoxin concentrations ≥0.1 IU/mL are considered positive. Concentrations≥0.1 IU/mL indicate a good long-term protection.[5]

Currently WHO recommends in its 2006 position paper [1]to administer primary series of 3 doses of TTCV given during infancy (aged <1 year) as well as 2 booster doses- ideally, a booster dose should be offered at age 4–7 years followed by another booster in adolescence, e.g. at age 12–15 year. Therefore, in total, 5 doses of TTCV should be given during childhood. A sixth dose should be given in early adulthood to provide added to assure long-lasting, possibly lifelong protection. This sixth dose could be administered at the time of the first pregnancy or during military service. In countries

where maternal and neonatal tetanus (MNT) remains a public health problem, pregnant women for whom reliable information on previous tetanus vaccinations is not available should receive at least 2 doses of TTCV with an interval of at least 4 weeks between the doses. To ensure protection for a minimum of 5 years, a third dose should be given at least 6 months later. A fourth and fifth dose should be given at intervals of at least 1 year, e.g. during subsequent pregnancies, in order to ensure long-term protection. Pregnant women who have received only 3 doses of DTP in early infancy should receive 2 doses of a TTCV with a minimal interval of 4 weeks. Those who received 4 doses of TTCV during their childhood need only 1 booster dose, which should be given at the first opportunity. In both scenarios, to provide protection throughout childbearing age, a sixth dose would be needed after at least 1 year.

This review of scientific literature aims at identifying systematic reviews on the available evidence of the duration of continued protection conveyed by specific immunization schedules targeted at the prevention of MNT related morbidity and mortality.

2. Methods

To identify relevant literature, the following search strategy to answer the specific Population (P), Intervention (I), Comparison (C), Outcome (O)- question was applied:

Population/Setting	Intervention	Comparison	Outcomes
All individuals globally, with focus on low- and middle income countries.	Specific schedules of TT (containing) vaccination	No intervention/ alternative interventions.	Duration of (continued) protection convened by a specific schedule. • Efficacy. • Effectiveness. • Immunogenicity.
PICO Question: What is the duration of continued protection (efficacy, effectiveness or immunity) against tetanus conveyed by a specific schedule of TTCV vaccination.			

The specific search strategy can be found in Annex 1 Search terms Databases searched were Pubmed and the Cochrane library. The search was conducted in July 2016 without time or language restrictions for reviews published by 30 July 2016. In addition, references of eligible reviews were screened to identify further publications. Experts of the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on maternal and neonatal tetanus elimination and broader tetanus control were consulted to provide further relevant articles. Titles and abstracts of all identified publications were reviewed and screened for eligibility. Reviews were included when the following inclusion criteria were met:

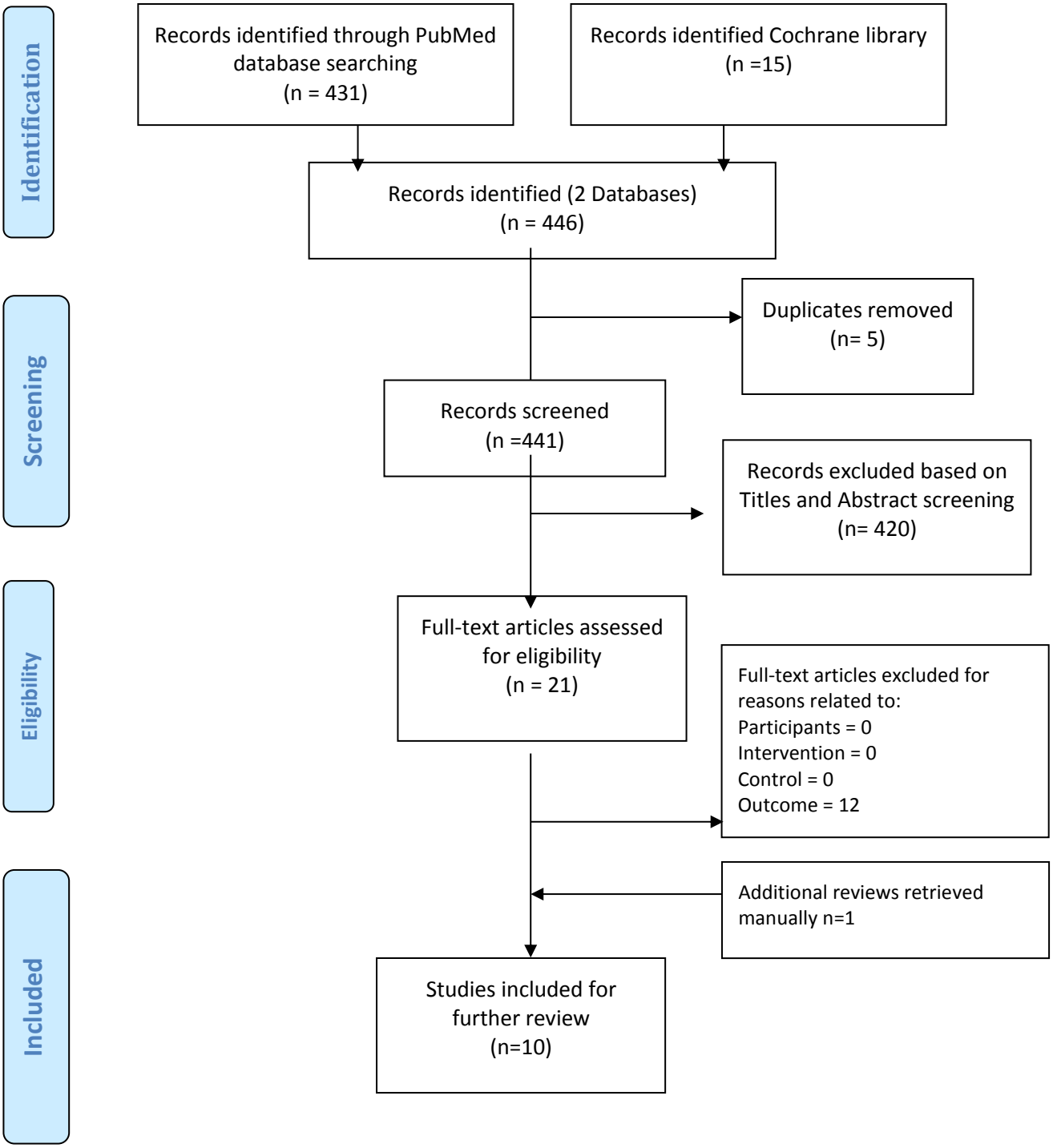
Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
a) were systematic or descriptive reviews or meta-analysis; b) were published in journals, books or websites; c) were published in English language; d) reported on TT vaccine or TTCV; e) included effect estimates efficacy, effectiveness, immunogenicity conferred by tetanus immunization.	a) Original studies b) Guidelines c) Letters d) Editorials

3. Results

The search yielded a total of 431 reviews. After screening of titles and abstracts, 21 full-text articles were assessed for eligibility of which 9 were considered as relevant to potentially address the research question. One review was manually retrieved and included for further review (see Figure 1).

Figure 1: PRISMA flow diagram



None of the reviews provided a systematic retrieval of evidence on the effect estimate of specific schedules of TTCV on the outcome of continued (>5 years) duration of protection conveyed by specific schedules of TTCV containing vaccine.

The included 10 reviews may nevertheless help inform policy and highlight gaps of the available evidence. Therefore, a synopsis of the retrieved evidence is provided below. The reviews were grouped into evidence providing information on the impact of childhood immunization schedules, evidence on the effectiveness of vaccination of WRA and pregnant women, the need for (re-) vaccination of adults and elderly individuals and reviews that had been conducted to information vaccination policy. Of the retrieved reviews, 5 were published within the last 4 years [6-10], the remaining 5 reviews were published in 2010 [11], 2009 [12], 2004 [13], 2003 [14] and 2001 [15] .

Reviews of vaccination schedules for infants and children

A systematic review of literature was conducted in the context of WHO's Optimizing Immunization Schedules project 2014 [6]to inform on the comparative efficacy or effectiveness of different immunization schedules during the first 5 years of life against diphtheria and tetanus among children during the first five years of life. The objectives were to provide the best evidence on primary vaccination against diphtheria (full antigen) and tetanus for children <18 months of age as to compare a. the effect of the number of doses on the outcomes (e.g. 3 vs 2 doses); b. the effect of age at initiation of vaccination on the outcomes (e.g. 6 weeks vs birth dose); c. the effect of the length of vaccine dosing intervals on the outcomes (e.g. 4 weeks vs 2 months); d. the effect of any vaccination on the outcomes (compared to no vaccination; absolute effectiveness); and to provide the best evidence, on booster vaccination against diphtheria (full antigen) and tetanus among children <5 years of age as to compare e. the effect of age at the booster on the outcomes (e.g. 12 vs 18 months) ; f. the effect of any booster on the outcomes (compared to no booster; absolute effectiveness); where the outcomes were assessed among <5-year-old children.
The WHO review found that two primary doses result in substantially lower tetanus antitoxin titers compared to three doses after completion of the primary series. However, this difference does not persist into the second year of life after a booster dose. Nor does the initial titre difference clearly translate into a difference in clinical protection (low quality of the evidence). On the other hand, a schedule leaving a long interval (6 months) between second and third dose provides substantially higher antitoxin titers for the second year of life (very low quality of the evidence). A birth dose (in addition to a three-dose primary series) does not provide higher tetanus antitoxin titers (very low quality of the evidence). At low level of evidence, only one moderately large study suggested that 3,4,5 and 2,3,4-mo-schedules provide similar antitoxin seroprevalence above a threshold of 0.01 IU/ml against tetanus, at one month post third primary or booster dose. Booster vaccination at 18 months of age yields slightly higher antitoxin concentrations than earlier boosting, but this difference does not translate into better protection (moderate quality of the evidence). Booster vaccination during the second year of life after a 3-dose primary series substantially increases antitoxin titers (very low quality of the evidence).

Bar-On et al 2012 [7] compared combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HiB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenza* b (HIB). No long term follow-up data were available to assess the duration of protection. No studies reported on the primary outcome measures as defined in the systematic

review (i.e. incidence of tetanus). Three studies reported on immunogenicity, defined as antibody concentration responses to tetanus, which was one of the review's secondary outcome measures. Systematic and local adverse events were the other secondary outcome measures. The three studies included a total of 28 events in the combined vaccine and 18 in the separate vaccines on the impact on anti-tetanus titers below the assay cut-off. Most events were contributed by one study with 27 events in the combined vaccine and 13 events in the separate vaccines (Marshall 2010 [16]) and one study with five events in the separate vaccines (Ortega-Barria 2007 [17]).
Across all studies, no significant difference on the anti-tetanus titers below the assay cutoff (no seroprotective antibody titers) was observed (risk ratio (RR) 0.56; 95% confidence interval (CI): 0.04 to 8.95) between DTPa-HBV-HIB and DTPw-HBV-HIB combined and separate vaccines.
There were significant differences (RR 2.22; 95% CI 1.21 to 4.06) between combined and separate DTPa-HBV-HIB vaccines. (Marshall et al 2010[16]). Marshall et al 2010[16] used a primary immunization schedule at 2, 4, and 6 months of age followed by a booster dose at 18—19 months. After DTPa-HBV/HIB booster vaccination, 100% (95%CI: 96.8—100%) of subjects had seroprotective antibody concentrations against tetanus one month after booster. No long term follow-up data were available.
No significant difference (RR 0.20; 95% CI 0.00 to 9.94) was reported between combined and separate DTPw-HBV-HIB vaccines. (Ortega-Barria 2007 [17], Rao 2009[18]). Ortega-Barria 2007 [17] within clinical Phase III trials compared primary immunization schedules at 2, 4, and 6, at 3,4,5 months and at 6, 10, 14 weeks. Seroprotection, defined as the percentage with anti-tetanus titers ≥0.1 IU/ml one month after primary immunization, was high (97.2 (95%CI: 93.6–99.1)- 100.0 (95%CI: 99.3–100.0)) for all schedules and vaccines (combined and separate). No long term follow-up data were available. Rao 2009 [18] administered the vaccine 6 to 8 weeks, 10 to 12 weeks and 14 to 16 weeks after birth. It was observed that 98.32%-100% of the subjects had pre-vaccination titers ≥0.1 IU/ml (protective levels) for tetanus toxoid; this may be related to the vaccination of the mothers with two doses of tetanus toxoid during gestation leading to passive transfer of antibodies in the neonates. All these subjects had seroprotective levels after the third dose of the vaccines.

Dhillon et al 2010 [11] reviewed the immunogenicity and effectiveness of Infanrix hexa™ (DTPa-IPV-HBV), as primary or booster vaccination, compared to other combined and separate vaccines. The vaccine was administered as a two- or three-dose primary vaccination course in the first year of life and as booster vaccination in the second year of life. The primary vaccinations were administered at 2, 3 and 4 months [19], 3, 4 and 5 months [20], 2, 4 and 6 months [21], or 3 and 5 months [22;23]. Seroprotection rates after primary immunization against tetanus were 100% across all but one control arm (pentavalent DTPa-combination vaccine) within one trial (seroprotection: 99.4% (95% CI: 96.7-100)) [23].
100% seroproection was achieved by boosting at age 11 months [22;23] and 12-19months [24;25]. Dhillon further described the long-term persistence of immune response against vaccine antigens in children who previously received primary and booster vaccination with a total of three or four doses of Infanrix hexa™ [24;26]. Heininger et al [24] assessed seroprotection rates against the tetanus component 3.8±0.17 years (range 3.50–4.08 years) after booster vaccination at age 12-18 months and primary immunization at 3, 4 and 5 months of age. Data were available for 89 subjects who had received four consecutive doses of DTPa-HBV-IPV/Hib and 36 subjects who had received four consecutive doses of separate DTPa-IPV/Hib and HBV vaccines. Anti-tetanus antibody concentrations were $\geqslant$0.1 IU/ml in 76.4% of subjects in the DTPa-HBV-IPV/Hib group and 80.6% in the DTPa-

IPV/Hib plus HBV group. Zinke et al. [26] conducted a serological follow up of two studies [24;25] at 4-6 years of age (n=203) (after 4 doses of tetanus containing vaccine) and at 7-9 years of age (n=200) (4 doses +/- booster at 5-6 years). Primary schedules used were 2, 4 and 6 months of age/ or 3,4 and 5 months plus a booster at 12-23/24 months. At age 4 to 6 years, or after a mean of 3.63 years (standard deviation: 0.48 years) following booster dosing in the second year of life, 74.7% continued to have seroprotective antibody levels against tetanus. At 7-9 years, in non-boosted individuals, seroprotective antibody levels against tetanus were approx. 64.7%, whereas they reached 100% for those boosted at 5-6 years.

Review of impact of vaccinating WRA and pregnant women

Demicheli et al 2015 [10] assessed the effectiveness of tetanus toxoid, administered to women of reproductive age (WRA) or pregnant women, to prevent cases of, and deaths from, neonatal tetanus. One study (1182 infants) [27] assessed the effectiveness of tetanus toxoid with influenza vaccine as control in preventing neonatal tetanus deaths in a rural area of Colombia. A single dose did not provide significant protection against neonatal tetanus deaths, (RR 0.57 (95% CI: 0.26 -1.24); 494 infants; GRADE: low-quality evidence). However, a two- or three-dose course did provide protection against neonatal tetanus deaths, (RR 0.02 (95% CI 0.00-0.30); 688 infants; GRADE: moderate-quality evidence). Administration of a two- or three-dose course resulted in significant protection when all causes of death are considered as an outcome (RR 0.31 (95% CI 0.17-0.55); 688 infants; GRADE: moderate-quality evidence). Cases of neonatal tetanus after at least one dose of tetanus toxoid were reduced in the tetanus toxoid group, (RR 0.20 (95%CI 0.10 -0.40); 1182 infants; GRADE: moderate-quality evidence). Another study [28], involving 8641 infants born to immunized mothers (1 or 2 doses of tetanus-diphtheria toxoid vaccine or Cholera vaccine as control), assessed the effectiveness of tetanus-diphtheria toxoid in preventing neonatal mortality after one or two doses in rural Bangladesh. Four to 14 days neonatal mortality was reduced in the tetanus-diphtheria toxoid group compared to the cholera vaccine group (RR 0.38 (95% CI: 0.27- 0.55). 1 dose of tetanus-diphtheria toxoid significantly reduced neonatal mortality between day 4-14 of life when the mothers was vaccinated 9-20 months before delivery. No significant difference to the cholera vaccine group was observed in when delivery occurred month 21-32 after vaccination. Participants were controlled for earlier reception of tetanus vaccine. The quality of evidence as assessed using GRADE was found to be low.

Review of the need for TT vaccination of adults and older individuals

Bourée 2003 [14] provided an overview of the immunity and immunization in elderly individuals. In industrialized countries, patients are mostly elderly with women more affected than men, some of whom received obligatory vaccination given to the drafted military personnel. [29] In geriatric patients with accidental wounds one study suggested that vaccination is useful if the last vaccination dates back to more than 10 years. When the seroprotection is high, a single booster for secondary immunization is sufficient. Seroconversion was assessed 4 weeks after the last vaccination, and no long-term immunogenicity or effectiveness data were available. [30]

Weinberger et al 2016 [9] also assessed the European perspective on tetanus-specific antibody concentrations in adults and elderly people as well as the immune responses conferred by a booster dose of tetanus-containing vaccine. In studies conducted in Austria and Israel [31;32], tetanus specific antibody concentrations were lower in elderly compared to young adults and even reported

as being below the threshold of protectively (<0.1IU/ml) [33-36]. On the immune response conferred by a single booster dose, Weinberger et al concluded a single booster dose of TTCV conferred high levels of protective antibodies, though higher seroprotection in younger adults (<40years) compared to older age groups, with not noted differences across different formulations[35;37;38]. A meta-analysis showed that tetanus vaccine-induced antibody responses were lower in an older age group (65-93 years), compared to adults aged 55-64 years (88.9%, 95%CI:82.1–93.8 versus 98.8%, 95% CI:95.7–99.9, respectively) [39]

Olander et al 2009[12] assessed the tetanus and diphtheria antitoxin concentrations in Finnish adults. In the country, after primary doses, tetanus boosters have been offered to men in military service and decennial boosters recommended for all through the adult life. The immunization programme started in 1957. Since then four to five priming doses of DTPw vaccine in the first 4 years of life were recommended plus a booster dose during adolescence. Since the initiation of the programme, Finland reported high primary tetanus and diphtheria vaccination coverage rates in infants. In 1989 diphtheria–tetanus (dT) booster vaccines for adolescence and adults were introduced. Serum samples of 990 subjects from 30 years of age, participating in a population survey in 2000–2001, were used to assess the tetanus and diphtheria antitoxin concentrations. Results showed that all individuals 30–39 years old and most males even up to 50–59 years of age had tetanus antibodies more than 1 IU/mL. In females 40–49 years of age 76% had tetanus antibodies ≥1 IU/mL. In the older age groups the percentage of individuals fully protected (>0.1 IU/mL) gradually declined to 77% and 64% in the male and female age groups 60–69 years, respectively, and to 46% and 35% and among men and women over 70 years of age. The authors suggested that in the younger population (30-49 years) seropositivity levels were high (>1IU/ml in almost the entire cohort) which would convey continuing protection for 20 years making a decennial booster obsolete. Whereas, in the older age group (≥50years), in particular females, lack of seroprotective antibody levels indicates the need for re-vaccination.

Reviews to inform policy

In their review of literature forming the evidence-base for tetanus immunization policy in England and Wales, Bracebridge et al 2004 [13] assessed the antibody production and duration of immunity following tetanus vaccination. The authors indicated, that the third dose conveys sustained protection. [40;41] Further, they noted that there are few data published on the long-term immunity following tetanus immunization. After primary immunization with 3 doses of tetanus containing vaccine, protection persists for up to 10 years.[42-44] One Danish study assessed anti tetanus toxin levels in adults (25-30 years) who had received only a primary vaccination series. In those vaccinated more than 25 years ago, 28% had no sufficient tetanus protection, in those vaccinated in the previous 20 years, 10% were not protected. [45] Statistical modelling concluded, with high confidence levels, that duration of protection is greater than 12 years after 4 or more doses of tetanus vaccination. [46] The authors noted that a booster dose given 5 years after primary immunization, will protect children for up to 20 years, though when this booster is administered to elderly individuals, duration of continued protection will decrease to 13 years. [47] The review concluded that there are no published studies on the long term immunity to tetanus after a 5 dose schedule.

Gardner 2001 [15] reviewed issues related to the decennials Td booster recommendations in adults in the United States of America (USA). A population based serologic survey conducted from 1988-1991 demonstrated that tetanus immunity declined from >80% in the age-group 6-39 years to 28% in persons 70 years or older. [48] Nevertheless, tetanus cases decreased in the USA, beyond immunization due to better wound management and reduced risk of exposure. The author concluded that the relative contribution to the reduction of tetanus cases in the USA since 1975 was only in parts attributable to the decennial combined tetanus-diphtheria vaccine (Td) booster as serological evidence indicated non-adherence to receipt of the booster dose. The review suggested that in the US the decennial booster policy is not cost-effective compared to other preventive measures. [49;50]

Capua et al 2013 [8] conducted a literature review to provide a clinically relevant synopsis of recent research findings and adolescent immunization policy in the USA. One study indicated that a booster dose of Tdap or Td in adolescents and adults, humoral immune response to all included antigens continued to exceed pre-immunization levels 10 years later with levels of tetanus antitoxin remaining protective (≥0.10 IU/ml) in ≥96.7% of adolescents and adults. [51] The review concluded that there are limited data on the duration of protection conferred by combined tetanus-diphtheria-acellular pertussis (Tdap) vaccination during adolescence.

Risk of bias assessments were provided for WHO's Optimizing Immunization Schedules review[6], Bar-On et al [7], Dhillon et al 2010 [11] and Demicheli et al. [10]. Bourée 2003[14], Weinberger et al. [9], Garder 2001 [15], Bracebridge et al 2004 [13], Capua et al 2013 [8]and Olander et al[12] didn't report on any risk of bias assessment.

4. Discussion

This review aims at synthesis of knowledge of available systematic reviews to inform the SAGE Working Group on maternal and neonatal tetanus elimination and broader tetanus control. It was truncated to include only readily accessible published systematic reviews identified by small number of electronic databases searched. Hence, it may be subject to limitations such as risk of publication bias.

The review of systematic reviews yielded some studies looking into antibody levels for duration of protection, but not enough evidence to compare duration of protection conferred by specific schedules of tetanus vaccines. We do not have sufficient evidence to propose any change from current WHO recommendation of 5 doses of TTCV during childhood, with a 3-dose primary schedule and 2 booster doses. The review supports the current recommendation of immunizing with a 3 dose primary schedule leading to a high percentage of infants with anti-tetanus titers ≥0.1 IU/ml for all assessed schedules.[6;7;11]

This review further confirms the need for immunizing WRA and pregnant women, to prevent cases of, and deaths from, neonatal tetanus. Regarding the need for TT vaccination of adults and older individuals, the retrieved evidence suggests that older individuals, in particular females, are at higher risk of tetanus. [12;14] The literature suggests that a single booster dose of TTCV after a primary

series conferred high levels of protective antibodies in adults, though protective antibody levels were higher in younger adults versus older adults.[9]

Within the reviews conducted to inform policy, duration of continued protection after a booster dose following primary immunization was demonstrated to be higher in children than in adults. [8;13]The review concluded that there are no published studies on the long term immunity to tetanus after a 5 dose schedule. [13] One review suggested revisiting a recommendation for a decennial booster dose which is in place in some, mainly high-income, countries. [15]

In conclusion, as no systematic review on the outlined PICO question could be retrieved, it might be advisable to conduct a systematic literature review of original studies. These may contain information on effectiveness, duration of protection and potential break-through cases after receipt of a specific number of TTCV doses and may assist with determining the impact of a specific schedule on the duration of protection.

5. Annexes

Annex 1 Search terms

Search terms used for search:

PubMed

("tetanus"[MeSH Terms] OR "tetanus"[All Fields] OR "tetanus toxoid"[MeSH Terms] OR ("tetanus"[All Fields] AND "toxoid"[All Fields]) OR "tetanus toxoid"[All Fields]) AND (("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]) OR ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]) OR ("immunisation"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] OR "immunization"[MeSH Terms]) OR ("immunisation"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] OR "immunization"[MeSH Terms])) AND (protection[All Fields] OR ("immunity"[MeSH Terms] OR "immunity"[All Fields]) OR effectiveness[All Fields] OR efficacy[All Fields]) and filtered by reviews

Cochrane Database of Systematic Reviews (CDSR)

#Tetanus

6. Reference List

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