## EVIDENCE TO RECOMMENDATIONS TABLE AND GRADE TABLES

Detailed evidence related to the evidence to recommendation table can be found in the background paper[1] produced by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on Maternal and Neonatal Tetanus Elimination (MNTE) and Broader Tetanus Prevention.

**Question:** *While maintaining a total of 3 booster doses of tetanus toxoid (TT) containing vaccine (TTCV), should children receive the first booster dose during the second year of life, at school-entry (4-7 years), and in pre-adolescence/adolescence (9-15 years) reduce tetanus-associated morbidity and mortality in the total population?*

**Population:** Children and adolescents.

**Intervention:** Three TTCV booster doses after primary immunization, given during the second year of life, at school-entry (4-7 years), and in pre-adolescence/adolescence (9-15 years).

**Comparison:** Three TTCV booster doses after primary immunization, given at school-entry (4-7 years), in pre-adolescence/adolescence (9-15 years), and in early adulthood.

**Outcome:** Tetanus cases and deaths in the total population

**Background:**
The main objective of tetanus vaccination is to reduce the risk of maternal and neonatal tetanus and related deaths in low-resource settings. Introduction of tetanus toxoid containing vaccines (TTCV) in routine childhood programmes has together with clean delivery and cord care practices eliminated neonatal and maternal tetanus in many countries. However, in the late 1980s there was an increased recognition of the magnitude of neonatal tetanus deaths persisting worldwide. In 1989, the World Health Assembly endorsed a resolution for all countries to eliminate neonatal tetanus by 1995. Beyond the goal of maternal and neonatal tetanus elimination (MNTE), tetanus vaccination can be used to provide protection from injury-related tetanus across the life course.

Three priming doses of TTCV mainly protect during the first few years of life; for long-term immunity three booster doses are needed. Pregnant women are protected if they received 6 documented doses in childhood (3 primary; 3 booster). Booster doses were recommended in the 2006

[1] http://www.who.int/immunization/sage/meetings/2016/october/presentations_background_docs/en/, accessed February 2017

WHO tetanus position paper at 4-7 years of age, at 12-15 years of age and in early adulthood [1]. However, up until October 2016, 49 of the 194 WHO Member States have not included childhood and adolescent booster doses in their national immunization schedules. In countries where MNT remains a public health problem, pregnant women who did not receive any booster dose after primary immunization with 3 dose of TTCV during childhood should receive 2 doses of TTCV; those who received one booster dose during childhood require only one additional booster during the current pregnancy . In both scenarios, to provide life-long protection including throughout childbearing age, a sixth dose would be needed after at least 1 year.

In 2015, SAGE formed a Working Group on MNTE and Broader Tetanus Prevention which reviewed the available evidence on the duration of protection induced by TTCV to define immunization schedules that would facilitate a better implementation of the 3 dose booster strategy. An early first booster dose given during the second year of life could be a measure to facilitate the implementation of booster doses, at the same time ensuring protection of all individuals across their life course if duration of vaccine-induced protection is sufficiently long.

| | CRITERIA | JUDGEMENTS | | | | RESEARCH EVIDENCE | ADDITIONAL INFORMATION |
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| PROBLEM | Is the problem a public health priority? | *No* ☐ | *Uncertain* ☐ | *Yes* ☐ | *Varies by setting* ☒ | • Case-fatality varies from 25 to 70% depending on treatment, age and general health of the patient.<br>• Despite a 94% reduction in neonatal tetanus deaths over the past 25 years, there is still a considerable number of deaths due to neonatal tetanus (estimated 49,000 in 2013, which compares to 780,000 in 1988) [2].<br>• As of September 2016 there are 18 countries that have yet to eliminate maternal and neonatal tetanus.<br>• Many countries have not included childhood and adolescent booster doses in their national immunization schedules despite already long standing WHO recommendations. As a consequence, adult males reveal disproportionally higher immunity gaps | • There are no reliable estimates of non-neonatal tetanus cases and death, including maternal tetanus |

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| | | | since they are not targeted during supplementary immunization activities or in maternal immunization programs. | |
| BENEFITS & HARMS OF THE OPTIONS | Benefits of the intervention<br><br>*Are the desirable anticipated effects large?* | *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐ | It is expected that –while maintaining the total of 3 booster doses of TTCV–<br>the second year booster dose will:<br>• increase tetanus protection lasting until school-entry compared to the three-dose primary series only [3]<br>• increase towards the 6-dose TTCV coverage overall, thereby ensuring protection throughout most of reproductive age, potentially beyond though no data could be retrieved on the continued duration of protection.<br>• decrease the number of booster doses necessary to be given during antenatal care<br>• decrease the inequity related to tetanus immunity between adult males and women<br>• harmonize schedules with recommended diphtheria and pertussis booster doses<br>• provide a platform for vaccination against several other diseases including pertussis, measles, and meningococcal A conjugate vaccines. | |
| | Harms of the intervention | *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐ | 1) Safety<br>TTCV used alone or in various fixed combinations is considered safe. It causes | There are no studies that compare head-to-head the |

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| | *Are the undesirable anticipated effects small?* | | minor local reactions such as pain and erythema in about 25–85% of cases. Mild systemic reactions including fever, aches and malaise occur in 0.5–1% of vaccinees following booster injections. Serious adverse events such as anaphylactic reactions and brachial neuritis are extremely rare, 1–6 and 5–10 per million administered doses, respectively [4].<br>In general, both local and systemic reactions increase with increasing numbers of doses. Studies do not indicate an increased risk for vaccination administered during the second year of life versus having the first booster dose at school entry age.<br><br>2) Waning immunity<br>Robust immunity across age groups and persisting 20-30 years after the last vaccination was evident from serologic data related to schedules containing six total TTCV doses in the Netherlands (3, 4, 5 and 11 months; 4 and 9 years) [5], Australia (2, 4, 6 and 18 months; 4 and 10–15 years) [6], and England (2, 3 and 4 months; 12 months [Hib-Men C-TT conjugate]; 3.5–5 years and 13–18 years) [3].<br>In a cross-sectional analysis of serum antibody titers in the US, mathematical models combining antibody magnitude | safety of different schedules with 3 booster dose. On theoretical grounds, there is no reason to believe that the new proposed schedule of booster doses will result in an increased risk of benign or serious adverse reactions. |

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| | | | and duration predict that 95% of the population will remain protected against tetanus and diphtheria for ⩾30 years without requiring further booster vaccination [7]. It remains uncertain, if protection is maintained beyond the reproductive age. | |
| | Balance between benefits and harms | *Favours intervention* ☒ \| *Favours comparison* ☐ \| *Favours both* ☐ \| *Favours neither* ☐ \| *Unclear* ☐ | The expected benefits cannot be quantified in terms of number of prevented tetanus cases and deaths. Still, since no harm is anticipated, the expected benefits clearly favour the change in the schedule. This includes that further deaths are expected to be prevented through higher coverage. | |
| | What is the overall certainty of this evidence for the critical outcomes? | Effectiveness of the intervention<br>*No included studies* ☐ \| *Very low* ☒ \| *Low* ☐ \| *Moderate* ☐ \| *High* ☐<br><br>Safety of the intervention<br>*No included studies* ☐ \| *Very low* ☐ \| *Low* ☐ \| *Moderate* ☐ \| *High* ☒ | GRADE very low certainty evidence that six doses of TTCV will protect from tetanus throughout the reproductive age (see GRADE table 1a).<br><br>GRADE high certainty evidence that the serious adverse events following immunization with TTCV are rare (see GRADE table 2). | No direct comparison of the 2 proposed schedules with 3 booster doses. But based on immunological grounds it can be assumed that after 6 TTCV doses in total the duration of vaccine induced protection is similar. |

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| VALUES & PREFERENCES | How certain is the relative importance of the desirable and undesirable outcomes? | *Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐ | No evidence available, though it is assumed that there is no important uncertainty or variability in respect to the desirable and undesirable outcomes. | |
| | Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *<u>Varies</u>* ☐ | Even though the desirable effects cannot be quantified (e.g. the real effect on the uptake of TTCV and other vaccines potentially administered in the second year of life), they are assumed large as compared to no anticipated harms. | |
| RESOURCE USE | Are the resources required small? | *No* ☐ *Uncertain* ☐ *Yes* ☒ *<u>Varies</u>* ☐ | No additional vaccination required, so no extra cost are expected. Creating an additional platform for vaccination during the second year of life may be an opportunity to administer several antigens within one health care visit and therefore even reduce overall costs to the health care system. | |

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| | Cost-effectiveness | *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐ | The number of recommended TTCV booster doses remains the same. By increasing vaccine uptake, total costs of vaccination might increase but more tetanus-related cases and deaths will be prevented. Increasing routine vaccine uptake might also result in decreasing the need for supplementary immunization activities. However, a formal cost-effectiveness analysis has not been conducted. | |
| EQUITY | What would be the impact on health inequities? | *Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐ | Occurrence of tetanus is a shameful reminder of health inequality everywhere but in particular in resource-constrained settings where neonatal tetanus is still prevalent in 18 countries [8]. In addition, studies have shown significantly higher immunity gaps in adolescents of both sexes and adult male. The proposed intervention is likely to reduce such inequalities to some degree. | |

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| ACCEPTABILITY | Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)? | *Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐ | The number of recommended TTCV booster doses and required healthcare visits remains the same. Since this intervention aims at increasing tetanus vaccination coverage, at achieving MNTE, at aligning with other recommendations (diphtheria, pertussis, measles-rubella, meningococcal A), and providing a platform for other vaccines, such change in the schedule should be acceptable to most key stakeholders. This would also reduce the number of vaccinations necessary for pregnant women. | |
| | Which option is acceptable to target group? | *Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐ | Better access to TTCV boosters and reducing the number of health care visits by administering several antigens during a second year of life platform may be favourable to the target population. | |
| FEASIBILITY | Is the intervention feasible to implement? | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐ | The second year of life booster will integrate in the already promoted second year of life platform. In some countries this platform still needs development. | |

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| Balance of consequences | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒ |
| Type of recommendation | We recommend the intervention ☒ | We suggest considering recommendation of the intervention<br>☐ Only in the context of rigorous research<br>☐ Only with targeted monitoring and evaluation<br>☐ Only in specific contexts or specific (sub) populations | | We recommend the comparison ☐ | We recommend against the intervention and the comparison ☐ |
| Recommendation (text) | All immunization programmes should review and adjust their routine immunization schedules to achieve MNTE and to ensure tetanus protection over the life course for all members of the population. Three priming doses in infancy and 3 booster doses in childhood/adolescence are recommended. The 3 TTCV booster doses should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age. Ideally, there should be at least 4 years between booster doses.The total of six doses by adolescence is expected to achieve protection from tetanus throughout reproductive age. However, little evidence exists related to the question if additional booster doses late in life may be needed. | | | | |

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| Implementation considerations | Some countries will require technical and programme guidance to smoothly transition to these new schedules, and to establish or utilize existing platforms to offer a package of vaccination along with other health services. WHO confirms its earlier recommendation to shift from the use of single-antigen TT to combinations containing diphtheria toxoid, i.e. DT or Td vaccines, which has not yet been implemented in many countries despite the negligible price differential between TT and DT/Td vaccines. |
| Monitoring and evaluation | Improved national surveillance and reporting systems, with district-level data analysis, are essential for rational planning of immunization efforts, including high risk approaches in support of MNTE. The need for improved surveillance systems is underscored by the absence of reliable global estimates of non-neonatal tetanus cases and deaths including maternal tetanus. |
| Research priorities | Sero-surveys should be used to validate assessment of tetanus risk to guide vaccination strategies, especially in high risk districts.<br>Close attention should be paid to sampling strategies and laboratory methods to ensure that results are valid and interpretable. |

**Reference List**


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