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: *Should a total of 6 doses of tetanus toxoid containing vaccine (TTCV) to infants, children, (pre-)adolescents compared to a total of 6 doses of TTCV to infants, children, (pre-)adolescents and adults be recommended to avert tetanus deaths.*

Population: Infants, children, (pre-)adolescents and adults.

Intervention: Six TTCV doses, including a primary series of 3 doses of DTP (DTwP or DTaP) given in infancy (age <1 year) plus booster doses during the second year of life, at school-entry and in pre-adolescent/adolescent.

Comparison: Six TTCV doses, including a primary series of 3 doses of DTP (DTwP or DTaP) given in infancy (age <1 year), with a booster dose of a tetanus toxoid-containing vaccine ideally at age 4–7 years, another booster in adolescence, e.g. at age 12–15 years and an additional booster in early adulthood.

Outcome: Tetanus deaths

Background:

Introduction of tetanus toxoid vaccine in routine childhood programmes with or without catch-up campaigns of older individuals has together with clean delivery 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. Following a 1989 World Health Assembly resolution for all countries to eliminate neonatal tetanus by 1995 routine maternal immunisation programmes any time during pregnancy were introduced.

In 2015, SAGE formed a Working Group on MNTE and Broader Tetanus Prevention which reviewed the available evidence of the duration of protection induced by TTCV in order to define immunization schedules that would provide protection across the life course. Further, high

[1] http://webitpreview.who.int/entity/immunization/sage/meetings/2016/october/presentations_background_docs/en/index.html, accessed October 2016

immunity gaps in adults, in particular males are observed in several settings.

Three priming doses of TTCV mainly protect during the first few years of life and for long-term immunity, booster doses are needed. Booster doses were recommended in the 2009 WHO tetanus position paper at 4-7 years of age, at 12-15 years of age and in early adulthood. However, 49 of the 194 WHO Member States have not included childhood and adolescent booster doses in their national immunization schedules. In addition, when booster TTCV doses are included in the national schedules, implementation and monitoring of coverage with booster doses have sometimes not been a priority. In some WHO regions more than 80% of the population lives in countries where diphtheria vaccination beyond 5-6 years of age is not included in the national schedule.

A booster dose during the second year of life is currently not mentioned while both diphtheria and pertussis are recommended at this age. The Working Group revisited these current recommendations.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies by setting* ☒	In 1999, there were 59 high risk countries targeted for elimination of maternal and neonatal tetanus. In 2016 there are 41 of these high risk countries that have eliminated maternal and neonatal tetanus through routine immunisation of pregnant women, clean delivery and cord care practices, and supplementary immunisation of all women of reproductive age where necessary in most countries. As of September 2016 there are 18 countries that have yet to eliminate maternal and neonatal tetanus. Recent data reveal disproportionately high immunity gaps in males. Many countries have not included childhood and	

			adolescent booster doses in their national immunization schedules despite the already long standing WHO recommendations. There is a clear difference in immunologic protection against tetanus between adult men and women since adult males do not receive booster doses of TTCV in many countries, whereas adult females are more likely to receive booster doses, either during supplementary immunization activities (SIA) or during pregnancy. Data further illustrates declining sero-protection rates in older children (5-15 years) in the absence of booster doses.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention *Are the desirable anticipated effects large?*	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Opportunities for integration of TTCV boosters will differ among countries. The second year of life provides a platform for vaccination against several diseases including pertussis, measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes opportunities for administration of Human Papilloma Virus (HPV) vaccination. 2009 serologic data from the United Kingdom showed that introducing a TTCV booster in the 2nd year of life	

			increases tetanus protection lasting until school-entry compared to the three-dose primary series only. Serologic data from Kenya, Tanzania and Mali support the need for a TTCV booster at school-entry related to substantial drop in seroprotection at ≥5 years of age. 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[1] (3, 4, 5 and 11 months; 4 and 9 years), Australia [2] (2, 4, 6 and 18 months; 4 and 10–15 years), and England [3](2, 3 and 4 months; 12 months [Hib-Men C-TT conjugate]; 3.5–5 years and 13–18 years). Further, India[4], which was able to achieve MNTE in 2015, has introduced TTCV during infancy and childhood, including three primary doses of DTP at 6, 10, and 14 weeks, booster doses at 16-24 months, at 5-6 years, at 10 and 16 years. Another example of achievement of MNTE is Indonesia[5], where the TTCV vaccination schedule consists of a primary series of TTCV in infancy, DTP4 at 18 months, diphtheria and tetanus toxoid	

			vaccine (DT) in first grade of school, and diphtheria and tetanus toxoid vaccine (Td) in second grade and third grade. Adding a booster dose in the second year of life is expected to increase immunity and ensure protection throughout (likely) most of reproductive age.	
	Harms of the intervention *Are the undesirable anticipated effects small?*	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Tetanus toxoid (TT) used alone or in various fixed combinations is considered safe. Tetanus toxoid causes minor local reactions such as pain and erythema in about 25–85% of cases, occasionally nodules and, very rarely, sterile abscesses (1–10 per million doses administered). Mild systemic reactions including fever, aches and malaise occur in 0.5–1% of vaccinees following booster injections. In general, both local and systemic reactions increase with increasing numbers of doses. Severe generalized adverse events such as anaphylactic reactions and brachial neuritis are extremely rare, 1–6 and 5–10 per million administered doses, respectively. [6] Studies do not indicate an increased risk for vaccination administered during the second year of life.	

	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Adding an additional booster dose to be administered to children and (pre-) adolescents is favoured when balancing the benefits and harms is favoured over maintaining the current 5 dose recommendation.	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	GRADE low certainty evidence for duration of continued protection. GRADE high certainty evidence that the serious adverse events following immunization are rare.	

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 in general there is no important uncertainty or variability.	
	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>* ☐	Though no evidence is available, adding an additional booster dose may be in the interest of the vaccine recipient/ caregiver to ensure continuing protection. Nevertheless, adding an additional visit to the health facility may be perceived as a burden for some caregivers or vaccine recipients.	
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *<u>Varies</u>* ☐	The vaccine price varies for different markets. The opportunity costs for an additional health care visit are assumed to be acceptable to be carried by immunization programs.	

	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Formal cost-effectiveness analyses has not been conducted, but vaccination programmes have reported very low costs for delivering TTCV vaccines even in a low resource setting. [7] 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 reduce overall costs to the health care system.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Occurrence of tetanus is one of the most visible signs of health inequality [8], and improving uptake of TTCV and likely other vaccine antigens and ensuring continued protection likely during most of child-bearing age, in particular in resource-constrained settings will reduce such inequalities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Adding an additional dose and potentially an additional health care visit is assumed to be a comparably small investment towards achieving MNTE and therefore an acceptable option to key stakeholders.	

	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Ensuring (continued) protection is likely to be acceptable to the target group. 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. However, individuals and communities need to be engaged in a continuous manner to maintain a high level of acceptability of vaccination services.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	Adding the additional booster dose may require the need to establish or utilize existing platforms which may be feasible yet challenging in some settings.	

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	We recommend the comparison	We recommend against the intervention and the comparison
	☒	☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)popul	☐	☐
Recommendation (text)	All immunization programmes should review and adjust their routine immunization schedules to ensure tetanus protection over the life course for all members of the population. The booster dose schedule should be adjusted to include three booster doses, giving a total of six doses to achieve protection throughout reproductive age, probably lifelong protection. These should be given preferably during the second year of life, between 4-7 years of age, and between 9-15 years of age. Ideally there should be at least a 4-5 year interval between doses. Further, booster doses late in life may be needed due to waning immunity.			
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.			
Monitoring and evaluation	Steps should be taken to improve the quality of monitoring, case investigation, and reporting of tetanus cases as part of broader process towards MNTE.			
Research priorities	Sero-surveys should be used to validate assessment of tetanus risk, in order to guide vaccination strategies, especially in high risk districts. Close attention should be paid to sampling strategies and laboratory methods to ensure that results are valid and interpretable.			

GRADE TABLE 1

Population: Infants, children, (pre-)adolescents and adults

Intervention: Six TTCV doses, including a primary series of 3 doses of DTP (DTwP or DTaP) given in infancy (age <1 year) plus booster doses during the second year of life, at school-entry and in pre-adolescent/adolescent.

Comparison: Six TTCV doses, including a primary series of 3 doses of DTP (DTwP or DTaP) given in infancy (age <1 year), with a booster dose of a tetanus toxoid-containing vaccine ideally at age 4–7 years and another booster in adolescence, e.g. at age 12–15 years plus an additional booster in early adulthood.

Outcome: Tetanus deaths

PICO Question: *Should the TTCV booster doses be administered during the second year of life, at school-entry and in pre-adolescence/adolescence compared to the administration of booster doses at school-entry, in adolescence and in early adulthood?*				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		5 Observational[2]	2
	Factors decreasing confidence	Limitation in study design	None serious[3]	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of evidence			**2**
Summary of Findings	**Statement on certainty of evidence**			Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			To achieve protection throughout reproductive age, the schedule should be adjusted to include three primary booster doses to infants plus three booster doses to children, (pre-)adolescents.

[2] [1] de Melker HE, Conyn-van Spaendonck MA, Rumke HC, van Wijngaarden JK, Mooi FR, Schellekens JF. Pertussis in The Netherlands: an outbreak despite high levels of immunization with whole-cell vaccine. Emerg Infect Dis 1997 Apr;3(2):175-8.

[2] ncirs. Fact Sheet Pertussis Vaccines For Australians: Information For Immunisation Providers. 2016 Mar.

[3] Wagner KS, White JM, Andrews NJ, et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine 2012 Nov 19;30(49):7111-7.

[4] Rakesh Kumar of the Government of India. Presentation on "India: Achieving MNT Elimination – Health Systems Approach" 2016.

[5] Jane Soepardi. Presentation on "Critical operational challenges to achieving at least 80% protection at birth from MNT in high risk districts". 2016.

[3] Review of literature could not retrieve any head-to-head comparison suggesting longer duration of continued protection using a 6-dose over a 5-dose schedule (primary 3 dose series plus 3 vs 2 booster doses). Nevertheless, country experience suggests a benefit of using a 6 dose schedule vs a 5 dose schedule.

GRADE TABLE 2
Population: Immunocompetent individuals
Intervention: TTCV
Comparison: No vaccine or control
Outcome: Serious adverse events following immunization

PICO Question: *In immunocompetent individuals, is there an increase in the incidence of serious adverse events following immunization with any dose of TTCV vaccine compared to not giving a TTCV vaccine?*				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4 RCT[4]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of evidence			4
Summary of Findings	**Statement on certainty of evidence**			Evidence supports a high degree of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion			Tetanus toxoid is one of the most extensively used antigens in vaccinations with an excellent safety profile. Severe adverse events are extremely rare. TTCV using various presentations have demonstrated to be safe to use in immunocompetent individuals of various age and population groups including infants, children, adolescents, adults and pregnant women.

[4] [1] The immunological basis for immunization series; Module 3: Tetanus; http://apps.who.int/iris/bitstream/10665/43687/1/9789241595551_eng.pdf, accessed October 2016.
[2] Bar-On ES, Goldberg E, Hellmann S, Leibovici L. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB). Cochrane Database Syst Rev 2012;(4):CD005530.
[3] Demicheli V, Barale A, Rivetti A. Vaccines for women for preventing neonatal tetanus 1. Cochrane Database Syst Rev 2015;(7):CD002959.
[4] Ortega-Barria E, Kanra G, Leroux G, Bravo L, Safary A, Lefevre I. The immunogenicity and reactogenicity of DTPw-HBV/Hib 2.5 combination vaccine: results from four phase III multicenter trials across three continents. Vaccine 2007 Dec 5;25(50):8432-40.
[5] Zepp F, Knuf M, Heininger U, et al. Safety, reactogenicity and immunogenicity of a combined hexavalent tetanus, diphtheria, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate vaccine, for primary immunization of infants. Vaccine 2004 Jun 2;22(17-18):2226-33.

Reference List

[1] de Melker HE, Conyn-van Spaendonck MA, Rumke HC, van Wijngaarden JK, Mooi FR, Schellekens JF. Pertussis in The Netherlands: an outbreak despite high levels of immunization with whole-cell vaccine. Emerg Infect Dis 1997 Apr;3(2):175-8.

[2] ncirs. Fact Sheet Pertussis Vaccines For Australians: Information For Immunisation Providers. 2016 Mar.

[3] Wagner KS, White JM, Andrews NJ, et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine 2012 Nov 19;30(49):7111-7.

[4] Rakesh Kumar of the Government of India 3Mt1A2. Presentation on "India: Achieving MNT Elimination – Health Systems Approach" 2016. Ref Type: Online Source

[5] Jane Soepardi 3Mt1A2. Presentation on "Critical operational challenges to achieving at least 80% protection at birth from MNT in high risk districts" . 2016.

[6] Weekly epidemiological record No2288. Tetanus vaccine, WHO position paper. 21-7-2016.

[7] Mvundura M, Kien VD, Nga NT, et al. How much does it cost to get a dose of vaccine to the service delivery location? Empirical evidence from Vietnam's Expanded Program on Immunization. Vaccine 2014 Feb 7;32(7):834-8.

[8] Blencowe H, Lawn J, Vandelaer J, Roper M, Cousens S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus 3. Int J Epidemiol 2010 Apr;39 Suppl 1:i102-i109.

[9] The immunological basis for immunization series; Module 3: Tetanus; http://apps.who.int/iris/bitstream/10665/43687/1/9789241595551_eng.pdf., accessed October 2016.

[10] Bar-On ES, Goldberg E, Hellmann S, Leibovici L. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB). Cochrane Database Syst Rev 2012;(4):CD005530.

[11] Demicheli V, Barale A, Rivetti A. Vaccines for women for preventing neonatal tetanus 1. Cochrane Database Syst Rev 2015;(7):CD002959.

[12] Ortega-Barria E, Kanra G, Leroux G, Bravo L, Safary A, Lefevre I. The immunogenicity and reactogenicity of DTPw-HBV/Hib 2.5 combination vaccine: results from four phase III multicenter trials across three continents. Vaccine 2007 Dec 5;25(50):8432-40.

[13] Zepp F, Knuf M, Heininger U, et al. Safety, reactogenicity and immunogenicity of a combined hexavalent tetanus, diphtheria, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate vaccine, for primary immunization of infants. Vaccine 2004 Jun 2;22(17-18):2226-33.