Report of the SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention

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List of Abbreviations

ANC	Antenatal care
DHS	Demographic and Health Survey
DOV	Decade of Vaccines
EPI	Expanded programme on immunization
HIV	Human immunodeficiency virus
MCH	Maternal and child health
MICS	Multiple Indicator Cluster Survey
MNCH	Maternal, Newborn and Child Health
MNT	Maternal and neonatal tetanus
MNTE	Maternal and neonatal tetanus elimination
NT	Neonatal tetanus
PAB	Protection at birth
PICO	Population, Intervention, Comparator, Outcome
RMNCH	Reproductive, maternal, newborn, and child health
SAGE	Strategic advisory group of experts on immunization
SBA	Skilled birth attendant
SIAs	Supplementary immunization activities
Td	Tetanus and low-dose diphtheria toxoid vaccine
TTCV	Tetanus-toxoid-containing-vaccines
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
WRA	Women of reproductive age

Executive Summary

In 1999, 59 countries with high incidence of maternal and neonatal tetanus were targeted for elimination of maternal and neonatal tetanus (MNT). Currently, 41 of the 59 of these countries have achieved elimination of MNT through routine immunization of pregnant women, clean delivery and cord care practices, together with supplementary immunization of all women of reproductive age (WRA), as and where necessary, in most countries. As of 26 September 2016, there are 18 countries that have yet to eliminate MNT and several face challenges such as lack of political commitment, insufficient funding, and insecurity. In 2015, SAGE convened a working group to examine why previous elimination target dates were missed and how to reset the agenda and comprehensively address tetanus risk across the life course.

The working group met by six teleconferences and twice in person (30 March – 1 April and 17 – 19 August, 2016) to discuss the current state of progress toward MNTE, challenges and solutions for countries yet to achieve elimination, strategies for sustaining MNTE, and strategies for broader tetanus prevention that will support the MNTE goal but also protect all other age groups against tetanus.

Tetanus prevention is achieved through immunization in all age groups besides continued clean delivery and cord care. Natural infection does not induce protective antibody response. Immunization only provides individual protection.

The working group examined strategies of countries that had successfully achieved elimination and the challenges faced by those who had failed to do so and discussed ways for overcoming these challenges. The working group also discussed strategies to sustain MNTE and the broader tetanus prevention, including the use of sero-surveys to monitor immunity gaps and reviewed evidence of the duration of protection induced by tetanus toxoid containing vaccines (TTCV) in order to define immunization schedules that would provide protection across the life course.

After examining the evidence, the working group developed recommendations for countries yet to achieve elimination, recommendations to sustain MNTE for priority countries that achieved elimination since 1999, and recommendations for achieving tetanus prevention across the life course through routine immunization programmes and, if needed, supplementary immunization campaigns.

Background

Tetanus disease

Tetanus is caused by bacterium *Clostridium tetani*. The bacterial spores generally enter through a break in the skin such as a cut or puncture wound by a contaminated object. In the presence of anaerobic (low oxygen) conditions, the spores germinate. Toxins are produced and disseminated via blood stream and lymphatic system. Toxins act at several sites within the central nervous system, including peripheral motor end plates, spinal cord, and brain, and in the sympathetic nervous system. The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses. The bacteria are commonly found in soil, dust and manure irrespective of geographical location. The incubation period varies between a few days to several weeks after tetanus bacteria enter through a break in the skin. Common signs and symptoms of tetanus include: spasms and stiffness in the jaw muscles (trismus). Tetanus diagnosis is based on physical exam, medical and immunization history, and the signs and symptoms of muscle spasms, stiffness and pain. Laboratory tests generally are not helpful for the diagnosis.

Tetanus is a medical emergency requiring hospitalization, immediate treatment with human tetanus immune globulin (TIG) or equine antitoxin if human immune globulin is not available, a tetanus toxoid booster, agents to control muscle spasm, and aggressive wound care and antibiotics. Mortality varies with access to advanced health care.

Tetanus disease burden

No good overview of number of tetanus cases worldwide is available. Surveillance systems have mainly focused on maternal and neonatal tetanus deaths, and in particular the neonatal deaths. However, existing surveillance systems in areas with well-functioning immunization programmes such as in the European Union (n=31 countries with a population of ~500 million) identify 50-100 reported cases per year. Whether these cases are a result of no vaccination or waning immunity is unknown.

Neonatal tetanus: In 1988, an estimated 780,000 deaths were attributable to neonatal tetanus. Through extensive efforts providing TTCV in routine immunization programmes targeting children and pregnant women, the estimated number of neonatal tetanus deaths had declined to 49,000 by 2013. This represents a 94% reduction in mortality during this 25 year period[1,2] (see figure 1). There are no estimates for subsequent years. However, these remaining tetanus-related neonatal deaths each year reveal distressing health inequities, as no child should die from neonatal tetanus given the availability of a safe, effective and inexpensive vaccine.

[1] WHO/UNICEF database. http://www.who.int/immunization/diseases/MNTE_initiative/en/index7.html.
[2] CHERG Reports March 2015. http://www.who.int/immunization/diseases/tetanus/Lancet-2013-Global-child-mortality.pdf.

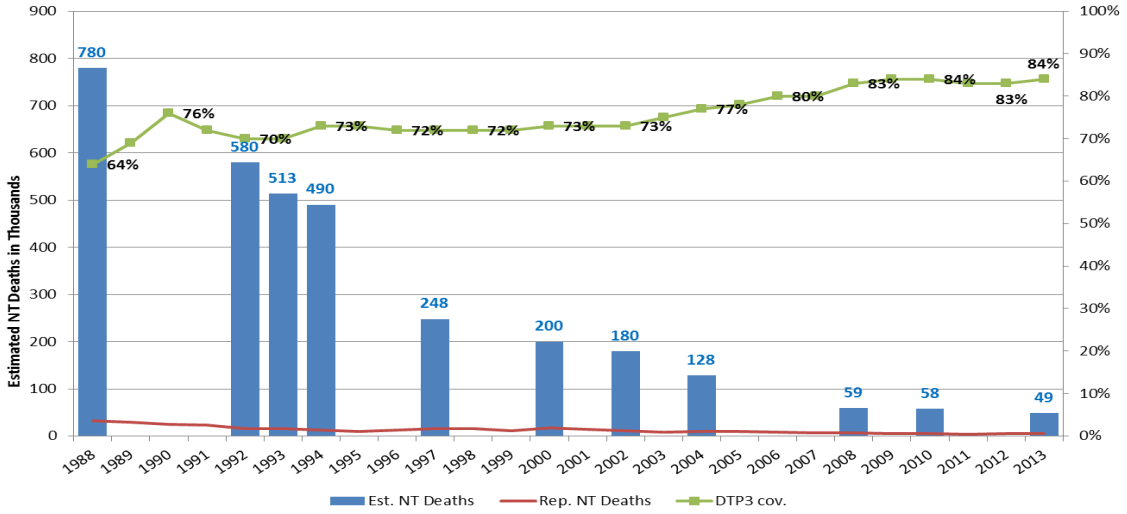

Figure 1.Trends in global estimated and reported neonatal tetanus deaths, 1988-2013 depicted on the left y axis and global estimates of DTP3 coverage in infants
Source: WHO/UNICEF database and CHERG Reports March 2015

Maternal tetanus: There are no reliable estimates of the burden of maternal tetanus, though it is generally considered to be prevalent in areas where neonatal tetanus remains endemic.

Prevention against tetanus

Clean care: Before tetanus vaccines became available in the late 1930s, protection against tetanus disease and mortality was dependent upon appropriate wound care and clean delivery and cord care practices.

Immunization: Tetanus vaccines became available in the late 1930s and were slowly introduced in childhood immunization programmes throughout the world. The scale up of TTCV in low and middle income countries began with the launch of the expanded programme on immunization (EPI) in 1974 and further reduced the number of susceptible children. Coverage worldwide for the three first doses of TTCV was estimated to 84% in 2013 (see Figure 1). The three priming doses mainly protect the first few years of life and for long-term immunity, booster doses are needed. Booster doses were recommended in the 2009 WHO position paper at 4-7 years of age, at 12-15 years of age and in early adulthood. Maternal immunization programmes were initiated in 1995 (see below). TTCV are available as monovalent TT or in combination with other antigens such as D, d, P, aP, IPV, Hep B, Hib (e.g. DTP, Td, DTPHepB,Hib, DTaPIPVHib, DTaPIPVHibHepB).

Experience acquired from the established MNTE programme

In the late 1980s there was an increased recognition of the magnitude of neonatal tetanus deaths persisting in many countries worldwide and following a 1989 World Health

Assembly resolution for all countries to eliminate NT by 1995 (later defined as reduction of NT to less than 1 case per 1,000 live births in every district in each country), routine maternal immunization with TTCV during pregnancy was introduced. In addition, supplementary immunization campaigns targeting all women of reproductive age (usually 15-49 years) have been conducted extensively.

Significant achievements but targets not fully met

The target set by the 1989 World Health Assembly resolution calling for the elimination of neonatal tetanus by 1995 was not achieved. In 1999, UNICEF, UNFPA and WHO launched a new initiative targeting 59 priority countries in which neonatal tetanus remained a significant public health problem[3]. Recognizing the close link between neonatal and maternal tetanus, the scope of the elimination programme was then broadened to include both maternal and neonatal tetanus. Strategies to attain MNTE include clean delivery and cord care practices, and ensuring protection at birth through immunization, including routine immunization of pregnant women during each pregnancy and immunization of all women of reproductive age (15-49 years) in high risk districts during SIAs. While surveillance for neonatal tetanus was part of the strategy, the quality of reporting of cases has remained inadequate. The global protection at birth (from tetanus) estimate that is based on TTCV coverage in pregnant women is 83% for 2015, and has been at 80% and above since 2006. By the end of 2015, over 140 million women of reproductive age had been reached by SIAs with at least two protective doses of tetanus vaccine. However, there are still an estimated 72 million women of reproductive age remaining who have not yet been targeted with SIAs for immunization with TTCV in the remaining 18 countries at risk.

As described above in addition to TTCV vaccination, strategies such as clean delivery, and cord care are important for the elimination of MNT. Evidence suggests that clean delivery practices can reduce the incidence of NT by 55-99%[4]. Skilled birth attendants (SBAs) can prevent about 2/3 of deaths among women and newborns, including tetanus[5]. Increasing institutional deliveries can also play an important role in reducing NT, provided there is adequate attention to quality of care and infection control practices in health facilities. Although evidence illustrates the efficacy of appropriate antenatal care (ANC), including immunization, and clean delivery by an SBA in reducing MNT, the least developed countries have low SBA and ANC coverage (Figures 2 and 3). Furthermore, primipara compared to multipara were found to have received fewer doses of TTCV during ANC [6].

The application of all or most appropriate strategies has enabled 41 of the 59 priority countries initially identified for MNTE to achieve elimination as of August 2016 (Figure 4).

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[3] Initially 57 countries that became 59 after independence of Timor Leste and South Sudan in 2002 & 2011 respectively

[4] "The challenges to boost ANC coverage & clean delivery and cord care to achieve MNTE in all districts." Presentation by Neelam Bhardwaj, UNFPA on March 30 to April 1, 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

[5] UNFPA. State of the World's Midwifery 2014. http://www.unfpa.org/sowmy.

[6] Peter Bjerregaard, Robert Steinglass, DM Mutie, et. al. "Neonatal Tetanus Mortality in Coastal Kenya: A Community Survey." International Journal of Epidemiology. Vol 22, no. 1. 1993. http://www.ncbi.nlm.nih.gov/pubmed/8449639.

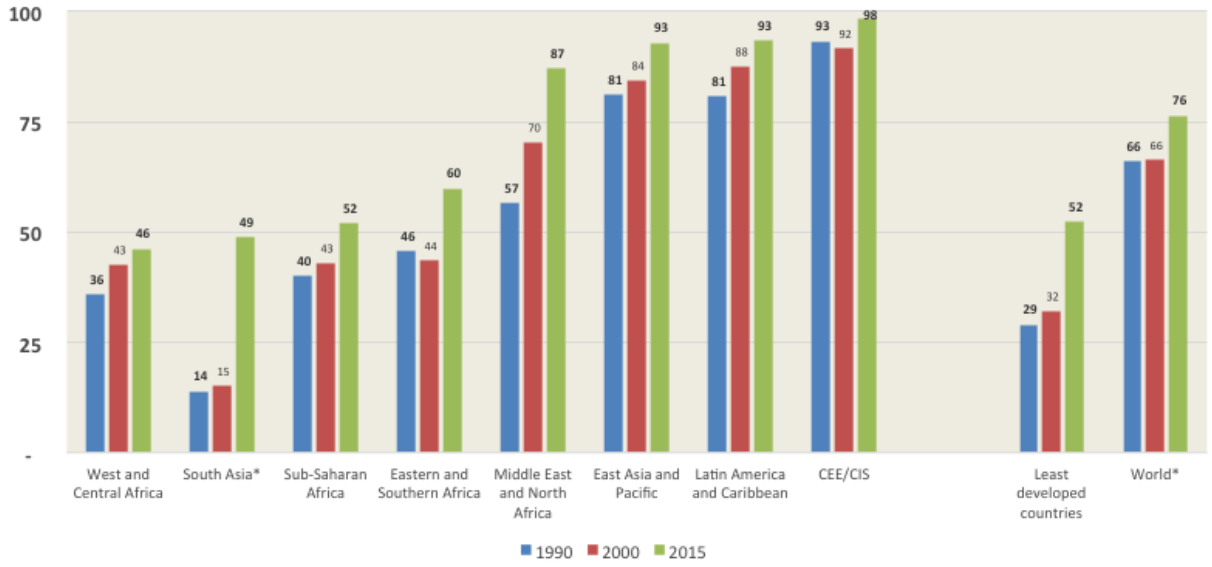

Figure 2. Percentage of births attended by skilled health personnel. Regional trends 1990, 2000, and 2015[7]. Source: UNICEF global databases 2015 based on MICS, DHS, and other nationally representative sources.

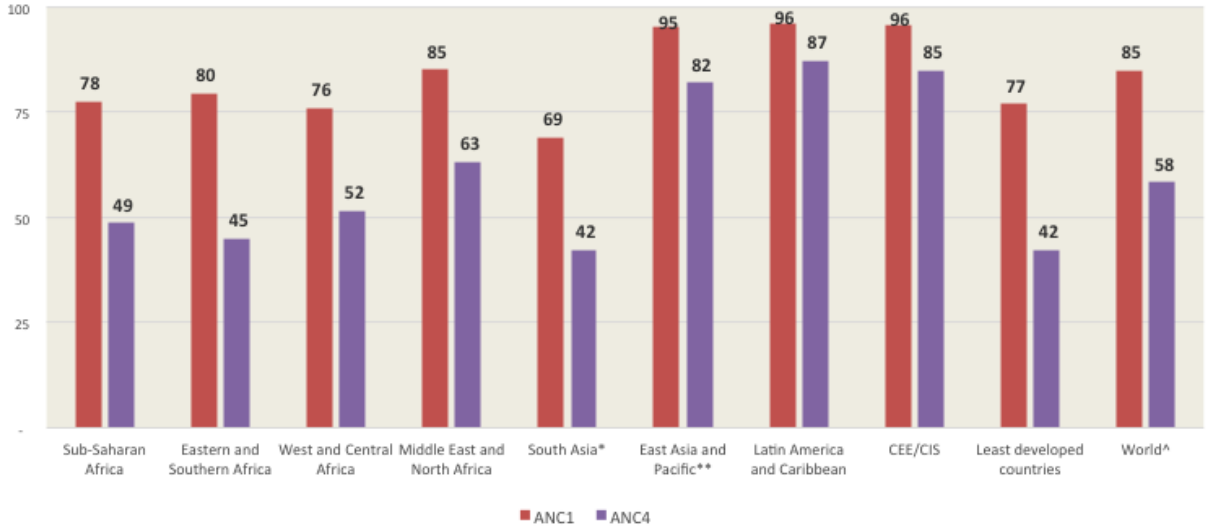

Figure 3. Percentage of women aged 15-49 years attended at least once (ANC1) during pregnancy by skilled health personnel (doctor, nurse or midwife), and percentage attended by any provider at least four times (ANC4) 2010-2015[8]. Source: UNICEF global databases 2015 based on MICS, DHS, and other nationally representative sources.

[7]1990 (1986-1997 median year 1992), 2000 (1998-2009 median year 2000) and 2015 (2010-2015, median year 2013). *South Asia region excludes India. Global estimates are based on a subset of 103 countries, covering 76% of births in 2015. Regional estimates represent data from countries covering at least 50% of regional births.

[8] ANC1 estimate for South Asia does not include India. ANC4 estimate for East Asia and the Pacific does not include China. Estimates are based on a subset of countries with available data for the period 2010-2015. The ANC1 analysis includes 107 countries covering 85% of births worldwide, and the ANC4 analysis includes 119 countries covering 85% of births worldwide. Estimates represent data from countries covering at least 50% of regional births.

The 18 countries that remain to eliminate MNT are Afghanistan, Angola, Central African Republic, Chad, Democratic Republic of the Congo, Ethiopia, Guinea, Haiti, Kenya, Mali, Nigeria, Pakistan, Papua New Guinea, Philippines, Somalia, Sudan, South Sudan, and Yemen (see Figure 4). The risk for MNT is often restricted to few districts in most of the remaining countries as a result of the elimination activities that have been implemented over the years (see Figure 4). However, there are six countries facing challenges in achieving MNT due to insecurity: Afghanistan, Central African Republic, Mali, Nigeria, Pakistan, and Yemen. Some of these countries have also struggled to eliminate polio.

Besides the difficulty with insecurity mentioned above, MNTE targets have been repeatedly missed due to insufficient funding, ineffective communication and community engagement, ineffective integration of RMNCH and EPI platforms, weak health systems and competing priorities. Insecurity remains a major obstacle to access populations in need of vaccination. The use of compact single-dose pre-filled auto-disable injection device would permit not only trained health professionals but also community workers to provide TTCV to susceptible women living in such insecure areas. The studies conducted in several countries (Afghanistan, Burkina Faso, Ghana, Mali [9], Somalia, and Southern Sudan) showed that also community workers could successfully deliver vaccine using these devices outside of the cold chain to vaccinate individuals against tetanus during SIAs[,10,11]. The use of such devices was tested and shown to be effective in TT SIAs in pilot studies in several countries that include Afghanistan, Chad, Ghana, Mali and Somalia among others. These devices would be especially useful in achieving MNTE countries such as: Afghanistan, Central African Republic, Chad, Nigeria, Pakistan, Somalia, South Sudan, Sudan, and Yemen. Forty percent of women of reproductive age, as estimated by UNICEF, in these nine countries are inaccessible to either routine or supplementary TTCV immunizations (~18 million women)[11].

In order to accelerate the achievement of MNTE through SIAs in the remaining 18 countries, 98 million USD is required to conduct SIAs in high risk districts using regular injection practices and additional 50 million USD for compact single-dose pre-filled auto-disable injection devices to reach inaccessible populations in areas of insecurity. Given the current funding pledged, there is a shortfall of 87 million USD. Timely securing of funding support is essential to achieve MNTE in the remaining 18 countries.

[9] Presentation by BASICS II for WHO TechNet Consultation March 22-25, 2003, Antalya, Turkey. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.
[10] Glenton, C., Khanna, R., Morgan, C. and Nilsen, E. S. (2013), The effects, safety and acceptability of compact, pre-filled, autodisable injection devices when delivered by lay health workers. Trop Med Int Health, 18: 1002–1016. http://onlinelibrary.wiley.com/doi/10.1111/tmi.12126/full.
[11] "TT Uniject: Programmatic Needs vis-á-vis Availability." Presentation by Azhar A Raza, UNICEF on August 17, 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

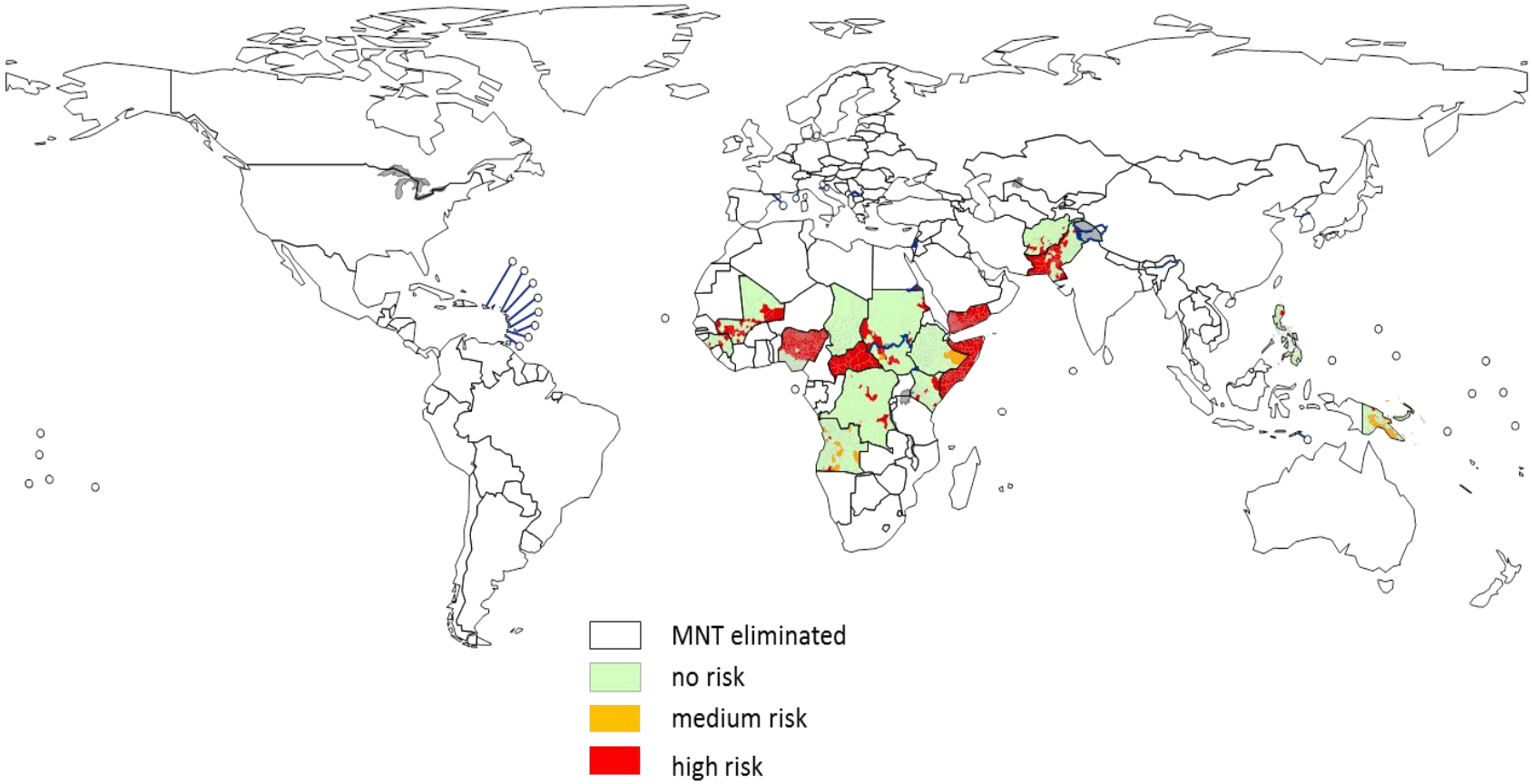

Figure 4. District MNT risk status in remaining 18 countries yet to attain elimination. Source: WHO/UNICEF database. Map production: Immunization, Vaccines, and Biologicals (IVB), World Health Organization

Factors contributing to achievement of MNTE

Many of the target countries identified in 1999 have achieved MNTE due one or several factors including: national commitment, timely availability and disbursement of resources, detailed micro-planning and quality implementation of SIAs, effective community engagement, monitoring and supervision of implementation, and integrated delivery of maternal and child health services, including clean delivery and cord care. Six[12] out of 41 validated countries achieved elimination without any supplementary vaccination campaigns, and basically relied on efforts to strengthen the health system.

There are several country examples of successfully overcoming challenges to eliminate MNT. India was able to achieve MNTE in 2015. Following the recognition of a significant burden of NT (150,000 to 200,000 estimated cases per year in the 1980s) in India, the country introduced TTCV immunization for pregnant women using ANC in the 1980s. In the last decade, India also created demand through conditional cash transfers for institutional delivery, strengthened the supply side, and conducted an intensive behavior change communication campaign, including the use of community mobilizers to promote clean cord care practices. Pregnant women are currently given two doses of TTCV four weeks apart. If the next pregnancy is within three years, one booster dose of TT is provided. India 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. India also used TT SIAs among women of reproductive age in a few selected high risk areas[13].

Indonesia is another example of a country that has achieved MNTE. Besides maternal immunization programme Indonesia introduced tetanus immunization using a school-based platform. In 1979, two doses of TT for pregnant women were introduced, and school immunization was introduced in the 1980s. The TTCV vaccination schedule in Indonesia is the primary series of TTCV in infancy, DTP4 at 18 months, DT in first grade of school, and Td in the second grade and third grades. There is a plan to postpone the third grade dose until fifth grade to prolong protection. This schedule is expected to provide protection against tetanus for approximately 25 years, which is most of the reproductive age of women. School based immunization against tetanus and diphtheria is routinely conducted nationwide every November in all public and private schools. Additionally, short term TT SIAs have been conducted in high risk districts for maternal and neonatal tetanus. Indonesia recently introduced universal health coverage for facility based delivery in 2015. The country has also focused on improving clean delivery and cord care practice and improving sensitivity of NT surveillance[14].

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[12] *China, Eritrea, Namibia, Rwanda, South Africa, Zimbabwe*

[13] Presentation on "India: Achieving MNT Elimination – Health Systems Approach" by Rakesh Kumar of the Government of India, 30 March to 1 April 2016.
http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

[14] Presentation on "Critical operational challenges to achieving at least 80% protection at birth from MNT in high risk districts" by Jane Soepardi, 30 March to 1 April 2016.
http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

These country examples illustrate that MNT can be successfully eliminated with appropriate strategies for immunization, clean delivery and cord care, as well as NT surveillance, combined with political commitment and resource allocation. Furthermore, Indonesia has shown that a school-based immunization platform can be an effective tool for certain countries to deliver TTCV for both sexes and provide high levels of long-lasting population immunity to tetanus. A 2009 WHO review of Indonesia, Malaysia, Sri Lanka, Syria, and Tunisia[15], noted several factors that contributed to successful school vaccination programmes, including high enrollment of both sexes, a strong primary health care system, strong central government support for supplies and equipment, collaboration between the Ministry of Health and the Ministry of Education, appropriate guidelines and training, cooperation of school and health care staff, and trust in the public health and education systems[16]. Countries that have achieved MNTE provide lessons on the important factors for success and potential strategies that can be used.

Sustaining MNTE

The working group reviewed a draft guide for sustaining MNTE in countries that have achieved MNTE. The guide proposes review of performance of tetanus elimination strategies in each district annually. This annual review exercise should be a joint exercise by the immunization programme, Maternal, Newborn and Child Health (MNCH), and surveillance managers together with partner representatives. The objectives of this review are: (i) to identify and classify districts that could potentially revert back to at risk for MNT; (ii) to select and tailor relevant corrective strategies and interventions to sustain MNTE in the short, and longer term; and (iii) to use this review as an opportunity to improve EPI and MNCH programmes with particular attention to optimizing the use of ANC and immunization platforms. The review of district performance aims at classifying districts' risk status for MNT that will guide the implementation of the corrective action to maintain the districts' elimination status.

The decision on corrective measures and immunization, ANC, SBA and NT surveillance approaches will have to take into account the country policy/strategy and local context, the district classification in "low risk" or "at risk" (medium and high risk) and specificities (main reasons for the low TT protection, assessing if it is a district wide or health facility catchment area specific issue) and the feasibility of implementing the corrective measures.

The Working Group's review of a draft UNICEF/WHO guidelines concluded that the draft document was complex and needed to be presented in two parts with one part focusing on the policy issues to sustain MNTE and the second part focusing on the operationalization of the required corrective activities to sustain elimination. There may also be a need for pilot testing or public consultation of the guidelines. The maternal newborn health group may

[15] School-based immunization http://www.who.int/immunization/programmes_systems/policies_strategies/school_based_immunization/en/.
[16] Presentation of "'New' Vaccination Platforms and Opportunities for TTCV Boosters" by Tracey Goodman of WHO, 18 August 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

also provide feedback. The emphasis on district level risk assessment is important, and it is important to sustain MNTE in a way that broadens the prevention of tetanus. Opportunities that include second year of life, adolescence, and school-based vaccination should be maximally utilized.

Sero-surveys could be used post-elimination to supplement the data from the reviews of district data and provide information immunity profiles in women of child bearing age and identify subpopulations with immunity gaps for corrective actions. However, in an ideal situation sero-surveys should aim to conduct comprehensive surveys that provide information of immunity profiles in both genders and all age groups, generate evidence for the need to introduce or scale up the coverage with booster doses, and identify areas and age groups for corrective action, as discussed later in this report.

Community engagement and effective communication are essential to achieving and sustaining MNTE. A review of systematic reviews was conducted to assess the impact of community-based interventions targeted at preventing MNT morbidity and mortality. The PICO (Population, Intervention, Comparator, Outcome) question was "What is the impact of community-based interventions on pregnant women and/or neonates compared to no intervention or alternative interventions in preventing maternal and neonatal deaths or increasing maternal immunization coverage?" The review yielded six systematic review articles. Of these, 3 assessed the impact of community based interventions on cause-specific neonatal mortality due to tetanus and 4 assessed the proportion of women with tetanus protection at birth. The review confirms that community-based interventions in low and middle-income settings are a valid strategy to decrease maternal and neonatal mortality and improve health outcomes in mothers and infants. However, the retrieved reviews provided little specific information on the effect of these interventions on reducing maternal and neonatal tetanus related mortality and little information on the impact on maternal tetanus immunization status.

In addition to improving immunization coverage, clean delivery and cord care practices, it is important to strengthen surveillance and reporting of neonatal tetanus, as part of more comprehensive surveillance for tetanus, and ensure that corrective action is taken when a neonatal tetanus case is documented.

Broader Tetanus Prevention

The working group also considered strategies for broader tetanus prevention, including a re-examination of routine immunization schedules. Strengthening implementation of routine immunization schedules will help sustain MNTE and prevent tetanus in other groups, including adolescents and adults, particularly males who currently do not receive the full complement of booster doses in many countries.

The current WHO position paper recommends three primary doses of DTP in infancy, a booster dose of dT at 4-7 years of age, a booster dose of dT at 12-15 years of age, and a

booster dose of dT in early adulthood[17]. 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.

Long term immunity

A review of published systematic reviews was conducted to examine vaccination schedules used for preventing tetanus and duration of vaccine-induced protection. The PICO (Population, Intervention, Comparator, Outcome) question was "What is the duration of continued protection (efficacy, effectiveness or immunity) against tetanus conveyed by a specific schedule of TTCV vaccination?" No publication on the continued duration of protection (>5 years after immunization) conferred by specific schedules of tetanus containing vaccines could be retrieved. However, sero-surveillance data were presented from multiple countries with different vaccination schedules and supported the understanding that several booster doses of TTCV after the primary infant series are necessary for life-long protection[18].

Population immunity following routine immunization and SIAs

Serological studies and case reporting in the European Union (n = 31 countries, population ~500 million) suggest that women of older age groups are most susceptible to tetanus but significant immunity gaps have also been identified in population groups refraining from vaccination due to religion or vaccine hesitancy and migrants from other parts of the world upon arrival in Europe[19].

Newer serologic data and case reports of tetanus from Africa illustrate an immunity gap in adult males as compared to females since females are primarily targeted for adolescent and adult vaccination due to MNT risk and many countries have not included childhood and adolescent booster doses in their national immunization schedules despite the already long standing WHO recommendations[20]. Among the 11.6 million Voluntary Medical Male Circumcisions (VMMC) performed under a programme for HIV prevention from 2008 to 2016, fifteen cases of tetanus were reported during 2012 to 2016, illustrating an immunity gap in adult males[21]. Routine reporting of tetanus cases is extremely inadequate in large parts of the world.

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[17]WHO. Tetanus vaccine: WHO position paper. Weekly Epidemiological Record, 2006. 20:81, 197-208.
[18] R Borrow, P Balmer, and MH Roper. The immunological basis for immunization series. Module 3: Tetanus Update 2006. http://apps.who.int/iris/bitstream/10665/43687/1/9789241595551_eng.pdf.
[19]Steens A, Mollema L, Berbeers GAM, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine 2010;28:7803-9. And the ECDC Annual report 2015. https://www.ncbi.nlm.nih.gov/pubmed/20875496.
[20]Presentation on "Tetanus serosurveys," by Heather Scobie and Alison Ridpath of CDC, 17-19 August 2016.
[21] Presentation on "HIV prevention through voluntary medical male circumcision and TTCV gaps for males," by Liz Miller of Public Health England and Julia Samuelson of WHO Department of HIV/AIDS, 18 August 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

Following the first reports of tetanus in newly circumcised men, the WHO HIV/AIDS Department examined hospital studies of non-neonatal tetanus in Sub-Saharan Africa published from 2003-2014 and found that 71% of the hospitalized tetanus cases were in males[22]. Recent data from sero-surveys conducted in Kenya, Tanzania, and Mozambique reveal disproportionately high immunity gaps in males 15 years and older (Figure 5). 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.

Furthermore, these data illustrate declining sero-protection rates in older children (5-15 years) in the absence of booster doses. Since early 2000, the national immunization programme in Mozambique has included two TTCV booster doses in first and second grades of school to boys and girls while Kenya and Tanzania do not. In the sero-survey Mozambique has high rates of seroprotection among children aged 5-14 while Kenya and Tanzania have lower rates of seroprotection[23].

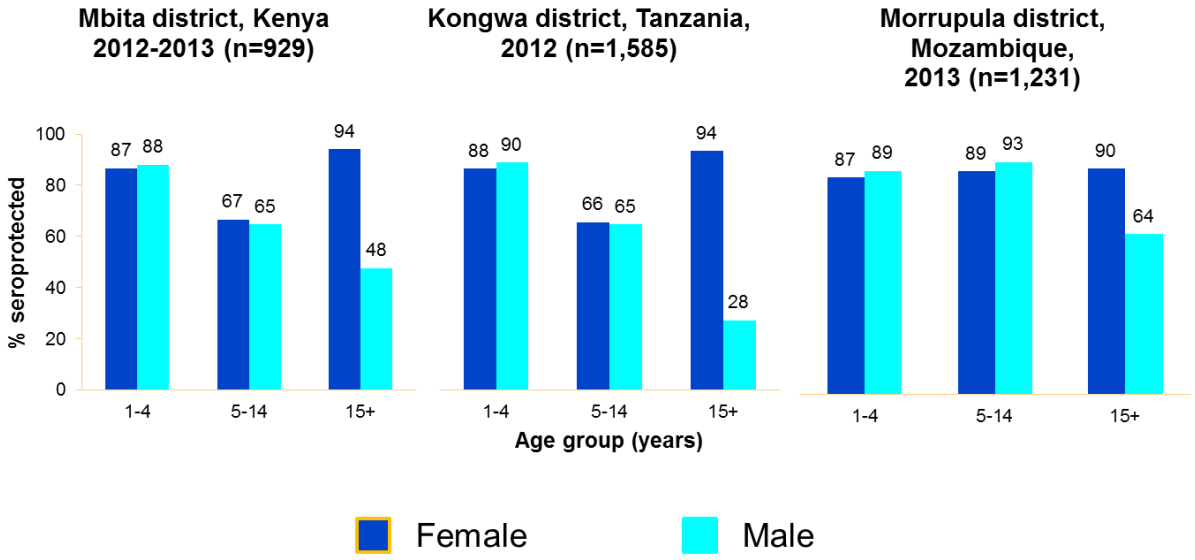

Figure 5: Results of percentage of sero-protected individuals at district level in three eastern and southern African countries. Source: Scobie et al, in press

Evidence shows need for improving coverage for primary doses of TTCV

The WHO UNICEF Estimates for National Immunization Coverage (WUENIC) show a global average coverage of DTP3 of 86% in 2015. Sero-surveys conducted in Eastern and Southern African countries support the JRF results that 85-90%, irrespective of gender, were shown to have protective levels of tetanus antibodies in the age group 1-4 years. Only

[22] Dalal S, Samuelson J, Reed J, Yakubu A, Ncube B, Baggaley R. Tetanus disease and deaths in men reveal need for vaccination. *Bulletin of the World Health Organization*. 2016;94(8):613-621. doi:10.2471/BLT.15.166777. https://www.ncbi.nlm.nih.gov/pubmed/27516639.

[23] Tetanus immunity gaps among adult men in Kenya, Tanzania, and Mozambique revealed by multiplex serologic surveillance by Scobie et al., In press, American Journal of Tropical Medicine & Hygiene.

if coverage reaches close to 100% for the primary series can elimination of all tetanus including MNT be achieved. The primary series is the basis for life long immunity. Noting the historical low coverage with the primary series of TTCV in many countries, all opportunities for providing primary series for those who missed these doses in infancy should be fully utilized.

Evidence shows need for providing booster doses of TTCV

A 2nd year of life booster is recommended for pertussis and diphtheria, and 2009 serologic data from 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[24]. Serologic data from Kenya, Tanzania and Mali supported the need for a TTCV booster at school-entry related to substantial drop in sero-protection at ≥5 years of age[25]. 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), Australia (2, 4, 6 and 18 months; 4 and 10–15 years), and England (2, 3 and 4 months; 12 months [Hib-Men C-TT conjugate]; 3.5–5 years and 13–18 years).

Opportunities for platforms to be used for booster doses

There are several platforms that provide opportunities to immunize with TTCV booster doses, including the second year of life, school-based vaccination, pre-adolescent and adolescent vaccination:

Opportunities for integration of TTCV boosters will differ among countries[16]. 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 HPV vaccination. Introduction of tetanus toxoid-conjugate vaccines where TT vaccine is used as a carrier protein, including meningococcal group A (MenAfriVac), meningococcal group C (Men-C), *Haemophilus influenzae* type b (Hib) represent another possible opportunity for a boost in population immunity to tetanus. Increased tetanus sero-protection has been shown in affected age cohorts following Hib/Men-C routine introduction in England, a Men-C catch-up campaign in the Netherlands, and MenAfriVac catch-up campaign in Mali[25].

Improved surveillance for tetanus cases needed

It was mentioned already in the background that many countries in the world do not have adequate surveillance for tetanus cases, including neonatal tetanus. As with other diseases

[24] Wagner KS, White JM, Andrews NJ, Borrow R, Stanford E, Newton E, et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine. 2012;30:7111–7. http://www.ncbi.nlm.nih.gov/pubmed/23022148.
[25] Basta NE, Borrow R, Berthe A, et al. Higher Tetanus Toxoid Immunity 2 Years After PsA-TT Introduction in Mali. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2015;61(Suppl 5):S578-S585. http://www.ncbi.nlm.nih.gov/pubmed/26553691.

targeted for elimination, due attention should be paid to improving surveillance and reporting of tetanus cases as part of national integrated disease surveillance efforts.

The working group noted that the neonatal tetanus elimination rate of 1 case per 1000 live births is high compared to other disease targets that often are in the range of 1 case per 100,000 or even lower. However, it would be difficult to change the target so late in the MNTE process so it was viewed better to find ways to capitalize on the current elimination environment. It was also noted that in the absence of high quality surveillance, incidence rates below this level would be difficult to measure. Currently, lot quality assurance surveys in the worst performing districts are used for validating that the threshold of less than 1 case per 1000 live births is met. Surveys to detect lower thresholds would be extremely resource intensive.

Using NT surveillance to monitor MNTE can be a powerful tool and can reveal health system failures. NT shows failure to reach women with TTCV, failure to provide service for clean delivery, and failure to provide adequate clinical services when mothers or newborns are affected by tetanus. NT finds the vulnerable, such as women that have no ANC and no TTCV vaccination, women who attend ANC but do not receive TT vaccination, and women who deliver at a health facility or with a midwife but the practices are unclean. Surveillance has a critical role to reveal causes of MNT and assist in finding practical solutions.

Community based NT surveillance can help to identify NT cases that die in the community and may not be reported to health care workers. However, it requires an extensive network, training, supervision, and investigation. An option may be to do community sensitization so the community will report cases to the health center and the health center can investigate or obtain district level support.

Improving NT surveillance may require integration with vital event registration and reporting, including neonatal deaths, that can then be investigated. This needs to be seen in the context of child survival, not only neonatal tetanus. A feasible imperfect solution is better than a perfect unrealistic option. It is important to have realistic expectations for NT surveillance. Rather than finding every last case, finding a few cases can provide important information. There is also no background rate like with AFP surveillance so it can be difficult to measure surveillance quality.

NT surveillance needs to play a relevant role to identify continued risk areas and corrective actions after validation. Surveillance needs to be supplemented by other relevant data on immunization, ANC, delivery, and cord care practices. The aim is to comprehensively understand and assess systems aspects. There are feasible and practical actions that can be taken to improve NT surveillance. The investigation of one NT case can provide information about the needs of the community.

Maternal deaths audit can also provide useful information on maternal tetanus.

Monitoring immunity gaps

Sero-surveys may play an important role in assessing immunity gaps across all age groups in both genders to inform corrective actions (e.g., catch-up campaigns of groups shown to have immunity gaps or introduction of booster doses). Data from sero-surveys could also be used along with other data in assessing risks and taking required corrective actions to sustain MNTE.

Sero-surveys may give a more accurate measure of tetanus immunity than administrative coverage or surveys. One study assessed administrative DTP3 coverage, surveyed DTP3 coverage, and sero-protection among 12-23 month old children in three districts in Ethiopia and found that serology showed lower percentages of protected individuals than administrative coverage data but higher percentages than coverage survey data, probably due to faulty maternal recall and incomplete documentation of vaccination records (Figure 6)[26]. Studies in Burundi, Central African Republic, and Cambodia comparing protection at birth (PAB) to sero-protection in women of reproductive age have also shown differences in the two measures[27,28,29]. For example, in Cambodia, sero-protection in parous women 15-39 years of age was 97% while PAB using coverage data was estimated to be 83%[29]. In some cases, PAB may underestimate the percentage of women protected when compared to serology results due to residual immunity from TTCV in infancy, booster doses given outside routine immunization services, and misclassification when using the PAB method due to lack of documentation and recall bias.

Furthermore, tetanus serology could be performed using a multiplex testing platform, which would allow for the testing of multiple antigens across public health programmes to reduce the cost. However, the choice of laboratory test used is important for validity of sero-survey results.

In-vitro tests exist that have been validated as accurate at the accepted standard for sero-protection (≤0.01 IU/ml based on *in-vivo* neutralization), but they are not commercially available (e.g., competition ELISA, double-antigen ELISA, toxin-binding inhibition, multiplex bead assay). Indirect ELISAs are not accurate <0.2 IU/ml because they detect both neutralizing and non-neutralizing antibodies, requiring use of a higher cutoff (e.g., 0.2 IU/ml)[30]. Commercial options for indirect ELISA exist, but none has been validated against

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[26]Travassos MA, Beyene B, Adam Z, Campbell JD, Mulholland N, Diarra SS, et al. (2016) Immunization Coverage Surveys and Linked Biomarker Serosurveys in Three Regions in Ethiopia. PLoS ONE 11(3): e0149970. http://www.ncbi.nlm.nih.gov/pubmed/26934372.

[27]WHO. Expanded programme on immunization –estimating tetanus protection of women by serosurvey. Weekly Epidemiological Record, 1996, 71(16): 117-24. http://www.ncbi.nlm.nih.gov/pubmed/8775796.

[28] Deming MS, Roungou J-B, Kristiansen M, et al. Tetanus toxoid coverage as an indicator of serological protection against neonatal tetanus. *Bulletin of the World Health Organization*. 2002;80(9):696-703. http://www.ncbi.nlm.nih.gov/pubmed/12378286.

[29]Scobie HM, Mao B, Buth S, Wannemuehler KA, Sørensen C, Kannarath C,Jenks MH, Moss DM, Priest JW, Soeung SC, Deming MS, Lammie PJ, Gregory CJ. 2016. Tetanus immunity among women aged 15 to 39 years in Cambodia: a national population-based serosurvey, 2012. Clin Vaccine Immunol 23:546–554.10.1128/CVI.00052-16. https://www.ncbi.nlm.nih.gov/pubmed/27053629.

[30] Matos D.C.S., Marcovistz R., Cabello P.H., Georgini R.A., Sakauchi D., Leite L.L. Immunogenicity test of tetanus component in adsorbed vaccines by Toxin Binding inhibition test. Mem Inst Oswaldo Cruz.2002;97:909–913. https://www.ncbi.nlm.nih.gov/pubmed/12386721.

in vivo or *in vitro* tests accurate at the 0.01 IU/ml threshold for sero-protection. In addition to concerns of misclassification bias related to using higher cutoff for indirect ELISA, performance of individual tests appears variable with some commercial tests having documented issues with accuracy and precision[31].

WHO could play a crucial role in establishing a tetanus laboratory network supporting diagnostics and sero-surveys.

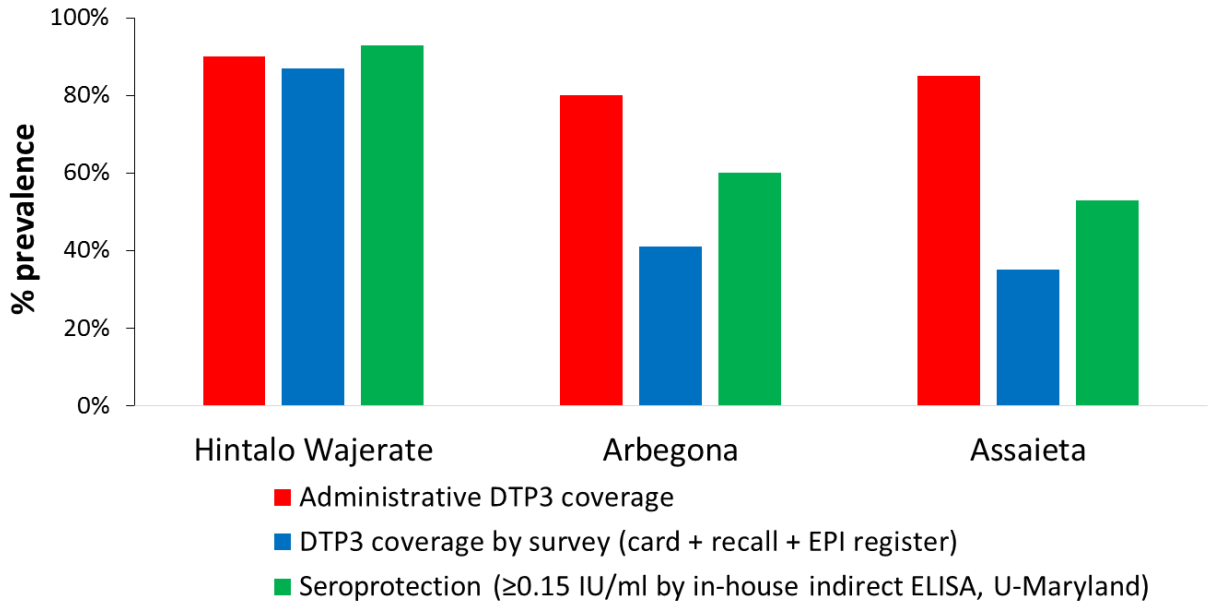

Figure 6. DTP3 coverage by administrative data and survey and tetanus seroprotection among 12-23 month old children in three districts in Ethiopia, 2013. Data source: MA Travassos, B Beyene, Z Adam, JD Campbell, N Mulholland, SS Diarra, et al. Immunization coverage surveys and linked biomarker sero-surveys in three regions in Ethiopia. PLoS ONE 2016; 11(3): e0149970.

Proposed revision of the WHO Tetanus position paper

The Working Group agrees on the need to revise the tetanus position paper with the understanding of the need for a clear decision from SAGE if any recommendation from the position paper needs to be changed or if any new recommendations are added. The Working Group would need to present SAGE with necessary evidence if any recommendation needs to be changed.

The justification for updating the position paper is based on:

[31] Van Hoeven KH, Dale C, Foster P, Body B. Comparison of Three Enzyme-Linked Immunosorbent Assays for Detection of Immunoglobulin G Antibodies to Tetanus Toxoid with Reference Standards and the Impact on Clinical Practice . *Clinical and Vaccine Immunology : CVI*. 2008;15(12):1751-1754. doi:10.1128/CVI.00254-08. https://www.ncbi.nlm.nih.gov/pubmed/18845832.

- Need to clarify for countries what type of vaccine they can use for different booster doses (options for TTCVs including DTP, DT, Td, pentavalent, hexavalent, etc.; no clarity on age at which Td can be used)
- A booster dose during the second year of life is currently not mentioned while both diphtheria and pertussis are recommended at this age
- Current age range recommended for administration of booster doses do not correspond to opportunity platforms as, for example, the adolescent booster
- Provision for catch up in older children, adolescents and adults if desired schedule not met during childhood
- The technical contents in the tetanus, diphtheria, and pertussis papers need to be harmonized.

Conclusions & Recommendations

Based on its review of the evidence, the WG concluded that the recurrent failure to meet MNTE targets was a reminder of persisting inequities in access to health services. The review also exposed immunity gaps in older age groups, especially among males because of focusing solely on maternal and neonatal tetanus.

The working group proposes the following draft recommendations for consideration by SAGE.

General Recommendations for MNTE

- Countries, international organizations and development agencies should consider prioritizing the implementation of all adopted strategies to achieve and maintain MNTE, including routine immunization of pregnant women, routine antenatal care (ANC), clean delivery and cord care and surveillance of MNT cases

- Achievement and maintenance of MNTE should be seen as a key indicator of universal health coverage since the disease mainly affects the most underserved and marginalized populations.

- There should be greater involvement and oversight by the WHO Regional Offices and regional immunization technical advisory groups in monitoring progress and ensuring that the global goal of MNTE is achieved, especially in the WHO regions with countries yet to achieve elimination. The regional immunization technical advisory groups should play an important role in advocating for the actions required from countries and partners especially WHO, UNICEF and UNFPA.

Specific recommendations for countries yet to achieve elimination

- Countries yet to achieve MNTE should establish/update and implement their operational plans to meet required timelines as indicated in Table 1. MNTE by 2020 to coincide with the end of the Decade of Vaccines (DOV) is feasible if timely availability of financial resources and innovative technologies (injection devices) is made available to reach the most marginalized.

- Countries should reinforce surveillance for MNT to assure accurate measurement of progress towards MNTE.

- UNICEF, UNFPA, and WHO should support countries in securing the necessary resources to implement their national elimination plans, including for procuring vaccines and for covering operational costs for SIAs.

- UNICEF, UNFPA, and WHO should make all efforts to secure timely supply of the available WHO pre-qualified tetanus toxoid vaccine in compact single-dose pre-filled auto-disable injection devices to facilitate vaccination of inaccessible populations by community workers.

- Should the supply of TT vaccine in this latter presentation be less than expected, a clear plan for prioritizing and allocating available doses should be established.

UNICEF, UNFPA, and WHO should urgently develop an MNTE investment case and resource mobilization strategy to secure funding support from potential donors, as predictable and timely resources are needed to fund operational costs of TTCV SIAs, compact one dose pre-filled auto-disable injection devices and validation surveys in the remaining 18 countries, if the 2020 elimination timeline is to be met.

Table 1. Prospect toward attainment of MNTE for the remaining 18 countries

Country category and definition	***List of countries in this category***	**Required action**	**Proposed Timelines**
Countries at lower risk and likely to attain MNTE by 2018 – • Funds available for completion of all planned MNTE activities	Angola, Chad, DRC, Ethiopia, Guinea, Haiti, Kenya, Philippines, South Sudan	Conduct SIAs for WRA in targeted high risk areas with close monitoring to assure quality	By mid-2017
		Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach.	By end-2017
		Validation of elimination	By mid-2018
		Development and implementation of sustainability plan	By end-2018
Countries at moderate risk and likely to attain MNTE by 2019 – • Most funds available • Relatively large proportion of WRA still to reach with quality SIAs • Low to medium level of insecurity	Papua New Guinea, Somalia, Sudan	Advocacy to secure funding (domestic & donor) to conduct TTCV SIAs in high risk areas	By end-2016
		Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach	By mid-2018
		Improve access to TTCV with the compact single-dose pre-filled auto-disable injection devices	By mid-2018
		Complete SIAs for WRA in targeted high risk areas with close monitoring to assure quality; use lessons learnt from experiences with polio vaccination in conflict affected areas	By end-2018
		Validation of elimination	By mid-2019
		Development and implementation of sustainability plan	By end of 2019

Country category and definition	***List of countries in this category***	**Required action**	**Proposed Timelines**
Countries at substantial risk and likely to attain MNTE by 2020 -· • Most funds not yet available • Existing substantial level of insecurity including active conflict • Weak health systems with serious access issues with relatively large proportion of WRA still to reach with quality SIAs • Other public health emergencies including polio	Afghanistan, Central African Republic, Mali, Nigeria, Pakistan, Yemen	Enhance advocacy to secure funding (domestic & donor) for conducting TTCV SIAs for WRA in high risk areas	By end of 2017
		Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach.	By end-2018
		Provide TT in compact single-dose pre-filled auto-disable injection devices to improve and enhance access to TTCV	By end-2018
		Conduct SIAs with close monitoring to assure quality in all high risk areas; use lessons from polio vaccination in areas of conflict.	By end-2020
		Validation of elimination	By mid-2021
		Development and implementation of sustainability plan	By 2021

Specific recommendations to sustain MNTE for all priority countries that achieved elimination since 1999

- UNICEF, UNFPA and WHO should work with countries to generate and sustain political interest in the continuing elimination of MNT to guard against complacency once a country has been declared to have eliminated the disease.
- 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. All countries should also scale up and sustain the coverage with clean delivery and improve clean cord care practices.
- Annual monitoring of MCH, Surveillance and EPI district performance through joint desk review of core[32] and surrogate[33]. MNT risk indicators is a useful and appropriate method to identify high risk districts and monitor potential MNT risk. Findings should be used to implement corrective measures for immunization and MCH services.
- TT campaigns should be conducted in the districts identified as high risk, based on core and surrogate risk indicators to fill immunity gaps.
- Steps should be taken to improve the quality of monitoring, case investigation, and reporting of tetanus cases as part of broader process; these data, rather than other surrogates, should eventually be the mechanism for monitoring sustained MNTE

Recommendations for achieving broader tetanus prevention

- 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. 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. Further, booster doses late in life may be needed due to waning immunity.
- WHO should re-emphasize the previous recommendations[34] on the number of doses needed in pregnant women and clarify that pregnant women are protected when they have six documented doses (by card, immunization registry and/or history) during the time of reproductive age in order to avoid unnecessary repeat vaccinations for protection during pregnancies. A standard algorithm for determining tetanus protection based on vaccination history and expected duration

[32] TT2+ coverage, Skilled birth attendance coverage, neonatal tetanus rate per 1000 live births
[33] ANC coverage, DTP1 & DTP3 immunization coverage, and percentage of population urban vs. rural
[34] WHO. Tetanus vaccine: WHO position paper. Weekly epidemiological record, 2006. 20:81, 197-208. http://www.who.int/immunization/policy/position_papers/tetanus/en/.

of protection should be employed to determine whether a dose is needed in the current pregnancy.

- Available sero-survey data and disease burden show declining sero-protection with increasing age and shift in ages of cases in the absence of booster doses. These data, as well as recent tetanus cases in the Voluntary Medical Male Circumcision programme, highlight the immunity gap in both females and males in different parts of the world. Updated WHO recommendations should reinforce the need for booster doses for both males and females across the life course and opportunistic catch up immunization, especially among males and the elderly. A booster dose is needed in all when exposed to specific risks.

- WHO should re-emphasize and track adoption of the recommendation that age appropriate combinations of tetanus and diphtheria toxoids should be used to promote and sustain diphtheria immunity across the life course and for both sexes and should clarify that tetanus antigen combined with low-dose diphtheria antigen (Td) is the preferred programme option for children who are 4 years of age and older.

- The use of sero-surveys to validate assessment of risk from other data sources should be considered 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.

- WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in sero-surveys.

- WHO should also provide guidance on sampling methods; sample collection and testing; and analysis, interpretation and use of sero-survey data.

- Achieving and sustaining tetanus elimination in every district is a signal of a country's ability to universally and equitably reach its underserved populations.

Annex 1: SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention Membership

SAGE members

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Experts

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- Robert Steinglass, Director Immunization Center, John Snow, Inc., USA

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