MALE CIRCUMCISION FOR HIV PREVENTION

MEETING REPORT

WHO INFORMAL CONSULTATION ON TETANUS AND VOLUNTARY MEDICAL MALE CIRCUMCISION

9 – 10 MARCH 2015, GENEVA, SWITZERLAND

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ACRONYMS AND ABBREVIATIONS

AE	adverse event
DTP 3	diphtheria-tetanus-pertussis vaccine (third dose)
IgG	immunoglobulin G
PEPFAR	The United States President's Emergency Plan for AIDS Relief
SIA	supplementary immunization activity
TAG	Technical Advisory Group on Innovations in Male Circumcision
TTCV	tetanus toxoid-containing vaccine
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VMMC	voluntary medical male circumcision
WHO	World Health Organization

EXECUTIVE SUMMARY

Since the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended in March 2007 that male circumcision should be regarded as an additional method of HIV prevention, voluntary medical male circumcision (VMMC) programmes have been implemented in 14 priority countries in east and southern Africa that have generalized HIV epidemics and low prevalence of male circumcision. By the end of 2014, an estimated cumulative total of 8.9 million male circumcisions had been performed, over 95% using the forceps-guided or dorsal slit surgical procedures. Innovative methods using circumcision devices are being developed, evaluated and rolled out. They have the potential to simplify the procedure and to increase the acceptability of circumcision.

By 2014 as part of the ongoing safety monitoring of VMMC programmes by WHO and The United States President's Emergency Plan for AIDS Relief (PEPFAR), nine cases of tetanus were reported, of which six resulted in death. WHO issued an Information Note (8 December 2014) suggesting interim actions for national programmes and partners, including on the currently WHO-prequalified elastic collar compression device which expanded on the manufacturer's Field Safety Notice issued November 2014. In addition, WHO convened a consultation on 9–10 March 2015 to assess tetanus risk associated with VMMC and different circumcision methods (surgical, elastic collar compression-type devices and collar clamp-type devices). The consultation also considered various clinical risk mitigation strategies, including tetanus immunization, in the context of the 2007 WHO recommendations on VMMC for HIV prevention and the 2006 WHO position paper on tetanus vaccination for general population protection.

This consultation report:

- shares details on the discussions on VMMC and tetanus risk;
- provides advice from WHO, based on the inputs of the experts, to programmes for their consideration concerning near-term risk mitigation of tetanus by VMMC services;

This report supersedes the Information Note of 8 December 2014, mentioned above.

The meeting held an in-depth discussion of the different circumcision methods available, their known safety profiles, the tetanus cases occurring after circumcisions performed for HIV prevention within VMMC programmes, the pathogenesis and burden of tetanus, the immunology of tetanus vaccination and vaccination policies in some VMMC focus countries. Following this discussion, the experts advised WHO and national programmes to minimize the risk of these rare but life-threatening events through interventions that would limit the burden on clients, providers and programmes and that would maintain the momentum of VMMC scale-up to further reduce the incidence of HIV. The risk of tetanus infection for all circumcision procedures, including circumcision with devices, may be mitigated through a **dual approach** of "clean" care and vaccine interventions for improved infection prevention and control.

The **clean care approach** includes:

- Encouraging personal cleanliness, which includes asking the client to wash his genital area, including under the foreskin, before circumcision and encouraging him to wear clean undergarments;
- Following standard surgical protocols on skin preparation of the genital area, which is relevant for all circumcision methods.
- Enhancing individual and community education on clean wound care after circumcision, which includes clear and understandable instructions on wound care and genital hygiene, clean/sterile dressings to use at home, clear instructions on when to return to the health-care facility for post-procedure care, and education on the benefits of vaccination against tetanus and the dangers of applying potentially *Clostridium tetani*-containing substances (such as animal dung poultices, herbal remedies) to wounds.

In addition to the risk mitigation steps outlined above, the following steps were advised when using the currently available elastic collar compression device:

- Providers should be trained to fully retract the foreskin without forcing, and to thoroughly clean with an appropriate antiseptic such as povidone-iodine, unless the client is allergic, three times on the genital area including under the foreskin followed by a two-minute wait prior to device placement; and at the time of device removal, clean with an antiseptic before cutting away necrotic foreskin, again before removing the O-ring and inner rings, and again after removal of the rings and prior to applying the dressing.
- Clients whose foreskins cannot be fully retracted easily should be offered conventional surgical circumcision under local anaesthesia.
- Any new clean care procedures should be properly validated for safety, effectiveness and feasibility before their addition to the instructions for use, including mitigation of odour while wearing the device.

Mitigating the risk of tetanus through vaccination was also advised for all circumcision methods.

- The primary goal of tetanus vaccination in the context of VMMC for HIV prevention is to reduce risks of tetanus

associated with circumcision to as low as possible, including risks related to contamination through poor hygienic conditions and practices. Tetanus vaccination in VMMC services will additionally benefit the implementation of WHO vaccination recommendations for children, adolescents and adults to reduce the risk of tetanus from other wounds.

- Ministries of health are advised to develop and phase-in effective and practical delivery strategies for providing tetanus vaccination in the context of their VMMC for HIV prevention and vaccination programmes. The most suitable schedule and delivery strategy would ideally be informed by reliable data on immunity levels in the community. But, as there is no herd immunity to tetanus, the individual's documented personal vaccination history remains a critical consideration on the doses needed, together with the feasibility of different VMMC service delivery approaches.
- The WHO schedule on tetanus toxoid-containing vaccine (TTCV) for adolescent and adult men serves as the basis for decision-making on the timing and number of doses needed for protection. The consultation recognized the limited data available, and the uncertainties related to the lack of individual vaccination history and the timing of an antibody response in the context of VMMC. When an individual's tetanus toxoid vaccination status is known, however, his status should guide decisions on vaccination dose needs
- The consultation advised that, unless an individual has documented evidence of receipt of a full five- to six-dose TTCV series, at a minimum, a single TTCV dose be administered prior to or at the time of male circumcision, recognizing that this dose will provide varying levels of protection, depending on the individual.
- In an individual who received a three-dose infant series or who received a previous dose in adolescence or adulthood:
  - **where feasible,** a TTCV booster dose should be given preferably 14 (but at least 7) days before the VMMC procedure (conventional surgery or device placement) for adequate protection.
  - Providing the TTCV booster dose at the time of the procedure may allow, but cannot guarantee, the production of some anti-tetanus toxin antibodies for partial protection within a few days.
- In an individual who never received any TTCV dose, a single dose does not provide protection. Two TTCV doses four weeks apart, with the second dose preferably 14 days, but at least 7 days, before the VMMC procedure are needed for protection against tetanus. This most cautious vaccination strategy should be considered: where few men are likely to have had prior TTCV doses and the tetanus burden is moderate to high.
  - A TTCV could also be provided at a post-operative follow-up visist, at least four weeks after the previous dose.

Based on the above information, the consultation participants advised that, in addition to infection prevention through rigorous surgical skin preparation including improved device-specific protocols, and interventions to improve good wound care, VMMC programmes should consider phasing-in TTCV prior to, or at the time of, circumcision. Circumcision services provide an opportunity to enhance both aspects of the dual approach to tetanus risk reduction by improving "clean" care and offering tetanus vaccination for males. Post-market surveillance for all devices and safety monitoring for all circumcision methods should include reporting of serious adverse events (AEs) such as tetanus cases to the national programme, the manufacturer and WHO.

INTRODUCTION

Since World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued recommendations in March 2007 that male circumcision should be regarded as an additional method of HIV prevention, voluntary medical male circumcision (VMMC) programmes have been implemented in 14 priority countries in east and southern Africa with generalized HIV epidemics and low prevalence of male circumcision. By the end of 2014, it is provisionally estimated that a cumulative total of 8.9 million male circumcisions had been performed, the great majority using the forceps-guided and dorsal slit surgical procedures.

Meanwhile, innovative methods using circumcision devices are being developed. They have the potential to simplify the procedure and increase the acceptability of circumcision. WHO developed the *Framework for clinical evaluation of devices for male circumcision* (*1*) that defines the characteristics of such devices and the clinical evidence necessary to demonstrate their safety, efficacy, suitability and acceptability in VMMC programmes. WHO initiated a prequalification programme for male circumcision devices to assess the safety and performance of the devices and the quality of the manufacturing system to ensure safe, good quality devices for purchase and use in public health VMMC programmes for HIV prevention. WHO also developed a *Guideline on the use of devices for adult male circumcision for HIV prevention* (*2*), which conditionally recommended the use of WHO-prequalified devices by trained providers. The *Guideline* advised a phased rollout with post-market surveillance, including safety monitoring to identify events that may be rare but serious.

Several manufacturers of male circumcision devices have requested assessment of their products through WHO's Prequalification of Male Circumcision Devices Programme.[1] WHO prequalified an elastic collar compression type device in 2013. A second device, a collar clamp type, had almost completed all prequalification components at the time of this consultation and was subsequently prequalified on 8 June 2015. (Up-to-date information on circumcision devices is available on the WHO website.[2])

As part of the ongoing WHO and PEFPAR safety review of VMMC procedures, WHO requested data from VMMC programmes on serious and moderate AEs that had occurred during 2013–2014. PEPFAR also requested and compiled reports of deaths and serious adverse events from all implementing partners. Among the results (some reported events occurred prior to 2013) nine cases of tetanus were reported – two in 2012, one in 2013 and the remaining six in 2014. The cases included six clients circumcised by a conventional surgical method and three by the currently available elastic collar compression device.

Tetanus is a severe and potentially fatal infection caused by the bacterium *Clostridium tetani,* spores of which are found in soil, dust and faeces of animals and humans. These bacterial spores can germinate in anaerobic conditions often found in wounds and produce a powerful neurotoxin that impairs inhibition of motor neuron activity. As a result severe muscle spasms ensue, producing the characteristic signs of tetanus disease, muscle spasms and paralysis of the voluntary muscles. The case fatality rate from tetanus can be high, particularly in low-resource settings. Among the nine cases, three recovered and six resulted in death.

In response to the reported tetanus cases, WHO issued an Information Note (8 December 2014) to programmes and partners on the situation and suggested interim actions including on use of the current elastic collar compression device, aligning with the manufacturer's Field Safety Notice issued November 2014.[3] In addition, WHO (through the Department of HIV, the Department of Essential Medicines and Health Products and the Department of Immunization, Vaccines and Biologicals) convened a consultation on 9–10 March 2015 to assess the potential risk of tetanus associated with circumcision and to advise on risk management strategies.

During the consultation the WHO Secretariat noted the success of the maternal and neonatal tetanus elimination initiative, which has reduced neonatal tetanus deaths by 94% since the 1980s. This has been achieved through a focus on tetanus toxoid vaccination, including boosters in pregnant women. A total of 37 among 59 countries still at high risk for maternal-neonatal tetanus have formally achieved elimination status by 2015 (defined as less than one case per 1000 births in every district). Countries have also given attention to providing the series of three diphtheria-tetanus-pertussis vaccines to infants. Given the challenges to ensure high vaccine coverage rates for infants, booster doses in childhood have received less attention. Similarly, there has been little emphasis on tetanus booster doses for male adolescents and men, leaving these people without protection, as the recent series of tetanus cases in the VMMC programmes illustrates. Integrating tetanus booster vaccination into circumcision programmes would be an important opportunity to boost tetanus immunity in this poorly served and vulnerable group. Moreover, this approach might help to allay negative rumours circulating in some communities that tetanus vaccination in pregnant women was designed

1 Information available at http://www.who.int/diagnostics_laboratory/evaluations/prequalification_male_circumcision_devices/en/

2 http://www.who.int/diagnostics_laboratory/evaluations/PQMCdevices_list/en/

3 Information available at www.prepex.com/wp-content/uploads/2014/12/CMT_FSN_001_2014.pdf.

to cause sterility. The WHO Secretariat also stressed the importance of maintaining the high safety record of the VMMC programmes, which is essential to their success and acceptability in the community. Through this consultation, WHO responded rapidly to the new challenges uncovered by the recently reported tetanus cases; WHO appreciates the contributions of the experts who participated.

Purpose

The purpose of the consultation was to provide information on tetanus risk associated with VMMC and specific circumcision methods (surgical, elastic collar compression-type devices and collar clamp-type devices), different proposed clinical risk mitigation strategies, host immune response with vaccination and the evidence required to demonstrate the safety, adequacy, timing and feasibility of risk mitigation approaches, including tetanus immunization in the context of VMMC programmes. Annex 1 presents the meeting agenda.

Participants and declarations of interests

The consultation participants had a range of experience and skills. They included infectious disease physicians, epidemiologists, immunologists, vaccinologists, medical microbiologists, surgeons directly involved in providing VMMC services, public health officials from countries implementing VMMC programmes and representatives of global HIV prevention and immunization programmes. Annex 2 presents the full list of participants.

Sixteen participants, as well as WHO staff and consultants from the three WHO departments, participated in the consultation. All external experts were asked to declare to WHO whether they had any financial, commercial or academic interests related to the subject matter of the consultation. Based on their submissions, WHO determined that three experts were considered to have potential conflicts of interest, and as a result, their participation was limited to the general discussions only. They did not participate in the formulation of advice and recommendations to WHO. For more information, see Annex 2.

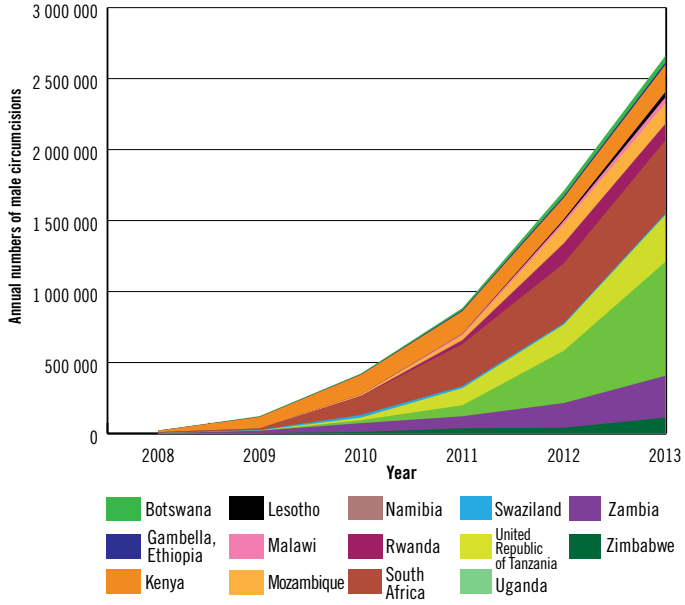
BACKGROUND

Voluntary medical male circumcision for HIV prevention

The meeting summarized the evidence demonstrating that circumcised men have a lower risk of acquiring HIV infection than uncircumcised men and the biological mechanisms that explain this lower risk; the conclusions and recommendations issued following the WHO and UNAIDS consultation on male circumcision for HIV prevention held in 2007 to review this evidence (*3*); the costs and impact which suggested that expanding circumcision services to 80% of adult men in 14 priority countries in east and southern Africa within five years would avert 3.4 million new HIV infections and result in a net savings of US$ 16.5 billion by 2025 in treatment costs averted (*4*). Since VMMC programmes began, evidence has shown that HIV incidence in the community has decreased in South Africa and Uganda (*5,6*).

In 2013 a total of 2.7 million male circumcisions were performed in the 14 priority countries, for a cumulative total of 5.8 million by the end of that year (Fig. 1). Provisional data show a cumulative total of 8.9 million male circumcisions through 2014.

Fig. 1: Annual number of medical male circumcisions performed in 14 priority countries in east and southern Africa, 2008–2013



Source: WHO/UNAIDS/UNICEF Global AIDS Response Progress Reporting

Male circumcision methods

An overview was provided of the procedures involved in performing circumcision by conventional surgical methods (as described in the WHO *Manual for male circumcision under local anaesthesia* (*7*)), by an elastic collar compression device and by a collar clamp compression device. While over 95% of all circumcisions in VMMC programmes have been performed using the forceps-guided method or the dorsal slit surgical methods, for men in whom it was not possible to fully retract the foreskin and clearly visualize the glans before the procedure, the dorsal slit is preferred. The sleeve resection method, another surgical method, was successfully used in one of the randomized trials on the efficacy of circumcision for HIV prevention, but it has not been widely used in VMMC programmes.

The elastic collar compression device, which had been prequalified by WHO in 2013, has been used in research studies and pilot implementation programmes. It is being progressively rolled out under active surveillance. By September 2014 approximately 25 000 circumcisions had been performed using this method. The collar clamp device has been evaluated in research studies and field studies in well-controlled environments.

The most important differences between the three methods are summarized in Table 1. In particular, the devices remain on the body for about seven days; the foreskin may or may not be removed at the time of device placement, depending on the device's mechanism of action. In contrast with surgical methods, neither device requires suturing to close the wound.

Table 1. Key differences between conventional surgical and device circumcision methods

Requirement	Conventional surgery	Elastic collar compression device	Collar clamp device
Anaesthesia	Injectable local anaesthesia required before the procedure.	Topical anaesthesia (cream) applied just before device placement.	Injectable local anaesthesia required before the procedure.
Sterility	Procedure performed under sterile conditions using sterile instruments and supplies.	Procedure requires clean, not sterile, environment.	Procedure performed under sterile conditions using sterile device, instruments and supplies.
Haemostasis	Diathermy or (absorbable) haemostatic sutures required.	Slow compression results in occlusion of circulation, ischaemia and necrosis; devitalized tissue removed after 7 days.	Clamp mechanism ensures tight compression and haemostasis.
Sutures	Absorbable sutures placed for wound closure.	No sutures required.	No sutures required.
Device and foreskin	Foreskin removed at time of procedure.	Device and foreskin removed at one week.	Foreskin removed immediately after device placement; device removed at one week.
Follow- up visit	Advisable but not required.	Visit on day 7 is required to remove necrotic foreskin and device. Further follow-up visits advisable but not required.	Visit on day 7 is required to remove device. Further follow-up visits advisable but not required unless complications.

WHO guidance on male circumcision methods

The WHO Secretariat summarized for the meeting WHO guidance on male circumcision methods and the data available on the safety of surgical and device circumcision methods. The incidence of AEs following surgical circumcision was low in the three randomized controlled trials that established the effectiveness of circumcision for HIV prevention. WHO's 2007 guidance that male circumcision be considered an additional method for HIV prevention included recommendations to carefully monitor circumcision safety as programmes were scaled up to reach large numbers of young men.

The WHO *Manual for male circumcision under local anaesthesia* (*7*) strongly emphasizes the safety of the surgical procedure; this was reiterated in the quality assurance guide and monitoring procedures (*8-10*). Given strong interest in innovative methods, including devices that might accelerate and expand access to circumcision for HIV prevention while maintaining safety, WHO developed the *Framework for clinical evaluation of devices for male circumcision* (*1*). The framework defines the minimum clinical evidence necessary to establish the suitability of devices for use within public health VMMC programmes, as well as procedures to monitor safety as programmes using circumcision devices expand beyond well-controlled research settings.

In 2013 WHO issued a conditional recommendation that WHO-prequalified devices can be used as an additional method of circumcision for HIV prevention among men at least 18 years old (*2*). This recommendation was based on data on safety, efficacy and acceptability from direct comparisons between circumcisions performed with elastic collar compression and collar clamp devices and conventional surgery as well as cohort studies in settings like those expected in programmes. The recommendation advised phased implementation, initially through pilot studies and then under surveillance for AEs – active then passive – as the new method is increasingly used in programmes. Since devices have different mechanisms of action and risk profiles, each must be monitored separately.

During safety monitoring in 2014, WHO noted that several tetanus cases had occurred within two weeks of circumcision. Given the high risk of death from tetanus and the need to ensure the lowest possible risk associated with circumcision performed on healthy men to prevent future HIV infections, the WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) recommended an in-depth investigation of circumcision and tetanus, which was initiated in October 2014.

Under the procedures for Prequalification of Male Circumcision Devices, WHO evaluates the clinical performance and technical characteristics of new technology as well as the manufacturer's quality management system. All manufacturers with a WHO-prequalified device are required to undertake post-market surveillance, which includes notifying WHO of all AEs associated with their device, reviewing all AEs, reviewing the risk assessment and taking corrective actions as necessary. Actions may include updating the device risk assessment, issuing field safety corrective actions and updating instructions for use. The manufacturer of the prequalified elastic collar compression device followed these procedures after the reported tetanus cases. WHO shared with the consultation participants proposed revisions to the instructions for use provided by the manufacturer, inputs of their experts and other materials.

MALE CIRCUMCISION AND TETANUS

Pathogenesis of tetanus infection

Tetanus is a severe and potentially fatal infection caused by the anaerobic bacterium *Clostridium tetani*, spores of which are found in soil, dust and faeces of animals and humans. The drumstick-shaped spores (Fig. 2) are widespread in nature, particularly in well-manured and alkaline soils. The spores are highly resistant and can survive in extreme conditions such as 10–15 minutes in boiling water, as well as alcohol, phenol and formalin disinfectants. The spores can be killed by iodine, sodium hypochlorite (household bleach), hydrogen peroxide and extreme heat. The spores may contaminate wounds and germinate in hypoxic environments. The vegetative *C. tetani* bacteria thrive and multiply in anaerobic conditions before releasing the potent neurotoxin tetanospasmin from the bacterial cell. In contrast to the spores, the bacteria are susceptible to and easily killed by common antiseptics.

Fig. 2. *C. tetani* bacteria and spores

Source: Phil.cdc.gov. Content provider - United States Centers for Disease Control

C. tetani is not an invasive organism and remains at the site of initial inoculation. The neurotoxin is absorbed from the site of infection into the lymphatic system and bloodstream, travels throughout the body and is taken up by the peripheral nerves. From there the neurotoxin may move into the central nervous system, where it impairs inhibition of motor neuron activity and gives rise to the typical clinical signs of muscle spasms and paralysis of the voluntary muscles. The severity of disease depends on the amount of toxin reaching the central nervous system. The incubation period from initial inoculation to onset of clinical symptoms is about seven days (range three to 21 days).

Tetanus is unique among vaccine-preventable diseases as it is not communicable (*11*). All individuals are susceptible to tetanus disease unless immunized with a proper course of TTCV, including booster doses to sustain protective immunity. Once tetanus toxin (tetanospasmin) has entered the central nervous system, it cannot be neutralized by circulating anti-toxin. To prevent tetanus, immunoglobulin must be present before toxin production and release to provide any degree of protection.

Tetanus risks by circumcision method

Possible risk factors common to all circumcision methods include individual and environmental factors such as personal hygiene, cleanliness of the home and environment, occupation and wound care practices. Before use of sterilized equipment was introduced, solutions and dressings, medical procedures, including surgeries and injections, were frequent causes of tetanus infections in industrialized countries (*11*). Possible procedural and facility-related risk factors include the effectiveness of skin preparation prior to circumcision and the sterility of instruments and consumables, including materials used for wound dressing. Wound complications that might increase tetanus risk include wound infection, infected haematoma and wound dehiscence.

Potential factors specific to conventional surgical methods include the quality of the suturing technique and of the diathermy or ligation of blood vessels, as well as the sterility of the suture materials (*12*). With the forceps-guided method, there is a small area of crushed tissue under the forceps before the foreskin is cut away; this is not present following dorsal slit or sleeve resection circumcision. It is unknown if this crushed tissue would the effect risk of tetanus. Potential risk factors identified with the collar clamp device include tissue remnants distal to the device after placement and excision of the foreskin. These remnants can become necrotic.

Risk factors for tetanus infection with the elastic collar compression device include the anaerobic environment between the necrotic foreskin and the healthy glans and potentially in the junction between the healthy tissue and the elastic compression ring on the proximal side of the device. The necrotic foreskin itself, while in theory isolated from the body by compression under the elastic compression ring, could be a risk factor, including the area under the foreskin against the glans. Other risk factors include tears or other skin breaches under the inner ring, particularly at the fraenulum at the time of placement or while wearing the device, due to movement and/or rubbing on garments, as well as possible skin breaches at the time of ring removal as the device is levered away from the healing tissue. Some bleeding during removal has been reported.

No literature was found on whether wounds healing by secondary intention were more or less prone to tetanus infection than wounds healing by primary intention, as occur following conventional surgical circumcision. However, wounds with devitalized tissue have been noted to provide the conditions for developing *C. tetani* infection and toxin production (*11*).

Penis microbiome

The meeting considered the data from the Rakai Health Sciences Program and the Johns Hopkins School of Medicine study on the microbiome of the uncircumcised and circumcised penis and a preliminary study among 22 men undergoing circumcision with the current elastic collar compression device. The first study assessed the microbiome at the coronal sulcus of men in the immediate and deferred circumcision arms of the randomized controlled trial conducted in the Rakai District, Uganda, at enrolment and after one year. At enrolment (before circumcision) the area under the foreskin was characterized by multiple anaerobic bacteria. The specimens taken from the coronal sulcus one year after circumcision revealed an environment typical of aerobic skin-associated bacteria and a decreased absolute abundance of penile bacteria (7.2-fold reduction in prevalence). There was no change in microbiota after one year among men in the group not yet circumcised (*13,14*). Additionally, the study team collected specimens from under the necrotic foreskin before removal of the elastic collar compression device from 22 men.[4] This showed a 6.2-fold higher prevalence and abundance of anaerobic bacteria prior to device removal compared with uncircumcised men from the previous study. While the team did not specifically probe for *C. tetani* bacteria, *C. perfringens* and other *C. spp.*, definite indicators of an anaerobic environment, were detected.

Adverse events with potential implications for risk of tetanus

In preparation for the TAG meeting in September 2014, WHO compiled data on AEs reported with the current elastic collar compression device that may be relevant to tetanus risk. The data on serious and moderate AEs came from 12 pilot studies conducted in eight countries, active surveillance with device introduction in Uganda and Zimbabwe and routine surveillance during implementation in Rwanda, totalling 24 640 placements. The overall rate of AEs was 8.6 per 1000 placements but was considerably higher in the pilot studies (31.7 per 1000 placements), possibly due to less experience on the part of the providers, more complete follow-up of clients or more careful AE reporting.

The most common serious and moderate AEs were associated with bleeding that required medical or surgical intervention such as cautery or sutures (44). The majority of these events occurred after device removal, but a small number occurred while wearing the device or during removal. A verbal report from the Botswana pilot programme indicated that bleeding on removal did occur and may have been related to the level of provider experience and skill at removing the device.

The most serious AEs associated with the prequalified elastic collar compression device were due to premature device removal or displacement within the first three days after placement. These cases involved acute pain and discomfort and gross swelling and blistering. They required prompt management by an experienced surgeon capable of managing the distorted anatomy. No cases of tetanus were reported following these events, but they imply a risk, given the devitalized tissue and open integument.

A small number of AEs occurred during device removal that required surgical intervention or special pressure dressing. In the pilot studies a large proportion of clients reported short, transient pain at the time of removal. This pain may be caused by the stretching of healthy tissue as the inner ring is freed from scar tissue, but this removal process also may cause minor tears in the skin proximal to the inner ring. It is not clear whether these tears might allow entry of any *C. tetani* bacteria present.

Two pilot studies in Uganda reported that about 75% of clients volunteered that they smelled an unpleasant odour while wearing the device, sometimes sufficiently unpleasant to interfere with normal daily activities. The odour was first noted at a median of four days after placement. Anecdotal reports indicated that the unpleasant odour was characteristic of anaerobic bacterial growth, although no definitive cultures or characterization were performed in the two studies (*15,16*). Gas production and associated fetid odour are also reported when *C. tetani* are grown in the laboratory (*11*).

Infections and wound disruptions were rare following device circumcision. In the randomized comparative trials and field studies reviewed by the TAG in January 2013, severe and moderate infection and disruption AEs occurred in six of 1983 placements of the collar clamp device used in the study (3.0 per thousand) and four of 2417 placements of the elastic collar compression device (1.7 per thousand) (*17*). In all subsequent studies, there were 22 severe and moderate infections and disruptions in 24 640 placements (0.89 per thousand – 2.6 per thousand in pilot studies and active surveillance and 0.23 per thousand from routine surveillance during implementation in Rwanda). By comparison, the total number of severe and moderate AEs due to infection and wound disruption reported in the three randomized controlled trials of surgical circumcision was 15 in 5230 procedures (2.9 per thousand) (*18-20*).

4 Liu CM et al., manuscript in preparation.

Reported tetanus cases

The meeting undertook a detailed review of the nine tetanus cases that were reported by VMMC programmes. The limited detail on clinical history, including the presence and appearance of wounds (at the circumcision site and other wounds), environmental conditions and wound care practices precluded a definitive classification. The cases were reported from Kenya, Rwanda, Tanzania, Uganda and Zambia and had occurred following conventional surgical circumcision (six cases) and circumcision with the current elastic collar compression device (three cases). Eight cases were consistent with circumcision as a contributory factor, due to the clear temporal association, wound site infection and/or lack of alternate explanations for the infection, and one was "indeterminate" (see the criteria in Table 2). An additional death following an elastic collar compression device circumcision was described, but it had been assessed by an in-country team as not related to tetanus.

Table 2. Criteria for classifying association between tetanus cases and circumcision

Type of association	Criteria
A: Consistent with causal association	Signs and symptoms of tetanus following circumcision that occur within a plausible incubation period for *C. tetani* (at least one and no more than 112 days) PLUS one or more of the following: i) circumcision site wound infection ii) history of applying substance potentially containing tetanus spores to circumcision wound iii)a reportedly normal healing wound and no alternative tetanus entry points (for example, punctures or wounds conducive to tetanus) evident elsewhere on body. OR surgical equipment demonstrated to contain *C. tetani* spores.
B: Indeterminate	Signs and symptoms of tetanus following circumcision that occurred within a plausible incubation period for *C. tetani* (at least one and no more than 112 days) AND presence of another wound, whether or not infected, and the circumcision wound site was normal; or there was a possible breach in the sterilization process or procedures.
C: Inconsistent with/ not likely to be a causal association	Circumcision occurred but the date of onset of symptoms is inconsistent with circumcision wound or healing process as a source of contamination with *C. tetani.*

Tetanus in Uganda

In November 2014 the Ministry of Health of Uganda, supported by WHO and the Office of the United States Global AIDS Coordinator, conducted an investigation into tetanus cases and deaths. In Uganda two of the four tetanus cases followed circumcision with the elastic collar compression device. In 2011 the country was declared to have eliminated maternal and neonatal tetanus (*21*), but there was no vaccination policy for boys and men after the primary series in infancy. Tungiasis infection due to the *Tunga penetrans* flea (jigger) was considered to be common, particularly in rural areas and homes with compacted earth floors, and could lead to tetanus infection. Data extracted from the National District Health Information System 2 for 2012–2014 showed an annual inpatient incidence of 3.0 per 100 000 population. No age disaggregation was available, nor could the completeness of the reporting be verified. A retrospective review of tetanus cases in St. Francis Hospital over four years, from 2005 to 2008, revealed that two-thirds of hospital admissions for tetanus were males over five years of age; the case fatality rate was almost 50%. National statistics reported to WHO and the United Nations Children's Fund (UNICEF) for the period 2006–2013 indicate that over 90% of tetanus cases occurred outside the neonatal period.

Findings were reported on a retrospective investigation into tetanus cases at Masafu Hospital, Busia District, in early 2015 identified 25 cases, all males, over a four-year period, the majority occurring after road traffic accidents. The case fatality rate was almost 50%. One-third (35%) of cases requested early discharge or discharged themselves when it became clear that treatment options were limited. Detailed information in records was limited.

TETANUS VACCINATION

Immunological basis for tetanus vaccines

The meeting summarized the immunological basis of tetanus immunity and discussed in vitro assays for tetanus including rapid diagnostic tests, different vaccination schedules and antibody responses among adolescents and adults with diverse vaccination histories. The review was informed by the WHO module on tetanus from the series on the immunological basis for vaccination, which was last updated in 2006 (*22*), and by a systematic review of tetanus vaccination presented in 2014 to the WHO Strategic Advisory Group of Experts (SAGE): working group on pertussis considering optimal schedules for diphtheria-pertussis-tetanus (DTP) vaccination (*23*). The systematic review confirmed that there were no differences in tetanus immunogenicity between different vaccine formulations, there was no evidence of differences in antibody response between adolescents and adults, and the highest levels of susceptibility to tetanus in low- and middle-income countries was now in adolescent and adult males. Tetanus vaccines are low-cost (about US$ 0.25 per dose including the syringe and needle) and highly efficacious.

Neutralizing immunoglobulin G (IgG) antibodies to tetanus toxin are protective against tetanus, with a generally accepted threshold for protective immunity of 0.01 IU/mL (determined by in vivo neutralization assay). With enzyme immunoassay tests a threshold level of around 0.10 – 0.16 IU/mL is used because these assays also measure the levels of non-neutralizing antibodies, resulting in an over-estimation of protection at low antibody levels. There is no herd immunity to tetanus, as the disease is not spread from human to human. Immunity to tetanus can be acquired by passive immunization either by transplacental transfer of maternal antibodies (which lasts a few months), by administration of tetanus immunoglobulin or by active immunization with TTCV. Tetanus vaccines available in low- and middle-income countries consist of tetanus toxoid formulated either alone or with diphtheria toxoid for maternal immunization; and for use in children, combined with diphtheria and pertussis vaccines (DTP), or in a pentavalent formulation with diphtheria, pertussis, *Haemophilus influenza* type B and hepatitis B vaccine, or conjugated to polysaccharide from meningococcus A (MenAfriVac).

The duration of protection against tetanus depends on the dosing schedule and the time since last dose (Table 3) (*24*). Only limited data are available on the kinetics of immune responses to booster doses. A study in 1987 in Danish military recruits vaccinated with a primary series against tetanus 17 to 20 years earlier measured a detectable increase in antibodies at four days (antibody levels were not assessed daily after boosting), but in general it takes six to seven days to reach substantial antitoxin levels (*25*). Thus, revaccination at the time of exposure to a tetanus-prone wound cannot be relied on to prevent a currently incubating tetanus infection. Other studies demonstrate that antibodies continue to rise after seven days, reaching a maximum at around 14 days after a booster dose (*26,27*).

Of importance when considering tetanus toxoid vaccination in the context of VMMC programmes, an antibody response may be elicited decades after a primary series (a common feature of inactivated vaccines). Even after many years, an interrupted primary or booster dose schedule should not be restarted; the schedule is simply continued with the next dose that is due (*24*).

Given that the time to symptoms of tetanus was five to 12 days among the tetanus cases reported following male circumcision, the kinetics of the immune response suggest that the booster dose should be given preferably 14 days, but at least seven days, before the circumcision procedure. A booster dose at the time of circumcision may provide some circulating antitoxin antibodies, but of unknown magnitude. A single TTCV dose in an individual who has never received any vaccination (vaccine-naïve) is inadequate. At least two doses four weeks apart are needed to have confidence in the level of antibody protection, and a third dose at least six to 12 months later is required for protection that lasts several years.

Table 3. Duration of immunity to tetanus

Dosing schedule	Duration of protection
Three doses in infancy (primary series) with no subsequent boosters	Approximately 3–5 years
Three doses in infancy plus one subsequent booster after an interval of at least 12 months	Into adolescence, approximately 10–20 years
Three doses in infancy plus two boosters (second year of life or school entry and adolescent or adult booster)	Through most of adulthood, 20–30 years

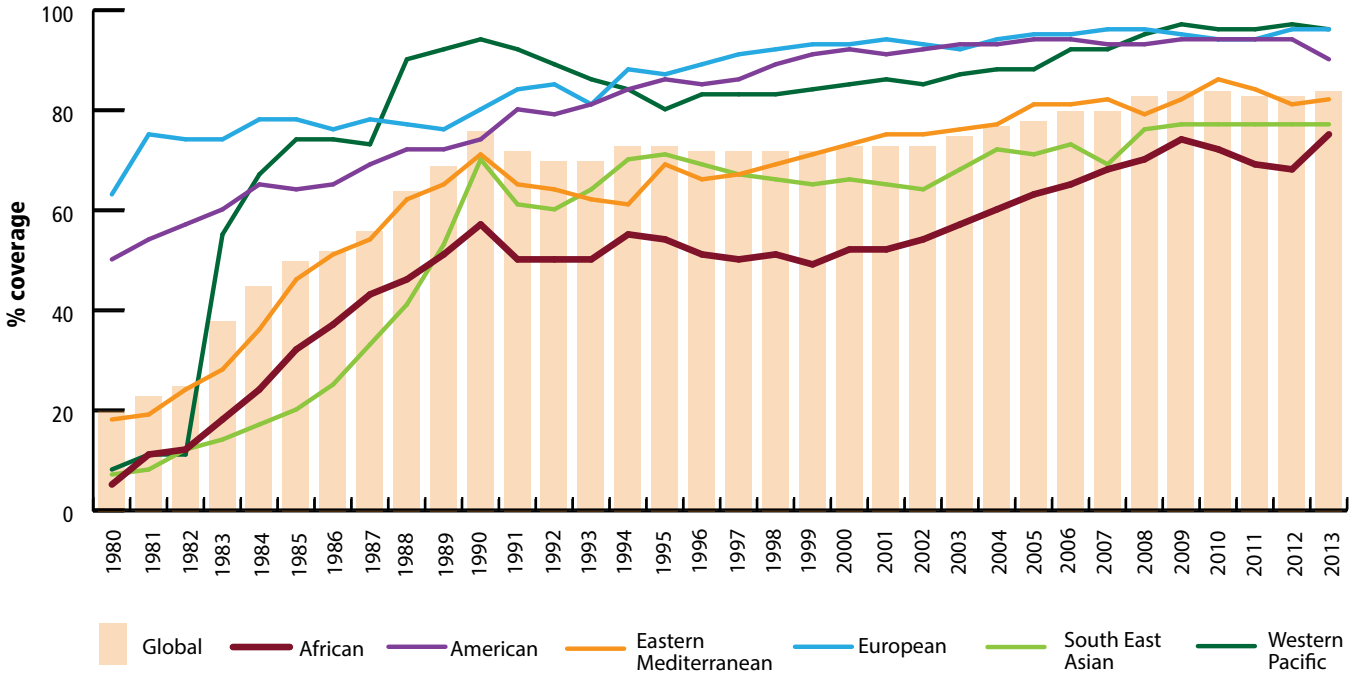
Vaccine policies and coverage

The meeting considered information on neonatal and non-neonatal tetanus, with particular reference to the African region and the global initiatives to eliminate maternal and neonatal tetanus. In 1988 WHO estimated that 787 000 newborns died of neonatal tetanus, with an annual global mortality rate of approximately 6.7 neonatal tetanus deaths per 1000 live births. In 2013 an estimated 49 000 newborns died from neonatal tetanus, a 94% reduction from the late

1980s. This has been achieved by offering pregnant women routine immunization with tetanus toxoid-containing vaccine and promotion of clean deliveries and clean cord care practices. While considerable progress had been made towards reducing neonatal tetanus deaths, as of February 2015, 24 countries had not achieved the status of neonatal tetanus elimination (less than 1 case per 1000 live births in each district in the country).[5] Neonatal tetanus is a reportable condition, but it has been estimated that WHO and UNICEF receive notification of only about 11% of cases. Data on tetanus cases occurring outside the neonatal period, including adolescent and adult tetanus cases, are even less reliable, as these cases are not routinely reported.

Since the mid-1980s the global initiative on expanding infant vaccination has meant that a larger proportion of newborns have received a primary series of at least three doses of TTCV. Estimated global coverage in 2013 was 84%; coverage in the African region was lower, at 75%. DTP 3 coverage in the African region was only 50% in the 1990s and was even lower in the 1980s (Fig. 3). Such regional averages hide national and subnational areas that have considerably lower immunization coverage. Thus, large numbers of men 15 years or older (born prior to 2000) may not have had the TTCV primary series. In addition, to ensure continued protective immunity against tetanus, booster doses must be given during childhood, adolescence and ten years later in adulthood. While many young women have received TTCV doses during pregnancy, there have been no equivalent systematic vaccination programmes for adolescent or young men, who in general might receive a vaccination only following a wound injury or accident or during military services (*22*).

Fig. 3. Global and regional DTP 3 immunization coverage, 1980–2013



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014. Immunization, vaccines and biologicals, WHO.

Further, 75% coverage with the third dose of the diphtheria-tetanus-pertussis vaccine (DTP 3 (or Penta3)) in the African region in 2013 means that until even recently, on average in the region, 25% of infants had not received the series of three TTCV doses (some had received no vaccination, others only one or two TTCV doses). Coverage of TTCV booster doses during childhood and adolescence is even lower.

Documented tetanus cases after circumcision suggests that many male adolescents and men were not adequately immunized against tetanus in some of the 14 focus countries in east and southern Africa that are implementing VMMC programmes for HIV prevention. This reflects slow implementation of the WHO 2006 position on tetanus vaccination among the general population and an ongoing focus on maternal and neonatal tetanus elimination without a shift to expanding the booster tetanus vaccination requirements in boys and young men.

5 http://www.who.int/immunization/diseases/MNTE_initiative/en/

WHO-recommended TTCV vaccination schedule

The WHO-recommended vaccination schedule for long-term immunity includes three booster doses after completion of the infant primary series, for a total of six doses (Table 3 and Table 4). Those who receive their first tetanus vaccine doses as adolescents or adults require a total of only five appropriately spaced doses to obtain long-term protection (*24*). For previously non-immunized adolescents and adults, the recommended schedule is two doses administered at least four weeks apart followed by a third dose administered at least six months after the second, and two subsequent boosters at least one year apart.

Table 4. WHO-recommended tetanus toxoid vaccination to obtain long-term immunity

	DTP 1	DTP 2	DTP 3	dT	dT	dT
Recommended Schedule	Before age one or as early as possible after age 6 weeks with >4 wks interval			e.g 4 to 7 yrs	e.g 12 to 15 yrs	Early adulthood
	dT	**dT**	**dT**	**dT**	**dT**	
Adolescents and adults with no previous immunization	As early as possible	At least 4 weeks after first dose	At least 6 months after second dose	At least 1 year later	At least 1 year after last dose	
	dT	**dT**	**dT**	**dT**	**dT**	
Pregnant women with no previous immunization (unreliable immunization)	As early as possible in first pregnancy	At least 4 weeks after first dose	At least 6 months after second dose (in next pregnancy)	1 year after 3rd dose (in next pregnancy)	At least 1 year after 4th dose (in next pregnancy)	
	dT	**dT**	**dT**	**dT**	**dT**	
Supplementary immunization activities in high risk areas (women of childbearing age)	During round 1	Round 2: 4 weeks after round 1	6 months after round 2	At least 1 year after 3rd dose (in next pregnancy)	At least 1 year after 4th dose (in next pregnancy)	

DTP: diphtheria-tetanus-pertussis vaccine; DTP 1, DTP 2, DPT 3: first, second and third DTP doses; dT: preparation of diphtheria and tetanus toxoid with a lower amount of diphtheria toxoid than DTP, for adolescents and adults; SIAs: supplementary immunization activities.
Source: WHO, 2006 (24)

Country reports

The meeting considered data from the Hospital of Tropical Diseases in Ho Chi Minh City, Vietnam, where an immunization programme was established in 1981 and the maternal and neonatal tetanus elimination programme was adopted in 1995. Although the officially reported national vaccination coverage rate has been greater than 90% since 2000, and usually over 95%, the hospital has seen 10 neonatal tetanus cases annually between 1997 and 2003 and about five cases annually since 2004. By contrast, the number of adult tetanus cases has remained stable at about 200 to 250 admissions per year, with about 80% of cases among men. The modal age of male cases increased from 15–19 years in 1993 to 21–25 years in 2002 and to 40–44 years in 2012. The modal age of female cases in 2012 was 75–79 years.

Unpublished data on tetanus antibody levels from serosurveys conducted in rural areas in Kenya, Mozambique and the United Republic of Tanzania in 2012 and 2013 (manuscript in preparation) show similar prevalence of tetanus antibodies between males and females in the age strata 1 to 4 years and 5 to 14 years but considerably lower prevalence of a protective level of antibodies in men than women over age 15 years. These observations are similar to those reported from a serosurvey in rural Kenya, published in 2006, which found similar prevalence of protective antibody levels among men and women except in the 18–45 year age group, where 30% of men and 70% of women were protected. This difference was attributed to the impact of the Expanded Programme on Immunization, introduced 20 years previously in this area, which provided booster doses to pregnant women (*22*).

Zimbabwe has been working towards, and achieved, officially validated elimination of maternal-neonatal tetanus in 2000; as well as reportedly eliminating tetanus under 14 years of age. Since 1980 the programme has included tetanus vaccinations at ages 6, 10 and 14 weeks and boosters at five years of age. The current schedule recommends a booster at age 18 months, but none at age five years. Coverage with the primary three-dose series has been high at over 80% since 1985 with the rate declining to 65% in 2006 and returning to over 80% in 2010. Tetanus is a reportable condition in Zimbabwe, with compulsory case notification within 14 hours. Recent reported data showed an average of five to six tetanus cases per year with no deaths. No tetanus cases have been reported in the VMMC programme, which has had a high rate of return for the post-circumcision follow-up visit.

A similar vaccination schedule is followed in South Africa, supplemented with TTCV doses at ages six and 12 years as a requirement for admission to primary and secondary school. According to information provided by the National Department of Health, no tetanus cases have been reported among VMMC clients in South Africa. Coverage data were not available.

RISKS AND RISK MITIGATION

Given that the new male circumcision methods use devices, the meeting considered the principles of risk management processes that should be integrated into the design of all medical devices and regularly updated throughout the life cycle of the product. An initial risk assessment should be conducted at the design stage, with the objective of identifying risks, putting in place procedures or making changes to or adapting the design to ensure that the risks are as low as reasonably possible. As experience with the initial prototype products accumulates, new information on risks becomes available; some potential adverse outcomes previously considered high have been mitigated and new risks identified. The baseline risk assessment may have an initial focus on engineering (materials, identification of potentially hazardous manufacturing processes, physical aspects of storage and distribution and disposal of the device after use), but clinical data supplements this once the product is used routinely. Usually, the first clinical use involves the intended user (e.g. medical doctor or mid-level health care provider) and intended setting (e.g. district health care facility), and it may provide information on foreseeable misuse and use error. But, as clinical use expands, new information on the frequency and magnitude of foreseen risks may emerge and new, not previously foreseen risks may be identified. In all cases the manufacturer must have a process to formally review such new information and consider whether the original risk assessment and balance of harms and benefits remain valid and within acceptable limits. If not, appropriate risk mitigation steps need to be put in place, for example, by product redesign, revised instructions for use and/ or updated training materials. Risk assessment and risk management are ongoing processes that pervade all steps in the development, production, marketing and disposal of a medical device and are formally codified in medical device regulations and standards (for example, ISO 14971). They are also part of WHO prequalification assessment of medical devices and maintenance of prequalification status.

WHO applies the principles of risk management in considering how new methods should be monitored and rolled out rapidly while keeping risk as low as reasonably possible. The new information on a small number of tetanus cases occurring soon after circumcision in VMMC clients required reassessing risks and minimizing actual and/or potential harms for all methods while ensuring that the balance of benefits and risks of circumcision for HIV prevention remains favourable. Safety monitoring in VMMC and post-market surveillance of WHO-prequalified devices is an important activity and has led to advice on mitigating this newly identified, rare – and preventable but potentially fatal – risk.

The manufacturer of the currently WHO-prequalified elastic collar compression device has followed the steps required by the WHO Prequalification of Male Circumcision Devices Programme, in line with international standards, by reassessing risk and proposing risk mitigation measures for use of their elastic collar compression device method. The experts at the WHO consultation considered these measures. The consultation took into account the earlier discussion on the potential for rapid germination and multiplication of *C. tetani* once in an anaerobic environment, which may be within 24 to 48 hours, based on laboratory experience. The proposed revisions to the manufacturer's instructions for use included the addition of povidone-iodine skin preparation, which is consistent with standard surgical protocols and other in situ medical devices. However, as per the WHO recommendations on basic surgical care, the prophylactic use of topical antibiotics as proposed by the manufacturer is not recommended without further evidence (*28*).

In addition to mitigating tetanus risk by enhanced attention to standard protocols for skin preparation and cleanliness by individuals who undergo the circumcision procedure, irrespective of VMMC method, tetanus risk could be mitigated by ensuring that all VMMC clients are adequately protected against tetanus by vaccination before circumcision. The meeting considered arguments for and against different immunization strategies that VMMC programmes could consider, including **(1)** providing one or two TTCV doses prior to circumcision, **(2)** timing of the first TTCV dose within VMMC, **(3)** considering individual risk or population/ groups at risk and **(4)** considering delivery strategies (routine or campaign).

The meeting participants also discussed various technologies for vaccine delivery, including the compact pre-filled autodisable syringe that has been used successfully for vaccination programmes in remote areas. However, there were no such supplies available at the time of the meeting, and there would be a delay of approximately one year before suitable production could be re-established. Other formats for TTCVs are readily available in developing countries, particularly for vaccination of pregnant women in the context of maternal and neonatal tetanus elimination programmes. These should be available for VMMC programmes. The meeting also briefly considered the availability of rapid diagnostic tests for assessing antibody levels using serums or whole blood. If rapid diagnostic tests were used for pre-MC screening, high specificity would be needed to avoid false positives. In an assessment in the United Kingdom, the test performance was deemed adequate for identifying non-immune subjects but not for serosurveys.

CONCLUSIONS AND ADVICE TO NATIONAL PROGRAMMES

Conclusions

The meeting participants held an in-depth discussion of the different circumcision methods available, their known safety profiles, the tetanus cases occurring after circumcisions performed in VMMC programmes, the pathogenesis and burden of tetanus, the immunology of tetanus vaccination and vaccination policies in some VMMC focus countries. The experts advised WHO and national programmes to minimize the risk of these rare but life-threatening events through interventions that would limit the burden on clients, providers and programmes but would maintain the momentum of VMMC scale-up to reduce further the incidence of HIV. The experts reached consensus on advice to WHO and programmes in support of implementation of the WHO recommendations on VMMC for HIV prevention, vaccination and clean care for tetanus prevention. The group noted that, in contrast to the progress in implementing the WHO/UNAIDS 2007 recommendations on scaling up VMMC for HIV prevention in high incidence countries, little progress has been made in implementing the WHO 2006 recommendation for tetanus immunization in adolescents and adults. The VMMC programmes, through careful safety monitoring, had uncovered vulnerability to tetanus among adolescents and young men in some eastern and southern African countries. The coordinated response of WHO's HIV, prequalification and immunization programmes has led to a combined risk mitigation approach that could enhance the quality of VMMC services for men, reinforce vaccination programmes, promote safer surgery and improve clean wound care by the individual and in the community. Similar coordination across national programmes will be essential for effective responses. Prevention of tetanus is achievable by use of TTCVs as well as by clean care, use of standard surgical practices and proper wound care.

Skin preparation prior to all circumcision procedures

- All surgical procedures carry some risk of infection and contamination with *C. tetani*, which can lead to tetanus. These risks must be minimized as much as reasonably possible given the context and purpose of the procedure.
- The safety and risk of circumcisions performed on healthy men in VMMC programmes for the purpose of reducing the risk of HIV infection must be addressed even more rigorously than the safety and risk of surgery for a condition that addresses an individual's immediate health need.
- Principles of infection prevention and control for skin preparation prior to any surgery and for post-operative wound management must be applied in all procedures, including circumcisions performed by conventional surgery and circumcisions with a male circumcision device.

Biological evidence on risks

- The microbiome under the foreskin before circumcision differs from the microbiome of the circumcised penis, in particular with regard to the greater prevalence and abundance of anaerobic bacterial species.
- The microbiological environment under the necrotic foreskin prior to removal of the currently prequalified elastic collar compression device differed from that of the uncircumcised penile microbiota with regard to a higher abundance of anaerobic species, indicating an environment that provides the opportunity for germination of *C. tetani* spores, proliferation of *C. tetani* bacteria and subsequent toxin production.
- The main risks of tetanus contamination following conventional surgical methods of circumcision were attributed to post-surgical wound infection.
- Inappropriate wound care practices that include application of substances containing *C. tetani* spores appear to be a risk in all types of circumcision procedures.

Epidemiological evidence on risks

- Determination of a causal association between male circumcision and tetanus infection in the retrospective case review was limited by the quality of information on each case, particularly regarding potential entry wounds (circumcision site and other wounds) and wound care practices. However, eight cases were assessed as being consistent with circumcision as a contributory factor, due to the clear temporal association, infection at the site of the wound and/or lack of alternate sites of *C. tetani* contamination.
- Epidemiological comparison of tetanus risks associated with different circumcision methods was limited by the small number of cases and uncertainties about the reporting of cases prior to 2014. Better information is needed from active surveillance (for example, selected sentinel surveillance sites), preferably through prospective recording of an individual's vaccination status, concomitant wounds elsewhere on the body, wound care practices and outcomes, to more conclusively quantify the level of risk by method.
- Other potential risk factors, such as occupation, type and geographic location of residence, and personal hygiene, may contribute to understanding tetanus risk; such information should be recorded when available.

Host immunity

- Each individual must be protected through vaccination as *C. tetani* spores are ubiquitous in the environment posing a risk to all individuals. The disease is noncommunicable, and no herd immunity is possible.
- In order to be fully protected against tetanus infection, each individual must have adequate anti-tetanus antibody levels, which can be ensured only following proper immunization with TTCV. Protection is achieved through active vaccination that stimulates neutralizing immunoglobulin G antibodies to tetanus toxin, conferred initially by a minimum of two TTCV doses at least one month apart. Over the lifetime of an individual, a series of immunization doses consisting of an initial three-dose primary series in infancy followed by booster doses (one at age 5–7 years, one during adolescence and one in adulthood) are required to maintain protective levels of antibodies and provide long-term protection. A single dose of TTCV provides little, if any, protection. In an unvaccinated adolescent or adult, two TTCV doses at least four weeks apart are sufficient to provide short-term protection.
- An antibody response in an individual who has received the primary three-dose series in infancy or at least one TTCV dose in adolescence or adulthood will be elicited regardless of age (adolescent or adult), as the response occurs even decades after the last dose. However, the magnitude and speed of response may vary depending on several factors, such as vaccine history. A measurable increase in antibody levels has been detected after four days, although generally it takes six to seven days to reach substantial protective antibody levels and at least 14 days to achieve the maximum level.
- Data on timing and magnitude of response are very limited, but considerable variation among individuals can be expected according to vaccination history. Thus, in the near term, for adolescent and adult males seeking VMMC, there will be uncertainty concerning level of tetanus protection.

Neonatal tetanus reduction through vaccination and clean care

- Programmes on maternal and neonatal tetanus elimination have succeeded in reducing neonatal tetanus over the past 20 years through immunization of pregnant women and, in some countries, by focusing primarily on clean umbilical cord care.

Gender inequity of tetanus protection

- While some countries require and provide tetanus doses for children ages 5–7 years, often linked with primary education, coverage for school-age boys and girls is far less than the coverage of the three-dose infant vaccination schedule.
- Most young women receive doses of TTCV during pregnancy as part of maternal and neonatal tetanus elimination initiatives, but there are no equivalent systematic booster immunization programmes for adolescents (girls and boys) and adult men, who may be offered tetanus vaccination only after wound injuries or, in some countries, at recruitment into uniformed services.
- Serosurveys in resource-limited settings in three countries of east and southern Africa confirm a substantially higher prevalence of protective tetanus anti-toxin antibody levels in adult women than in adult men.

Country context

- Few countries where VMMC programmes for HIV prevention are being implemented have tetanus vaccination programmes that include the childhood and adolescent booster doses. Even in countries with currently high coverage of three infant doses, where one subsequent booster dose in VMMC services would stimulate increased protective antibody levels, there remain large in-country differences in tetanus toxoid coverage. In addition, higher coverage levels (approaching 80%) of infant DTP 3 doses have been achieved only in the past 15 years, leaving large proportions of men born earlier with no or inadequate protection unless they receive at least two doses prior to circumcision. Furthermore, most men seeking circumcision will not have documented evidence of the TTCV doses they received in the past.

Advice to national programmes

In the context of the WHO 2007 recommendation on VMMC for HIV prevention and the WHO 2006 recommendation on vaccination against tetanus, and in light of the above consultation inputs, WHO provides the following implementation advice to national programmes.

This advice is based on principles of risk reduction, perspectives for the near term and medium term time considerations on feasibility, national context regarding tetanus burden and coverage, and TTCV immunogenicity. A **dual protection approach to risk reduction** is advised: tetanus toxoid-containing vaccination and clean care (both at the facility and by the individual). In the future adolescents will more likely have received the primary TTCV vaccination series. VMMC services could provide a platform for a booster dose, or VMMC services could be coordinated with adolescent immunization programmes so that adolescents arrive at VMMC services with adequate protection.

Infection prevention and control for all circumcision procedures

- For all circumcision procedures, including circumcision with devices, risk of tetanus infection may be mitigated through improved infection prevention and control, in line with the WHO/UNAIDS/Jhpiego *Manual for male circumcision under local anaesthesia* (*7*), the WHO's *Surgical care at the district hospital* (*28*) and the *WHO guidelines for safe surgery 2009* (*29*).
- By reducing the bacterial load, personal cleanliness before any surgical procedure is an important first step in the prevention of infection. This ideally includes washing the genital area, including under the foreskin, to remove any dirt and debris before the procedure. Encouraging clients to wear clean undergarments also is important.
- Standard surgical protocols on skin preparation of the genital area should be followed for all circumcision methods. This includes use of an appropriate antiseptic, such as povidone-iodine, unless the client is known to be allergic. The provider should apply the antiseptic to the skin at least three times and then wait two minutes before the procedure or device placement.
- Careful attention needs to be paid to clean care of the wound after circumcision. For the client, provision for clean care includes clear and understandable wound care and genital hygiene instructions, provision of clean/sterile dressings to use at home and clear instructions about returning to the health-care facility for post-procedure care and when to return urgently if specific symptoms suggestive of tetanus are noted.
- Communication in the community should improve understanding about the benefits of tetanus vaccination and the dangers of applying substances that might contain *C. tetani* spores (such as animal dung poultices, herbal remedies) to wounds. An assessment of local wound care practices will be useful.

Elastic collar compression devices

Other risk mitigation steps are advised with use of the prequalified elastic collar compression device:

- Providers must be trained to: **(1)** fully retract the foreskin without forcing; **(2)** thoroughly clean with an appropriate antiseptic such as povidone-iodine unless the client is allergic, three times on the genital area including under the foreskin, followed by a two-minute wait prior to device placement; **(3)** at device removal, clean with antiseptic before cutting away necrotic foreskin; and **(4)** again before removing the O-ring and inner rings and after removal of the rings prior to applying the dressing. Close monitoring is necessary as programmes implement revisions to protocols.
- Clients whose foreskins cannot be fully retracted easily should be offered conventional surgical circumcision under local anaesthesia as this will allow a small dorsal slit to be made and any adhesions can be broken, allowing proper skin preparation before the conventional surgical procedure.
- Any new procedures need to be properly validated for safety, effectiveness and feasibility before their addition to the instructions for use, including procedures for mitigation of odour while wearing the device.

Collar clamp devices

- No cases of tetanus have been reported following circumcision with the collar clamp device, but safety data were limited, as the method has not been used beyond well-controlled research settings. Standard surgical skin preparation protocols should be followed. Post-market safety monitoring and active and passive surveillance phases with introduction of collar clamp devices should include reporting of infections and tetanus cases.

Mitigating tetanus risk through TTCV vaccination

With all circumcision methods, mitigating the risk of tetanus infection through tetanus toxoid vaccination is advised. The current WHO schedule of TTCV for adolescent and adult men serves as the basis for decision-making on the timing and number of doses needed for protection, along with considerations of the tetanus burden at national (and local) levels and evidence on historical DTP 3 coverage relevant to the age of men presenting for VMMC. In addition, TTCV will provide protection against tetanus from other wounds.

- The primary goal of tetanus vaccination in the context of VMMC for HIV prevention is to reduce risks associated with the circumcision procedure and its wound to as low as possible, including risks related to contamination through poor hygienic conditions and practices. Tetanus vaccination in VMMC services would also benefit the implementation of the WHO vaccination recommendation for children, adolescents and adults to reduce the risk of tetanus from other wounds in unprotected adolescents and adults (*24*).
- Ministries of health are advised to develop and phase-in, collaboratively between VMMC and immunization programmes, effective and practical delivery strategies for providing tetanus vaccination in the context of their VMMC services to reduce the risk of circumcision site contamination and infection. Phasing in additional vaccination doses will require engagement of both programmes and coordinated planning.

- The most suitable TTCV strategy should be informed by:
  - **Population-level considerations**: There is no herd immunity to tetanus; only individual immunization assures protection. In the absence of TTCV booster(s), adolescent and adult males seeking VMMC are at risk of tetanus. Determining the best strategy includes: **(1)** assessing tetanus burden, past tetanus vaccination policies including for school entry and adolescent boys and historical DTP 3 coverage at national levels; **(2)** considering a conservative strategy of vaccination before circumcision (that is, a strategy that provides greater certainty of the level of protective antibodies) even if the school-age and adolescent TTCV doses have been routinely provided in the population but a moderate to high tetanus burden is suspected. The most cautious strategy should be considered where DTP 3 coverage since 1985 has remained low to moderate (for example less than 80%) and the tetanus burden is moderate to high.
  - **Individual-level considerations**: Among men presenting for VMMC, knowledge of their own vaccination history, as well as vaccination records, is frequently limited. If documented information is available, however, it should be used to determine the TTCV doses that the individual needs. Men opting for VMMC by any method have the right to receive full information on the benefits and risks of the procedure, including the risk of tetanus infection and the protection offered by tetanus vaccination.
  - **Feasibility**: While TTCV is usually available in government health facilities, vaccination delivery in VMMC services needs to be planned and phased in with relevant health-care staff. This phase-in should include sensitization of clients and communities to this new opportunity for tetanus protection in advance of circumcision.

Number and timing of TTCV doses in the context of VMMC programmes

Considering the number and timing of vaccine doses to be given in the context of VMMC programmes and the level of protection thus afforded to VMMC clients, the group noted the following:

- It is uncertain exactly where and when the highest risk of *C. tetani* inoculation occurs, the timing for germination and release of the neurotoxin that causes disease.
- If *C. tetani* spores are present at the time of placement of an elastic collar compression device or while the device is in situ, it may take one to two days for the spores to germinate and bacteria to multiply within the anaerobic environment.
- The first symptoms of tetanus disease among the cases reviewed occurred between five and 12 days following circumcision or device placement, informing the timing of TTCV for MC protection.

When an individual's tetanus vaccination status is known, his status should guide decisions on vaccination dose needs. Immunological kinetics vary but suggest that:

- Unless an individual has documented evidence of having received a full five-dose series of TTCV, it is advised that a single dose of TTCV be added, prior to or at the time of male circumcision, recognizing that this dose will provide varying levels of protection, depending on the individual.
  - In an individual who previously received three infant doses or one dose during adolescence or adulthood, where feasible, a TTCV booster dose should be given preferably 14, but at least 7 days, before the circumcision procedure (conventional surgery or device placement) for adequate protection.
  - Providing the TTCV booster dose at the time of surgery or device placement may allow, but cannot guarantee, the production of some circulating antibody within a few days; antibody levels will reach their maximum in about 14 days.
- In a vaccine-naïve individual (has never received any TTCV doses) a single TTCV dose would be inadequate to induce protective antibody levels. Two TTCV doses at least four weeks apart, with the second dose preferably 14 days, but at least 7 days, before the VMMC procedure are needed for tetanus protection.
  - If the first dose is provided at the time of circumcision, recognizing that no protection is provided during circumcision healing, a TTCV booster dose could also be offered at a post-operative follow-up visit, at least four weeks after the first dose. This would provide protection for wounds other than the circumcision wound. For longer term protection, the individual should be provided with a third dose in 6 months and additional doses subsequently 1 year apart.
  - Where few men are likely to have had prior TTCV doses and the tetanus burden is moderate to high, the most cautious strategy should be considered - providing two TTCV doses four weeks apart with the second dose preferably 14 (but at least 7) days prior to VMMC; and encourage subsequent booster doses as noted above.

Summary advice

Based on the consultation participants advised **a dual approach** to reducing the risk of tetanus infection, through **(1)** rigorous surgical skin preparation for all circumcisions, including device methods, and good personal wound care education ("clean care") and **(2)** provision of tetanus toxoid vaccination.

In the near term the vaccination advice reflects an assumption that individual tetanus toxoid vaccination status is unknown for many men. Thus, in deciding a strategy for tetanus prevention in VMMC programmes, countries will need to consider the tetanus burden and the historical vaccination coverage levels of DTP 3, particularly

in the birth years of clients seeking VMMC. When an individual's tetanus toxoid vaccination status is known, however, his status should guide decisions on vaccination dose needs.

For the medium term the consultation participants advised that ministries of health institutionalize TTCV (booster) doses, for both girls and boys, in childhood and adolescence through routine vaccination programmes, following current WHO recommendations.

Given the limited coverage of tetanus vaccination in adolescent and adult men in many countries where VMMC programmes are implemented, the background burden of tetanus in these settings and the potentially high risk of tetanus infection from any injury or infected wound, circumcision services are an opportunity to offer tetanus vaccination for males, thus reducing the gender inequity in tetanus immunity and contributing to universal coverage. Surveillance of tetanus should include both neonatal tetanus and non-neonatal tetanus (after 28 days), and this surveillance should be incorporated in a planned manner into routine immunization programme surveillance systems with systematic recording and reporting.

Information gaps identified and proposed actions

The consultation participants identified several key information gaps that should be addressed by ministries of health, other key partners and researchers to improve VMMC services, given the newly identified risk of tetanus infection. They advised the following steps to improve knowledge:

- Obtain better information on the tetanus burden through retrospective hospital-based record reviews of all suspected and confirmed tetanus cases in a specified time period, including, but not limited to, cases following VMMC.
- Review historical coverage of TTCV, in particular DTP 3 coverage and school-age and adolescent booster doses. Consider local population dynamics, such as immigration of men from settings where vaccination coverage is limited.
- Assess local wound care practices and community understanding of and adherence to proper wound management practices. Identify best practices for care instructions and maintaining a clean dressing. Adapt and revise information and training materials for clients and providers if necessary.
- Improve surveillance and analysis of adverse events occurring in VMMC programmes. Reinforce routine safety monitoring in all VMMC programmes, including notification of all suspected tetanus cases and deaths.
- Set up an adverse event technical working group in each country to review adverse events in the VMMC programme. This review should include all tetanus cases that occurred within 30 days after VMMC. Cases should be investigated and assessed for causality.
- Inform device manufacturers of adverse events including any cases of tetanus occurring after use of their product.
- Closely monitor the effect of revised instructions for use and hygienic interventions for all methods, particularly in countries with a high background burden of tetanus.
- Consider developing a network of case-based sentinel hospital surveillance sites in urban and rural settings to measure tetanus burden and conduct more in-depth case investigations. This may be facilitated by linkage with current surveillance programmes for other diseases. Assess the impact on uptake of VMMC of adding TTCV to VMMC services. Uptake may be influenced positively, negatively or not affected.
- Assess antibody titres prior to TTCV and antibody response based on the number and timing of TTCV doses among adolescent and adult men presenting for circumcision. Assess the correlation between antibody titres and individual documented vaccination status.

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ANNEX 1. MEETING AGENDA

Day 1: Monday, 9 March 2015		
Time	**Topic**	**Chair/Presenter/ Facilitator**
8:00 – 8:30	Registration – welcome coffee	
8:30 – 9:00	**Opening** • Welcome and introductions • Objectives and expected outcomes, review of agenda • Declaration of conflict of interests	**R. Baggaley, M. Zaffran, J. Samuelson**
9:00 – 10:30	**Session I: Background information** • VMMC for HIV prevention recommendations, progress and potential impact • Description of male circumcision methods, device classification and mechanisms of action • WHO guidance on male circumcision methods, data on safety and device prequalification • Pathogenesis of C. tetanus Discussion and clarifications	**Chair: D. Tarantola** **B. Ncube** **T. Hargreave, D. Rech, S. Watya** **J. Samuelson, A. Sands** **I. Poxton**
10:30 – 11:00	Coffee break	
11:00 – 12:30	**Session II: Tetanus and medical male circumcision** • Microbiome analysis • Biological plausibility and potential points of tetanus contamination with each method: conventional surgery, elastic collar compression and collar clamp device • Rates of reported adverse events with potential implications for tetanus risk Questions for clarification	**C. Liu** **I. Poxton, T Hargreave** **T. Farley**
12:30 – 13:30	Lunch break	
13:30 – 15:30	**Session III: Exchange of information and views on relatedness of tetanus and MC** • Summary of line list and criteria to classify relatedness • Description of individual cases • Discussion on relatedness of tetanus to MC for each case and risk factors Key points • Epidemiological data: » Global: neonatal and non-neonatal » Background burden in select countries and method specific data in Uganda Clarifications • Risk management	**A. Hesse** **T. Adamu, S. Watya, J. Reed** **L. Thwaites** **A. Yakubu , L. Thwaites, D. Rech, O. Mugurungi, S. Dalal** **M. Maier**
15:30 – 16:00	Coffee break	
16:00 – 17:30	**Session IV (limited participation): Deliberations on evidence for risks and risk mitigation** • Non-vaccine, clean approaches: » Mitigation of risks associated with » conventional surgery » VMMC devices Discussion • Balance of harms – benefits • Evidence, research and/or monitoring to demonstrate safety without additional tetanus vaccination Discussion	**T. Hargreave, A. Sands** **J. Samuelson, R Baggaley, T. Farley**
18:00 – 19:00	Reception at Château de Penthes	

Day 2: Tuesday, 10 March 2015		
Time	**Topic**	**Presenter/Facilitator**
8:00 – 8:30	Welcome coffee	
8:30 – 10:30	**Key points from Day 1** **Session V: Risk mitigation: tetanus vaccination** • Immunological basis of tetanus vaccines; antibody measurement, response and protection for adolescents and adults • Vaccine policies and coverage » Global and regional » Country : Uganda, South Africa, Zimbabwe Discussion on vaccination timing considerations • by MC method • by individual characteristics: vaccination history, age	**Chair: D. Tarantola** **L. Miller, T. Tiwari** **A. Yakubu** **S. Watya, D.Rech, O. Mugurungi**
10:30 – 11:00	Coffee break	
11:00 – 12:30	**Session VI: Technical considerations on vaccination approaches** • Role of compact pre-filled auto disposable (cPAD) or other technologies and supplies • Other considerations Discussion and key recommendations	**A.A. Raza**
12:30 –13:30	Lunch	
13:30 – 14:30 14.30 – 15:30	**Session VII (Limited participation): Considerations on tetanus mitigation strategies in the context of voluntary medical male circumcision** • Strategies on immediate VMMC service delivery: adolescent and adult focus • Strategies on medium- and longer-term VMMC delivery for sustained coverage: focus on adolescents and infants Discussion	**F. Gasse**
15:30 – 16:00	Coffee break	
16:00 – 17:00	**Session VIII (Limited participation): Key points and next steps** Discussion Summary of key points and next steps Closing	**J. Samuelson** **R. Baggaley, M. Zaffran**

ANNEX 2. LIST OF PARTICIPANTS

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* Did not participate in the formulation of recommendations.

Unable to attend; provided inputs electronically: Dr Marty Roper, independent consultant on tetanus and vaccines

Declarations of interests

All experts were required to complete the WHO Declaration of Interests form. Eight of the 17 experts declared the following interests:

Tigistu Adamu: He works with Jhpiego, which has received US government funds to assess the safety and acceptability of current elastic collar compression devices, for which he was co-investigator. This was not considered to give rise to a potential conflict of interest.

François Gasse: He acted as an advisor to the company Becton Dickinson on vaccine vial technology improvement. This was not considered to give rise to a potential conflict of interest.

Braden Hale: His work with the United States Department of Defense has included technical advice on research studies of the current elastic collar compression device. This was not considered to give rise to a potential conflict of interest.

Cindy Liu: works with John Hopkins University on studies of penile microbiome including under conditions of use of the current elastic collar compression device. This was not considered to give rise to a potential conflict of interest.

Dino Rech: His research unit at CHAPS performed USAID-sponsored research on the current elastic collar compression device. In addition, he participated in organizing dinner meetings funded by the manufacturer of this device. This was considered to give rise to a potential conflict of interest, and as a result Dino Rech did not participate in the formulation of recommendations.

Jason Reed: He has made numerous public statements about the programmatic efficiencies of medical devices for male circumcision. He works with PEPFAR, which has funded a number of safety and acceptability studies. This was considered to give rise to a potential conflict of interest, and as a result Jason Reed did not participate in the formulation of recommendations.

Renée Ridzon: She acts as a consultant to the Bill and Melinda Gates Foundation, which is involved in the testing of male circumcision devices. This was considered to give rise to a potential conflict of interest, and as a result Renée Ridzon did not participate in the formulation of recommendations.

Stephen Wyata: He is an employee of the company Uro Care, which is involved in offering private medical services. This was not considered to give rise to a potential conflict of interest.

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