World Health Organization

Tetanus and voluntary medical male circumcision: risk according to circumcision method and risk mitigation

Report of the WHO Technical Advisory Group on Innovations in Male Circumcision – consultative review of additional information,
12 August 2016

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Key points

On 7 July 2016, the World Health Organization (WHO) issued a report on the risk of tetanus associated with different male circumcision methods and specific mitigation measures according to circumcision method. In a teleconsultation on 12 August 2016, the WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) reviewed additional information submitted since the publication of the report. The information was submitted in writing by interested parties, following an open request by WHO. These parties included representatives of the manufacturer of the currently prequalified elastic collar compression device, a researcher of the currently prequalified collar clamp device, an expert on tetanus and the Ministry of Health of Uganda. In addition, during an open session of the teleconsultation, verbal presentations were made to TAG by several interested parties. TAG members were given all written submissions in advance of the teleconsultation; also, all submissions (except for confidential and copyrighted materials) were posted on the WHO public website. After the open session, TAG deliberated on the presentations made and the documentation submitted in a closed session, and provided its recommendations to the WHO Secretariat.

After careful consideration of all documentation submitted and information provided in the open session, the TAG members unanimously endorsed the conclusion reached in June 2016 (reported 7 July 2016) of a higher risk of tetanus following circumcision with the elastic collar compression device compared with other circumcision methods that removed the foreskin at the time of the procedure. This conclusion was based on an analysis of the epidemiological evidence that recognized reporting limitations and was supported by a plausible biological mechanism. Tetanus incidence was estimated to be more than 30 times higher following circumcision with the elastic collar compression device compared with surgical circumcision. TAG considered that, although underreporting of tetanus cases following circumcision was possible, differential underreporting was unlikely to account for the magnitude of the difference. No new evidence was presented that undermined the validity of this conclusion.

TAG members confirmed their previous advice of July 2016:

- Circumcision with a device method where the foreskin is left in situ and removed several days after application should be undertaken only if the client is adequately protected against tetanus by immunization with tetanus-toxoid-containing vaccine (TTCV) that includes:
    a) two TTCV doses at least 4 weeks apart, with the second dose at least 2 weeks before device placement; or
    b) if a client has previously received three infant doses, or one dose during adolescence or adulthood, a TTCV booster at least 2 weeks before device placement (a booster at the time of placement provides only limited protection as it takes 7–14 days for antibodies to rise to protective levels); or
    c) a series of five doses of TTCV.
- For conventional surgical methods in which the foreskin was removed at the time of the surgical procedure, TAG members recommended no modification to the 2015 consultation advice on vaccination. Ministries of health were advised to develop and phase in effective and practical delivery strategies for providing tetanus vaccination in the context of their programmes for voluntary medical male circumcision (VMMC) for HIV prevention and for vaccination. The strategies used would depend on the country's TTCV schedule and practices, and its tetanus burden. Unless an individual has documented evidence of having received a full five-dose TTCV series, it is advised that, at a minimum, a single TTCV dose be administered before or at the time of circumcision.
- A clean care approach should be followed for all circumcision methods, as noted in 2015. This approach includes the following:

- 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; this is relevant for all circumcision methods.
- Enhancing individual and community education on clean wound care after circumcision. This includes giving clear and understandable instructions on wound care and genital hygiene, clean or sterile dressings to use at home, clear instructions on when to return to the health-care facility for post-procedure care, education on the benefits of vaccination against tetanus and education on the dangers of applying substances that may contain *Clostridium tetani* (e.g. animal dung poultices or herbal remedies) to wounds.

As part of ongoing monitoring of the safety of VMMC programmes, TAG stressed the importance of countries to systematically collect and compile information on all deaths and inpatient hospitalizations that occurred within 30 days of circumcision, irrespective of method or potential causal link to the circumcision procedure. This safety monitoring is an essential component of VMMC programmes that are implementing an elective procedure for HIV prevention.

1 Background

1.1 Tetanus and voluntary medical male circumcision, consultation March 2015

In March 2015, WHO convened an informal consultation on tetanus and voluntary medical male circumcision (VMMC) to discuss recent cases of tetanus that had been reported following circumcision through VMMC services within HIV prevention programmes. At that time, a total of nine cases had been reported, six of which had occurred after conventional surgical circumcision and three after use of the elastic collar compression device, which was prequalified by WHO in May 2013.

The WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) and tetanus experts reviewed in detail each male circumcision method, safety profiles, the pathogenesis and burden of tetanus, and different approaches to mitigating tetanus risk. The experts recognized limited coverage of tetanus-toxoid-containing vaccination (TTCV) among adolescent and adult men in most of the countries implementing VMMC programmes. They recommended a dual approach to reducing tetanus risk through:

- promoting good personal wound care and standard surgical skin preparation for all male circumcision methods; and
- phasing in strategies to provide TTCV as relevant to their context, including as a minimum a single dose at the time of circumcision.[1]

1.2 Additional tetanus cases since 2015 – consultation June 2016

By May 2016, WHO had received reports through VMMC programmes of an additional six cases of tetanus. WHO therefore convened a technical consultation on 3 June 2016 to receive further advice.

A total of 15 cases had been reported, 12 of which occurred since 2014, when active monitoring for adverse events including tetanus had been reinforced. Of those 12 cases, six had occurred following conventional surgical circumcision and six following use of the elastic collar compression device,

[1] WHO Informal consultation on tetanus and voluntary medical male circumcision: report of meeting convened in Geneva, Switzerland, 9–10 March 2015. World Health Organization; 2015. ISBN 978 92 4 150923 7. (http://apps.who.int/iris/bitstream/10665/181812/1/9789241509237_eng.pdf, accessed 15 August 2016)

which leaves the foreskin to necrotize in situ for up to 1 week before removal. Over the same period, an estimated total of 3.04 million surgical circumcisions and 90 500 circumcisions with the elastic collar compression device had been performed in the four countries that had reported tetanus cases following circumcision.

TAG members and tetanus experts reviewed the evidence and concluded that the epidemiological evidence about these rare serious adverse events, supported by biological plausibility, was sufficient to consider that the risk of tetanus with use of the elastic collar compression device differed from that assessed during earlier safety reviews[1,2] and was higher than the risk with surgical circumcision.

TAG revised its 2015 advice. Specifically, it advised that circumcision with a device method where the foreskin is left in situ and removed several days after device application should be undertaken only if the client is adequately protected against tetanus by immunization. For conventional surgical methods in which the foreskin is removed at the time of the surgical procedure, TAG recommended no modification to the 2015 advice.

2 Technical consultation 12 August 2016

In response to statements that additional information was available and had not been considered by TAG, WHO convened a further consultation with TAG by teleconference to review any additional submissions (data and documentation) that were related to the safety of male circumcision methods. The consultation included an open session that allowed interested parties to present their position, followed by a closed session restricted to TAG members, with WHO providing secretariat support.

2.1 Documentation received

Before the consultation, WHO issued a public call for submission, in writing, of additional relevant information that should be considered by TAG. A notice requesting submissions was placed on the WHO public website and individuals were invited to register if they wanted to present during the open (public) session of the TAG teleconsultation. Submissions were received from the manufacturer of the elastic collar compression device; EngenderHealth (involved with clinical evaluation of the collar clamp device); Dr Louise Thwaites, Oxford University, United Kingdom; and the Uganda Ministry of Health (Annex B). These submissions were circulated to TAG members and, with the exception of those designated confidential or copyright protected, were posted on the WHO public website. Links to additional relevant documents and publications were provided (Annex C). TAG members, interested parties who participated in the open session and WHO Secretariat staff are listed in Annex A.

2.2 Open session

The first part of the teleconsultation was an open session where interested parties could call into the teleconsultation; participants included those registered to present and others who simply wished to listen to the proceedings. Following welcome remarks and introductions by the WHO Department of HIV, the TAG Chair invited participants who had submitted requests to present their position to TAG members.

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1 Male circumcision for HIV prevention: WHO Technical Advisory Group on Innovations in Male Circumcision: evaluation of two adult devices, January 2013: meeting report. World Health Organization; 2013 (http://www.who.int/hiv/pub/malecircumcision/tag_devices/en/, accessed 15 August 2016).

2 WHO Technical Advisory Group on Innovations in Male Circumcision, meeting report, 30 September – 2 October 2014, Geneva, Switzerland. World Health Organization; 2015 (http://www.who.int/hiv/pub/malecircumcision/innovations-mc/en/, accessed 15 August 2016).

2.2.1 EngenderHealth

The representative of EngenderHealth summarized the status of recent method-change studies of the collar clamp device among men and boys aged 10 years and over in Kenya. These studies were designed to improve and simplify the method, and involved use of topical anaesthesia and the "no-flip technique", which avoids eversion of the foreskin. A study of the penile microbiome before circumcision, before device removal and 6 weeks after circumcision was under way, and permission was awaited for export of swabs for microbiological analysis in the United States (US).

There had been no reports of tetanus following over one million circumcisions with the collar clamp device in China, but the country had high current and historical immunization rates. Similarly, there had been no tetanus cases in over 4100 circumcisions with the collar clamp device in four African countries (Kenya, Malawi, Uganda and Zambia). EngenderHealth attributed the absence of tetanus cases to removal of the foreskin immediately after device placement, thus avoiding an environment conducive to anaerobic growth. No clients or providers had reported strong odour while wearing the device or at removal.

2.2.2 Manufacturer of the elastic collar compression device

Representatives of the manufacturer of the elastic collar compression device welcomed the opportunity to present new information to TAG, and summarized the key points on biological plausibility and risk differences by circumcision method made in their written submission. They stated that there was no evidence supporting a plausible biological mechanism for a higher risk of tetanus with the elastic collar compression device compared with other circumcision methods. Specifically, they noted that:

- there was no proof that *C. tetani* was present;
- an anaerobic environment was not proof of an increased risk of *C. tetani*;
- the updated instructions for use of povidone-iodine for placement and removal had not been properly implemented in any of the three most recent tetanus cases following use of the elastic collar compression device; and
- epidemiological data and relative incidence calculations of tetanus risk were erroneous because of serious underreporting of tetanus cases after surgical circumcision.

Consequently, the manufacturer stated that the recommendation for tetanus risk mitigation should be the same for all circumcision methods, and that the recommendation for immunization with two TTCV doses before circumcision with the elastic collar compression device but not with surgical circumcision was not justified.

In response to questions from TAG members on the documents submitted, the manufacturer's technical experts restated their opinion that compression by the O-ring rapidly and completely cut off blood supply and isolated distal tissue including the nervous system, thus preventing any possibility of progression of tetanus toxins from germinated *C. tetani* spores. The effect of this mechanical barrier was reinforced physiologically by "scar (granulation) tissue that gradually formed during the previous seven days (due to the pressure exerted by the [device] band)" which "provides protection from deep tissue invasion by potential pathogens, including *C. tetani*."

Further clarification was sought by TAG members about observations by providers of wounds on the proximal side of the device; that is, bleeding, friable tissue and oozing at the time of device removal, and necrotic tissue remaining after removal. In response, the company's experts stated that local uptake of tetanus toxins at the site of the device was not possible, that no cases of localized tetanus had been reported and that generalized tetanus could not occur because of tissue necrosis. They noted that tetanus could only occur if tetanus toxins entered the circulatory system and were thus disseminated throughout the body. However, one of the company's experts acknowledged that microabrasions were possible and could not be excluded.

TAG posed questions about discrepancies in the number, details and geographical locations of tetanus cases following conventional surgical circumcision put forward by the company and those reported to WHO. In response, the company stated that, in addition to the four cases reported in Appendix G of the submission, a further case following surgical circumcision had occurred in Uganda in 2014. The company offered to share the detailed reports it had received from the Uganda Ministry of Health. The manufacturer was also asked to confirm details of the 11 tetanus cases following surgical circumcision (Appendix F of the submission), and to provide details of the four cases reported in Appendix G. The Uganda *Ministry of Health safe male circumcision (SMC) death audit report* (November 2014; posted on the WHO website) listed one of these four cases as an infant who had died of causes other than tetanus.

2.2.3 Professor Ian Poxton, University of Edinburgh, United Kingdom

As an expert on anaerobic microbiology who had participated in the March 2015 technical consultation, Prof Poxton stressed that all wounds had the potential for growth of anaerobic bacteria, and that microenvironments provide a sufficiently large environment for *C. tetani* production. He compared the foreskin meatal opening and the anaerobic environment under the foreskin to the anaerobic environment present in plaque and subgingival tissue at 1 mm depth, situated in the well-aerated oral cavity. Prof Poxton also noted that facultative anaerobes absorb oxygen and create anaerobic spaces, and that the microenvironment just proximal to the device was anaerobic (see Liu *et al*.[1]) in addition to the anaerobia created in necrotic foreskin. An anaerobic environment is necessary for germination of *C. tetani* spores; thus, the environment created by the elastic collar compression device increases the risk of tetanus and any other anaerobic bacterial infections. Prof Poxton noted that toxin may gain entry through the circulatory and lymphatic systems through which it is then carried to the nervous system.

In Prof Poxton's view, careful skin preparation with povidone-iodine would help to reduce the risk of tetanus with use of the elastic collar compression device, as it does for other circumcision methods. It is not known whether povidone-iodine applied at the time of removal would penetrate into the few millimetres of remaining necrotic tissue even if the surface was cleaned. In addition, Prof Poxton noted that povidone-iodine was unlikely to inactivate the neurotoxin.

Following presentations by the three registered parties and an opportunity to raise questions for clarification, the speakers were thanked and the open session was closed.

2.3 Closed session

After the open session, the teleconsultation was reconvened as a closed meeting of TAG members, with secretariat support provided by WHO. TAG members were informed of written declarations of interests of TAG members received by WHO and were asked to declare any further interests that may have arisen. Two members had declared (in writing) interests relevant to the subject matter of the consultation. These declarations (Annex A) were not considered to require exclusion of these members from the meeting.

The TAG members reviewed and discussed the written documentation received from interested parties. They also considered the view put forward by the manufacturer of the elastic collar compression device that there was no biological plausibility for an increased risk of tetanus compared with other circumcision methods, as well as the epidemiological evidence.

2.3.1 Biological plausibility

TAG members noted that the key points made by the manufacturer of the elastic collar compression device and its experts in the written submission and during the open call had been stated previously, and had been available at the March 2015 and June 2016 consultations (included as Appendix H of

[1] Liu CM, Prodger JL, Tobian AA, Serwadda D, Galiwango RM, Nalugoda F *et al*. Genital anaerobic bacterial overgrowth and the PrePex male circumcision device, Rakai, Uganda. *J Infect Dis*. 2016;214(4):595–598.

the submission). For the reasons given below, TAG members did not agree with the argument put forward by the manufacturer that there was no "plausible biological heightened risk of tetanus" with the elastic collar compression device.

- *Generalized or local tetanus*
  The discussion during the open session, which noted that localized tetanus infection was not possible following circumcision with the elastic collar compression device, was deemed not relevant because all six documented cases following circumcision with the device were generalized tetanus, as were all cases following surgical circumcision.

- *Potential contamination with spores before placement and while wearing the elastic collar compression device*
  Tetanus spores are widespread in the environment. Without standard surgical skin preparation, spores may remain present before device placement. There was also potential for contamination under the foreskin while wearing the device. Among the six documented cases following circumcision with the elastic collar compression device, the occupations (farmers, brick layer and motor cycle driver) and living environment would be likely to expose individuals to spores.

- *Potential germination of C. tetani spores and multiplication of C. tetani bacteria*
  The foreskin distal to the device rapidly became anaerobic as the blood supply was constricted by the O-ring. This by itself was a risk for spore germination and growth of facultative and obligate anaerobic bacteria. The microbiome study of Liu *et al.* was not designed to specifically recover *C. tetani* from individuals wearing the elastic collar compression device. However, the study did detect multiple anaerobic bacterial species under the foreskin, demonstrating the creation of an anaerobic environment, which is necessary for *C. tetani* germination and growth. Although specific documentation was not available, TAG members hypothesized that there may be micropockets where bacterial growth could occur. Given a possible incubation period as short as 1 day, rapid bacterial colonization is likely. Clients and providers have reported strong odour during wearing and at the time of removal of the elastic collar compression device. Odour is a by-product of anaerobic bacterial growth. In addition, *C. tetani* are motile due to the presence of flagella and may migrate into the subpreputial space.

- *Toxin entry into the body*
  TAG members disagreed with the arguments put forward by the manufacturer regarding complete separation of foreskin tissue from the body and elimination of risk based on a mechanical barrier and physiology. In particular, tissue necrosis was noted as incomplete 4 days after placement (Bitega *et al*. described the mechanism of action of the device method in the first safety and efficacy study).[1] Also, no evidence had been presented to demonstrate that adequate and consistent pressure was maintained around the entire circumference of the O-ring while in situ. No histological information is available on the integrity of the skin during the 7 days the device remains in situ.

  There was clear observational evidence that bleeding and oozing occurred during device removal, although not in all cases and usually in small amounts. Subclinical lesions or microabrasions could not be excluded, and provided an additional potential portal for tetanus toxin to enter the lymphatic or circulatory systems. Granulation tissue was observed to be friable, and healing has been noted to take longer than surgical methods. In her written submission, Dr Thwaites noted that tetanus usually occurred where entry sites were

[1] Bitega JP, Ngeruka ML, Hategekimana T, Asiimwe A, Binagwaho A. Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited settings. *J Acquir Immune Defic Syndr*. 2011;58(5):e127–134.

presumed to be avascular or where scar tissue was present; also, that entry may be facilitated through the action of cytopathic toxins produced by *C. tetani* and other bacteria present. Given that in many tetanus cases no identifiable entry site was apparent, the above evidence was considered to support the potential for several portals of toxin entry and subsequent dissemination in the body through haematogenous spread before neuronal uptake.

- *New instructions for use including the povidone-iodine skin preparation protocol*
  The manufacturer of the elastic collar compression device reported that no tetanus cases had occurred following use of the new povidone-iodine skin preparation protocol developed in March 2015 (Appendix J of the submission), and claimed that this new protocol would eliminate any possibility of higher tetanus risk with the device. While the new clean protocol had been developed in early 2015, three tetanus cases had occurred with the elastic collar compression device since September 2015. Povidone-iodine was used (but apparently with insufficient wait time) in the most recent case, who was also given one TTCV dose. This raised questions about the practicality of implementing the new protocol. TAG members considered that it was not possible to eliminate all tetanus risk with the elastic collar compression device.

2.3.2 Epidemiological evidence

TAG members reviewed the totality of the epidemiological evidence available on tetanus cases following circumcision, and the number of procedures that had been performed. They noted that the number of confirmed tetanus cases following circumcision remained unchanged from June 2016. Also, they acknowledged the new information on the number of circumcisions with the elastic collar compression device by year and country to end June 2016 provided by the manufacturer (Appendix I of the submission), and the official number of circumcisions performed each year by country from the WHO VMMC 2016 progress brief.[1] Only partial information and estimates had been available in June 2016. TAG members reviewed the documentation and considered the conclusions provided by the manufacturer of the elastic collar compression device that:

- tetanus incidence following circumcision with the elastic collar compression device is of the same magnitude as in the general population;
- tetanus incidence following surgical circumcision is of the same magnitude as in the general population; and
- tetanus incidence following circumcision with the elastic collar compression device is of the same magnitude as that following surgical circumcision.

Tetanus incidence in the general population

In two separate calculations using "the most up-to-date official report", the manufacturer of the elastic collar compression device stated that, in 2014, the true tetanus incidence among males aged 5 years and over was 9 (95% confidence interval [CI]: 4.7, 17.3) cases per 100 000 population and the incidence in males aged 15 years and older was 7.1–11.6 per 100 000. These incidence rates were 30–40 times higher than those reported by WHO, for the following reasons:

- The manufacturer quoted the paper by Nanteza *et al.*[2] (Appendix E of the submission), which extracted outpatient tetanus cases from the national District Health Information Software-2 (DHIS-2) for the years 2011–2014. This was the source used by WHO in 2015,

[1] Voluntary medical male circumcision for HIV prevention in 14 priority countries in east and southern Africa: Progress brief. June 2016, WHO/HIV/2016.14 (http://www.who.int/iris/bitstream/10665/246174/1/WHO-HIV-2016.14-eng.pdf, accessed 15 August 2016).

[2] Nanteza B, Galukande M, Aceng J, Musinguzi J, Opio A, Mbonye AK *et al*. The burden of tetanus in Uganda. Springerplus. 2016;5(1):705.

except that inpatient (not outpatient) admission statistics were extracted for the years 2012–2014. Inpatient statistics were regarded as a better benchmark against which to compare hospitalized tetanus cases following circumcision, in that they avoided likely multiple counting as outpatient cases are referred to higher level facilities for specialized care. However, a recognized limitation of inpatient data was that some cases may be missed, such as those who died before or during transfer to higher levels of care, or were never admitted.

- From the 1311 outpatient tetanus cases among males aged 5 years and above in 2014 (Table 1 in Nanteza *et al.*) and an estimated 2014 population of 15 293 000 males aged 5 years and over, the annual outpatient incidence was 8.6 (95% CI: 8.1, 9.0) per 100 000 males aged 5 or more years, based on a Poisson distribution for rare events. This differed from the annual incidence of 9 (95% CI: 4.7, 17.3) per 100 000 computed by the manufacturer.

Data extracted by WHO in early 2015 from the same Uganda DHIS-2 for 2012–2014 showed an annual male inpatient incidence of 3.0 per 100 000 population.[1] Since the risk of tetanus following circumcision is restricted to a period of about one month, the relevant comparison is tetanus incidence per month, not per year. The annual inpatient incidence is equivalent to 3 male inpatient tetanus cases per 1 200 000 months, or 0.25 per 100 000 months. A similar calculation using the DHIS-2 statistics cited above results in an estimated outpatient tetanus incidence in Uganda among males aged 5 years and above of 0.71 (95% CI: 0.68, 0.75) per 100 000 months. Given the limitations of both inpatient and outpatient data, these estimates provide a range for the likely background incidence of tetanus in the population.

Number and location of tetanus cases following surgical circumcision

Between 2012 and 2016, 15 confirmed tetanus cases following circumcision had been identified and reported to WHO. Two cases from Zambia in 2012 and one from Uganda in 2013 had occurred before active monitoring of tetanus had been reinforced by VMMC programmes. Between 2014 and 2016, 12 confirmed tetanus cases following circumcision had been reported from Kenya (two surgical), Rwanda (four elastic collar compression device), Uganda (two elastic collar compression device, three surgical) and Tanzania (one surgical) – giving a total of six cases after circumcision with the elastic collar compression device and six after surgical circumcision. Four cases survived, seven died and the outcome in one case was unknown. The number of confirmed tetanus cases following circumcision was unchanged from June 2016.

The manufacturer stated that Uganda was the only country where the Ministry of Health conducted active surveillance of tetanus following safe medical circumcision. However, all countries implementing VMMC programmes reported data on moderate and serious adverse events to WHO and the US President's Emergency Plan For AIDS Relief (PEPFAR). In addition, since 2014, all countries had been requested to report all deaths and inpatient hospitalizations occurring within 30 days of any circumcision method as part of ongoing safety surveillance of the VMMC programmes.

Appendix G of the report submitted by the manufacturer stated that four fatal tetanus cases following surgical circumcision were identified in Uganda in 2014–2015. These cases had been previously reviewed by WHO and the Ministry of Health. They included two fatal cases, one survivor and one infant aged 8 weeks who died of "aspiration pneumonia secondary to anaphylactic shock following SMC" (see *Ministry of Health safe male circumcision (SMC) death audit report*, November 2014).

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[1] WHO Informal consultation on tetanus and voluntary medical male circumcision: report of meeting convened in Geneva, Switzerland, 9–10 March 2015. World Health Organization; 2015. ISBN 978 92 4 150923 7 (http://apps.who.int/iris/bitstream/10665/181812/1/9789241509237_eng.pdf, accessed 15 August 2016).

The report submitted by the manufacturer (Appendix F: *General SMC updates*, April 2016) mentioned 11 tetanus cases after surgical circumcision but provided no details. In response to WHO's request for further information, the Ministry of Health had responded that the *General SMC updates* report was provisional. In early August 2016, the Ministry of Health informed WHO that the number of post-circumcision tetanus cases was seven, of which two cases followed circumcision with the elastic collar compression device and five followed surgical circumcision. Six of these cases were in the WHO case series; clinical details of the seventh case were awaited, to confirm that it met the criteria for association and occurred within a relevant time period. Data available on the location of five of the six confirmed tetanus cases showed that they came from the central (two surgical, one elastic collar compression device), eastern (one elastic collar compression device) and northern (one surgical) regions.

Underreporting of tetanus cases following surgical circumcision

The manufacturer of the elastic collar compression device stated that the absence of cases following surgical circumcision in Rwanda was evidence of underreporting because the country had similar demographics and vaccination policies to Uganda. However, alternate valid explanations included the following:

- Rwanda having higher historical diphtheria-tetanus-pertussis (DTP3) coverage rates than Uganda (e.g. Figure 2 in Dalal *et al*. 2016[1]).
- If the tetanus incidence following surgical circumcision observed in Uganda – 3 cases in 1 712 928 surgical circumcision or 0.18 (95% CI: 0.04, 0.51) per 100 000 – applied to Rwanda, the number of cases expected in Rwanda since 2014 was 0.48 (95% CI: 0.10, 1.40) based on an estimated 273 515 surgical circumcisions performed.

The manufacturer stated: "… causes of underreporting Tetanus cases after surgical MC are not related to Tetanus diagnosis … but rather, among others:

a) The fact that these cases do not return to the healthcare setting where they had originally been surgically circumcised (unlike with [the device]).
b) Inspection of the penis as possible point-of-entry for men with Tetanus is not acceptable socially in rural health clinics and is not currently part of routine procedure for care providers diagnosing a patient with Tetanus.
c) Reporting mechanism that does not include cause of admission, but cause of death – which in many cases, are complicated following Tetanus."

After analysing the available evidence, TAG members considered that these statements were not compelling for the following reasons:

- The Uganda *Ministry of Health safe male circumcision (SMC) death audit report* (November 2014) reconstructed the clinical history of each case and noted that "the SMC facilities were not the tetanus care providers because the patients did not make contact with the providers" (pages 12 and 13). After the onset of symptoms, the three men who subsequently died of tetanus first presented to health-care facilities other than those where the circumcision had been performed, and one of them even provided a different name. Two of the tetanus deaths occurred after circumcision with the elastic collar compression device and the other after surgical circumcision. This particular patient had been reviewed at the VMMC site on days 2 and 7 after device placement.
- Although Appendix J submitted by the manufacturer did not provide details of referral pathways, the first tetanus symptoms appeared 10–13 days after device placement, or 3–

[1] Dalal S, Samuelson J, Reed J, Yakubu A, Ncube B, Baggaley R. Tetanus disease and deaths in men reveal need for vaccination. *Bull World Health Organ*. 2016;94(8):613–621.

6 days after removal. The routine day 7 removal visit was of no value in these cases for detecting tetanus following circumcision with the device.

- Although the signs and symptoms of tetanus are quite specific, an initial misdiagnosis (e.g. of meningitis or neck pain) might occur. However, symptoms of tetanus would become apparent within a short time and the patient would probably be referred for specialized tetanus care. Misclassification of cause of death is possible in a patient whose symptoms were not observed at a health facility, but is less likely in health-care settings.

Tetanus incidence after surgical circumcision in Uganda

According to the manufacturer of the elastic collar compression device, the true incidence of tetanus following surgical circumcision in Uganda was 4 per 97 000 procedures (95% CI: 1.5, 10.7). This was based on four tetanus deaths following circumcision (listed in Appendix G of the submission) and the reported number of circumcisions performed in the central region in two specific quarters, but excluding all other quarterly time periods and regions. According to the manufacturer, the absence of cases in other regions and time periods was evidence of underreporting. However, the manufacturer's estimate was considered by TAG members to be an overestimate because:

- Appendix G actually contained three, not four, tetanus cases, and one of those listed was an infant aged 8 weeks who had died of other causes;
- tetanus cases actually occurred in regions other than the central region, following surgical circumcision as well as circumcision with the device;
- in the absence of objective a priori reasons by which reporting was known to be better in the central region and in specific time periods, post-hoc selection of time periods and locations overestimates true incidence; and
- for rare adverse events like tetanus, there will be time periods and regions with no cases.

Comparison of tetanus incidence with surgical circumcision and circumcision with the elastic collar compression device

Over the period January 2014 to June 2016, an estimated 113 662 device and 3.72 million surgical circumcisions were performed in Kenya, Rwanda, Uganda and the United Republic of Tanzania. The estimated incidence of tetanus was 5.3 (95% CI: 1.9, 12) per 100 000 device circumcisions and 0.16 (95% CI: 0.06, 0.35) per 100 000 surgical circumcisions (Table 1), resulting in an estimated incidence rate ratio of 33 (95% CI: 8.7, 120). Restricted to Rwanda and Uganda, the only countries from which tetanus cases following device circumcision had been reported, the incidence rates and incidence rate ratios were similar to those in the four countries combined. At the review conducted in June 2016, the estimated total number of surgical and device circumcisions in the four countries were 18% and 20% lower, respectively, than those in Table 1.

Table 1. Tetanus incidence and incidence rate ratio by circumcision method, 2014 – June 2016

Countries	Elastic collar compression device cases/circs	Incidence per 100,000 (95% CI)	Surgery cases/circs	Incidence per 100,000 (95% CI)	Incidence rate ratio (95% CI)
Kenya, Rwanda, Uganda and the United Republic of Tanzania	6 / 113,662	5.28 (1.94, 11.5)	6 / 3,717,338	0.161 (0.059, 0.351)	32.7 (8.74, 122)
Rwanda and Uganda only	6 / 110,800	5.45 (1.99, 11.8)	3 / 1,986,443	0.151 (0.031, 0.441)	35.9 (7.66, 222)

Based on the epidemiological evidence, TAG members concluded that the incidence of tetanus following conventional surgical circumcision was similar to the background rate, but the incidence following circumcision with the elastic collar compression device was about 30 times higher. They recognized that there may have been underreporting of tetanus cases following surgical circumcision. However, differential underreporting was considered unlikely to account for the magnitude of the difference between circumcision methods, because about 190 unreported tetanus cases following surgical circumcision would have been needed since 2014 in the four countries for the two methods to have the same estimated incidence rate. Underreporting on this scale was deemed not plausible, particularly given that case fatality was high and such a pattern of mortality would have been noticed and reported by field workers even in the absence of active surveillance.

Conclusion on epidemiological evidence

Having reviewed the evidence submitted by the manufacturer of the elastic collar compression device, TAG members disagreed with the manufacturer's finding that incidence of tetanus following surgical circumcision was similar to that following circumcision with the elastic collar compression device. They also disagreed that the incidence following circumcision with the device was of the same magnitude as in the general population. TAG members noted in particular that the manufacturer's approach to estimating tetanus incidence overestimated the risk following surgical circumcision.

Countries should be supported to systematically collect and compile information on all deaths and inpatient hospitalizations that occurred within 30 days of circumcision, irrespective of method and irrespective of potential causal link to the circumcision procedure. Compiling such events at the global level permitted timely identification of rare adverse events associated with circumcision, and implementation of appropriate risk mitigation measures.

3 TAG conclusions and recommendations

Having reviewed the documents submitted by interested parties and having considered the presentations made during the open session, TAG advised WHO that the conclusion reached in June 2016 remain. TAG concluded that:

- tetanus incidence was more than 30 times higher following circumcision with the elastic collar compression device than with surgical circumcision; and
- although underreporting of tetanus cases following circumcision was possible, differential underreporting was unlikely to account for the magnitude of the difference.

TAG confirmed its previous advice of July 2016:

- Circumcision with a device method where the foreskin is left in situ and removed several days after application should be undertaken only if the client is adequately protected against tetanus by immunization with TTCV that includes:
    a) two TTCV doses at least 4 weeks apart, with the second dose at least 2 weeks before device placement; or
    b) if a client has previously received three infant doses, or one dose during adolescence or adulthood, a TTCV booster at least 2 weeks before device placement (a booster at the time of placement provides only limited protection as it takes 7–14 days for antibodies to rise to protective levels); or
    c) a series of five doses of TTCV.
- For conventional surgical methods in which the foreskin was removed at the time of the surgical procedure, TAG recommended no modification to the 2015 consultation advice on vaccination. Ministries of health were advised to develop and phase in effective and practical delivery strategies to providing tetanus vaccination in the context of their programmes for VMMC for HIV prevention and for vaccination. The strategies used would

depend on the country's TTCV schedule and practices, and its tetanus burden. Unless an individual has documented evidence of having received a full five-dose TTCV series, it is advised that, at a minimum, a single TTCV dose be administered before or at the time of circumcision.

- A clean care approach should be followed for all circumcision methods. This approach includes the following:
    - 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; this is relevant for all circumcision methods.
    - Enhancing individual and community education on clean wound care after circumcision. This includes giving clear and understandable instructions on wound care and genital hygiene, clean or sterile dressings to use at home, clear instructions on when to return to the health-care facility for post-procedure care, education on the benefits of vaccination against tetanus and education on the dangers of applying substances that may contain *C. tetani* (e.g. animal dung poultices or herbal remedies) to wounds.

As part of ongoing monitoring of the safety of VMMC programmes, TAG stressed the importance of countries systematically collecting and compiling information on all deaths and inpatient hospitalizations that occurred within 30 days of circumcision, irrespective of method or potential causal link to the circumcision procedure. This safety monitoring is an essential component of the VMMC programmes that have implemented an elective procedure for HIV prevention.

TAG stressed the importance of continued global level monitoring of the safety of VMMC programmes, and offered to reconvene if additional relevant information became available. This is in addition to the requirement for manufacturers of prequalified devices used for male circumcision to maintain their own systems for detection, investigation and action related to adverse events at the patient level and incidents at the device level.[1]

[1] Relevant international guidance includes: *Guidelines on medical devices vigilance system,* MEDDEV 2 12-1 rev. 8 Vigilance, January 2013; and ISO 13485 *Medical devices -- quality management systems -- requirements for regulatory purposes*.

Annex A: Participants

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Declarations of interests

All members were required to declare interests related to the subject matter of the discussion. Two declared interests as follows (these interests were the same as those declared for earlier consultations that were deemed not to require exclusion from the meeting):

> **Tigistu Adamu** works with Jhpiego, which has received US government funds to assess the safety and acceptability of elastic collar compression devices, for which he was co-investigator. This was not considered to give rise to a potential conflict of interest.
>
> **Christopher Samkange** consulted with PSI on male circumcision training to the national VMMC programme and served as specialist urological consultant for delivery processes

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Annex B: Documents received by WHO August 2016

Submitted based on request for additional information on tetanus and male circumcision methods

Document	Content
CMT data and analyses for WHO TAG re-evaluation 120816.pdf (13 pages)	The risk of tetanus following a male circumcision procedure – key evidence and analyses, July 2016. Memo from Eddy Horowitz, CEO CircMedTech to WHO, Attention VMMC Technical Advisory Group dated 31 July 2016
CMT Appendix A -J Infect Dis -2016-Liu-infdis-jiw182 (002).pdf (13 pages)	Genital anaerobic bacterial overgrowth and the PrePex male circumcision device, Rakai, Uganda. Accepted manuscript by Liu et al., *J Infect Dis* Advance Access published May 13, 2016 [now published *J Infect Dis* 2016; 214: 595–8, doi: 10.1093/infdis/jiw182] Abstract available and full-text links at: http://jid.oxfordjournals.org/content/214/4/595.abstract Not posted publicly due to copyright restrictions
CMT Appendix B - JID Response to Liu article Letter Editor- Brook - Accepte....pdf (4 pages)	Letter to the Editor, *J Infect Dis* from Itzhak Brook MD, Georgetown School of Medicine, Washington DC (not dated) Extract available at: http://jid.oxfordjournals.org/content/early/2016/07/31/infdis.jiw276.extract?sid=86f2adae-0491–42b7–98c9-bc30f85b74e4 Not posted due to copyright restrictions
CMT Appendix C - 2016 Schiavo_Review of Dr Liu Article.pdf (4 pages)	Letter from Prof Giampietro Schiavo, University College London to Alon Kushnir, VP Regulation & Clinical Affairs, Circ MedTech Ltd dated 26 July 2016
CMT Appendix D - Correspondence Letter by Cindy M Liu_Ockham's Razor and th....pdf (4 pages)	Ockham's razor and the PrePex male circumcision device. Accepted manuscript by Liu et al., *J Infect Dis* Advance Access published July 11, 2016 Available at http://jid.oxfordjournals.org/content/early/2016/07/31/infdis.jiw277.extract Not posted publicly due to copyright restrictions
CMT Appendix E - Uganda Tetanus Burden Paper June 2016.pdf (7 pages)	Nanteza, B *et al*. The burden of tetanus in Uganda. *SpringerPlus* 2016; **5**:706, http://dx.doi.org/10.1186/s40064–016–2309-z (Open Access)
CMT Appendix F - Final SMC Updates April 8 2016 Uganda MoH.pdf (16 pages)	Slides titled 'General SMC Updates' by Barbara Nanteza, 8 April 2016, Lourdel Towers Not posted on WHO website since presentation considered confidential and not approved by Uganda Ministry of Health (MoH)
CMT Appendix G - 4 surgical TT cases in Uganda (003).pdf (1 page)	Table of four fatal tetanus cases following surgical MC in Uganda Not posted on WHO website as considered not yet official by MoH
CMT Appendix H - Experts Risk Analysis on Tetanus and VMMC with PrePex 2015.pdf (48 pages)	Tetanus and VMMC with PrePex risk analysis: findings & recommendations for expert consultation with WHO, March 9th 2015
CMT Appendix I - CONFIDENTIAL CONFIDENTIAL PrePex Procedures to Date by Coun....pdf (1 page):	Table of number of PrePex procedures performed by year and country (to end of June 2016) Not posted in WHO website since details are confidential to CMT

Document	Content
CMT Appendix J – Data on tetanus cases following PrePex rev.pdf	Clarifications and data on tetanus cases following PrePex, CMT. Received 5 August 2016 and exceptionally accepted. Details on specific dates and occupation removed for reasons of confidentiality
EngenderHealth 2Aug16.pdf (1 page)	Email from Mark Barone, EngenderHealth (2 August 2016)
MC-and-tetanus-documents-review_CLTresponse-Aug16.pdf (1 page)	Note on biological plausibility mechanism from Dr C. Louise Thwaites, Clinical Fellow, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam, Centre for Tropical Medicine and Global Health, University of Oxford, United Kingdom, dated 10 Aug 2016
MoH Final SMC Death Audit (No Names).pdf	This Uganda *Ministry of Health safe male circumcision (SMC) death audit report* (November 2014) provides details on four cases investigated by the safety monitoring committee in 2014. Two cases occurred after surgical circumcision and two after PrePex circumcision; one case was an infant who died of causes other than tetanus

Note: All above documents shared with TAG members, as well as the document of 11 August 2016 'Circ MedTech (CMT) reply to: Question for CircMedTech experts'

Annex C: Additional documents posted by WHO August 2016

Document	Content
Dalal Bull WHO 2016.pdf (9 pages)	Dalal, S *et al*. Tetanus disease and deaths in men reveal need for vaccination. *Bulletin World Health Organ* 2016; **94**:613–621, http://dx.doi.org/10.2471/BLT.15.166777 (Open Access)
WHO reports • WHO Update to consultation on tetanus VMMC 7 Jul 2016 • WHO MC Tetanus_Consult Report Final 2015 • WHO MC TAG Report_2014 • WHO_MC_TAG Mtg Rpt Jan13 • WHO MC Devices Use Guideline Oct13	Reports from WHO consultations and meetings (WHO website) • Report on update to the 2015 technical consultation of tetanus and VMMC. • This consultation report shares details on the discussions on VMMC and tetanus risk, and provides advice to programmes for their consideration concerning near-term risk mitigation of tetanus by VMMC services. • This report describes the TAG review of new information on the safety of circumcision, including by specific device methods from pilot implementation studies and programme roll-out; the safety and suitability devices for circumcision in adolescents; other new innovative methods for adult circumcision; and the safety and clinical performance of infant circumcision devices used in African settings. • This report describes the TAG January 2013 meeting review of the clinical performance of two specific male circumcision devices as part of the product review in the WHO Prequalification of Male Circumcision Devices Programme. It was based on clinical data collected in the context of the Framework for clinical evaluation of male circumcision devices (WHO). • Guideline on the use of devices for adult male circumcision for HIV prevention, October 2013, WHO
Bitega2011_Prepex	Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited setting, Bitega et al. JAIDS, Vol 58, no. 5, Dec 15, 2011. Provides description of method mechanism of action and timing of device removal. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/21909032 doi: 10.1097/QAI.0b013e3182354e65.

Note: All documents shared with TAG members