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,
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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