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Original Article

Closing the Gap Toward Zero Tetanus Infection for Voluntary Medical Male Circumcision: Seven Case Reports and a Review of the Literature

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Abstract

Background: Voluntary medical male circumcision (VMMC) is important for HIV prevention, providing up to 60% protection. Although VMMC is usually a safe procedure, it is not free of associated serious adverse events. In the Uganda VMMC program, which is available to males 10 years of age and older, 11 individuals were reported with tetanus infection out of almost 3.5 million circumcisions over an eight-year period (2009–2018). The majority had received tetanus vaccination prior to VMMC. Disproportionately and statistically significantly, the elastic collar compression method accounted for half the tetanus infection cases, despite contributing to only less than 10% of circumcisions done. This article describes gaps in presumed tetanus vaccination (TTV) protection along with relevant discussions and recommendations.

Case Presentations: We present seven tetanus case reports and a review of the literature. We were guided by a pre-determined thematic approach, focusing on immune response to TTV in the context of common infections and infestations in a tropical environment that may impair immune response to TTV. It is apparent in the available literature that the following (mostly tropical neglected infections) sufficiently impair antibody response to TTV: human immunodefiency virus (HIV), pulmonary tuberculosis, nematode infections, and schistosomiasis.

Conclusions: One of seven patients died (14% case fatality). Individuals with prior exposure to certain infection(s) may not mount adequate antibody response to TTV sufficient to protect against acquiring tetanus. Therefore, TTV may not confer absolute protection against tetanus infection in these individuals. More needs to be done to ensure everyone is fully protected against tetanus, especially in the regions where risk of tetanus is heightened. We need to characterize the high-risk individuals (poor responders to TTV) and design targeted protective measures.

Keywords: post-voluntary medical male circumcision; safe male circumcision; Uganda; wound care

Voluntary medical male circumcision (VMMC) for prevention of human immunodeficiency virus (HIV) is performed on relatively healthy adult and adolescent males between 10 and 49 years of age [1]. However, those older than 49 years with no contraindications may be circumcised if they so desire. The intention is to maintain as low an adverse event (AE) rate as is practically possible while focusing on the age group most vulnerable to HIV infection. The most serious although extremely rare risk associated with this procedure is death, which is also true for other minor surgical procedures, mostly because of developing tetanus, which carries a case fatality rate of 42%–67% in sub-Saharan Africa [2–4]. Other causes of life threatening-adverse events associated with VMMC include uncontrolled hemorrhage in those with bleeding disorders, anaphylactic drug reactions, and surgical site infections/sepsis [5]. These are, however, associated with much less morbidity and mortality compared with tetanus. The other causes of death in the period of up to

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30 days after VMMC may not be related directly to circumcision (e.g., malaria or enteric infection).

Protection against tetanus infection is multi-layered. The first line of defense is providing tetanus vaccination (TTV) to the unvaccinated or immune-impaired is initiated on the day of VMMC, and is followed subsequently by the second and third dose. The initial three doses in infancy plus two boosters at four to seven years of age and 12 to 15 years of age are intended to provide maximum protection [6].

The second layer of protection proper post-operative care, which is critical for healing and preventing contamination with unauthorized topical applications. This responsibility is shared with the client. However, the health care provider must provide clear information on surgical site care during the first week or two. Physical inspection of the surgical site and interaction with the service provider are required during the follow-up period in the Uganda VMMC program. Should tetanus occur, it is essential to provide crucial clinical care to treat and prevent death. We outline these measures, emphasizing that they are not foolproof, and provide the next steps.

Voluntary medical male circumcision is important for HIV prevention, providing up to 60% protection [7]. Although VMMC is usually a safe procedure, it is not entirely free of serious AEs and even death [4].

Background

In the VMMC program, proper screening, when well guided and strictly performed, may exclude those who are clearly vulnerable to tetanus acquisition. This includes those who had not been vaccinated at all or had been vaccinated insufficiently, those who have open wounds that may be potentially contaminated with spores (e.g., wounds from trauma after traffic accidents or from jigger infestations (*Tunga penetrans*). Many boys in rural Africa go to school barefoot and are therefore prone to minor cuts. However, the point of entry may heal long before tetanus manifests and the individual may not recall having a wound or may not be in position to report it even if they remembered. This presents a screening challenge or gap. We have no clear guidelines on what to do with men or boys with healed or healing minor wounds on their extremities who present for VMMC.

Although limited, the available evidence from a recent Ugandan study suggests that adequate antibody response would be up to 94% by day 14 after TTV, 97% by day 28, and 100% by day 42 [8]. The current practice (from 2017) is to give one VVT dose on the day of VMMC. Therefore, up to 6% of individuals (1/16) shown to have an inadequate antibody immunologic response to VVT [8] by day 14 are vulnerable to tetanus. No explanations for the inadequate antibody response were provided in that study.

Case Presentations

Case 1

In September 2017, a 50-year-old casual laborer in a semi-urban location had VMMC via the sleeve resection method; he received TTV on the day of circumcision. The patient did not return for the mandatory day two and day seven follow-up visits as was recommended to him and could not be contacted by telephone because he did not own one. There were no immediate family members available. The patient was discovered ill on day 18 after VMMC in an abandoned shelter. He was underweight and had a jigger infestation that had burrowed in callosities on both feet making it difficult to see. A clinical diagnosis of tetanus was made based on the signs of moderate trismus, marked generalized rigidity, short-lasting tachypnea, and mild dysphagia but no fever. He was negative for HIV-1/HIV-2 antibodies. We admitted the patient to a dark quiet room at a tertiary private hospital; debridement was performed to reduce the jigger burden. He died on the fourth day after admission from sudden cardiorespiratory arrest that did not respond to cardiopulmonary resuscitation. Prior treatment included feeding via nasogastric tube, anti-convulsant drugs (intravenous diazepam and intravenous magnesium sulfate), antibiotic agents (intravenous metronidazole), and intravenous fluids. Tetanus immunoglobulin 3000 IU had been given. The postmortem findings revealed presence of pulmonary tuberculosis (PTB) lesions in the lungs.

Case 2

In June 2018, a 12-year-old student who lived with both parents in an urban location had VMMC via the dorsal slit method; he received TTV on the day of VMMC. The patient was negative for HIV-1/HIV-2 antibodies; he returned on day two and day seven for follow-up. He developed symptoms suggestive of tetanus on day 11 post-VMMC. He manifested severe trismus, generalized increased tone, and spontaneous, frequent, and prolonged spasms lasting more than 15 seconds. Respiratory distress with tachypnea, dysphagia, and tachycardia of more than 120 beats per minute, with moderate autonomic nervous system dysfunction but with no fever was present. He had old scars on his feet and legs (post-minor trauma) and a clean-healing circumcision. The patient was admitted to the intensive care unit (ICU) for 30 days; the patient was on ventilator support for 25 days. Potent anticonvulsants including intravenous magnesium sulfate, diazepam, midazolam, and also intravenous fentanyl and metronidazole were given. We administered nutritional support of 1,800–2,500 kcal/d and tetanus immunoglobulin (TIG) 500 IU. He stayed an additional seven days in the general ward post-ICU for physical therapy and monitoring. Twelve months later, the patient was in good health and was going to school with no sequela.

Case 3

In September 2018, a 21-year-old casual laborer in an urban location had VMMC via the dorsal slit method and received TTV on the day of the VMMC. He presented on day seven after VMMC with mild to moderate trismus, generalized increased tone, no respiratory distress, short-lasting spasms and mild dysphagia, intermittent tachycardia less than 120 beats per minute, and no fever. We admitted him to the ICU, although he did not need ventilator support. The patient had healed leg/feet scars/wounds (post-minor trauma) and a clean-healing frenulum post-VMMC. He was negative for HIV-1/HIV-2 antibodies. The patient received TIG 500 IU, anticonvulsants, analgesics, antibiotic agents, and nutritional support up to 2,000 kcal/d. He was discharged from the ICU after 15 days; the patient then stayed on a general ward for four more days before being discharged home. One month

later, the patient was in good health, back to work, with no sequela. At last follow-up six months later, he remained well.

Case 4

In March 2019, an 11-year-old boy from an urban location had VMMC via the dorsal slit method 15 days prior to admission to the ICU with a diagnosis of severe tetanus. The fourth-born in family of six, the patient lived in a one-room rented house with a cement floor. The symptoms presented three days prior to the ICU admission. He had experienced generalized and frequent spasms lasting more three minutes. He had a pulse rate of 176 beats per minute, oxygen saturation as measured by pulse oximetry (Spo_2) of 91%–94%, a respiratory rate of 36 breaths per minute, and a temperature of 37.6°C. His mother accompanied him and provided his history. The mother denied applying any topical medicines or concoctions on the penis. However, she reported occasional tiny wounds on his feet from minor trauma and a history of occasional jiggers; no jigger entry points were seen on physical examination. The patient had no comorbid conditions.

The patient initially presented to a local clinic where he received five unknown tablets; no improvement was observed overnight. He visited another local clinic from which he received intravenous medicines, again without improvement. His mother took him to a public tertiary hospital where they spent two days. The patient was subsequently transferred to a private tertiary hospital with an ICU. He required mechanical ventilation for 22 days. Included in the treatment were multiple broad-spectrum antibiotics. He had received TIG while at the public tertiary hospital. Anticonvulsants included magnesium sulfate, phenobarbital, diazepam, midazolam, atracurium, and rocuronium. All doses were titrated to response and in various combination and times. The patient also received fentanyl, clexane, omeprazole, and chloropromazine. For nutritional support, he received high-calorie feeds (1,500–2,500 kcal/d) via nasogastric tube.

Laboratory tests included arterial blood gases, full blood count (FBC), liver function tests (LFTS), renal function tests, and chest radiographs. The patient received rehabilitative physiotherapy. Four days after transfer to the ICU he was discharged home in satisfactory condition with baclofen and paracetamol. Follow-up at two weeks and again at six months was unremarkable. The patient continues to do well and has gained weight.

Case 5

In August 2019, a 42-year-old fisherman from a rural location had VMMC via the dorsal slit method. He had received TTV on the day of circumcision. He was negative for HIV-1/HIV-2 antibodies. After VMMC he was seen on the second post-operative day and was well. On the seventh postoperative day he presented to a local hospital with a high fever, tetanus, and dysphagia, and generalized painful spasms. He was moved to the next-level hospital and subsequently to a private facility with an ICU.

At this facility, 21 days after VMMC, the patient was conscious with a nasogastric feeding tube in place. The patient presented with risus sardonicus and generalized spasms. The frequency and duration of each spasm were monitored and noted. He was normothermic, with normal oxygen saturation of 98% on room air, he had a normal radial pulse of 73, and was normotensive. There were no signs of surgical site infection. The patient was found to be HIV-negative, have a normal complete blood count, an elevated γ-glutamyl transferase, features of a urinary tract infection (UTI; >10,000 leucocytes in urine), and had negative blood smear for microfilariae. He was treated in the ICU for 11 days without ventilator support and then on the general ward for seven days before being discharged.

During hospitalization, the patient received TIG 2000 IU and antispasmolytic drugs including diazepam alternating with chlorpromazine CPZ). Intravenous antibiotic therapy was necessary for a severe UTI. He was treated with intravenous pantoprazole and placed in a dark ICU room to minimize stimulation from light, noise, and touch. A catheter was inserted, and urine output was monitored. Feeding was done via a nasogastric tube with high-protein feeds, target calories 1,500–2,000 kcal/d.

On day 15 he started physiotherapy, the nasogastric tube was removed, and he began eating. He was discharged on day 18 free of spasms and able to walk unsupported. The circumcision had healed completely. Six months later the patient was doing well free of any sequela.

Case 6

In October 2019, a 37-year-old subsistence farmer had VMMC via the dorsal slit method. He developed symptoms eight days after circumcision including neck pain, lockjaw, and spasms with associated fever. He spent several days at different facilities before being admitted to the ICU. A diagnosis of tetanus was made at admission. The patient scored 12 on the Glasgow Coma Scale and was tachycardic at 133 beats per minute with a blood pressure of 100/70 mm Hg. He had features of dysautonomia. The circumcision site was clean and healing. A brain computed tomography was free of space-occupying lesions or other pathology. Liver function tests were abnormal, however, he was negative for hepatitis B and C. He also tested negative for HIV-1/HIV-2 antibodies. The patient required mechanical respiratory support. He received TIG 6000 IU, noradrenaline infusion, magnesium sulfate infusion, fentanyl infusion, rocuronium infusion, and antibiotic therapy including metronidazole. In addition, nutritional support up to 1,500–2,500 kcal/d from protein, fat, carbohydrates, and multivitamin mixtures. He was placed in an enclosed room, with lights off, and minimal skin contact to minimize trigger of spasms. He had elevated liver enzymes suspicious for alcohol-induced hepatitis and low serum calcium and magnesium. The patient was hospitalized for 32 days, 24 of which were in the ICU. He was discharged in good health. Three months later he continued to be in good health with no sequela.

Case 7

In November 2019, a 48-year-old causal laborer from a rural setting had VMMC using the dorsal slit method and received TTV on the day of circumcision. Eleven days later he was a passenger on a motorcycle and involved in a traffic accident. He sustained a closed head injury, a pneumothorax, and fractures of the left second and third metatarsals. He was

admitted to a local hospital for several days, however, because of his deteriorating condition he was transferred to a tertiary facility with ICU care.

Upon arrival at this facility the patient was very ill, with tachycardic pulse 152 beats per minute, low oxygen saturation of 83% on room air, and a score of 9 on the Glasgow Coma Scale. He remained in the ICU for 38 days on a ventilator and then on the general ward for 20 days undergoing rehabilitation. The patient received intravenous antibiotic agents, sedation/antispasmolytics including magnesium sulfate, propofol, rocuronium, fentanyl, chlorpromazine (CPZ), midazolam, inotrope support with noradrenaline, and TIG. He was fed a high-calorie diet up to 2000 kcal/d. He was treated with highly active antiretroviral therapy (HAART) because of a new diagnosis of HIV while in the ICU. A cast was placed on his foot by an orthopedic surgeon. Four weeks after discharge he was settled with his family and was gaining strength, walking on crutches, and gaining weight.

Discussion

Voluntary medical male circumcision is a critical component of HIV prevention programs that seek to halt the transmission of HIV. Voluntary medical male circumcision protects the individual and the community. Although VMMC has a low rate of AEs, when tetanus is associated with it raises major concerns from the communities and their overseers. In this article we highlight the gaps in protection against tetanus. In part, these gaps are due to a delayed immunologic response to VVT (a vaccine), the delay is occasioned by some tropical infections. We also outline the next steps in bridging existing knowledge gaps.

The incubation period for these seven cases was seven to 18 days. However, the 18-day period might have been less, because day 18 was the day that the patient presented; he could have fallen ill earlier. From the prognostic perspective, an incubation period less than seven days indicates a grave prognosis. The entry site could be presumed to be the circumcision site, especially for case 1 who lived alone in squalid conditions. The VMMC program is unable to assess potential client's living conditions before offering the service.

The complicating factors for case 1 included being underweight, which was most likely caused by poor nutrition, squalid living conditions, and covert (subclinical) PTB, living alone, and not having a telephone. He apparently had had jiggers for many years, which cast doubt on whether this was the source of the infection. The extensive feet callosities obscured the presence of jiggers. Jigger infestations are not widespread and may not be confronted in routine training programs for most health workers in Uganda.

For case 2, the patient and his mother denied any application of any topical substances. There was evidence of minor healed wounds/scars on both feet. There is no current guide on what to do for such clients. It is estimated that up to 30% of clients, especially adolescent boys, have sustained scrapes and skin breaches in the weeks preceding VMMC [2]. Case 3 also had minor trauma of the leg and feet and a nonseptic post-operative frenulum wound. He admitted to applying a detergent on the surgical site to accelerate healing. Perhaps this was a potential entry mechanism. Case 4 had minor trauma wounds to the leg and feet and a healing nonseptic wound at the frenulum.

In terms of protection, all patients had records of tetanus vaccination on the day of circumcision. It was not ascertained if they had childhood vaccinations and subsequent booster doses.

Unfortunately, in the currently prevailing circumstances in sub-Saharan Africa, it may not be possible to reduce the risk of tetanus infection and death to zero. We are likely to see more tetanus cases with the advent of mass VMMC, assuming that they are duly reported. The premise for this prediction is that the known risk factors are not all readily controllable, although they can be minimized. The lack of a national mass TTV program including booster vaccinations is one such factor. Also, there is no control over what patients do to the circumcision site while at home [9,10]. Topical applications of any tetanus spore-containing materials, including but not limited to homemade herbs or animal waste heightens the tetanus risk tremendously. However, we can mitigate this risk by promoting the initial dressing change on day two to be health worker supervised and strongly discourage any unauthorized topical applications. Additionally, there are certain unknown uncontrolled risks that we have yet to discover.

Review of the literature

The concept of varied immunologic responses to vaccines, including TTV, is well documented [11]. The varied immune response fits into three categories: appropriate responders, slow responders, and non-responders. From the literature reviewed for this article, there are several known factors that would lead to a varied or impaired immune response to TTV and these include but are not limited to HIV, tuberculosis (TB), nematode infestation, schistosomiasis, and men (older than 35 years), as outlined below.

HIV

Immune responses to most vaccines are unknown to be impaired in patients with HIV infection [12]. Although studies have also shown that HIV-infected children are able to mount both cellular and humoral immune responses to commonly administered vaccines in the first two years of life [13], antibody levels tend to be lower and to decrease more rapidly over time compared with immunocompetent individuals [14]. This may have to do with the role of $CD4^+$ lymphocytes in antibody production [15]. The immunoglobulin response is lower in HIV-1 carriers than in controls. The proliferative responses to TTV are lower in HIV-1 carriers [16]. Testing for HIV is routine in the safe male circumcision program, however, guidance on VMMC for HIV-positive individuals as relates to tetanus risk is not clear.

Pulmonary tuberculosis

Tuberculosis is a multi-systemic disease with myriad presentations and manifestations and is the most common cause of infectious disease-related mortality worldwide. In 2009, two billion people were estimated to have latent tuberculosis [17]. Latent tuberculosis (LTB) infection occurs when a person is infected with *Mycobacterium tuberculosis* but does not have active TB. Adolescents, the same group targeted for VMMC, are a high-risk group for LTB infection, which is not treated routinely in low-income countries. The prevalence of LTB infection in a group of adolescents in eastern Uganda

was 16.1% (95% confidence interval [CI], 15.1–17.2) [18]. A nationally representative Kenyan survey of children six to 14 years of age reported the prevalence of LTB infection of 10.2%, a figure that did not change much over two decades between 1986 and 2006 [19]. Whereas an outright TB infection has an impact of the body's immunity in the context of TTV, the impact of latent PTB remains to be established. We also know that malnutrition can switch LTB infection over to TB. Malnutrition is not screened specifically in the VMMC program, however, case 1 had PTB undiagnosed at the time of administering VMMC and was underweight.

Uganda faces a high burden of TB. A national prevalence survey conducted in 2014–2015 in the population more than 15 years old, revealed the prevalence of sputum-positive TB was 174 per 100,000. A substantial proportion of patients with PTB do not present with typical symptoms. The prevalence of any cough was only 21.6%. The much higher TB prevalence in men and the highest prevalence to notification ratio among the adolescents and young adults highlight the need to develop strategies to diagnose TB in these sub-populations [20].

Soil-transmitted nematodes

More than one billion people may be infected with at least one soil-transmitted nematode (STN) and the prevalence among school-aged children may be as high as 90% [21-23]. These helminth infections include ancylostoma duodenale, ascaris lumbrocoides (enterobiasis, strongyliodasis, filariasis, trichinosis, hookworm, trichuriasis, ascariasis, angiostrongyliasis, and Throthers), and trichuris trichiura. Recent data suggest that approximately 60 species of roundworms parasitize human beings. Intestinal roundworms constitute the largest group of helminthic disease in humans. A substantial proportion of children and young adolescents in sub-Saharan Africa, including Uganda, have had a nematode infestation (Fig. 1).

Infection with *Wuchereria bancrofti* can diminish the immune response to an unrelated antigen by a mechanism that is likely to involve interleukin-10, as happens when TTV is given to filarial-infected individuals. A TTV-specific immunoglobulin G (IgG) response is low compared with non-filaria–infected individuals [24].

Most cases of helminthiasis are asymptomatic; co-infections occur with multiple helminths, or with one or more helminths and other disease. Helminth infections are commonly believed to result in unique disease susceptibility and outcomes [25]; helminth infections confound TTV efficacy [26,27] by secreting molecules that regulate the mammalian immune system [28]. One-third of the human population is infected with these parasitic worms. To avoid being eliminated, these parasites actively dampen the immune response of their hosts. This immune modulation also suppresses immune responses to third-party antigens such as vaccines [29].

Schistosomiasis

Schistosomiasis is an acute and chronic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*.

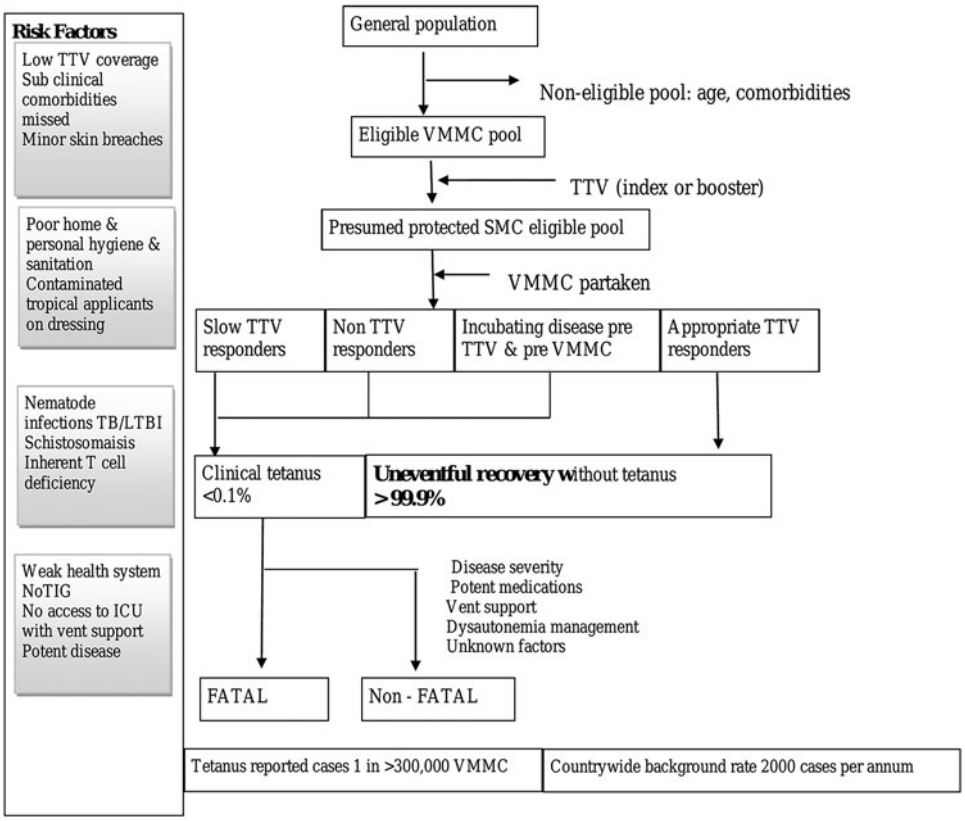

FIG. 1. Schema illustrating patient population and system factors for tetanus outcomes. TTV = tetanus vaccination; VMMC = voluntary male medical circumcision; TB = tuberculosis; LTBI = latent tuberculosis infection; TIG = tetanus immunoglobulin; ICU = intensive care unit.

Table 1. Contributors to High Tetanus Case Fatality in Sub-Saharan Africa

Patient factors
Severe baseline illness
Severe clinical form (dysautonomia, laryngospasm, and respiratory failure)
Outdoor risk: wounds and abrasions
High costs of care
Lack of health-seeking behavior
System factors
Suboptimal ICU care without ventilator support and potent medications
Cold chain failure
Community factor
Low disease awareness
Abundance of spores in rich organic soils
Vector factors
Highly virulent clostridia
Varied incubation period

This table outlines the factors that contribute to the higher than two-third case fatality in sub-Saharan countries.

Schistosomiasis is prevalent in tropical and sub-tropical areas, especially in poor communities without access to safe drinking water and adequate sanitation. Schistosomiasis affects agricultural and fishing populations. In Uganda, these would be in and around Lakes Victoria and Kyoga, both catchment areas for VMMC. Inadequate hygiene and contact with infected water make children especially vulnerable to infection. Estimates show that at least 206.4 million people required preventive treatment for schistosomiasis in 2016, of which more than 89 million people were reported to have been treated [30]. It is estimated that 91.4% of those requiring treatment for schistosomiasis live in Africa. There are two major forms, the intestinal and orogenital, caused by five main species of blood fluke. In Uganda, *Schistoma mansoni* is more prevalent.

In a survey recently conducted in Uganda in 2017 under PMA2020, schistosomiasis was found to be prevalent among all geographic and demographics throughout Uganda; three in 10 people were affected [31]. It is found in at least 23%–26% of primary and secondary schoolchildren in Uganda, inclusive of the target age for VMMC.

High background rate

There is likely to be a group that could possibly be otherwise good TTV responders, however, this was prevented by an incubating disease that got in prior to both VMMC and TTV. This plays on the platform of a high background rate in the country.

Corr

Last line of defense

As partially outlined in Table 1, successful treatment of the severe form of disease requires ICU facilities able to provide safe ventilatory support and potent medicines to control dysautonomia and convulsions. In the seven cases reported here, one patient who died had TB and malnutrition and he did not receive ventilatory support. The other patients with the severe form of disease received ICU care and all survived. However, this came at a cost (Table 2). The cost of care ranged from $5,000 to $40,000.

Table 2. Summarizing Characteristics of the Seven Cases of Tetanus, 2020 Tetanus Male Circumcision-Related Report, Uganda

Variable \ *Case*	1	2	3	4	5	6	7
Date	September 2017	June 2018	September 2018	March 2019	October 2019	September 2019	November 2019
Age (mean 30 y)	50	12	21	11	37	42	48
Address	Rural	Urban	Urban slum	Urban	Rural	Rural	Rural
Occupation	Informal	Student	Informal	Student	Informal	Informal	Informal
Incubation days	18[a]	11	7	12	8	7	11
Onset to admission in ICU (d)	NA	1	2	3	13	4	2
ICU admission	No	Yes	Yes	Yes	Yes	Yes	Yes
TTV given	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
TIG given	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ICU stay in days	4 in HDU	30	15	22	24	11	38
Total length of stay	4	37	19	26	32	18	58
Tetanus severity	Severe	Severe	Moderate	Severe	Severe	Moderate	Severe
Ventilator support	No	Yes	No	Yes	Yes	No	Yes
Schistosoma test	Not done	Not done	Not done	Negative	Not done	Negative	Negative
Microfiliariae test	Not done	Not done	Not done	Negative	Not done	Negative	Negative
TB test	Positive	Not done	Not done	Not done	Not done	Negative	Negative
HIV test	Negative	Negative	Negative	Negative	Negative	Negative	Positive
Mortality	Died	Lived	Lived	Lived	Lived	Lived	Lived
Cost of care (USD)	$5,626	$29,982	$5,622	$20,479	$16,668	$7,422	%40,552

All circumcisions were surgical, using the sleeve resection or dorsal slit methods.

[a]The number of days were most likely less.

NA = not available; HDU = high dependency unit; ICU = intensive care unit; TTV = tetanus vaccination; TIG = tetanus immunoglobulin; TB = tuberculosis; HIV = human immodeficiency virus.

Strategies to mitigate risk further

First, we need to close the knowledge gaps. How do we identify the slow or non-responders and those incubating tetanus before VMMC in high-risk subpopulations? In this article, we have identified the likely high-risk subgroups: those who are HIV-positive, those with TB, and the STN- and schistosomiasis-infected. These are high-risk subgroups because they would ordinarily have received TTV but would have responded slowly or not at all and therefore evoked suboptimal TTV-specific IgG levels to counter a tetanus toxin invasion successfully.

Could this be prevented by increasing the panel of pre-VMMC tests and expanding the ineligibility criteria? Would the increased logistical burden of the programs make it be unaffordable or reduce the uptake of the VMMC service? Testing for HIV is relatively easy, quick, and affordable. However, we need to clarify what to do with those who are HIV-positive. Should VMMC be delayed until the certainty of sufficient TTV-specific IgG presence? Testing for TB is more challenging, because there may be no overt symptomatology and the standard tests have low sensitivity. These may increase program expenses, prolong wait time, and perhaps deter many from taking part in the VMMC service. Pulmonary tuberculosis may not be easy to test for especially in the absence of a classic typical presentation. However, VMMC programs in high-burden countries should consider strengthening history review and intensify TB symptom screening prior to male circumcision services. We also need to investigate how best to screen for malnutrition and what to do with those who fail to meet whatever standard agreed upon.

Soil-transmitted nematodes are challenging. Empirical treatment without testing is perhaps most feasible for nematodes (deworming) and more complex for schistosoma and filariasis. It may be easy to test for nematode infestation or better still to deworm before male circumcision. The question is how long before VMMC do you deworm to eliminate impaired response. That work has not yet been done. Testing for schistosoma is more technically challenging. Also, it has not yet been determined how long after treatment for schistosomiasis should male circumcision be performed or first TTV be given. In Figure 2, we provide a possible gap-closing scheme. Failure to eliminate these tangible risks for tetanus will predispose to more cases of tetanus as the program develops and expands.

We need to study and understand community-based wound care practices from each locality. From routine field surveys, we find that clients apply topicals that are likely to contain tetanus spores and therefore risk tetanus infection. Such topicals include, but are not limited to sisal ash, rat feces, leaves, other herbal concoctions, cat fur, dirt, toothpaste, and detergents. These are culturally driven practices that may influence outcomes substantially. The work to be done here is sensitization and perhaps and understanding of why patients do as they do, against counsellor's advice.

Conclusions

At present, elimination of tetanus risk for VMMC programs in sub-Saharan Africa have not been successful because of associated tropical diseases that impair the effectiveness of TTV. In addition, it may not be possible to eliminate erroneous and risky home-based wound care practices, especially those that lead to wound contamination with tetanus spores. Public sensitization may be useful in mitigating some of these risky practices. More work is required to identify, characterize, and profile those who are slow responders or non-responders to TTV. The factors that impair the immune response to TTV need investigations as well as deworming, treating schistosomiasis, and testing for TB or LTB as part of the VMMC package. This may increase the likelihood that men will continue to undergo VMMC.

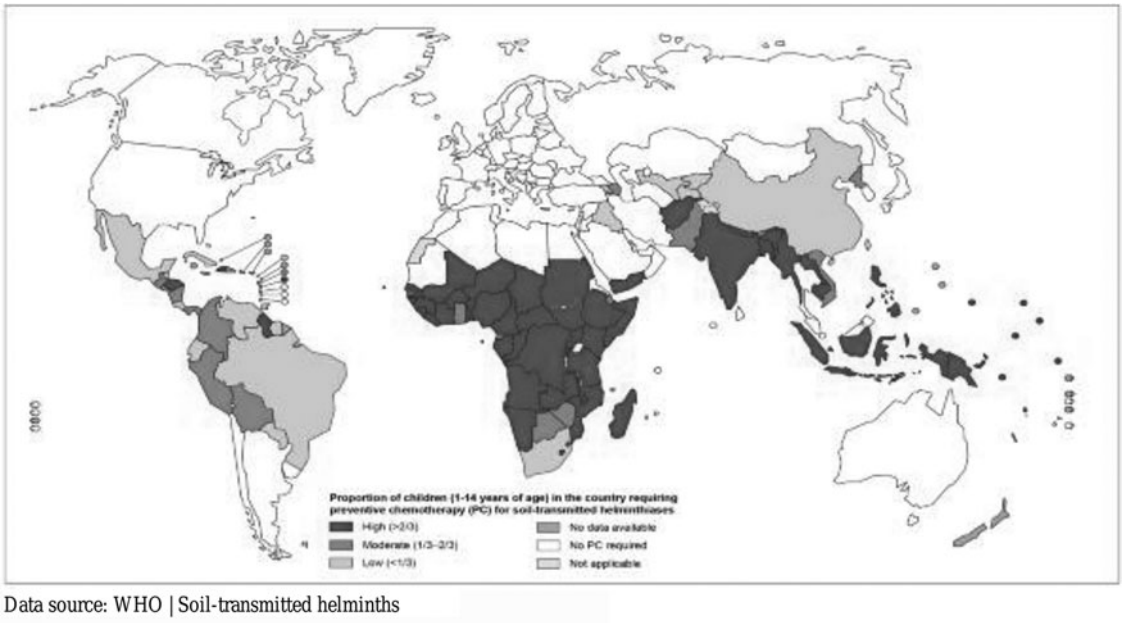

FIG. 2. Proportion of children (1–14 years) in the country requiring preventive chemotherapy (PC) for soil-transmitted helminthiases worldwide, 2014.

Acknowledgments

Individual consent was obtained to participate. Consent waiver for the deceased was obtained. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Author Contributions

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