The Risk of Tetanus
Following a Male Circumcision Procedure

Key Evidence and Analyses

July 2016
To: The World Health Organization  
Attention: VMMC Technical Advisory Group  
Subject: Data related to the WHO Review of the Risk of Tetanus following a PrePex MC Procedure

Circ MedTech Ltd. (CMT) welcomes this opportunity to present key evidence and analysis, relevant to the risk of Tetanus following use of the PrePex device, for consideration of the World Health Organization (“WHO”) VMMC Technical Advisory Group (TAG) at its meeting scheduled for August 12, 2016.

The initial evaluation of the WHO and its conclusion were shared with CMT in a public document “Tetanus and Voluntary Medical Male Circumcision: Risk according to Circumcision Method and Risk Mitigation Summary of Technical Consultation 3 June 2016; Switzerland, 7 July 2016 (“WHO July 2016 Report”). CMT commends the WHO’s HIV/AIDS Department, and particularly Mr. Gottfried Hirnschall, for taking rapid and decisive action to coordinate the present consultation after learning that evidence may have been inadvertently excluded from the initial consultation. CMT also appreciates the efficient diligence of the Ministry of Health of Uganda, and particularly the efforts of Dr. Barbara Nanteza, in seeking to gather the information needed to rectify the omission.

The information we herein present — supported by clinical and scientific evidence — demonstrates that both the epidemiological evidence and plausible biological mechanism presented to the experts lacked veracity, since they were based on improbable assumptions and imprecise data.

In Part 1 of our following document (Key Evidence and Analyses) we present clinical and scientific evidence demonstrating the inaccuracy of the plausible biological mechanism claim. The evidence shows that use of the non-surgical PrePex male circumcision (MC) device does not pose a higher risk of contracting Tetanus compared with surgical MC methods.

In Part 2, we demonstrate that the statistical risk ratio results presented in the June 3rd consultation are based on inaccurate data and erroneous analysis. Therefore, they do not represent the actual risk ratio. We also present our analysis on how the risk ratio should be calculated, taking into account the most up-to-date information available and the significant underreporting of Tetanus cases following surgical MC.

Based on all available evidence, we find that the incidence of Tetanus following a surgical MC is of similar magnitude as that following a PrePex MC, and both are of similar magnitude to the incidence of Tetanus in the male population. We are convinced that each MC method presents the same level of risk of Tetanus, and therefore believe that mitigation measures should apply equally across all MC methods.

Indeed, we know that the stringent reporting requirements applicable to PrePex procedures have drawn attention to the underreported prevalence of Tetanus in VMMC program countries. We believe this presents an opportunity to tackle the underlying problem, which should not instead be dismissed as a problem unique to PrePex patients.

At CMT, we remain committed to the shared objective of saving lives by safely reducing HIV transmission. We thank you for this opportunity to present our findings on this important issue. We are convinced that the TAG members — having reviewed all relevant and verifiable data and analyses — will reach different conclusions than those reached previously in the June 3rd consultation.

Respectfully yours,

Eddy Horowitz  
Chief Executive Officer
## TABLE OF EVIDENCE

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<td><strong>Evidence:</strong> Liu Et.al Article cannot be used for reasons detailed below (Pages 4-5).</td>
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<tr>
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<td>Complaints of Odor</td>
<td>Odor cannot be associated with the PrePex device.</td>
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<td><strong>Conclusion:</strong> There are increased anaerobes associated with the PrePex device.</td>
<td><strong>Conclusion:</strong> No evidence supporting biological plausibility.</td>
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<tr>
<td></td>
<td><strong>Claim:</strong> PrePex has plausible biological heightened risk of Tetanus.</td>
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<td></td>
<td><strong>No</strong> significant underreporting of Tetanus following surgical MC.</td>
<td><strong>There is significant</strong> underreporting of Tetanus following surgical MC (Page 7-9).</td>
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<td><strong>Conclusion:</strong> Tetanus incidence after Surgical MC is similar in magnitude to the Tetanus incidence in the general population, and both have lower magnitude of incidence for Tetanus compared with PrePex MC.</td>
<td><strong>Conclusions:</strong> Tetanus incidence after Surgical MC is similar in magnitude to the Tetanus incidence in the general population, and both have similar magnitude of incidence for Tetanus compared with PrePex MC.</td>
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<tr>
<td></td>
<td><strong>Claim:</strong> PrePex has higher risk ratio than surgical MC.</td>
<td><strong>Claim:</strong> PrePex has similar risk ratio as surgical MC.</td>
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</table>
Part 1: Plausible Biological Mechanism

From the WHO July 2016 report: "The PrePex associated increase in anaerobes may account for unpleasant odor and a possible heightened risk of tetanus." - Liu et al. Article (Appendix A).

On different occasions, CMT has supplied data emphasizing and demonstrating the inaccuracy of the above statement. Detailed and undisputed expert evidence and analyses were presented in the CMT experts’ report submitted to the March 2015 WHO experts meeting (Appendix H), explaining how the PrePex mechanism does not allow clinical Tetanus via the C. tetani known mechanism. Nothing has changed regarding the PrePex mechanism and regarding the C. tetani mechanism since then, and there is no evidence to support the contrary. We suggest the current TAG members review this report again.

The mechanism by which PrePex kills local nerves and thereafter blocks blood flow, along with lymphatic supply, eliminates the risk that the Tetanus toxin may enter the body via the necrotic foreskin (Appendix B, Appendix C and Appendix H). Moreover, after using the PrePex device, the wound is covered with granulation tissue below the eschar which creates an additional barrier between the blood stream and environment.

Yet even more evidence has come to light supporting the CMT experts’ report with the addition of new information presented in the Liu et al. 2016 article.

A correspondence review letter addressing the Liu et al. article was published by Dr. Brook (Appendix B). This letter raised several limitations within the aforementioned article which highlights the unreliability of Liu’s conclusion that PrePex presents a higher risk of contracting Tetanus. These limitations include:

- Significant flaws with the study design - specifically with regards to the sample size of the two study arms, demographics and significant time lapse of 10 years between the two arms.
- The authors did not identify any evidence of detecting C. tetani.
- The assumption that the abundance of anaerobic bacteria may pose a risk of infection is unsupported and unjustified.
- Liu et al. do not offer a scientific explanation as to how Tetanus toxin may enter the body following the PrePex procedure.
- The fact that Liu et al. did not use Povidone Iodine (PI) in the PrePex procedure, which is an integral part of performing a PrePex Procedure.

Dr. Schiavo Giampietro, Professor of Cellular Neurobiology (Appendix C), criticized the Liu et al. article by concluding that its findings could not support its conclusions.

Dr. Liu et al. responded (Appendix D) to Dr. Brook’s published correspondence, acknowledging that the study was hypothesis generating, rather than hypothesis testing. Importantly, Dr. Liu states: "our article does not and cannot prove that the PrePex device causes an enhanced risk of tetanus".

The authors of the article concur that their work was not intended to and does not prove that the PrePex device causes an enhanced risk of Tetanus compared with surgical Male Circumcision. Similar conclusions and scientific explanations provided in this document are expressed by other experts criticizing this work.
In 2014, CMT offered the WHO to carry out a study with the aim of testing the (then) new clean care procedure, in order to demonstrate a reduction in anaerobic load. WHO replied that such a study would only provide data on the existence of an anaerobic environment but could not be used to determine if, when using PrePex, the risk for contracting Tetanus is reduced once an anaerobic environment is also reduced. CMT agreed with the WHO position. By the same token, a study that finds an increased anaerobic environment is equally insufficient to determine whether PrePex presents an elevated risk for contracting Tetanus in the same environment.

In addition, the results of the Liu et al. article do not reflect the actual anaerobic microbiome environment of the PrePex procedure following the 2015 PrePex mitigation, which includes use of PI and waiting for 2 minutes between three PI scrubs. This mitigation is currently part of the PrePex procedure and was specifically recommended by the WHO TAG as a means by which to mitigate anaerobic bacteria.

**Odor complaints; the claim that odor is associated with increased risk of Tetanus**

Malodorous wounds are often polymicrobial, i.e. they contain both anaerobes and aerobes, and the level and type of bacteria present will affect the wound environment. Anaerobic bacteria that cause infection include bacteroides — such as *Bacteroides fragilis*, *prevotella*, *Fusobacterium nucleatum*, *Clostridium perfringens* and *anaerobic cocci* — which generate odor by emitting compounds such as putrescine or cadaverine.

Theoretically, devitalized tissue can play host to anaerobic and aerobic bacteria, increasing the risk of local infection. However, the presence of anaerobic and aerobic bacteria in the necrotic and devitalized foreskin following a PrePex Procedure does not pose a risk to the patient because the foreskin is separated from the rest of the body by the PrePex device’s Elastic band. This band, and the scar tissue that forms, also prevent dissemination of Tetanus toxin. Necrotic wounds tend to have a more offensive odor than clean wounds. Odors that are produced by necrotic or sloughy tissue may be due to the presence of dead, devitalized tissue, the proliferation of anaerobic micro-organisms, or the interaction between anaerobic and aerobic bacteria.

Therefore, a bad odor is not synonymous with the anaerobic bacteria. They may or may not be present. Moreover, the odor cannot be attributed to the presence of *C. tetani* or to an increased risk contracting Tetanus.

**From all the above we conclude that:**

1. The Liu *et al.* article cannot be used to support increased anaerobic environment under the foreskin with PrePex versus uncircumcised men.
2. There is no scientific evidence that PrePex is associated with an increase in *Clostridium tetani* or its spores.
3. There is no support to the claim that the use of the PrePex device may account for a possible heightened risk of contracting Tetanus.

Ref 1: Van Rijswijk, L. The language of wounds, In Krasner *et al* Chronic Wound Care 3rd Ed. 2001, HMP Communications.

Part 2: Statistical Risk Ratio (Epidemiological Evidence)

Rate of Tetanus Incidence in the General Population

The WHO July 2016 report states:

"The only country for which an official reported estimate of background risk of tetanus outside the neonatal period is available is Uganda, where an annual inpatient incidence of 3.0 per 100 000 population was reported over the period 2012–2014"

CMT agrees that Uganda is the only relevant country for which an official reported estimate of background risk of Tetanus outside the neonatal period is available. However, CMT uses the most up-to-date official report of Tetanus incidence outside the neonatal period, an official published article by the Uganda Health Ministry ("The burden of tetanus in Uganda," by Nanteza et al., SpringerPlus June 2016 [Appendix E]). In the article, the Ministry performed in-depth analysis and cross reference of sources, and concluded that the number of Tetanus cases in males aged 5+ years in 2014 was 1,311.

Formal data indicates that in 2014 there were 15,293,000 males of age 5+ years in Uganda. The reported Tetanus incidence in the Nanteza et al. article is 1,311 TT cases in 2014 for males aged 5+, resulting in an incidence of 9 cases per 100,000 males aged 5+ (95% confidence interval [CI]: [4.7–17.3] cases per 100,000).

In order to further subgroup the prevalence in the VMMC age population, per Nanteza et al., 18/25 of the Tetanus cases investigated were in the circumcising age range. The Wilson’s score 95% confidence interval (CI) is [52.42%; 85.72%], resulting for the year 2014 in an estimated range of between 687 and 1,124 Tetanus cases. Therefore, since the number of males aged 15+ in Uganda in 2014 was 9,678,000, the incidence of Tetanus in males age 15+ was between 7.1 and 11.6 per 100,000 in 2014.

From the Nanteza et al. article (Table 1), it is apparent that the number of reported Tetanus cases show an increasing trend over the years, increasing by 5% between 2013 and 2014. This increasing trend, which is higher than the 3% population growth, is expected to continue to show even higher incidence rate in the population.

Ref 3:
Rate of Tetanus Incidence after Surgical MC

From the WHO July 2016 report: "While there may have been some underreporting of tetanus cases following circumcision, particularly following surgical circumcision, differential underreporting was considered unlikely to account for the magnitude of the difference"

We disagree with this statement.

Underreporting of Tetanus cases following a surgical MC in Uganda

The WHO July 2016 report presents a calculation of Tetanus incidence rates after surgical MC based on the total number of surgical circumcision procedures performed in 4 countries since the initiation of the VMMC program. This manner of calculating the incidence is flawed as the reporting of the post-surgical MC Tetanus cases is severely lacking. To confirm this, CMT held face-to-face meetings with managers of several leading NGOs and other high-ranking individuals in the Uganda health system. All the individuals confirmed that in Uganda there is a real issue of under-reporting of post-surgical MC Tetanus cases. CMT maintains records of these meetings.

To determine the incidence rate, one should analyze country-by-country in a specific time period, where reliable reporting of Tetanus cases following surgical MC information is available. Underreporting is an acknowledged challenge and barrier in assessing incidence accurately.

Due to the large underreporting magnitude of post-surgical MC Tetanus cases, it is not possible to accurately estimate the incidence of Tetanus following surgical MC. However, we provide below the manner which, in our view, is most accurate and appropriate to assess the incidence rate of Tetanus after surgical MC.

The surgical MC Tetanus incidence analysis should be restricted to Uganda, the only country where the Ministry of Health conducted active surveillance during late 2014 and early 2015 to obtain data of un-reported Tetanus cases following surgical MC. A formal report from the Uganda Health Ministry dated 08 April 2016 (Appendix F) reported eleven (11) identified surgical MC-related Tetanus cases, a significantly higher number than the 3 cases presented in the WHO July 2016 report.

In order to highlight the considerable underreporting scope of Tetanus following a surgical MC; Table 1 below presents the quarterly data of surgical MC procedures in Uganda, per region. Marked in red are 4 cases of fatal Tetanus cases of which CMT was able to obtain death reports.

As seen in the table, following 97,000 surgical procedures, 4 Tetanus cases were identified in September 2014 and March 2015, obtained by MoH due to active surveillance efforts. For the additional 1.7 million procedures only one (1) tetanus case following surgical MC was formally reported.

The fact that all four Tetanus cases were identified in one region, over a limited period of time during active surveillance for Tetanus cases post-surgical MC, following a small number of surgical MC, whereas no cases were identified AT ALL in any region, and over a long period of time, following 17 times more surgical MC does not make scientific sense.

The only credible explanation for this unreasonable phenomena is a lack of Tetanus cases reporting following the other 1.7 Million surgical MC procedures in Uganda.
<table>
<thead>
<tr>
<th>Quarters</th>
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</tr>
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<tbody>
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<td><strong>454389</strong></td>
<td><strong>397689</strong></td>
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<td>52279</td>
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</table>

Table 1 – Number of Surgical Procedures per quarter per region in Uganda and the Actively-identified Tetanus Cases.
Underreporting of Tetanus Cases following Surgical MC in Rwanda

Rwanda has identified no cases of Tetanus for adult men in recent years. As the Rwandan population demographics and vaccination policy for men is similar to that of Uganda, it is improbable that Uganda has a Tetanus incidence of 9 to 100,000 in its 5+ male population while in Rwanda the incidence is 0. Reporting zero (0) cases of Tetanus suggests a malfunctioning Tetanus-reporting system in a country where the information clearly indicates that Tetanus cases do frequently occur.

The WHO country representative in Rwanda recently (June 12th, 2016) participated in a meeting where, among others, the lack of Tetanus reporting in Rwanda was discussed. The participants used terms such as "we see Tetanus on a regular basis in our hospitals".

Since it is reasonable to assume that the Tetanus incidence in Rwanda and Uganda are similar (same vaccination policy, same surgical MC technique, similar population demographics), the logical conclusion is that Rwanda lacks a reporting system for Tetanus in the general population, as well as for Tetanus following a surgical MC. Assuming a rate of 2 to 6 to 1000 for hospital admissions (as reported by Nanteza et al. for Uganda) for Rwanda, with 550,000 annual admissions Ref 4 translates into at least a few hundred cases of Tetanus in males aged 5+ which are not reported annually.

This lack of reporting system will lead to incorrect conclusions regarding the incidence of Tetanus following surgical MC and the general incidence in the population in Rwanda.

As a general comment, additional causes of underreporting Tetanus cases after surgical MC are not related to Tetanus diagnosis as mentioned in the WHO July 2016 report 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 PrePex).

b. Inspection of the penis as a possible point-of-entry for men with Tetanus is not acceptable socially in rural health clinics and is not currently part of the routine procedure for care providers diagnosing a patient with Tetanus.

c. Reporting mechanism that does not include the cause of admission, but the cause of death - which in many cases, are complications following Tetanus.

Ref4:
Rate of Tetanus Incidence after Surgical MC in Uganda

Having established the severity of underreporting of Tetanus cases following a surgical MC and the limitations involved, we now proceed to present our view on the most accurate method available to estimate the rate of Tetanus incidence following surgical MC.

CMT was able to obtain reports from 4 fatal Tetanus cases, as presented in Appendix G. We were also able to confirm that 1 additional fatal case occurred in mid-2013 and that an additional 4 cases occurred in the same period of time, and in the same region, as the 4 cases presented in Table 1. As CMT could not obtain full reports of the additional cases, they are not included in the incidence analysis. However, these additional cases can only reinforce the conclusions presented below as they occurred in the same period of time and in the same region when active surveillance of Tetanus cases following surgical MC was done.

From the formal reports shared by the MoH Uganda officials, at least 4 Tetanus cases occurred following 97000 surgical MC (Table 1). These 4 cases occurred in 1 region (Central) during two months of September 2014 and March 2015. From this we conclude the following:

a. Since Tetanus is not a communicable disease and the immunization levels, population demographics and the surgical MC methods in all 1.8M surgical MC procedures in Uganda were similar, the only practical explanation for 4 cases of Tetanus identified in 97000 circumcisions and none in other periods and regions can only be as a result of underreporting during other time periods. From this, we conclude that the incidence rate should be calculated based solely on this specific period, as it has the only reliable data regarding Tetanus following a surgical MC due to the active surveillance of Tetanus cases following surgical MC done in those periods.

b. The incidence of Tetanus after surgical circumcision in Uganda is 4 (95% confidence interval [CI]: [1.5-10.7]) cases per 100,000 circumcisions (4 actively-identified cases of 97,000 procedures).
Incidence of Tetanus after a PrePex Procedure

Unlike the underreporting following surgical MC, Tetanus events following a PrePex MC are stringently monitored and reported to the Health Ministries level as well as to the WHO, allowing a reliable calculation of Tetanus incidence rates following a PrePex procedure.

For the actual number of PrePex procedures performed to date per country, see Appendix I.

In Rwanda, a sufficient number of PrePex procedures were conducted to adequately calculate the Tetanus incidence (prior to PI mitigation implementation). There were 4 cases of Tetanus after a PrePex procedure, out of 116,000 PrePex procedures. The Tetanus incidence in PrePex procedures is 3.5 (95% confidence interval [CI]: 1.2-10.0) cases per 100,000 circumcisions.

CMT statisticians found the sample size of the PrePex procedures in Uganda not sufficient to determine a reliable incidence of Tetanus. Since Uganda and Rwanda have similar Tetanus vaccination coverage and population demographics, it allows inclusion of the Uganda Tetanus cases by combining Uganda and Rwanda data. This showed a total of 6 Tetanus cases following a PrePex procedure from 120,000 procedures, resulting in an incidence rate of 5 cases (95% confidence interval [CI]: 2.1-12.0) per 100,000 circumcisions.

Therefore, we conclude that the PrePex Tetanus incidence rate is between 3.5 per 100,000 to 5 per 100,000.
Conclusion of the Tetanus incidence analysis:

- Rwanda and Uganda have relatively low Tetanus immunization coverage, similar population demographics, and same surgical MC technique and thus expected similar Tetanus incidence both in population and post-surgical MC and post-PrePex MC.

- Reliable data for PrePex Tetanus incidence calculation obtained from Rwanda and Uganda—Incidence of 3.5 to 5 per 100,000.

- Reliable data for surgical MC Tetanus incidence can only be obtained from Uganda during specific periods and regions where MoH conducted active collection of Tetanus cases following surgical MC – Incidence of 4 per 100,000.

- Reliable data for Tetanus incidence in the general population of males in age of circumcision can only be obtained from Uganda for 2014 – Incidence of 7.1 to 11.6 per 100,000.

- Risk Ratio of Tetanus after PrePex procedures versus surgical MC is 1.20 (95% CI: [0.34-4.27], which is statistically similar.

- Risk Ratio of Tetanus after PrePex procedures versus the relevant male population is (0.70 95% CI: [0.31-1.56]), which is statistically similar.

These findings lead us to conclude that:

1. Tetanus incidence following PrePex MC is of the same magnitude as in the general population.
2. Tetanus incidence following Surgical MC is of the same magnitude as in the general population.
3. Tetanus incidence following PrePex MC is of the same magnitude following surgical MC.

Note - The Tetanus incidence calculation is applicable only to a prior PrePex procedure (i.e. one performed before the amended CMT protocol) that did not include the Povidone Iodine mitigation measure.
Conclusion of the key evidence and analyses

In this document, we have shown the statement in the WHO July 2016 report “the risk of tetanus was higher following PrePex compared with conventional surgery” is unsubstantiated, as the data and analysis supplied by CMT demonstrates that there is no evidence to support this claim. It is an unfounded theory.

We believe we have provided sufficient evidence and proof that the data used in the WHO July 2016 report was incomplete, inaccurate and outdated.

From our findings we conclude that, based on all existing and available evidence, the incidence of Tetanus following a surgical MC is similar to the Tetanus incidence following a PrePex MC — and both are similar to the Tetanus incidence in the male population.

Respectfully,

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Eddy Horowitz                                                                                                                Alon Kushnir
Chief Executive Officer                                                                                                  VP Regulation and Clinical Affairs