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The Uptake of the Prepex and Shang ring male circumcision devices by adolescent and adults in Africa: A systematic review and meta-analysis

Dr. Kakaire Menyha Rajab

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Supervisors:

Dr. Benjamin Kagina

Leila Hussein Abdullahi

Vaccines for Africa Initiative,

School of Public Health and Family Medicine

University of Cape Town.

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Student number: KKRRAJ001

Signature: Signed by candidate

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Abstract:

This dissertation focused on a systematic review and meta-analysis of the uptake of the Prepex and Shang ring devices among adolescent and adult males seeking voluntary medical male circumcision (VMMC) services in Africa. The dissertation is divided in 3 parts.

Part A is the research protocol of the systematic review. In this section, the research question, aim and methods are presented. The review aimed to explore the uptake and acceptability of two World Health Organization (WHO) prequalified devices by adolescent and adult men seeking services through programs in Africa using a systematic review approach. The search strategy, databases where searches were conducted, and the screening process are detailed. All searches were carried out on 12th May, 2017. Included studies must have been conducted between 2007 and 2017, to coincide with the period during which VMMC programs were operational. The assessment of the risk of bias of the included studies is also explained in this section. Statistical methods are also detailed in this section.

Part B is the literature review that discusses the programs put in place for the scaling up of VMMC in Africa. Part B also presents the challenges of the VMMC programs in Africa. This section presents the developments of VMMC, evidence linking the male circumcision to HIV prevention and the necessity for innovative methods to carry out male circumcision.

Part C describes the implementation of the protocol presented in Part A. The metaprop command in Stata version 14 was used for the pooled estimate of the uptake of device

methods. This section is written in a format that is suitable for publication in a peer reviewed journal (PLoS ONE). .

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List of abbreviations:

AIDS	Acquired Immunodeficiency Syndrome
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
ROB	Risk of Bias
STI	Sexually Transmitted Infection
TAG	Technical Advisory Group
UNAIDS	Joint United Nations Programme on HIV/AIDS
VMMC	Voluntary Medical Male Circumcision
WHO	World Health Organization

CHAPTER ONE: PROTOCOL

Background:

In 2007, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended Voluntary Medical Male Circumcision (VMMC) to become a part of the comprehensive HIV prevention strategy in countries with hyperendemic and generalized HIV epidemics and low rates of male circumcision.[1] In response to these recommendations, VMMC programs targeting adolescent and adults were initiated in fourteen countries in Eastern and Southern Africa including; Ethiopia, Kenya, Uganda, Republic of Tanzania, Rwanda, Malawi, Zambia, Zimbabwe, Mozambique, Namibia, Botswana, South Africa, Swaziland and Lesotho.[2] The implementation of VMMC programs aimed at increasing the uptake of circumcision services in the fourteen selected priority countries as well as among traditionally non-circumcising communities within these countries.[3]

A modelling study demonstrated that achieving VMMC coverage of 80% among men aged 15-49 years in the fourteen priority countries by 2016 would require the circumcision of around 20.1 million males.[4] The circumcision of the millions of males would in turn avert 3.4 million new HIV infections in these countries. According to the modelling study, the impact of such reductions in the new HIV infections would result to a net savings in treatment costs of US$ 16.5 billion by 2025.[4] Therefore, in Africa, increased uptake of adult male circumcision will have both public health and economic benefits.

From 2008 through 2015, VMMC programs provided 11.7 million males with VMMC for the purpose of HIV prevention in the fourteen priority countries.[5] Progress towards the VMMC target of 80% circumcision coverage varied in the fourteen countries with

Ethiopia (Gambella province), Kenya and the United Republic of Tanzania surpassing the targets set in 2011.[5] In addition, South Africa, Mozambique, Uganda and Zambia attained more than 50% coverage although this was below the VMMC coverage target.[5]

Uptake of circumcision services has been suboptimal in some of the VMMC priority countries which have recorded coverage of less than 50%. Understanding the strategies used in the countries where VMMC targets are met is important as the effective strategies may be used to increase the coverage of circumcision in the countries where VMMC targets are still unmet. As an example, if the method used to perform a circumcision procedure is highly acceptable among the target males, this may improve the circumcision coverage in a given setting.

The VMMC procedure is performed using either a surgical or a device based method.[6] At the start of VMMC programs, adolescent and adult male circumcisions were most commonly performed using conventional surgical methods. [7] These methods had been standardized and used successfully in randomized clinical trials that demonstrated the HIV prevention benefits of circumcision.[8-10] Surgical methods, however, require a certain level of surgical skill, prior injection of anaesthesia, heamostasis and wound closure.[6] These requirements as well as other challenges slowed the pace of scale-up.[11] The urgency for circumcision scale-up among adult males created a need for safe, fast and acceptable innovative methods.[12] It is therefore rational to propose that most of the current and future VMMC will be performed using innovative circumcision methods.

Male circumcision devices were evaluated for circumcision among adolescents and adults in the hope of increasing VMMC coverage. Certain device methods, different from those proposed for adult VMMC, had long been used successfully and safely

among infants. [13] Circumcision of adolescents and adults using device methods was anticipated to make the procedure simpler and quicker as devices had been found to require a shorter duration of procedure.[14, 15] Additionally, the circumcision devices would enable the procedure to be performed in the hands of much less qualified health workers and this would improve accessibility of circumcision services. Device circumcision methods were also thought to be more acceptable for males who had personal concerns or otherwise reluctant to be surgically circumcised.[12] Increase in the use of device methods have the potential to increase the uptake of circumcision services with subsequent positive impact on progression towards the set VMMC target of 80% circumcision coverage. The uptake of circumcision devices in the fourteen VMMC priority countries remain unknown. Furthermore, it is not known whether the availability and utilization of the circumcision devices may have an impact on the variable circumcision coverage observed in the fourteen countries.

The WHO stipulated an objective assessment for the prequalification of circumcision devices for use in public VMMC programs that includes evidence on clinical safety, performance and acceptability in the country of intended use.[16] Findings from initial clinical trials of the Prepex device in Rwanda[17], Zimbabwe[18] and Uganda[19] and the Shang ring device in Zambia and Kenya[15, 20] reported the two devices to be safe and acceptable among adult males. Subsequently the two devices received WHO-prequalification for use in the circumcision of adolescent and adult males in VMMC programs.[16, 21] The Prepex and Shang ring devices have been progressively rolled out under active surveillance since their prequalification. It is unclear if the prequalification of the circumcision devices plays a role in the uptake of circumcision services.

Why it is important to do this review

We are not aware of any systematic review study that has assessed the uptake of circumcision by the WHO-prequalified device methods in the fourteen VMMC priority countries. Similarly, there is a lack of existing review literature on the acceptability of device methods among adolescent and adult males in Africa. Our study proposes a systematic review of the literature on uptake of the prequalified circumcision device methods for VMMC from 2007 to 2017. Additionally, we will assess the factors that influence the choice of circumcision procedures among adolescent and adult males in VMMC priority countries. Information from the review results will generate knowledge on the uptake and acceptability of WHO-prequalified circumcision devices. This knowledge can be used to advocate for VMMC in an attempt to reach the VMMC targets of 80% in the fourteen priority countries.

Objectives

- To establish the uptake of the two WHO-prequalified circumcision devices in the VMMC priority countries
- To establish the proportion of adolescent and adult males choosing VMMC by a WHO-prequalified devices (Prepex and Shang ring) when offered as a choice instead of the conventional surgical methods in the VMMC priority countries
- To describe the acceptability of the WHO-prequalified device (Prepex and Shang ring) in the VMMC priority countries

Criteria for considering studies for this review:

Types of studies:

Non-randomized controlled trials, cohort, case-control and cross-sectional studies will be included. Randomized Clinical Trials (RCTs) will only be included to address objective number three to describe the acceptability of the WHO-prequalified device. Only primary studies will be included and reviews will be excluded.

Types of participants

Males aged 10 years and older that have been circumcised voluntarily at a health facility. The 10 years has been used as the target lower age for circumcision programs for HIV prevention in the priority countries. We will exclude neonates and infants as circumcisions in that age group are largely done for religious and therapeutic reasons, and not primarily for HIV prevention.

Types of interventions

Medical male circumcision using either of the two currently WHO-prequalified circumcision devices for use in adolescent or adult VMMC, that is, the Prepex™ (Circ MedTech, Israel) and the ShangRing® (Wuhu Snnda Medical Treatment Appliance Technology Company, China).

Comparison

Voluntary Medical male circumcision using any of the other methods which have been approved for the circumcision of adolescents and adults.

Types of outcome measures

Primary outcomes

-Circumcision coverage among adolescents and adult males in the fourteen VMMC priority countries. Alongside this we intend to establish the proportion of circumcisions that have been performed using the two WHO-prequalified device methods among the cumulative number of circumcisions in the VMMC priority countries.

-Proportion of participants selecting a device, either the Prepex or Shang ring, among adolescent and adult men when offered a choice between the device and another method in the VMMC priority countries. This will be measured by the proportion of individuals who chose circumcision by one of the two WHO-prequalified devices of all men who have sought circumcision in the period after 2007.

Secondary outcomes

-Acceptability of the WHO-prequalified devices (Prepex and Shang ring) by adolescents and adult males in the fourteen VMMC priority countries

Search methods for identification of studies

We will conduct a comprehensive search to ensure all published and unpublished studies are identified. The search will include all articles in English from April 2007 – February, 2017, in line with the period during which scale-up of MC services for HIV prevention has been ongoing following the WHO recommendations. Key words including MeSH, and free-text terms, relating to our review question will be developed, piloted, optimized and adapted to each individual database. These will then be combined with a relevant filter to select out countries from the African continent only.

Only studies enrolling adolescents and adults will be included and we will exclude studies among neonates and infants. The age restriction is used as adolescents aged 10 years and older and adults have been the primary target for VMMC programs.

We will conduct electronic searches using key search terms of circumcision and device names with appropriate Boolean operators (**Appendix 1 and Appendix 2**). We will search the following published databases for relevant studies; MEDLINE (PubMed), The Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), Databases of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment Database (HTA)), ISI Web of Science, CINAHL, Scopus.

For ongoing or not yet published studies, websites of clinical trial registries such as ClinicalTrials.gov (https://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/) will be searched. For progress reports and non-reviewed publications, databases of World Health Organization Library Information System (WHOLIS) (http://www.who.int/library/databases/en/), the Joint United Nations Programme on HIV/AIDS (UNAIDS resource library) (http://www.unaids.org/en/resources/), World Bank (www.worldbank.org/) will be searched for grey literature.

Searching other resources

We will also check reference lists of the included articles for other potentially eligible studies that may not have been identified through the search. Abstract proceedings of relevant meetings like the International AIDS society conference on HIV Science (IAS), the Conference on Retroviruses and Opportunistic Infections (CROI), the International

Conference on HIV/AIDS and Sexually Transmitted Infections in Africa will also be searched for completeness.

Data collection and analysis

Selection of studies

Using the search strategy, the identified titles and abstracts of eligible studies will be screened independently by two study team members. Full-text manuscripts of potentially eligible abstracts, retained after screening, will be independently read by the two study members to determine if they meet the inclusion criteria. When discrepancies arise over the inclusion of titles/ abstracts or full-text articles, two study team members will resolve disagreements by discussion and consensus failure to which the third study team member will arbitrate. We will classify retrieved studies as either included studies or excluded studies in accordance with the criteria for inclusion or exclusion of studies defined a priori. We will document reasons for exclusion of studies and present a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that shows the process of study selection.[22]

Data extraction and management

A data extraction form will be developed and used independently by two study team members to extract data from the included studies (**Appendix 3**). The data extraction form will first be piloted by the first study team member using some of the included studies to assess comprehension. A second study team member will review the pilot data extraction. In case of discrepancies with data extraction, a third study team member will be consulted and the differences resolved by consensus. The primary

reviewer will then use the standardized data extraction form to extract information from included articles and record the following;

1. Study design,
2. Period during which study was conducted,
3. Study settings and country,
4. Participant inclusion and exclusion criteria,
5. Participant details and baseline demographics,
6. Number of participants by study and study arm,
7. Details of relevant experimental and comparator interventions such as device type,
8. Relevant outcomes and their definitions,
9. Factors that may have influenced choice of circumcision method
10. Any relevant subgroups
11. Study funding
12. Declarations of interest by primary study authors.

Assessment of risk of bias in included studies

After relevant data is extracted from the included studies, the risk of bias will be assessed using the study-design specific criteria outlined by an appropriate tool. Intervention studies will be assessed using the Cochrane collaborations tool [23] for assessing the risk of bias while observational studies will be assessed using the risk of

bias and quality assessment tool developed by Hoy *et al.,* and modified by others.[24] The scoring tool by Hoy *et al.,* examines the internal and external validity by taking into account study design, methodology and the presence of bias. A version of this tool is shown (**Appendix 4**). Two review authors will independently assess the risk of bias for each included study with disagreements resolved through discussion. The selected interventional studies will be assessed for selection, performance, attrition, detection, reporting biases as well as other sources of bias. For each included study, we will report our assessment of risk of bias together with a descriptive summary of the information that influenced our judgment. We will judge the "Risk of Bias" in an included study as either 'low risk', 'high risk' or 'moderate risk'. We will present a 'Risk of bias' table to summarize these assessments.

Dealing with missing data

We will contact the authors of included studies to request for any additional missing information if unavailable.

Assessment of heterogeneity

Data will be pooled to assess heterogeneity. This will be assessed firstly by visually inspecting the forest plots. Secondly, the Chi-squared test for homogeneity with a significance level set at 10% will be used. Finally, the I^2 statistic will be used to quantify any statistically significant heterogeneity between study results and rated as 'low' for ≤ 49% and 'moderate' for 50-74% and 'high' for ≥ 75%.

Data synthesis

Data will be synthesized using Stata version 14. A summary table that presents data on the frequencies of circumcisions performed using each device method will be developed. Numbers of males that choose circumcision with a device method will be expressed as proportions of all males seeking VMMC that are offered a choice of circumcision method. Data from studies investigating the uptake of the two device methods will be pooled for analysis using a random effects model. Pooled statistics of device uptake will be expressed as estimated proportions/prevalence (ES) with 95% confidence intervals (CI). We will perform subgroup analysis to establish if the uptake proportions differed by device method and participant age. The WHO criteria for assessing acceptability will be used in the analysis of studies reporting this outcome. [12] Experiences that participants' liked or disliked about the device circumcision procedures or during the period following procedures will be described and explored using content analysis and narrative synthesis.

The overall risk of bias within studies will be scored using the risk of bias tool developed by Hoy *et al.,* and adapted by Werfalli *et al.* The adaptation by Werfalli and colleagues allows for a composite score to assist with relative comparison between studies thereby reducing reviewer's subjectivity. The quantitative scoring system added by Werfalli *et al.,* aids in analyzing the risk of bias in studies by categorizing the overall risk of bias in each study into low, moderate or high risk studies depending on the overall score for a study.

Subgroup analysis and investigation of heterogeneity

We anticipate heterogeneity between participants choosing different device methods. Subgroup analysis will be conducted by age (adolescents versus adults), by country grouping (divided into whether a country has surpassed the target, has met >50% of the 2011 target or is yet to achieve 50% of the 2011 target) and by device method.

Sensitivity analysis

Sensitivity analysis will be carried out where imputations were done for the primary outcomes and also to determine if the study designs, study period or publication type have an impact on the results of the meta-analysis

Dissemination:

The findings of this review will be circulated through peer-reviewed publications and in the university repository.

Ethical considerations:

Systematic reviews draw on publicly available data and do not directly involved human or animal subjects; therefore they do not require formal ethical review.[25] The study protocol will, however, be reviewed by the supervisors with extensive knowledge in systematic review methods and be submitted to the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee for approval.

Declarations of interest

There is no conflict of interest by any of the authors.

Discussion

Voluntary Medical Male circumcision (VMMC) program implementation has been met with challenges resulting into slow service uptake in a number of priority countries. Circumcision devices such as the Prepex and Shang ring have been promoted as a strategy to hasten the pace of VMMC scale-up. No systematic review of literature exists regarding the uptake of these methods and factors that may influence participants' acceptability for the WHO-prequalified circumcision devices. However, as VMMC programs continue to incorporate these WHO-prequalified device methods for the circumcision of adolescents and adults, it will be paramount to ensure that these methods are acceptable to the target population. Our systematic review therefore aims to understand the uptake and acceptability of the currently prequalified methods and factors that may have influenced acceptability of the device methods for VMMC. This information would help in advocacy for the use of these methods.

PART B: LITERATURE REVIEW

Introduction:

Voluntary Medical Male circumcision (VMMC) is the complete removal of the foreskin, the fold of skin that covers the glans penis.[6] It is routinely performed for religious and cultural reasons among infants and adolescents. Additionally, VMMC is performed therapeutically for the management of medical conditions like phimosis, paraphimosis, and inflammatory conditions of the glans penis and the foreskin.[26] It is therefore not surprising that the male circumcision has been performed since biblical times making it one of the oldest and known surgical procedures in the world. In a systematic review by Weiss *et al.,* it was further suggested that male circumcision might prevent HIV acquisition and other sexually transmitted infections (STIs). [27] The likely protective effect of male circumcision against HIV and STIs demonstrated through numerous observational studies, gave impetus to the need for further investigation of the public health benefits of male circumcision. [28, 29] Evidence confirming the effectiveness of male circumcision in prevention of HIV and STIs as well as the acceptability of male circumcision informed WHO policy recommendations and implementation in priority countries.

Purpose of the literature review:

- To describe the evidence linking voluntary medical male circumcision (VMMC) with reduced HIV acquisition and other health benefits
- To describe the recent developments in circumcision devices used for conducting VMMC
- To identify the gaps in the roll out of the circumcision devices used in the VMMC priority countries in order to reach the WHO target of 80%

Sections of the literature review:

The first section explores the public health benefits of VMMC among adolescent and adult males. The second section gives an overview of the process of identification of target countries and the implementation of VMMC scale-up service programs. The third section describes the challenges faced by VMMC programs and role that the introduction of circumcision devices into programs may play in increasing service uptake. The last section describes the process followed in the prequalification of devices for VMMC programs and details the mechanism of actions of the two currently prequalified device methods, whose brand names are Prepex and Shang ring.

Search strategy for the literature review:

Key terms such as adult, adolescent, male circumcision, non-surgical circumcision methods, uptake and acceptability of circumcision, device names (Prepex and Shang ring) and voluntary medical male circumcision (or VMMC) were used to identify the relevant literature. Electronic databases and websites searched for peer-reviewed journals or reports included: Medline (PubMed), Africa Wide, UpToDate, CINAHL, WHOLIS, CENTRAL the World Health Organisation (WHO) website and Google Scholar.

No restriction was placed on the type of study design, study period or language. Articles or documents that reported about the roll out of medical male circumcision among adolescents and adults were included as well as studies that focused on the use of the only WHO-prequalified device methods (Prepex and Shang ring).

The public health benefits of VMMC:

Voluntary Medical male circumcision and HIV infection risk:

Randomized controlled trials in three African countries demonstrated a compelling evidence of a reduced risk of heterosexually acquired HIV among circumcised men by 60%.[8-10] The clinical trial data were consistent with results from earlier observational studies which had demonstrated lower incidence and prevalence of HIV in circumcised men compared with those not circumcised, both at the population and individual levels.[28-30] By reducing HIV acquisitions among men, female sexual partners have reduced chances of encountering an HIV infected sexual partner.[12]

Voluntary medical male circumcision and the effects on other STIs:

In addition to the reduced risk of acquisition of HIV, male circumcision reduces other Sexually Transmitted Infections (STIs), including Human Papilloma Virus (HPV), and Herpes Simplex Virus (HSV)- Type 2. [8, 9, 31] The reduction in the risk of acquiring HIV and other STIs contribute to telling evidence for the inclusion of male circumcision as a public health intervention for preventing STIs, among men. Male circumcision confers benefits to the female partners of the circumcised men, including a reduced prevalence and incidence of high-risk HPV, and a lower incidence of bacterial vaginosis and severe bacterial vaginosis, trichomonas infection and genital ulceration.[10] Female partners of circumcised men are also at a reduced risk of cervical cancer.[32-34]

The impact of VMMC on the HIV epidemic:

It was shown by Halperin and Bailey in 1999 that countries in sub-Saharan Africa in which VMMC was not widely practiced also had the highest HIV prevalence. [28] Mathematical modelling undertaken following the clinical trial evidence of reduced HIV

acquisition among circumcised men also showed that VMMC scale-up would have a substantive impact on HIV incidence and prevalence if service uptake was optimal. Additionally, the mathematical models demonstrated that the reductions in HIV incidence and prevalence would be most significant in countries with generalized epidemics.[35-37]

Circumcision uptake in general:

In 2007, the World Health Organization (WHO) estimated the global prevalence of male circumcision to be 30% among males aged 15 years and older.[3] There were variations across countries with the practice almost universal in North and most of West Africa, but less common in southern Africa. Prevalence in central and East Africa varied from as low as 15% in Burundi and Rwanda to as high as 98% in Ethiopia.[3] Variations were also notable by ethnicity within countries. For example, although an estimated 84% of all Kenyan men were regarded as being circumcised, the percentage was much lower among the Luo and Turkana ethnic groups (17% and 40%, respectively).[3] To achieve the desired public health impact of VMMC, the acceptability of the circumcision procedure must be optimal among adolescents and adults.[38]

Voluntary Medical Male Circumcision (VMMC) Programs:

In response to the compelling evidence for HIV risk reduction through VMMC, the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), in 2007, recommended that VMMC become part of the comprehensive HIV prevention package in countries with a hyperendemic and generalized HIV epidemic and low rates of male circumcision.[1] In response to these recommendations, programs were initiated in fourteen countries in Eastern and Southern Africa with strategic plans and infrastructure

for the scale-up of male circumcision for HIV prevention.[2, 11] The priority VMMC countries are: Ethiopia, Kenya, Uganda, Republic of Tanzania, Rwanda, Malawi, Zambia, Zimbabwe, Mozambique, Namibia, Botswana, South Africa, Swaziland and Lesotho.[2] Alongside the provision of the procedure, the VMMC programs included promotion of condoms and safer sexual practices, treatment for STIs, HIV testing and counseling with linkage to HIV care and treatment.[39] The circumcision programs, targeted at adolescents and adult males, have been referred to collectively in most publications as "VMMC Programs", a terminology we use in this review. The widespread uptake of the VMMC services is critical for the realization of the public health benefits associated with the circumcision of males.

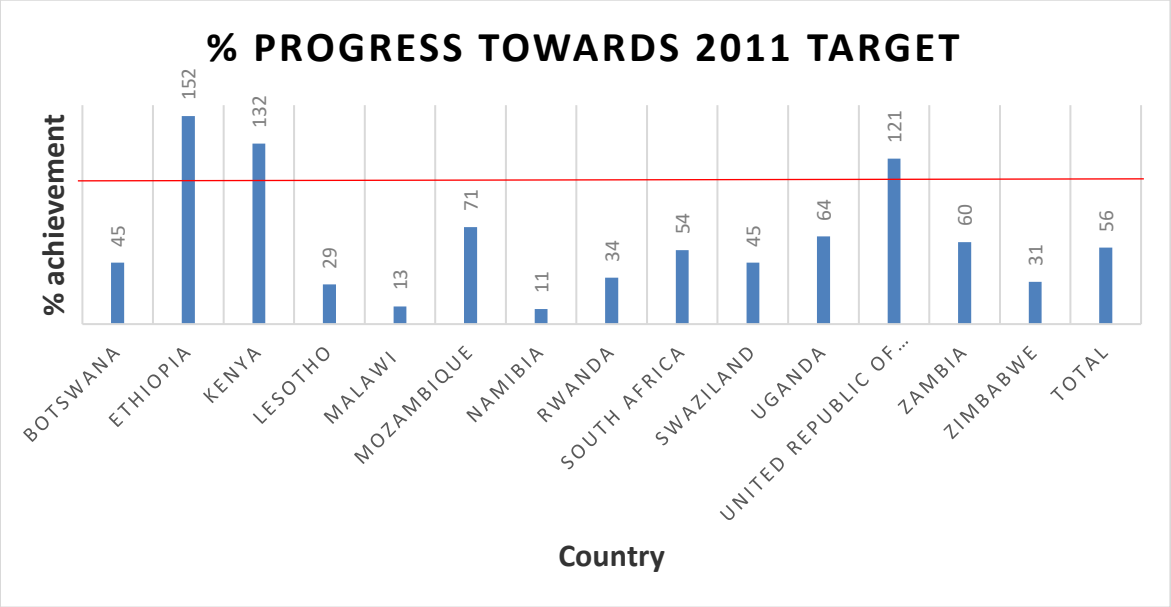
VMMC program targets for achieving public health impact:

A detailed impact and costing model called the Decision-Makers Program Planning Tool (DMPPT) was developed to help national policy makers decide the scope and pace of the individual country's VMMC scale-up. Using the DMPPT, the impact and cost of the VMMC scale-up in 13 high priority countries in eastern and Southern Africa was modeled in 2011.[4] The model estimated that 20.1 million circumcisions would be required to increase circumcision prevalence from 2011 baseline levels to 80% by the end of 2015 in men aged 15-49 years. The DMPPT further predicted that 80% prevalence in male circumcision would need to be maintained through 2025 (requiring an additional 8.4 million circumcisions over 10 years). The 80% prevalence in male circumcision would result to a total of 3.36 million HIV infections averted over the period 2011 – 2025. This made the procedure cost effective considering the treatment costs.[4]

Uptake of VMMC services:

By June 2015, VMMC programs in fourteen countries had been able to provide nearly 11.7 million males with medical circumcision for the purpose of HIV prevention (WHO, 2016).[5] This total of 11.7 million circumcisions was below the set target of 20 million by the end of 2015. Individual countries have reported variable progress (**Figure 1**) towards achieving 80% circumcision prevalence among males aged 15 years and older. For example Ethiopia (Gambella province), Kenya and the United Republic of Tanzania surpassed the targets of 80% VMMC rates. The cumulative number of VMMCs performed in four other countries—Mozambique, South Africa, Uganda and Zambia—attained more than 50% of VMMCs targeted. The remaining seven countries had, however, only managed less than 50% of the VMMCs targeted before the end of 2015 (**Figure 1**)

Figure 1: *Percentage achievement of VMMC numbers against 2011 targets in east and Southern Africa by country as at June 2015.* [40]



Red line represents 100% of achievement of the 2011 targets

Challenges facing VMMC programs in Africa.

The pace of scale-up has been slower than anticipated in some countries due to several challenges. Among studies investigating individual barriers to VMMC uptake, several barriers have been suggested to deter men from seeking VMMC services.

In a white paper published by the International Initiative for Impact Evaluation (3ie), possible barriers for VMMC uptake were categorized into individual level and social barriers.[41] Individual level barriers include; fear of pain or adverse events during or after surgery, the costs associated with VMMC, a period of sexual abstinence, and threats to masculinity, including loss of penile sensitivity or penile size, opportunity cost of procedure in the form of lost wages from undergoing the procedure. In other studies, it was reported that fear of an HIV test [42-44] as well as the perceived low risk for HIV acquisition [45] also deterred men from seeking VMMC.

Social barriers include culture and ethnic identity.[41] Different cultures within the priority countries hold varied beliefs regarding the practice of circumcision. In some cultures, men are circumcised as part of rituals for initiation into adulthood, making the procedure less foreign.[44] Among these traditionally circumcising communities, however, the procedure is often performed by traditional circumcisers. In these communities, VMMC performed in health facilities by trained health workers has at times faced resistance affecting its uptake. On other hand traditionally non-circumcising communities were also reported to have challenges of low uptake at the start of large-scale VMMC programs. In Zimbabwe, a traditionally non-circumcising country, considering circumcision were ostracized as the connotations regarding circumcision were largely negative.[42]

Concerns regarding the safety of the circumcision procedure have also been influential in its uptake. Men have expressed fear of injury to the penis as a deterrent for seeking VMMC services. [42, 45] The provision of safe circumcision services with few adverse events would improve confidence in the services. This is necessary to allay anxiety and increase demand for the service among the targeted men that may be skeptical about the service quality.

Fear of pain during the procedure has long been, and remains a deterrent to seeking VMMC. Studies on acceptability of VMMC prior to the initiation of VMMC programs had reported this as a barrier.[38, 46] In some settings, the pain known to be associated with the traditional circumcisions was imagined to be similar with the VMMC procedure.[42] Subsequent acceptability studies implemented after the VMMC programs were underway reported the fear of pain to remain a recurrent issue.[43] Ensuring that the experience of men undergoing VMMC is as painless as possible may therefore increase their uptake of the service.

To address the barriers identified through the white paper by the International Initiative for Impact Evaluation, demand-generation interventions have been implemented through pilots in 6 of the 14 priority countries.[47] These interventions were designed to address one or more potential barriers. Interventions included conditional compensation [48, 49] provision of information using influencers (such as partners, peers, role models) [50-52] messages delivered through cell phones[53]. Evaluations of the pilots reported mixed (both positive and null) results on VMMC uptake when interventions were implemented to address demand-side challenges.[47]

Circumcision methods and their likely role in VMMC service uptake:

The VMMC procedure is performed using either a surgical or a device based method.[6] The method used for performing the circumcision procedure may act as a contributor to the slow pace of service uptake. This may be the case if the time required to perform the procedure is long, such that few clients get the services. Another way through which the method of circumcision may affect uptake is through the perception that men have towards a method. Some studies have indicated that men opine some of the barriers mentioned above (including; concerns over pain, safety and side effects) to relate to the surgical methods of circumcision.[11] This perception of the procedure being risky and associated with pain may deter men from seeking VMMC services lowering the service uptake.

The majority of the adult and adolescent male circumcision procedures since the start of VMMC programs have been performed using one of three well described surgical methods namely: the dorsal slit method, the forceps-guided method or the sleeve resection method.[6] The forceps-guided method has been the most commonly used for scale up in East and Southern Africa.[7] The dorsal-slit method has not been as widely used by VMMC programs in sub-Saharan Africa; except for adolescent VMMC.[54] Being the most complicated of the three, no country program has used the sleeve resection method as the primary method for circumcision. All these methods require the prior injection of anaesthesia, haemostasis and wound closure, skills that require sufficient training time and prior surgical skills to be acquired. Due to the shortages of skilled health workers in the implementing countries that can perform these methods, the reliance on surgical methods alone may have contributed to the suboptimal uptake of

VMMC services. Simpler methods that minimize skills and have less technical requirements were and continue to be urgently needed. [12] Device circumcision methods may eliminate some of the challenges inherent to surgical methods, such as injection of anaesthesia, and suturing to achieve haemostasis and skin apposition. They may also be attractive to potential clients who have concerns or are otherwise reluctant to be surgically circumcised. Device circumcision methods, however, ought to be acceptable to the intended clients for the desired increase in service uptake to be achieved. It's therefore our desire to review the uptake of device methods among the population targeted by VMMC programs.

The advent of device methods for performing VMMC among adolescents and adults:

Prior to 2007, circumcision devices were routinely used by experienced health workers for infant circumcision as they made the procedure quicker and safer than the conventional surgical circumcision methods. A meeting report by Bakare in 2008 indicated that there were more than 20 commercially available devices.[13] In 2010, three devices (the Plastibell, the Mogen Clamp and the Gomco clamp) were described in the WHO guidance on early infant male circumcision.[55] These were recommended for use among infants on the basis of well-documented clinical experience with these methods in different regions of the world. Several other device methods used in infant circumcisions at the time lacked proper documentation of their safety and performance. Little clinical evidence existed regarding the use of devices in post-pubertal boys and adults, particularly in the countries in the African region where rapid expansion of male circumcision programs for HIV prevention is most urgent.

A number of country programs and researchers introduced devices into VMMC programs in a phased approach following the steps stipulated in the "*WHO Framework for the clinical evaluation of devices for male circumcision"* .[56] The device methods were intended to simplify the procedure and attract men who might have failed to seek services due to the fear of undergoing the surgical procedure. The successful uptake of these device methods would support rapid scale-up of VMMC services among adolescents and adults. To guide the use of devices in public funded VMMC programs for HIV prevention, WHO established the Prequalification of Male Circumcision Devices Programme.[16] This started by having an expert Technical Advisory Group (TAG) on innovations in male circumcision constituted. The TAG worked with other global partners to define a pathway for the evaluation of the efficacy and safety of innovations in male circumcision including devices. A device would be listed as prequalified after an objective assessment. Included in the assessment were the steps of; review of a product dossier, inspection of the manufacturing site(s), as well as evidence of clinical safety, performance and acceptability from initial studies in countries of intended final use. [16] Through the programme, the WHO prequalified the Prepex device for use in the circumcision of adult males aged 18 years and older in 2013.[21, 57] Subsequently, the prequalification was extended to include adolescents in 2015. The Shang ring device was similarly prequalified in 2015 for use among adolescents and adults.

The classification of VMMC devices:

The WHO classifies VMMC devices based upon the mechanism of action into elastic collar compression devices, clamp devices, crush devices and ligature devices. [57] Elastic collar compression devices, such as the Prepex, function by causing vascular

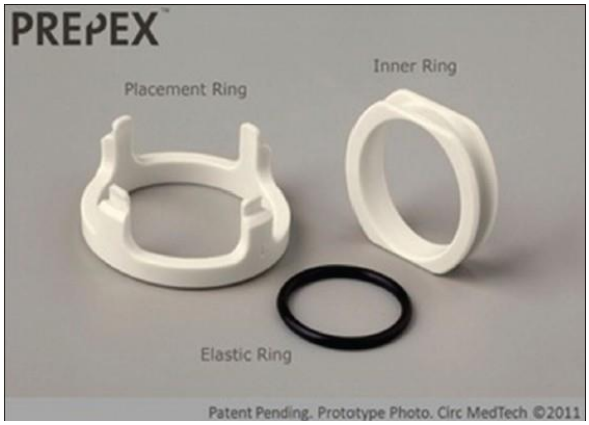
obstruction and gradual necrosis of distal foreskin tissue. Clamp devices, an example being the Shang ring, function by tightly compressing the proximal part of the foreskin to reach haemostasis.[57]

Crush devices, an example of which is the Mogen clamp, function by applying pressure to the foreskin tissue and cutting off the vascular supply to the distal foreskin. Ligature devices an example of which is the Plastibell function like the compression device methods.

The Prepex circumcision device:

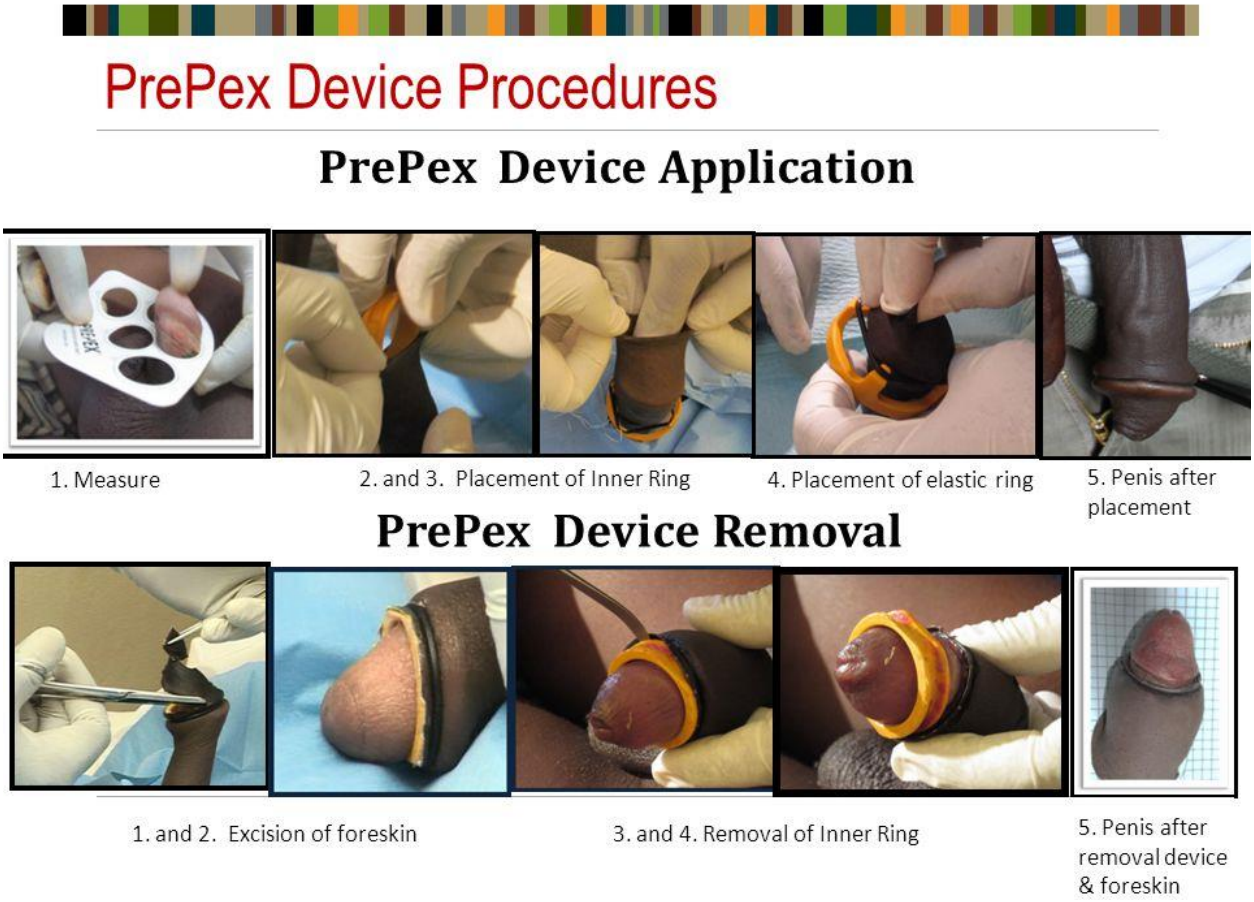
The Prepex device is classified as an elastic-collar compression-type device.[57] The device consists of an inner plastic ring, an outer elastic ring, a placement guide and a verification thread (**Figure 2**). The Prepex device works by providing slow compression between an elastic ring and a hard inner ring sufficient to cause ischeamic necrosis of the foreskin over a period of one week while the device remains in place.[57] **Figure 3** demonstrates the steps followed in placing and removing the Prepex device.

Figure 2: The Prepex device showing the components.



Accessed at http://www.circlist.com/instrstechs/prepex.html on 21st August, 2017

Figure 3: The Prepex device placement and removal procedure steps



Source: Excerpt from slide deck titled, "Experience with prepex device use with adults and adolescents in pilot implementation and active surveillance in Zimbabwe, Zambia and South Africa." [58]

The Shang ring device:

The Shang ring device is a novel disposable MC device classified among the Clamp type of circumcision devices. Like other clamp type devices, the Shang ring device works through the delivery of a rapid, tight compression of the foreskin sufficient to achieve haemostasis and prevent tissue slippage such that the foreskin can be removed at the time of device placement.[57] The foreskin is removed after the device is secured in place by a ratchet lock mechanism and the device left in place. Due to the

immediate foreskin removal with this method, injected local anaesthesia is required. It consists of two part, an inner ring and an outer ring (**Figure 4**).

Figure 4: The Shang ring device; showing the outer and inner ring (left), the outer ring alone (right)

The inner ring (**Figure 4**) has a shallow groove on its outer surface that is lined by a silicone band which confers a non-bioreactive surface against which the outer ring sandwiches the foreskin. The outer ring consists of two halves hinged together at one end and closes securely via a ratchet style closure. Details of the use of this device method have been summarized in **Figure 5**.

Figure 5: Shang ring device placement and removal steps:

Source: *Accessed at https://snnda.en.alibaba.com on 28th August, 2017* [59]

How Prepex and Shang ring devices might work to increase uptake of VMMC services:

The possible advantage of using the Prepex and Shang ring circumcision devices over surgical methods are several. These devices could accelerate the delivery of VMMC in resource-limited settings by decreasing the time taken to perform the procedure. The devices may also bring convenience as the procedure through device can be mastered and performed more easily, eliminating the highly technical steps inherent to surgical methods. A simpler procedure would in turn decrease the infrastructure required to provide the service so that it can be provided in a wider array of locations. In all, these advantages of the Prepex and Shang ring methods may potentially make the VMMC procedure more acceptable to clients than the conventional surgical methods. This

would effectively increase the reach of VMMC services. Being novel to the long established surgical methods of circumcision, the uptake of the two devices by the targeted clients shall be important to the attainment of the desired goal of reaching 80% circumcision coverage in countries yet to reach that milestone as well as maintaining that prevalence across the continent.

Conclusion:

The implementation of VMMC program has been met with diverse challenges that may have contributed to slow uptake in a number of the priority countries. Circumcision devices such as the Prepex and Shang ring have been promoted as a strategy to hasten the pace of VMMC scale-up. No systematic review of literature exists regarding the uptake of these methods and factors that may influence participants' acceptability for the WHO-prequalified circumcision devices. However, as VMMC programs continue to incorporate these WHO-prequalified device methods for the circumcision of adolescents and adults, it will be paramount to ensure that these methods are acceptable to the target population.

Our systematic review therefore aims to understand the uptake and acceptability of the currently prequalified methods and factors that may have influence their acceptability. This information would help in advocacy for the use of these methods.

PART C: JOURNAL MANUSCRIPT

The Uptake of the Prepex™ and Shang ring male circumcision devices among adolescent and adult males in Africa, a systematic review

Abstract:

Background:

Voluntary medical male circumcision (VMMC) programs have been implemented in fourteen countries in sub Saharan Africa since 2007. The uptake of services has been suboptimal in some of the countries partly due to the widespread use of surgical methods. Circumcision using device methods was postulated to increase the uptake of VMMC services by making the procedure quicker and more appealing to men. We conducted a systematic review to establish the uptake and acceptability of the Prepex and Shang ring male circumcision devices in VMMC program countries. A meta-analysis was also performed.

Methods:

A comprehensive literature search from several databases was carried out to identify studies reporting VMCC coverage, uptake or acceptability of either the Prepex or Shang ring device methods. Search terms included, “non-surgical methods, male circumcision instrumentation as well as the individual device names such as Prepex, Shang ring, Gomco, Mogen, Plastibell, Accucirc, Alisklamp, Ismail Clamp, Tara Klamp, Unicirc, Smartclamp”. Electronic searches were complemented by going through the reference lists of the included studies. All searches were carried out on 12th May, 2017. Included studies must have been conducted between 1st April, 2007 and 28th February, 2017.The search was limited to studies among adolescents and adults in VMMC implementing countries. Two reviewers independently reviewed, rated, and abstracted data from each article. Uptake estimates were pooled in a meta-analysis and stratified according to the device method and participant age using Stata. Acceptability of device

methods among recipients was summarized using four criteria and presented as proportions.

Results:

Of the 391 total articles retrieved, 25 studies incorporating observational and interventional study designs met the inclusion criteria. Of these 25 studies, 7 articles reported uptake of device method, 5 and 2 being on the Prepex and Shang ring devices respectively. The pooled uptake estimate was 75% (95% confidence interval 62% to 89%). Prepex uptake was estimated to be 73% while the Shang ring estimates were 82%. On stratification by population group, uptake of device methods among adolescents was 82% compared to 72% by adults. Majority (21) of the studies reported at least one of the criteria used to assess device acceptability. Acceptability of the two device methods was high: 95% of participants reported satisfaction with a device procedure. The devices were not associated with lengthy periods out of work, with 87% of participants reported to have resumed normal activities within two days after the procedure. Almost all (97%) participants circumcised with the device methods indicated they would recommend a device procedure to a friend or relative.

Conclusion:

Our findings showed a high uptake and acceptability of the two circumcision devices methods that have been prequalified by WHO for use among adolescents and adults. There is a dearth of evidence on the extent of utilization of devices for adolescent or adult circumcision and whether this has improved the overall uptake of VMMC services, thus emphasizing the need for more studies on this topic.

Background

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended Voluntary Medical Male Circumcision (VMMC) to be part of the comprehensive HIV prevention strategy in 2007.[1] The recommendation was for the countries with a hyperendemic and generalized HIV epidemic and low rates of male circumcision. The WHO and UNAIDS recommendations were instrumental to VMMC programs targeting adolescent and adults being initiated in fourteen countries in Eastern and Southern Africa. Based on the HIV epidemic, the priority VMMC countries are; Ethiopia, Kenya, Uganda, Republic of Tanzania, Rwanda, Malawi, Zambia, Zimbabwe, Mozambique, Namibia, Botswana, South Africa, Swaziland and Lesotho.[2] The VMMC programs target was to increase the uptake of circumcision services in the fourteen selected priority countries.

Historically, the uptake of circumcision services varied greatly across countries within Africa [3]. For example, countries in the North and West parts of Africa reported circumcision coverage exceeding 80% for adolescent and adult males while much lower rates were reported in the East and South Africa. [3] A modelling study demonstrated that achieving a circumcision coverage of 80% among men aged 15-49 years in the 14 priority African countries by 2016, it would require the circumcision of 20.1 million males.[4] Further, the modelling study showed that performing the 20.1 million male circumcisions would avert 3.4 million new HIV infections in the priority countries.[4] According to the modelling study, the impact of such reductions in the new HIV infections would result to a net savings of US$ 16.5 billion by 2025 in treatment costs. [4,

[5] Therefore, increased uptake of adult male circumcision will have both public health and economic benefits.

From 2008 through 2015, VMMC programs provided 11.7 million males with medical circumcision for the purpose of HIV prevention in the fourteen priority countries.[5] Progress towards the VMMC target of 80% circumcision coverage varied in the fourteen countries with Ethiopia (Gambella province), Kenya and the United Republic of Tanzania surpassing the targets set in 2011. In addition, South Africa, Mozambique, Uganda and Zambia attained more than 50% coverage. Uptake of circumcision services has, however, been suboptimal in the remaining seven VMMC priority countries, each recording circumcision coverage of less than 50% of the 2011 target. [5]

Factors contributing to the low uptake of circumcision services in some countries include concerns over pain, safety and side effects which many men opine to relate to the surgical methods of circumcision. [11] Understanding the strategies used in the countries where VMMC targets are met is important as these effective strategies may be used to increase the coverage of circumcision in the countries where VMMC targets are still unmet. As an example, if the method used to perform a circumcision procedure is highly acceptable among the target males, this may improve the circumcision coverage in a given setting.

The VMMC procedure is performed using either a surgical or a device based method. [6] At the start of VMMC programs, adolescent and adult male circumcisions were most commonly performed using conventional surgical methods. [7] These methods had been standardized and used successfully in randomized clinical trials [8-10] that demonstrated the HIV prevention benefits arising from circumcision. Surgical methods, however,

require a certain level of surgical skill including injection of anaesthesia, heamostasis and wound closure. [6] These surgical skill requirements may have partly slowed the pace of circumcision services scale-up. The urgency for circumcision scale-up among adult males created a need for safe, fast and acceptable innovative methods. [60] It is therefore rational to propose that most of the current and future VMMC will be performed using these innovative methods.

Male circumcision devices were evaluated for circumcision among adolescents and adults, in the hope of increasing VMMC coverage. Certain device methods, different from those proposed for adult VMMC, had long been used successfully and safely among infants.[13] Circumcision using device methods was anticipated to make the procedure simpler and quicker. Additionally, the use of circumcision devices would negate the need for a healthcare professional with skilled surgical skills. Device circumcision methods were also thought to be more acceptable among males reluctant to be surgically circumcised. High acceptance and widespread use of device methods would have the potential to increase the uptake of circumcision services, and in turn, positively contribute towards the set VMMC target of 80% circumcision coverage. The extents to which circumcision devices are utilized in the fourteen VMMC priority countries remain unknown. Furthermore, it is not known whether the utilization of the circumcision devices may have an impact on the variable circumcision coverage observed in the fourteen countries.

The WHO stipulated an objective assessment for the prequalification of circumcision devices for use in public VMMC programs that includes evidence on clinical safety, performance and acceptability in the country of intended use. [16] Findings from initial

clinical trials of the Prepex device in Rwanda [17], Zimbabwe [18] and Uganda [19] as well as the Shang ring device in Zambia and Kenya [15, 20] reported the two devices to be safe and acceptable among adolescents and adults. Subsequently both Prepex and Shang ring devices received WHO-prequalification for use in VMMC programs. [57, 61] The Prepex and Shang ring devices have been progressively rolled out under active surveillance since their prequalification. It is unclear if incorporation of the prequalified devices into circumcision programs plays a role in the uptake of circumcision services. It is of interest to ascertain whether device introduction into VMMC programs has translated into increased service uptake.

Why it is important to do this review:

To our knowledge, there are no systematic review studies that have assessed the uptake or acceptability of circumcision by the WHO-prequalified devices in the fourteen VMMC priority countries. In order to fill this evidence gap, we conducted a systematic review. Information from the review results will generate knowledge on the uptake and acceptability of the WHO-prequalified circumcision devices. This knowledge can be used to advocate for VMMC in an attempt to reach the VMMC targets of 80% in the fourteen priority countries.

Research question:

The research question was as follows:

What is the uptake of the two WHO-prequalified male circumcision devices among adolescents and adults in the countries scaling up VMMC for HIV prevention within Africa?

Objectives:

- To establish the uptake of the two WHO-prequalified circumcision devices in the VMMC priority countries
- To establish the proportion of adolescent and adult males choosing VMMC by a WHO-prequalified device when offered as a choice instead of the conventional surgical methods in the VMMC priority countries. A meta-analysis was performed to summarize the results for this objective from identified studies.
- To describe the acceptability of the WHO-prequalified device in the VMMC priority countries

Methods:

The review was registered with PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO) before searches commenced (registration number PROSPERO 2017:CRD4201705803). There were no substantive deviations from protocol. The review is presented in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance.[22]

Criteria for considering studies for this review:

Inclusion criteria: Studies conducted in VMCC priority countries and reporting the outcomes of interest. The outcomes of interest were the uptake or acceptability of the two WHO-prequalified circumcision devices. The summarized table 1 below provides elements of the different components used for search and inclusion of the studies.

Table 1: Inclusion criteria for the uptake and acceptability components of the systematic review:

Component	**Uptake component**	**Acceptability component**
Population	Adolescent (aged 10 -17 years) or adults aged older than 18 years	
Interventions	Circumcision using either the Prepex or Shang ring device for male circumcision	
Comparator	Circumcision using one of the surgical methods of circumcision	
Outcome	Uptake defined as the choice by a participant to receive circumcision by a device method including participants whose circumcision may eventually have been performed by another method due to reasons making them ineligible for circumcision with their chosen device method.	Among participants circumcised using a device method, client acceptability was estimated using one of the four measures predetermined by WHO in the framework for the evaluation of clinical devices including: • Client satisfaction with the procedure categorized as either very satisfied, satisfied, somewhat satisfied or not satisfied. • Average duration between device placement and resumption of activities of daily living assessed as the proportion return to work/school within the first 2 days. • Pain at different time points assessed by the Visual Analog Scale

		• Proportion of participants who would recommend the method to a friend or to the community
Study design	All study designs except Randomized controlled trials	Any study design
Time limitation	Conducted between 1st April, 2007 and 28th February, 2017	
Setting	Conducted in one of the VMMC priority countries	
Language	English language articles only	

Outcome measures for acceptability as recommended by WHO for studies assessing acceptability of circumcision device methods.[12]

Included studies must have been conducted between 2007 and 2017, to coincide with the period during which VMMC programs were operational.

The search strategy was broad and not limited to any particular study design. For studies reporting uptake, however, randomized studies were not considered for inclusion as the intervention had been assigned as opposed to being self-selected by the participant. Both published and unpublished (grey literature) articles in English were considered.

Studies were also excluded if they:

- Were conducted on infants or children aged younger than 10 years
- Did not report acceptability or uptake of Prepex or Shang ring devices
- Did not specify the circumcision methods used.
- Were review articles.

Primary and secondary outcome measures:

The primary outcome of this study was the proportion of circumcisions that have been performed using the two WHO-prequalified device methods in the VMMC program countries.

The secondary outcome was the proportion of adolescent or adult males that opt for a device method when offered a choice between the Prepex or Shang ring device methods and one of the conventional surgical methods. Along with this, the factors for choice of device method were investigated.

Information sources:

Search methods for the identification of the included studies:

We developed a comprehensive search strategy that incorporated a combination of free text and Medical Subject Headings (MeSH) terms. The search initially used the priority VMMC African countries search filter, however when applied during the search, this limitation resulted into an overall output of 17 articles which was too specific. Excluding the African countries filter made the search more sensitive. The detailed strategy is shown in **Appendix 5**. All search results from the individual databases were imported and screened using the rayyan software for managing systematic reviews (https://rayyan.qcri.org/). Endnote referencing software was used for managing references and indexing cited articles.

Electronic databases:

Studies were identified by searching major electronic databases using key search terms with Boolean operators. We searched the following databases for relevant studies:

MEDLINE (PubMed), The Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), Databases of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment Database (HTA)), ISI Web of Science, CINAHL, and Scopus. The search strategy developed for Medline was modified to suit the vocabulary of the other databases that were searched. **Appendix 5** shows a summary of search results retrieved from the PubMed database. Grey literature searches were conducted in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/), and databases of World Health Organization Library Information System (WHOLIS), (http://www.who.int/library/databases/en/), and the Joint United Nations Programme on HIV/AIDS (UNAIDS resource library) (http://www.unaids.org/en/resources/). Lastly, searches were done in Google Scholar. All searches were carried out on 12th May, 2017.

Study selection:

The identified titles and abstracts of eligible studies were screened independently by RK and BK for inclusion. Then, full-text manuscripts of potentially eligible abstracts were independently screened by the two study team members for inclusion based on the criteria described in table 1. Screened studies were classified as either included or excluded. The two reviewers discussed the included and excluded studies, resolving discrepancies by discussion and consensus. Reasons for exclusion of studies were documented and listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Data collection and data items:

A data collection form (**Appendix 3**) was developed and used independently by two reviewers RK and BK to extract data from the included studies. Prior to data extraction, we piloted the comprehension of the form by extracting data from 5 of the included studies. The extracted data was recorded into an MS Excel sheet with the fields indicated in the data extracted form.

Data Synthesis:

Males that chose circumcision with a device method were analysed as proportions of all males seeking VMMC where a choice of circumcision method was offered. Using Stata Version 14, data from studies reporting uptake of the two devices were pooled using the Freeman-Tukey double arcsine transformation metaprop model, a random effects model.[62] Pooled statistics of device uptake were expressed as estimated proportions/prevalence (ES) with 95% confidence intervals (CI).

Subgroup analysis:

The aggregate prevalence was stratified by device method (intervention used) and by age. Sub analysis based on the 2011 VMMC target by different countries (low, intermediate, exceeded) could not be performed due to data limitations. The WHO criteria for assessing acceptability, was used in the analysis of acceptability data. [12] Factors reported by participants for choosing or rejecting a device for circumcision were recorded where reported. Experiences reported by participants with regards to liking or disliking the device for circumcision procedures were assessed using content analysis and narrative synthesis.

Assessment of heterogeneity:

Heterogeneity between studies was determined to assess the extent of variation between studies during meta-analysis. Heterogeneity was assessed by inspecting the extent of overlap within the forest plots, and through the *I*-squared statistic (where 75% or higher values indicate high levels of heterogeneity).[63]

Risk of bias assessment of included studies:

The risk of bias was evaluated by the two reviewers (RK and BK) with disagreement resolved through discussion and consensus. Included studies were evaluated for risk of bias related to internal and external validity. The risk of bias in observational studies was assessed using the quality assessment tool for evaluating prevalence studies as suggested by Hoy and colleagues and adapted by Werfalli and colleagues, **Table 2**. [24, 64]

Table 2: Risk of bias assessment criteria for prevalent studies

Items	**Score**
External validity	
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 Point
2. Was the sampling frame a true or close representation of the target population?	1 point
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 point
4. Was the likelihood of non-response bias minimal?	1 point

Total	4 points
Internal validity:	
5. Were data collected directly from the participants (as opposed to a proxy)?	1 point
6. Was an acceptable case definition used in the study?	1 point
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
8. Was the same mode of data collection used for all participants?	1 point
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 point
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 point
Total	6 points

The adaptation of the tool by Werfalli and colleagues allows for a composite score to assist with relative comparison between studies thereby reducing reviewer's subjectivity. The quantitative scoring system added by Werfalli and colleagues was maintained in analyzing the risk of bias in these studies and categorizing the overall risk of bias in each study. [64] Studies with an overall score of 0-5 points were categorized high risk studies, 6-8 as moderate risk studies, while those with >8 points were categorized as low risk studies, **Table 3**.

Table 3: Overall scoring for the risk of bias assessment:

Overall score	Implication

0-5 points	High risk: Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate
6-8 points	Moderate risk; Further research is likely to have an important impact on our confidence in the estimate and may change the estimate
>8 points	Low risk; further research is very unlikely to change our confidence in the estimate

The Cochrane collaboration risk of bias (ROB) tool [23] was used for interventional studies and covers six domains of bias including: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias

Funding:

No funding was received for this study.

Ethics:

Systematic reviews draw on publicly available data and do not directly involved human or animal subjects; therefore they do not require formal ethical review. [25]The study protocol was however reviewed by the supervisors with extensive knowledge in systematic review methods and submitted to the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee for approval.

Dissemination:

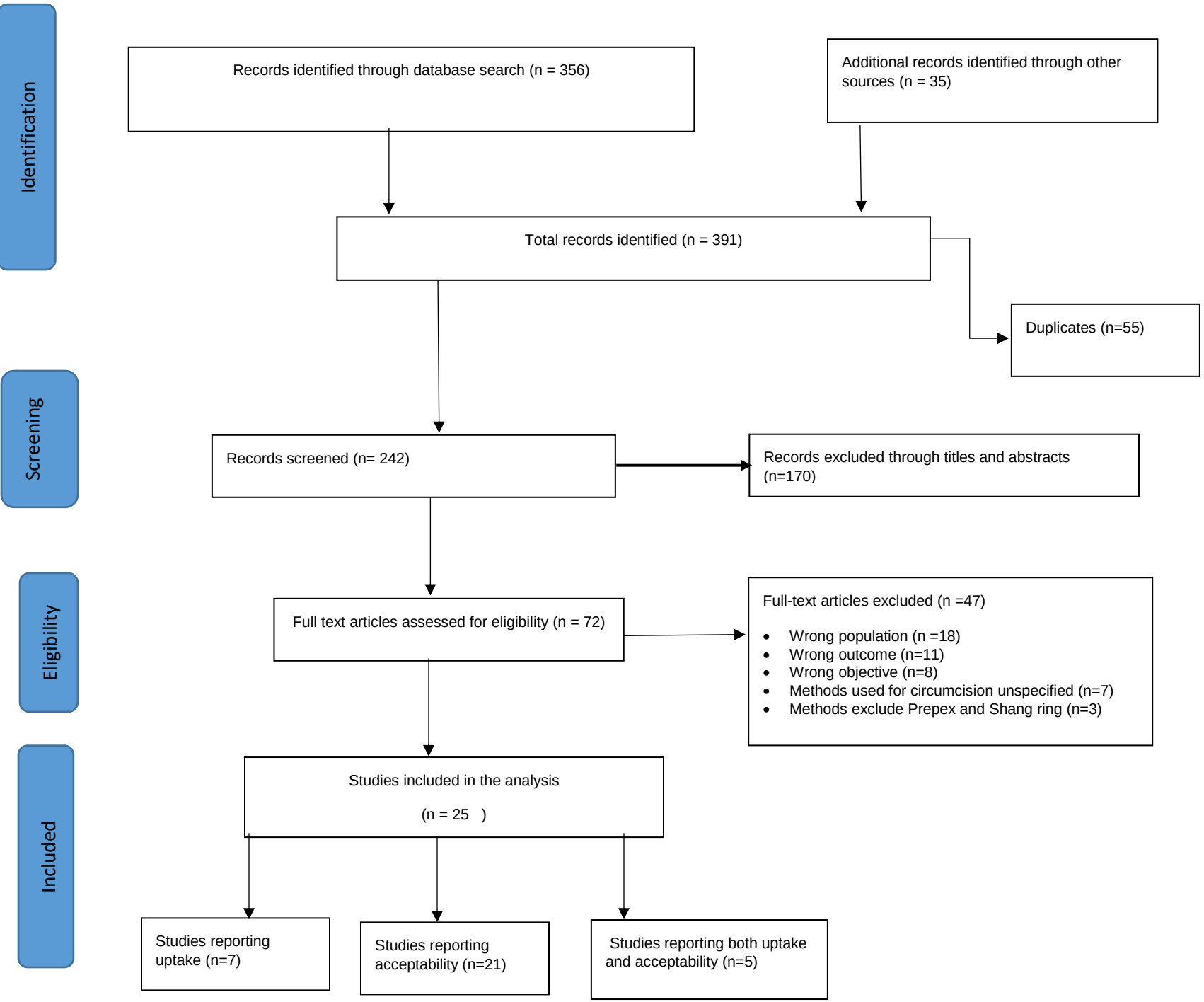
It is expected that this work will contribute to the knowledge on uptake and acceptability of VMMC devices. The study findings will be submitted to a peer-reviewed journal for publication.

Results:

Quantity of research available:

From all searches, 391 records were identified, which after duplicate records were removed, 242 records remained that were then screened for inclusion (**Figure 6**). The titles and abstracts of the 242 records were assessed for inclusion, resulting in 72 potential records retained for the next round of screening. The full-texts of the 72 records were obtained and screened further for inclusion. From the 72, we excluded 47 records. Thus twenty five (25) studies were included in the systematic review. In total, seven studies reported uptake of Prepex and Shang ring devices in VMMC and were included in the meta-analysis. A total of 5,998 participants were enrolled into the studies that were included in the meta-analysis. The two Shang ring studies enrolled 1,085 participants while the five Prepex studies enrolled 4,913 participants. Twenty one studies reported acceptability of the devices. Five studies reported both uptake and acceptability.

Figure 6. Flow-chart of studies included in the review:



Characteristics of the included studies

Included studies comprised 24 peer-reviewed journal articles and one conference abstract. [65] The studies were conducted in eight countries out of the fourteen VMMC countries. All the studies were conducted at health facilities.

Studies reporting uptake were all prospective cohort studies. Four studies enrolled only adults, two studies enrolled only adolescents while one study enrolled both adults and adolescents. The uptake studied were set in Uganda (4 studies), South Africa (1 study), and Zimbabwe (2 studies) (**Table 4**).

Twenty one studies reported acceptability of devices. [14, 15, 18, 20, 66-82] Studies comprised fourteen prospective observational studies [19, 20, 67-69, 71, 72, 74-76, 78, 79, 81, 82], six RCTs [14, 15, 18, 66, 70, 80], and one cross-sectional study [77]. (**Table 4**). Nineteen studies enrolled only adults, one study enrolled only adolescents [82], and one study enrolled both adults and adolescents [75]. Among acceptability studies, three were conducted in Kenya [20, 66, 69], four in Zimbabwe [18, 72, 76, 82], three in Uganda [71, 73, 80], two in Rwanda [14, 79], two in South Africa [75, 77], two in Malawi [68, 74], one in each of Zambia [70], Mozambique [67] and Botswana [78], while two articles reported results of studies that had enrolled participants in both Zambia and Kenya [15, 81].

Five studies reported both uptake and acceptability. (**Table 4**).[71, 73, 75, 76, 82] Two of these were conducted in Uganda [71, 73], two were set in Zimbabwe [76, 82] while the fifth was in South Africa [75]. Three studies enrolled only adults [71, 73, 76], with one study each enrolling only adolescents [82] or both adults and adolescents [75].

Table 4: Characteristics of included studies:

Study	Country	Study design	Population	Study setting	Intervention	Quantitative / Qualitative Outcome(s)	n (Sample size)
Sokal 2014 [81]	Kenya and Zambia	Prospective observational	Aged 18-54 years *Median ages 19 (IQR 18-24)(in Kenya) and 24 (IQR 21-30) (in Zambia)*	7 sites in Homa Bay district in Kenyan study, 3 sites in the capital, Lusaka in the Zambian study	Shang ring	Qualitative	1163 participants enrolled, 557 in Kenya and 606 in Zambia
Milovanovic 2016 [77]	South Africa	Cross sectional study	3 participant groups: Prepex recipients (15 years or older) Escorts of clients Prepex rejectors *Recipients median age -26 years(IQR 22-30)*	2 high volume sites (Tsakane and Witbank hospital) and Zuzimpilo, an HIV wellness and VMMC clinic in Johannesburg	Prepex	Qualitative	312 recipients, 117 escorts and 21 rejectors
Feldblum 2014 [69]	Kenya	Prospective observational	Healthy males aged 18-49 years *Median age -20 years*	One fixed Kisumu clinic (urban) and two outreach dispensaries (rural)	Prepex	Qualitative	427 participants
Galukande 2014 [71]	Uganda	Prospective observational	Healthy males aged 18-49 years *Mean age- 24 years*	Urban site at International Hospital, Kampala	Prepex	Both	1,040 participants, with 678 choosing Prepex

Mutabazi 2013 [79]	Rwanda	Prospective observational	Aged 21-54 years *Mean age – 25 years*	1 urban based site at Kanombe Military Hospital in Kigali	Prepex	Qualitative	518 participants in a three-phase study
Kigozi 2014 [19]	Uganda	Prospective observational	Aged 18 years and older *Mean / median age –not reported but majority (67%) were 18-25 years*	One site in rural area	Prepex	Quantitative	429 participants with 350 choosing Prepex
Kigozi 2013 [73]	Uganda	Prospective observational	Healthy adult males aged 18 years and older *Mean / median age –not reported but majority (65%) were </= 24 years*	One site in rural area	Shang ring	Both	621 participants, with 508 choosing Shang ring
Cummings 2016 [67]	Mozambique	Prospective observational	Healthy males aged 18-49 years *Mean / median age –not reported but majority (70%) were </= 24 years*	Jose Macamo health center in Maputo (urban)	Prepex	Qualitative	504 participants
Tshimanga 2016 [82]	Zimbabwe	Prospective observational	Adolescents aged 13-17 years	Spilhaus Prepex study site in Harare	Prepex	Both	934 participants of whom 710 consented
Kohler 2016 [74]	Malawi	Prospective observational	Adult males aged 18-49	3 sites, 1 urban static (Lilongwe), 1 rural static	Prepex	Qualitative	804 participants

			Mean / median age –not reported but majority (86%) were < 30 years	(Nsanje district) and 1 rural tent (Mulanje district)			
Musiige 2016 [78]	Botswana	Prospective observational	Adult males aged 18-49 years from areas within 50km radius of Gaborone *Mean age -27.7 years*	Block 8 clinic in Gaboorone and Nkoyaphiri clinic in peri-urban area bordering Gaborone	Prepex	Qualitative	802 participants
Mavhu 2016 [76]	Zimbabwe	Prospective observational	Adult males aged 18 years and older as part of the active surveillance phase *Age disaggregation not provided*	6 dedicated VMMC clinics in 4 provinces; 2 clinics in Harare, 2 clinics in Bulawayo, 1 clinic in Manicaland, 1 clinic in Mashonaland west	Prepex	Both	2156 participants
Barone 2011 [20]	Kenya	Prospective observational	Aged 18-54 years *Mean 20.5 (range 18-45)*	Homa Bay hospital in Kenya	Shang ring	Qualitative	40 participants
Kasprzyk 2016 [72]	Zimbabwe	Prospective observational	Aged 18-50 years *Mean age 32.5 years*	Ministry of Health VMMC center	Prepex	Qualitative	53 participants
Mutabazi 2012 [14]	Rwanda	Randomized controlled trial	Aged 21-54 years *Mean age 26 (SD 5.17)*	Nyamata district hospital, a rural area 35 km from Kigali	Prepex	Qualitative	217 participants
Feldblum 2016 [70]	Zambia	Randomized controlled trial	Aged 18-49 years *Median 23.5 (IQR 20-29) ; Mean 25.7 (6.9)*	3 clinics in Lusaka, University Teaching Hospital, Chilenje Clinic, Chawama district hospital	Shang ring	Qualitative	500 participants

Barone 2012 [66]	Kenya	Randomized controlled trial	Aged 18-54 years *Median 21 years (18-38)*	Homa bay district hospital	Shang ring	Qualitative	50 participants
Sokal 2014 [15]	Kenya and Zambia	Randomized controlled trial	Aged 18-54 years *median 19(18-36) in Kenya ; 22 (18-39) in Zambia*	Homa Bay district hospital in Kenya and New Start YWCA VMMC clinic in Lusaka	Shang ring	Qualitative	400 participants
Tshimanga 2016 [18]	Zimbabwe	Randomized controlled trial	Aged 18 years and older *Mean 29.1 (SD 9)*	Spilhaus center, a family planning clinic in Harare	Prepex	Qualitative	240 participants
Lebina 2015 [75]	South Africa	Prospective observational study	Both adolescents (14-17 years) and adults 18-49 years *Median adults (26), among adolescents (16)*	2 high volume sites (Tsakane and Witbank hospital) and Zuzimpilo, an HIV wellness and VMMC clinic. Substudy of adolescents was only done at Tsakane and Zuzimpilo clinics	Prepex	Both	454 participants
Feldblum 2016 [68]	Malawi	Prospective observational study	Aged 18-49 years *Mean 20.8 (SD 4.62), Median 19 (IQR 18-21), Range (18-48)*	St. Gabriel's Hospital, in Namitete village, a 45-minute drive from Lilongwe	Shang ring	Qualitative	500 participants
Kanyago 2013 [80]	Uganda	Randomized controlled trial	Aged 18 years and older *Median 22 (IQR 21-23)*	Mbarara district in South western Uganda (urban area)	Shang ring	Qualitative	138 participants
Kigozi 2014 [65]	Uganda	Prospective observational	Aged 13-17 years	Rakai district (rural)	Shang ring	Quantitative	464 participants, 384 chose Shang ring

Risk of bias within studies:

Observational studies:

All the sixteen observational studies had a moderate risk of bias.

Most of the studies (n=13) had a representative participant target in terms of the national population intended for VMMC services. In two studies, the participant target was assessed as not representative of the national population. In one study participants came from a highly urbanized setting.[71] In the other study, men were generally well educated and half were employed, which may not be representative of the men in the country the study was being conducted.[72]

In all studies, no random selection was used to select the sample. The likelihood of non-response bias was minimal in all studies. This was because all studies collected data directly from the participants as opposed to proxies.

Only two studies clearly stated having pretested the data collection instrument to ensure validity and reliability.[71, 72] In the remainder of the studies, however, mention was made of having used trained research personnel for data collection. The mode of data collection was the same for all subjects in each study.

Interventional studies:

All the seven studies employed some form of convenience sampling. It was not possible to blind participants to the intervention, which was a risk for performance bias in all the included interventional studies.

Table 5: Summary of risk of bias evaluation:

	Internal risk of bias				External risk of bias							
Study ID	Risk of Bias 1	Risk of Bias 2	Risk of Bias 3	Risk of Bias 4	Risk of Bias 5	Risk of Bias 6	Risk of Bias 7	Risk of Bias 8	Risk of Bias 9	Risk of Bias 10	Quality score	Overall risk of bias
Sokal 2014(1)	1	1	0	1	1	1	0	1	1	1	8	Moderate
Milovanovic 2016	1	0	0	1	1	1	0	1	1	1	7	Moderate
Feldblum 2014	1	1	0	1	1	1	0	1	1	1	8	Moderate
Galukande 2014	0	0	0	1	1	1	1	1	1	1	7	Moderate
Mutabazi 2013	1	0	0	1	1	1	0	1	1	1	7	Moderate
Kigozi 2013	1	1	0	1	1	1	0	1	1	1	8	Moderate
Cummings 2016	1	1	0	1	1	1	0	0	1	1	7	Moderate
Tshimanga 2016 (1)	1	0	0	1	1	1	0	1	1	1	7	Moderate
Kohler 2016	1	1	0	1	1	1	0	1	1	1	8	Moderate
Musiige 2016	1	1	0	1	1	1	0	1	1	1	8	Moderate
Mavhu 2016	1	1	0	1	1	0	0	1	1	1	7	Moderate
Barone 2011	0	0	0	1	1	1	0	1	1	1	6	Moderate
Kaspryzk 2016	0	0	0	1	1	1	1	1	1	1	7	Moderate
Feldblum 2016	1	1	0	1	1	1	0	1	1	1	8	Moderate
Lebina 2015	1	1	0	1	1	1	0	1	1	1	8	Moderate

Overall risk of bias score categorization: 0-5 high risk of bias; 6-8 moderate risk of bias; >8 low risk of bias

Data synthesis:

Uptake component:

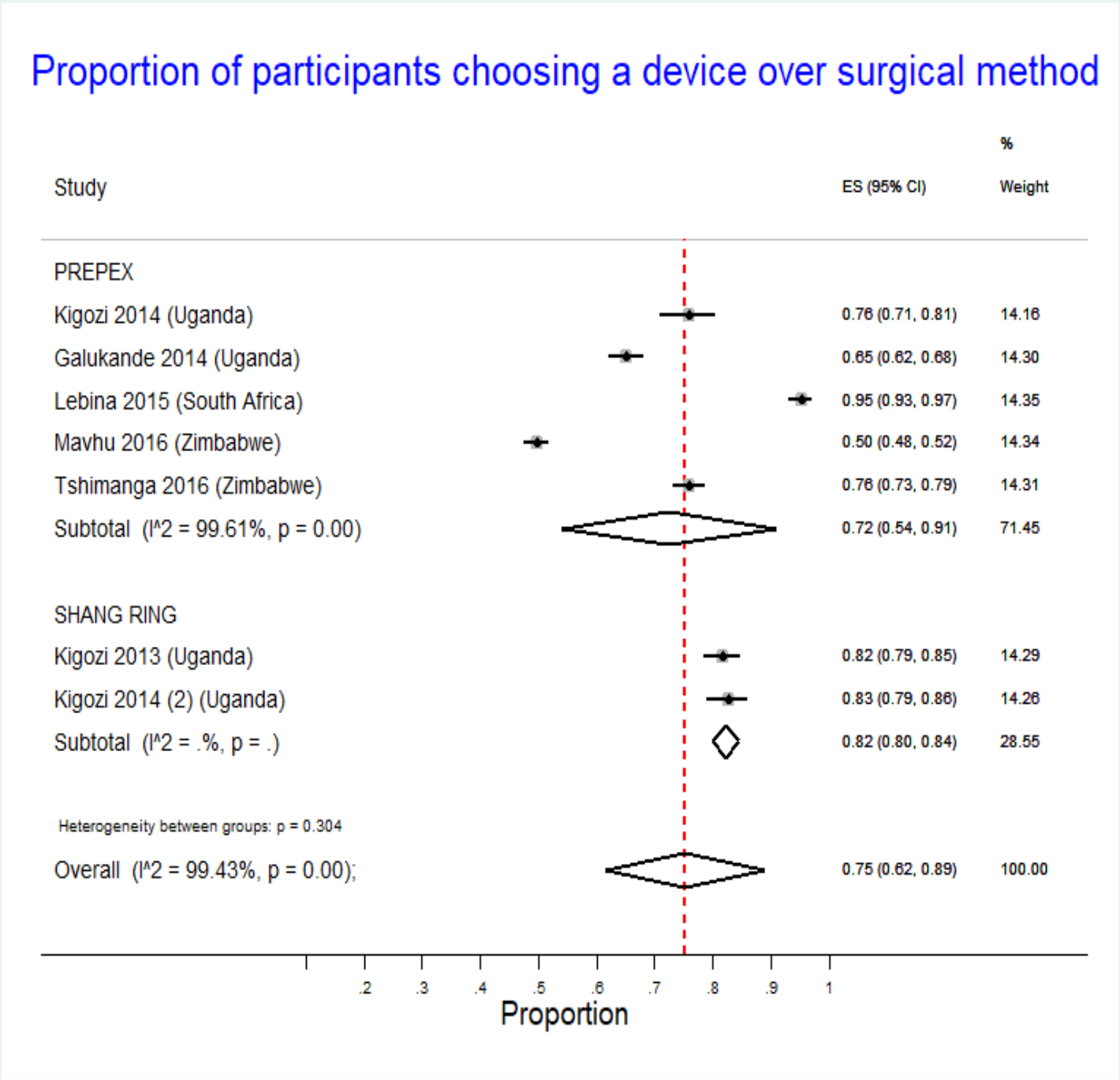
To calculate the uptake estimates, we double checked the proportions reported by individual studies by using the crude numerators and denominators of each study. Of the seven studies reporting uptake, three had explicitly presented an estimate for the uptake of the device method which was confirmed upon cross checking.[19, 65, 73] The remaining four articles didn't present the estimated proportions but crude numbers were used to calculate an estimate of the uptake.[71, 75, 76, 82]

Five studies used the Prepex device [19, 71, 75, 76, 82] as the intervention while the other two studies looked at Shang ring device [65, 73].

This review found the overall uptake of the two WHO-prequalified device methods to be 75% (95% confidence interval (CI): 62% to 89%) among adolescents and adults; test of heterogeneity, I^2 =99.43%, p=0.000; seven studies, total sample size = 5,998 (**Figure 7**). The uptake varied from 50% to 95%.

There was great similarity among the included studies in terms of design, populations, interventions, timeframe during which studies were conducted, and definition/reporting of outcomes which means it may be appropriate to compare outcomes across studies.

Figure 7: Overall choice of circumcision method among study participants:

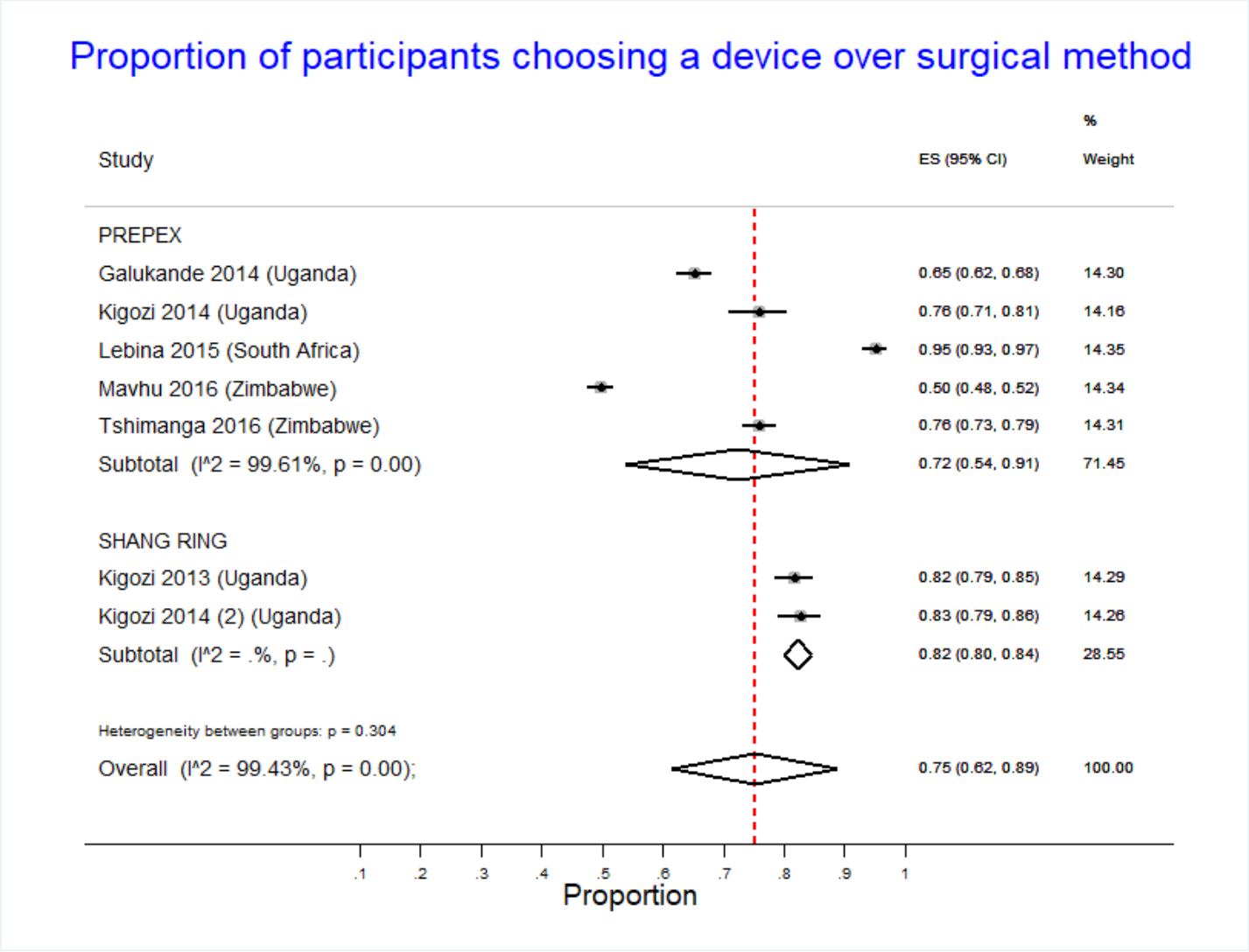


ES – Effect size; CI – Confidence Interval.

Sub analyses were subsequently performed to test the proportion estimates for uptake by either device method (Prepex or Shang ring) and by age of the participants. **Figure 8**

shows that the device specific uptake rates were 72% (95% confidence interval (CI): 54% to 91%) for the Prepex device; and 82% (95% CI: 80% to 84%) for the Shang ring device. The uptake of the Shang ring device appeared to be higher than that of the Prepex device and the difference between the proportions was statistically significant (p < 0.001). The difference may however, not be clinically significant due to the small number of studies reporting Shang ring uptake in comparison to the Prepex studies.

Figure 8: Overall choice of circumcision method among study participants stratified by device method:

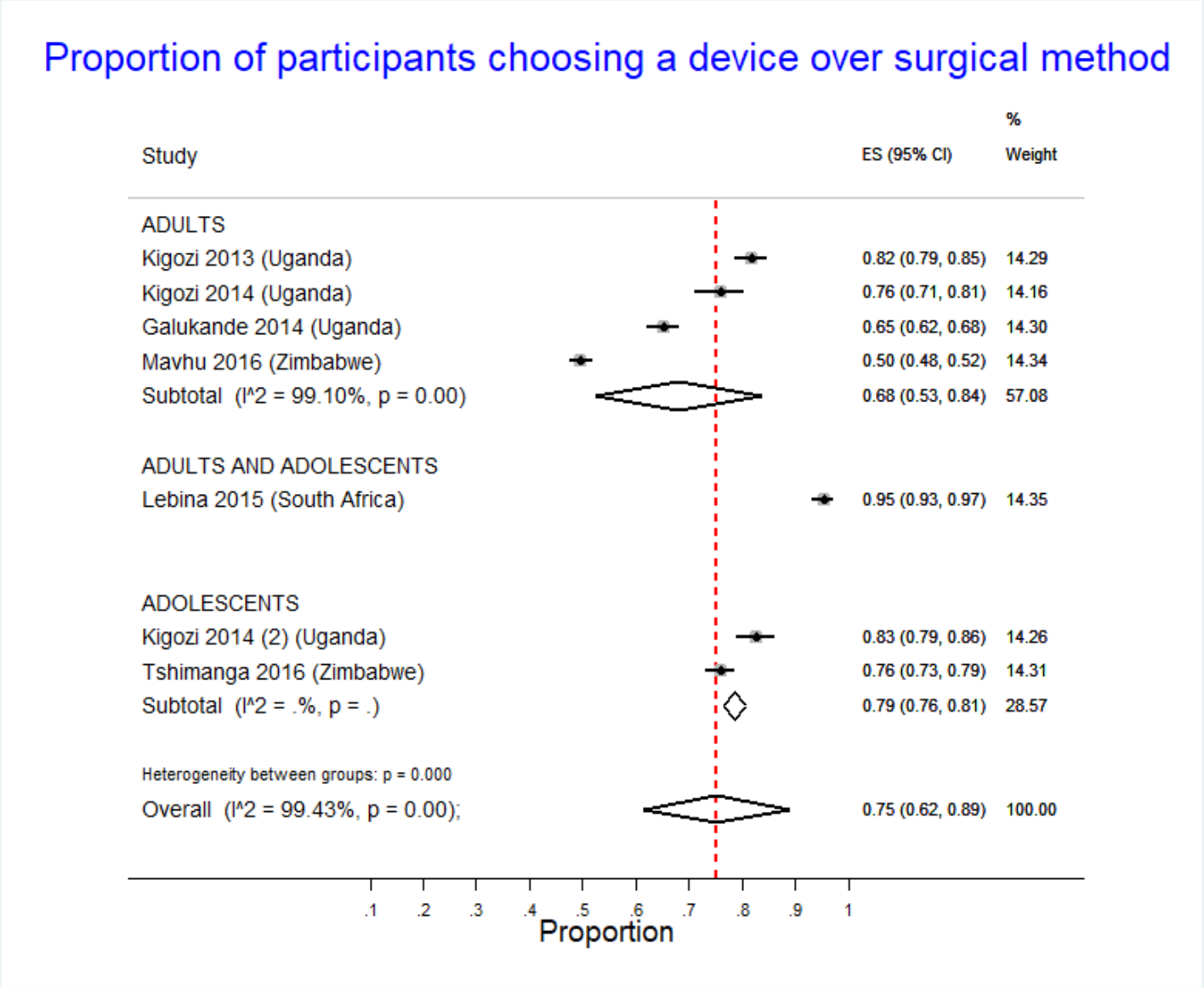


ES – Effect size; CI- Confidence Interval.

There were no studies reporting a direct comparison of uptake of the two devices. In one article the authors had intended to conduct a direct comparison study but they reported that the device manufacturers were unwilling to supply devices for a direct comparison study.[19]

When analysis was done by age groups, uptake of device methods among adolescents was slightly higher than among adults (**Figure 9**)

Figure 9: Choice of circumcision method among study participants by age category:



ES – Effect size; CI – Confidence Interval.

Heterogeneity of included studies:

There was substantial heterogeneity across studies included in the meta-analysis, I^2 = 99.43%. We intended to conduct a sensitivity analysis with respect to study quality, but this was not done as all studies had a moderate ROB. The heterogeneity between Prepex studies had an I^2 value of 99.61%. Limitations on the number of Shang ring

studies made it impossible to estimate the level of heterogeneity between Shang ring uptake studies.

Acceptability component:

Thirteen studies were based on the Prepex device while 8 explored the acceptability of the Shang ring device. Eighteen studies reported upon the proportion of participants expressing satisfaction with the device procedure or cosmetic outcome at the last study visit (**Figure 10**). Eleven studies reported on the proportion of participants that resumed their activities of daily living within 2 days of device placement (**Figure 11**). Fifteen studies reported a proportion of participants that would recommend the device procedure they had undergone either to a friend, relative or to their community (**Figure 12**). Only eight studies reported findings on all the three acceptability measures.

The fourth outcome measure of mean pain score at erection was reported in only seven studies. These studies used the visual analog scale (VAS) for assessing pain. The mean pain score on the VAS across the seven studies reporting upon pain was 3.4.

Figure 10: Acceptability of device circumcision: *Percentage of participants satisfied with the device procedure*

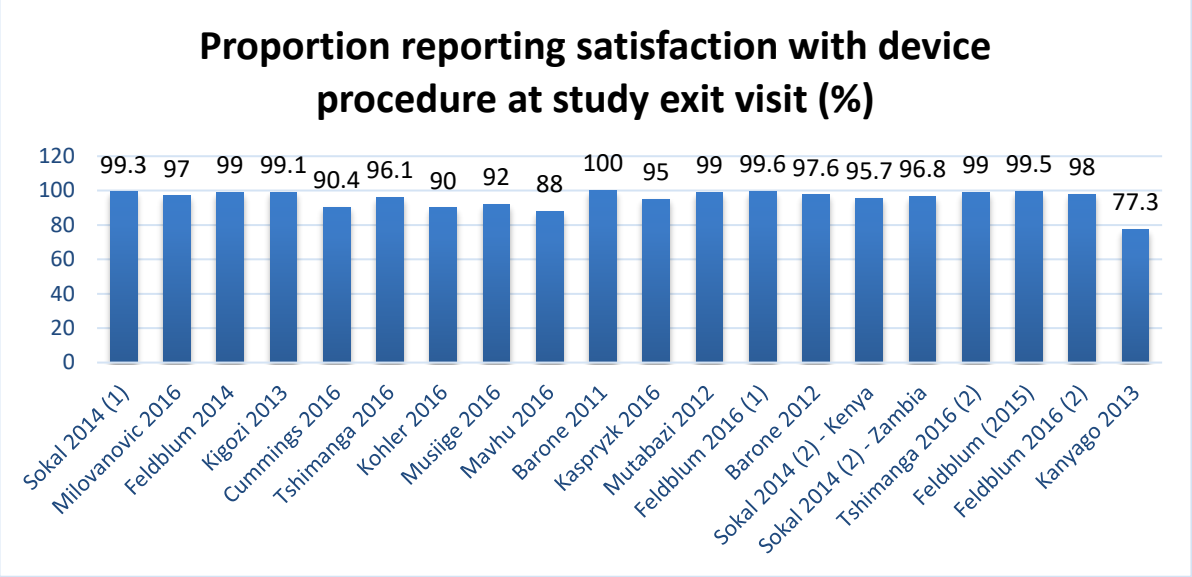
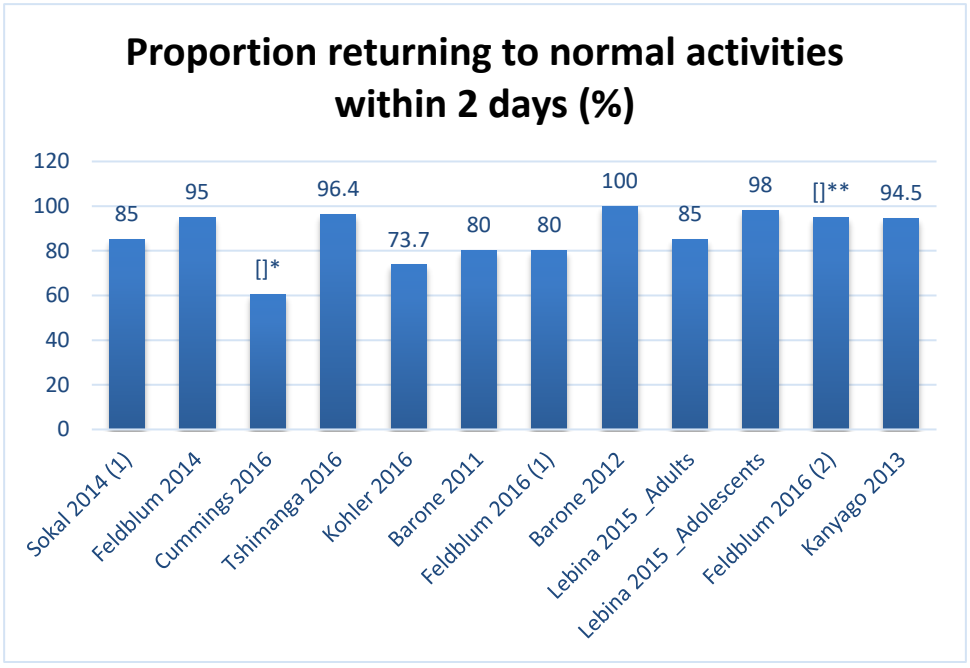
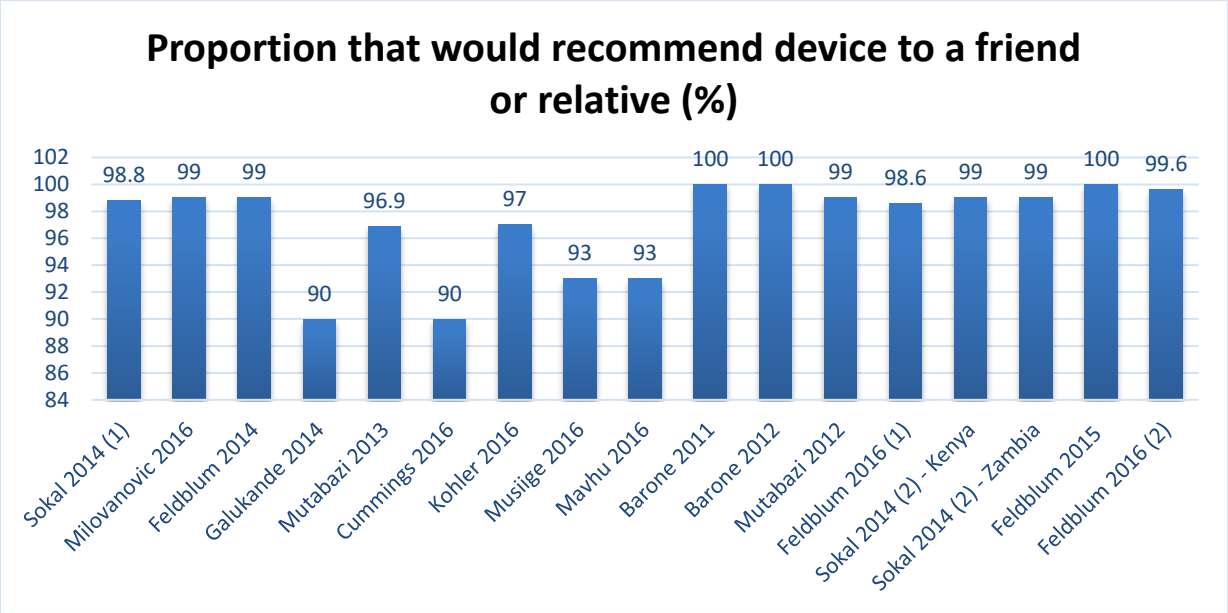


Figure 11: Acceptability of device circumcision: *Percentage of participants reporting resumption of activities of daily living within 2 days following the device procedure*



** Proportion returning to work within 1 day of the device placement; ** Proportion returning to work within three days of device placement*

Figure 12: Acceptability of device circumcision: *Percentage of participants that would recommend the device procedure to friends or their community*:



Age-range of participants:

Despite the intention to enroll participants up to the age of 54 in the adult studies, the median age of enrolled participants was generally low. This is similar to the client population seen in most VMMC programs which have recurrently had males over 25 years largely underrepresented [83]. It was not possible to test the potential contribution of age to heterogeneity because of very few studies enrolling only adolescents. The four studies that enrolled only adults, however, had significant heterogeneity with I^2= 99.1%

Discussion:

Summary of findings:

To our knowledge, this is the first systematic review to explore the uptake and acceptability of the two WHO-prequalified devices, Prepex and Shang ring among adolescent and adult males in Africa. Our review revealed that uptake of the two was very high among adolescents and adults. The two devices were also highly acceptable with majority of participants in the studies reporting favorable outcomes following circumcision using the device method. However, the overall risk of bias from the included studies was moderate implying that further research is likely to have an important impact on our confidence in the result.

All studies assessing the uptake of the circumcision devices reported had participants offered a choice of either surgical or device method following a detailed education session on the two methods. Participants in the uptake studies had no prior knowledge about the circumcision device methods before coming to the study facility. The high uptake of the two device methods was therefore observed in settings with little or no knowledge on different circumcision methods. The results suggest a high uptake of VMMC services is achievable in many settings if awareness of the circumcision devices is widespread. We were, however, unable to find evidence as to whether the high uptake of the devices had resulted into an increased uptake of VMMC services.

Our review found the uptake of the devices to be lower among older men in comparison to younger men. Utilization of VMMC services among older men remains low.[83] It was not surprising that younger men utilized VMMC services more than older men. The

younger men are a representative group of participants targeted by the VMMC programs.

Participants circumcised with either the Prepex or Shang ring devices were highly satisfied with the procedure and the post circumcision experiences, including wearing the device as well as after its removal. Men also reported high levels of satisfaction with the cosmetic outcome following complete healing. Men also reported to have resumed their normal activities of daily living within a short period following the device placement procedures. One reported dislike was the discomfort experienced due to pain on erection, but this was not reported to have deterred the participants from recommending the procedure to their friends or community.

We were limited in assessing the coverage of the two devices as the included articles lacked any primary study reporting the coverage of circumcision at country level by either of the prequalified device methods. Even the identified non-peer reviewed publications from the WHO could not be used to assess the coverage. The WHO publications did not report the coverage in numbers by methods used for circumcision. It was therefore not possible to establish proportions of circumcisions done by the two WHO-prequalified device methods, which had been a major intention of the review.

Most of the studies included in the review were conducted over a short duration of time which may not have been sufficient for comprehensive information relay, however, the implementation of VMMC programs has repeatedly demonstrated that interpersonal communication is a major way through which participants hear about services.

Strengths and limitations of included studies:

A major strength of this review is the comprehensive search that involved multiple databases including grey literature and a modification to the search strategy to ensure the inclusion of all relevant research. Piloting of the search strategy with all limitations to the data sources identified 23 papers for inclusion in this review. This was a surprisingly small number given the recent growth in research work regarding device circumcision among adults and adolescents. This however suggests there is paucity of published data on VMMC in the priority countries that were the study settings for the review. The search strategy was then broadened to include all articles reporting about the use of Prepex and Shang ring devices without any of the initially planned limitations. The broadened search strategy may have yielded a number of studies that did not address the search question, however, through vigorous screening, only those studies that were appropriate for answering one of this review's objectives were retained.

Another strength is that the data included in the review findings was cross-checked by another reviewer at various stages of the review process including screening, data extraction and quality of studies assessment. The rigorous screening and supplementation of the results of the electronic search with hand searching allows confidence in the conclusion that all relevant research was identified. The conclusions arising from this review can be therefore be regarded as based on a comprehensive synthesis of all available evidence.

We also systematically assessed all the available data using the most recently published standard tool for the assessment of quality in prevalence studies.

Significant heterogeneity in pooled prevalence estimates may be a limitation of this systematic review. The limited data did not however allow for us to completely explain the heterogeneity by carrying out further analysis. Thus caution must be exercised in drawing conclusions about the differences that were observed for uptake rates by device methods and by age group categorization.

Another potential limitation was that in nearly all studies, device circumcision procedures were performed as part of initial safety and efficacy pilot studies. A condition for these studies was that specific demand creation for device methods was not to be done, and this may have an effect on the uptake of device methods, information regarding which was only presented for the first time when participants arrived at the service sites.

Many of the included studies were performed for safety reasons and therefore, the uptake rates observed may be higher than those that would be obtained in surveillance studies.

Authors' conclusion and implications for programmatic considerations and research

The findings of this review provide encouraging results of the role that the two WHO-prequalified device methods could play in increasing uptake of services among the target population. All included studies reported a majority (50% or higher) of participants chose a device method when it was offered. Men that received a device circumcision procedure were highly satisfied with the procedure, able to resume their activities soon enough and were happy to recommend it to other people.

Although no evidence was found to demonstrate that devices increased VMMC uptake, the high uptake rates in a setting of non-device targeted demand promotion activities, may imply that the devices could increase overall uptake of VMMC services. Caution needs to be exercised however, because the studies were only done among participants that had voluntarily sought services and the attraction may not be similar among males that are undecided about undergoing circumcision.

The current evidence is insufficient to conclude whether or not the introduction of the WHO prequalified devices into VMMC programs are effective for encouraging the uptake of VMMC services. This was due to the non-availability of data regarding the proportion of circumcisions within VMMC programs performed using the two WHO prequalified device methods.

Lack of high quality evidence to suggest that the prepex and Shang ring device methods improve uptake of VMMC services within priority countries means there is insufficient evidence to support that conclusion. Future research should consider and address the methodological and conceptual limitations of currently published studies. It should aim to assess the proportions of all circumcisions within the priority countries that are completed using device methods. Such research should be adequately powered and should consider incorporating a longitudinal study design to ensure the most rigorous and conclusive findings.

Appendices:

Appendix 1: Key terms for each of the PICO components:

			Search terms
#1	Population	Adolescent and adult males circumcised	"Adolescent"[Mesh] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescents"[All Fields] OR "adolescence"[All Fields] OR "teenager"[All Fields] OR "teenagers"[All Fields] OR "Adult"[Mesh] OR "adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[
#2	Intervention	WHO-prequalified devices; Prepex device and Shang ring device	prepex[All Fields]) OR shang[All Fields] AND ring[All Fields]
#3	Comparator	Other circumcision methods	non-surgical[All Fields] OR methods"[Subheading] OR "methods"[All Fields] OR "techniques"[All Fields] OR "methods"[MeSH Terms] OR medical[All Fields] "Circumcision, Male/instrumentation"[Mesh] OR Gomco[All Fields] OR Mogen[All Fields] OR Plastibell* [All Fields] OR Accucirc[All Fields] OR Alisklamp[All Fields] OR Ali's Clamp[All Fields] OR Ali's Klamp[All Fields] OR Ismail Clamp[All Fields] OR Tara Klamp[All Fields] OR Unicirc[All

			Fields] OR Smartclamp[All Fields] OR SmartKlamp[All Fields]
	Outcome	Uptake	"Uptake"[Mesh] OR "Utilization"[Mesh] OR "Acceptability"[Mesh]
#5	Time	2000 to date	"2007/04/01"[PDAT] : "2017/02/28"[PDAT]

Appendix 2: Search strategy:

Database	Search Terms	Limits
PubMed	From key words above: #1 AND #2 AND #3 AND #4 AND #5	2007/04/01 to 2017/02/28
Cochrane Library	Adolescen* OR teenage* OR adult* in Title, Abstract, Keywords and Male Circumcision in Title, Abstract, Keywords and non-surgical techniques OR medical techniques OR prepex OR shang ring in Title, Abstract, Keywords (Word variations have been searched)	
EBSCO*host*	male circumcision AND adolescen* OR teenage* OR adult* AND prepex OR non-surgical techniques	
Web of Science	TOPIC: (Adolescen* OR teenage* OR adult*) AND TOPIC: (Male Circumcision) AND TOPIC: (non-surgical techniques OR medical techniques OR prepex OR shang ring	DocType=All document types; Language=English
Scopus	male circumcision AND adolescen* OR teenage* OR adult* AND prepex OR medical techniques OR non-surgical techniques	

Appendix 3: Proposed systematic review data extraction form:

The Uptake of the Prepex and Shang ring devices of male circumcision among adolescent and adult males in Africa			
Date form completed [dd/mm/yyyy]		[…. /…./……]	
A: General information			
Study ID (surname of first author and year of first full report of study was published e.g. Kakaire,2017)			
Name of extractor:			
Title			
Authors			
Contact details			
Publication type (e.g full report, abstract)			
References of potentially eligible studies from the reference list			
B: Eligibility			
Characteristics	**Yes**	**No**	**Comments**
Are participants aged 10 years and above			
Was a device method used to perform circumcision			

Does the study report uptake of device circumcision?				
Is the publication date between April, 2007 and Feb, 2017?				
Is it an English language article?				
Was circumcision performed in a health facility?				
Was the study conducted in a country among the 14 VMMC priority countries?				
If the answer to any of the above questions is NO, then exclude the study				
Decision taken	INCLUDE		EXCLUDE	
If no, give reason(s) for exclusion				
DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW				
C:Methods				
Aim(s) of the study				
Ethical approval obtained	Yes	No	Unclear	Not reported
	If yes, which institutional review board?(with approval number):			

D: Characteristics of study					
Type of study	Cross-sectional	Cohort studies		Case-control	
	Others(specify)				
Start date			End date		
Total study duration (from start of recruitment to end of study follow-up)					
Inclusion criteria					
Exclusion criteria					
Setting (e.g. rural /urban/semi-urban etc.)					
Method of recruitment of participants					
Informed consent	Oral	Written	Not done	Done, but method not reported	Not reported
Profession of circumcisers	Medical doctors	Professional nurses	Nursing assistants	Other cadre	
Participants	Description as stated in the paper				
Total number enrolled					

Withdrawals, exclusions and loss-to-follow up			
Give reasons for withdrawals, exclusions or loss-to-follow up			
Age	Range		
	Mean(standard deviation)		
	Median		
Intervention(s):			
Name of device method used			
Comparator: Yes / No			
Outcome measures			
Circumcision coverage		Number or % of males who requested VMMC and underwent a circumcision procedure among all males eligible	
Uptake of WHO prequalified circumcision devices		Number or % of individuals circumcised choosing either the Prepex and Shang ring devices of all circumcised patients	

Factors influencing choice of circumcision by a WHO prequalified device method	Facilitators				Barriers	
Outcomes:						
Total number of males seeking circumcision						
Number males eligible for medical circumcision						
Reasons for ineligibility						
Males circumcised by a device method	Prepex		Shang ring		Other device method	

E: Risk of bias assessment						
Does the study have a high risk of:						
Selection bias?	Yes		No		Unclear	
Performance bias?	Yes		No		Unclear	
Detection bias?	Yes		No		Unclear	
Attrition bias?	Yes		No		Unclear	
Reporting bias?	Yes		No		Unclear	
Other concerns about bias?	Yes		No		Unclear	
Are study results valid?	Yes		No		Unclear	

F Miscellaneous					
Funding source	Name				
	A source of bias?	Yes	Probably	Probably not	No
Key conclusions of the study authors					

Appendix 4: Risk of bias and quality assessment tool for prevalence studies:

Items	**Score**
External validity	
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 Point
2. Was the sampling frame a true or close representation of the target population?	1 point
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 point
4. Was the likelihood of non-response bias minimal?	1 point
Total	4 points
Internal validity:	
1. Were data collected directly from the participants (as opposed to a proxy)?	1 point
2. Was an acceptable case definition used in the study?	1 point
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
4. Was the same mode of data collection used for all participants?	1 point
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 point
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 point
Total	6 points

Appendix 5: Results of PubMed search:

Subject	Search terms	Output
English language limitation	English	240
Time limitation to 2007 and after	2007/01/01 to 2017/12/31	252
Outcomes included	acceptability OR acceptance OR utilization OR uptake OR coverage	328
Interventions	"Circumcision, Male/instrumentation"[Mesh] OR "Circumcision, Male/methods"[Mesh] OR "Circumcision, Male/standards"[Mesh] OR "Circumcision, Male/statistics and numerical data"[Mesh] OR "Circumcision, Male/therapy"[Mesh] OR male circumcision devices OR non-surgical circumcision OR male circumcision instrumentation)) OR "shang ring" OR prepex (1550)	689
Age of participants	adult OR adolescent OR teenager OR teenagers OR adults	7,291,509

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