Voluntary Medical Male Circumcision for Reducing HIV Incidence among Men Who Have Sex with Men

By

Chen Zhang

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Epidemiology

May, 2017

Nashville, Tennessee

Approved:

Dr. Sten H. Vermund, Ph.D., M.D.

Dr. Han-zhu Qian, Ph.D.

Dr. Bryan Shepherd, Ph.D.

Dr. David Penson, Ph.D.

Dr. Glenn Webb, Ph.D.

To my beloved family and parents

For their continuing encouragement and support

ACKNOWLEDGEMENTS

Striving through the vigorous and challenging trail of accomplishing the highest degree in my devoted area of interest, I have always been grateful for numerous people who have been providing me with valuable training, mentorship, assistance, opportunities and support. My progress would not be accomplished without these efforts and blessings.

First and foremost, I would like to express the most sincere gratitude to my research mentor and Chair of my dissertation committee, Dr. Sten H. Vermund. I greatly appreciate and learn from every conversation with Dr. Vermund to discuss my research projects and dissertation for his critical challenge, creative idea, visionary suggestions and tremendous patience. I am also very thankful for my mentor, Dr. Han-zhu Qian, for his great efforts to address every question I had during my research activities, and his timely revisions and feedbacks for all the manuscripts and dissertation drafts. I would also like to thank other committee members for their time and effort on my dissertation, including Dr. Glenn Webb, especially for his assistance to the mathematical building; Dr. Bryan Shepherd, especially for his statistical support; and Dr. David Penson for his assistance in decision analysis including the budget-impact analysis.

I sincerely owe my earnest thankfulness to the Ph.D. program in Epidemiology at Vanderbilt University that provided me a stage for further training; and the current/former faculty members at Vanderbilt (Drs. Katherine Hartmann, Robert Greevy, Aaron Kipp, Christ Slaughter, Meira Epplein, Alicia Beeghly-Fadiel, Melinda Aldrich, Pingsheng Wu, Kristin Archer, Stephen Deppen, and Yu Shyr) who provided me with

cutting-edge coursework training for the growing of my intellectual curiosity and academic ability. My thankfulness also goes to the former program coordinator, Ms. Amanda Harding, who offered generous assistance for all the academic logistics and management work.

I am also grateful for all the faculty and staff at Vanderbilt Institute for Global Health, with whom I felt embraced in a comfortable and supportive environment every day. Specifically, I would like to thank Ms. Jennifer St. Clair for her arrangements of my meetings with Dr. Vermund; Ms. Bea Smith for helping me with a variety of logistics; Ms. Holly Cassell for all the administrative efforts, and Donna Ingles and Donna Miller for their help on my DP5 application.

Finally, this work was supported the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award numbers R01A1094562(S. Vermund, PI), R34A1091446 (S. Vermund, PI), and P30A1110527(S. Mallal, PI). My stipend was supported by the Vanderbilt International Scholarship Program and by the endowment from the Amos Christie Chair in Global Health, held by Dr.Vermund.

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

Figure Page

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
HIV	Human immunodeficiency virus
MSM	Men who have sex with men
OR	Odds Ratio
RR	Relative risk
STD	Sexually transmitted diseases
STI	Sexually transmitted infection
VMMC	Voluntary medical male circumcision
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

CHAPTER I

BACKGROUND

HIV epidemic in China

Based upon a newly released report from the Chinese government, the number of people living with HIV/AIDS (PLWHA) in China was 501,000 by the end of 2014 (UNAIDS & MoH, 2015). Although the national HIV epidemic categorizes China as a low-prevalence country, the trend of increasing pattern remains. For instance, the reported cases of PLWHA has increased from 272,000 in 2009, 307,000 in 2010, 352,000 in 2011, 386,000 in 2012, 437,000 in 2013, to 401,000 in 2014 (NHFPC, 2014, 2015). The sharp increase of the epidemic among several high-risk groups indicates a serious and rapidly deteriorating situation (NHFPC, 2014).

Role of MSM in the HIV epidemic in China

The most common transmission route for the HIV/AIDS epidemic in China has been shifting from injection drug use and contaminated plasma collection to unprotected sexual contacts in the last decade (Guo, Li, & Stanton, 2011; UNAIDS & MoH, 2015). The rapid increase in homosexual transmission is of a particular concern (Chow, Wilson, & Zhang, 2011a; Lu et al., 2013; J. R. Wu et al., 2013; Ye et al., 2012). Although the dominant route is still heterosexual transmission, homosexual transmission among MSM

shows a marked uptrend. Accordingly, the male homosexual proportion of new infections increased from 2.5% in 2006 to 25.8% in 2014 (NHFPC, 2014, 2015). In addition, the homophobia is prevalent and stigma against MSM is significant. In addition to the unstructured surveillance system in China, makes the HIV epidemic among MSM very likely to be underestimated (Lou et al., 2014; Z. Wu et al., 2013; Y. Zhou et al., 2014).

Risk factors among MSM

A series of biological, behavioral and structural risk factors are embedded in the life context of MSM (Guo et al., 2011; Vermund & Qian, 2008). At the individual level, condomless receptive anal sex has been considered the most significant risk factor for HIV infection (Jin et al., 2010). Circumcised men who primarily conduct insertive sex have lower risk compared with their uncircumcised peers (Jin et al., 2010). Furthermore, MSM reporting substance use (Xu et al., 2014), multiple sex partners (Cheng et al., 2014; Chow et al., 2013), and psychological distress (Jiang, Cai, Pan, & Ma, 2014) are more susceptible to HIV infection. It is probably because these risk behaviors are markers for impaired decision-making, high risk taking, poor coping and low self-efficacy. At the intrapersonal and community level, MSM who encountered partner violence (Sabido et al., 2015), lacked access to HIV testing (Vutthikraivit, Lertnimitr, Chalardsakul, Imjaijitt, & Piyaraj, 2014), reported less social support from families and friends, and being socio-economically disempowered (Steward, Miege, & Choi, 2013), were more likely to contract with HIV.

At the social level, prevalent homophobia and stigma forces many MSM to hide their true identity and presents barriers for their seeking appropriate and timely healthcare (C. Wei et al., 2013). MSM experience even more severe stigma and discrimination in contexts highly influenced by Confucianism, such as China.

In China, men are supposed to fulfill their filial piety (In Confucian philosophy, filial piety is a virtue of respect for one's parents, elders, and ancestors). Therefore, majority of MSM will hide their true identity by getting married and having offspring to carry their family names (Steward et al., 2013). Homosexual behaviors are not viewed as a personal choice, but as evidence of moral weakness(Steward et al., 2013) Approximately more than half MSM in China live a "double life" by marrying with a woman to hide their true sexual identity, especially for the older ones (Pando et al., 2013a). The hidden identity may further exacerbate the epidemic by preventing MSM from seeking for health care and HIV prevention outreaches.

HIV prevention interventions among Chinese MSM

Although the ever-increasing HIV epidemic explodes among Chinese MSM, no effective interventions are available (Guo et al., 2011). Condoms can effectively prevent HIV transmission, but only 20% MSM consistently use condoms during sexual activities (Guo et al., 2011; Zheng, 2009). Pre-exposure prophylaxis (PrEP) can be used by uninfected MSM, but uninfected individuals do not like to take antiretroviral drugs, and side effects discourage adherence. Therefore, VMMC might be a biomedical prevention that provides lifelong protection after a single procedure(Vermund & Qian, 2008).

Mechanisms of VMMC in preventing HIV transmission

Circumcision is likely to protect men from acquiring HIV by eliminating the most vulnerable mucosal surface areas and HIV target cells in a minimally keratinized zone, the inner surface of the penile prepuce(Donoval et al., 2006; Vermund & Qian, 2008). Both observational studies and large randomized controlled trials (RCT) have shown that voluntary medical male circumcision (VMMC) reduces the risk of HIV acquisition by over half in heterosexual men living in high prevalence areas of Africa(Auvert et al., 2005; Bailey et al., 2007; R. H. Gray, Kigozi, et al., 2007). Although the evidence on the relationship between VMMC and HIV risk among MSM has been inconclusive, protective effects were observed among men who practiced insertive sex (Beyrer, 2010a; Doerner et al., 2013b; Fankem, Wiysonge, & Hankins, 2008; Gust et al., 2010; Jameson, Celum, Manhart, Menza, & Golden, 2010a; Jozkowski et al., 2010; Londish, Templeton, Regan, Kaldor, & Murray, 2010b; Sanchez et al., 2011; Schneider et al., 2012b; Wiysonge et al., 2011; C. Zhou et al., 2012). Therefore, circumcision may be considered a cost-effective biomedical tool, which is viable to add it to a critical layer of enhancing prevention intervention among MSM.

A series of observational studies and three randomized controlled trials (RCT) conducted in sub-Saharan Africa have proven the promising effectiveness of VMMC against HIV among heterosexual men (Auvert et al., 2005; Bailey et al., 2007; R. H. Gray, Kigozi, et al., 2007; Millett, Flores, Marks, Reed, & Herbst, 2008; Wiysonge et al., 2011). A meta-analysis of RCT data, suggested 56% reduction in the relative risk (RR=0.44, 95%CI=0.33-0.60) among circumcised men compared to their uncircumcised peers (Mills, Cooper, Anema, & Guyatt, 2008). Their conclusion gained support from

another meta-analysis of 27 studies based upon observational data (Weiss et al., 2008; Weiss, Quigley, & Hayes, 2000). After adjusting potential confounders, the authors found a strong association between VMMC and reduced relative risk (RR=0.42, 95% CI=0.34-0.54).

The role of VMMC in preventing HIV infection among MSM is controversial (Millett et al., 2008; Qian et al., 2015; Vermund & Qian, 2008). For instance, two studies conducted in areas with dense HIV prevalence, VMMC was found to reduce HIV risk significantly among MSM (Schneider et al., 2012a). Even among males who primarily conducted receptive sex, circumcision exerted a significantly protective effect (Schneider et al., 2012a). However, as indicated in a meta-analysis, the effects of VMMC against HIV infection were not significant among this at-risk population (Wiysonge et al., 2011). Furthermore, the potentially protective evidence of VMMC in MSM studies with the less rigorous study design, favors further investigators of this strategy for HIV prevention among this population. On the other hand, a most recent study conducted in 2015 among MSM in Beijing revealed the strongest protection effect among Chinese MSM who predominately practice insertive sex (aOR=0.15, 95%CI=0.04, 0.65). This study suggested that circumcision was significantly associated with lower odds of HIV infection among MSM practicing insertive anal sex, with a strong beneficial trend for other MSM as well, providing the strongest evidence to date that VMMC might be a useful biomedical tool for HIV risk reduction among MSM.

Feasibility of scaling up VMMC among MSM in China

Although VMMC has been considered as a medical practice that specifically applied to men with phimosis and redundant prepuce in China for a long time, with the increasingly scaling-up educational programs launched, many people have recognized its protective effects for HIV and other sexually transmitted diseases (STD). Based upon several studies conducted among Chinese males, the willingness of VMMC uptake ranged from less than one-third among male miners in Guangxi (F. M. Wei et al., 2012), to more than two-thirds among general male population who received an intervention for circumcision promotion (Luo et al., 2011; Ruan et al., 2009). In studies conducted specifically among MSM, their willingness for receiving VMMC is consistent with the general population, among whom two-thirds of them expressed their willingness of accepting the VMMC as a strategy to prevent HIV and other STD (Lau et al., 2011; Luo et al., 2011). In addition, younger MSM tend to be less influenced by the Chinese traditional culture and are more likely to accept new ideas and challenge the status-quo (Liu H, 2001). For instance, compared with MSM who were 40 years or older, only 11% of younger MSM got married, which was only one-fifth of the older MSM (11% vs. 64%) (Chow, Wilson, & Zhang, 2011b).

In addition, well-designed interventions can facilitate greater willingness of accepting VMMC among MSM in China (Lau et al., 2012). For instance, an intervention successfully increased the willingness of up-taking circumcision from 8.1% to 35.1% among a group of bisexual MSM in Southern China (Lau et al., 2012). Furthermore, newborn circumcision in western countries (e.g., United States) has made great contribution to curbing the HIV epidemic among at-risk population (Matar, Zhu, Chen, &

Gust, 2015; Young et al., 2012). Therefore, with appropriate strategies, the potential of promoting VMMC among of MSM in China is promising, especially among the younger generation.

CHAPTER II

SPECIFIC AIMS AND SIGNIFICANCE

Specific Aims

The primary objective of this research project is to evaluate the protective efficacy, epidemiological and economic impacts of voluntary medical male circumcision as an intervention strategy to reduce HIV infection among MSM population in China. Therefore**, (1)** we will conduct a systematic review and meta-analysis to evaluate the protective efficacy of the association between male circumcision and HIV infection among MSM with a series of sensitivity analyses; **(2)** we will employ a transmission model to assess the epidemiological impact of VMMC by projecting the HIV incidence for the next decade among MSM in Beijing; and **(3)** we will determine the budget-impact of VMMC program by a decision-modeling strategy.

Aim 1: To conduct a systematic review and meta-analysis to assess the association between VMMC and HIV infection among MSM. We will systematically review and conduct meta-analyses of outcomes in observational studies, and to summarize the magnitude of association between VMMC and HIV infection among MSM. In addition, stratified subgroup analyses will be employed to examine if the effect of VMMC differs by different characteristics of individuals and settings, including sex position (receptive vs. insertive), study design (cross-sectional vs. studies with follow-

ups), geographical regions (Asia vs. non-Asia; Asia+African vs. non-Asia/non-Africa), assessment methods (self-reported vs. medical exam), and sample size at baseline (<=3000 vs. >3000).

Aim 2: To project HIV incidence for the next decade among MSM in Beijing using a transmission model. We will employ a deterministic compartmental modeling procedure to fit prevalence from 2005-2015. We will project new HIV cases during 2016-2026 under different coverage rates ranging from 0.0001 (at baseline) to 0.15 (an optimistic assumption) with simulation on varying transmission rates, model calibration to match historical data, and sensitivity analyses for several assumptions. We hypothesize that projected HIV incidence among MSM in Beijing will be reduced by greater use of VMMC.

Aim 3: To assess the economic impact of scaled-up VMMC program in China. We will use a deterministic compartmental model to project new HIV cases (2016-2026) under circumcision coverage rates (λ) ranging from 0.0001 (very low coverage at baseline) to 0.15 (15% of MSM circumcised/year). We will conduct simulations using varying transmission rates. The ratio of the number of VMMC per new HIV case averted was the indicator used for the budget-impact analysis. The lower this ratio, the more economical VMMC would be for HIV prevention among MSM.

In summary, Aim 1 evaluates the protective efficacy of the VMMC and assesses whether VMMC is associated with lower HIV risks, and provides the efficacy data for the Aim 2 and Aim 3. Aim2 projects HIV incidence/prevalence for the next 10 years using a HIV transmission model, which can serve as the foundation for Aim 3. Aim 3

evaluates the economic impact of VMMC scale-up among MSM in China. With the assistance of Aim 1-3, decision-makers can comprehensively assess the efficacy and effectiveness of VMMC among MSM.

Significance of Aim 1

Two previous published meta-analyses have examined the efficacy of protection of VMMC among MSM in the past few years. The earlier meta-analysis of 15 studies from VMMC interventions demonstrated that there was insufficient evidence that male circumcision protected against HIV infection or other STIs among MSM (Millett et al., 2008). In the later meta-analysis of 21 studies examined the effect of VMMC by sexual position (insertive vs. receptive) and found a strong protective effect among MSM who primarily practice insertive anal sex (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.17-0.44) (Wiysonge et al., 2011). Since then, with the increasing emphasis on VMMC strategy among MSM, several more studies with rigorous design have been published (Pando et al., 2013b; Templeton, Millett, & Grulich, 2010; Thornton, Lattimore, Delpech, Weiss, & Elford, 2011; Zeng et al., 2014), including the study indicating the strongest protective effect of VMMC in Chinese MSM to date (Doerner et al., 2013a; Qian et al., 2015). In addition, neither of the meta-analysis have assessed the context specific characteristics (e.g., Asia vs. non-Asia; resource-rich vs. resource-limited settings; high-prevalence vs. low-prevalence; receptive vs. insertive), which can provided more specific and tailored information for interventions in future. The efficacy and effectiveness of VMMC may differ by settings with different social, cultural, and contextual

characteristics. To date, we have seven articles from Asia, twenty-four articles from non-Asian countries; eight addressed in the resource-limited settings vs 23 in resource-rich settings; five conducted among high-prevalence countries vs. 26 among low-prevalence countries; five examined the effect of insertive-position, and nine assessed the effect of receptive position. Therefore, we have sufficient resources to provide context-specific effect of circumcision among MSM. Furthermore, with the efficacy of protection from the meta-analysis, we can use them as parameters in the following mathematical model and cost-effectiveness analysis.

Significance of Aim 2

The Mathematical modeling approach has been used to estimate the impact of VMMC on reducing HIV risk among MSM in Beijing, China (Group, 2009).Several studies utilized parameters in published studies to project key factor pertaining to HIV epidemic including HIV incidence, prevalence, and number of male circumcision required for each infection averted (R. H. Gray, Li, et al., 2007; Group, 2009; Hallett et al., 2008; Nagelkerke, Moses, de Vlas, & Bailey, 2007; White et al., 2008; Williams et al., 2006). However, most available studies were conducted in African settings among heterosexual populations. Very few studies examined the impact of VMMC among MSM. One mathematical model simulated and projected HIV epidemic in the next ten years among MSM in Beijing under different scenarios of combination of intervention strategies including uptake of HIV testing, linkage, ART initiation, and condom use (Lou et al., 2014). Another recently published study specifically examined whether male

circumcision had an impact on HIV epidemic in MSM in Peru (Goodreau et al., 2014). By stratifying three levels of insertive sex (e.g., 100%, >80% or >60%) during condomless anal sex and two levels of uptakes of circumcision among eligible men (e.g., 25% or 50%), investigators concluded that introducing circumcision programs among MSM would not mitigate the HIV epidemic in Peru. However, authors made an assumption that overly underestimated the efficacy of VMMC among MSM without considering a most recent study with strongest efficacy to date (Qian et al., 2015).

Although these studies have either addressed the male circumcision or conducted among MSM, none of them specifically addressed the impact of VMMC among MSM in the setting of China, which has a significantly different social, cultural and epidemic environment, for example VMMC is not a traditional practice among Chinese men, and VMMC use is low. Establishing a HIV transmission model, we can evaluate the projected epidemiological impacts of VMMC among MSM in Beijing City, China

Significance of Aim 3

To assess long-term population-level impacts of expanding VMMC among MSM, we should consider the balance between costs (e.g., numbers of VMMC performed) and impact (e.g., numbers of new HIV cases averted). The United States Agency for International Development (USAID) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have developed a modeling tool called “Decision Makers’ Program Planning Tool” (DMPPT) to facilitate decision makers’ estimates of the epidemiological impact and cost of alternative programmatic options for scaling up

VMMC (Kripke & Njeuhmeli, 2016; Kripke et al., 2016; Njeuhmeli et al., 2011). However, these model-based studies only focused on heterosexual sexual men in specific settings with generalized HIV epidemics, e.g., African nations (Bollinger et al., 2009; Kripke & Njeuhmeli, 2016; Njeuhmeli et al., 2011; Stover et al., 2016).

The DMPPT model assumes the HIV incidence rate to remain constant during the prediction period, resulting in potentially over- or underestimating the impact of VMMC (Kripke et al., 2016). To date, no analogous modeling studies have specifically addressed the potential utility of circumcision programs targeting MSM; given the lower prevalence of VMMC in China and comparatively low to moderate risk profiles among MSM (Beyrer et al., 2012; Vermund & Qian, 2008; Zhang, Qian, Liu, & Vermund, Under review), it is conceivable that VMMC would have a greater impact than in areas of high circumcision prevalence (e.g., the United States) or in areas where at-risk MSM have higher risk behaviors. In order to assess context-specific impacts of VMMC among MSM in China, we conducted the current cost-minimization analysis assess the extent to which expanding VMMC programs might reduce HIV incidence among MSM, addressing costs and cost-effectiveness.

CHAPTER III

DATA AND METHODOLOGY

Aim 1

Overview

Aim 1 is to conduct a systematic review and meta-analysis to assess the efficacy of circumcision in preventing HIV infection presented in existing literature.

The **primary research question** is formulated as 'can VMMC effectively reduce acquisition of HIV among MSM?' VMMC is a procedure to remove the foreskin that covers the head of the penis. As the inner part of the foreskin is highly susceptible to HIV infection, removal of the foreskin of infants, adolescents and adults by trained health professionals can help reduce the chance of HIV acquisition among males (Reynolds et al., 2004; Vermund & Qian, 2008). Acquisition of HIV is measured by either self-reporting or blood testing. My overall hypothesis is 'MSM who receive the VMMC are less likely to have HIV acquisition compared to these who don't receive the VMMC'. My **secondary research question** is whether the effect of VMMC on preventing HIV infection varied by individual (e.g., receptive verse insertive sex positions), contextual (e.g., Asia vs. Non-Asia; Asia+Africa vs. non-Asia and non-Africa), and study-design characteristics (e.g., sample sizes, sampling strategies). Details are discussed in the following subgroup analyses.

Eligibility criteria

Generally, studies that meet the following criteria will be included in the systematic review and meta-analysis: (1) Original studies published in English or in other languages (e.g., English, Spanish) between 1985 and 2016; (2) provided quantitative measurement of the effect of circumcision on HIV infection; (3) provided sufficient information to calculate effect size estimates; (4) conducted exclusively among MSM, or MSM subgroup from the total sample of the study; and (5) used a rigorous study design (e.g., randomized control trials, cross-sectional studies, longitudinal studies, observational studies). More specific criteria are presented in the following PICOS table. Exclusion criteria include (1) descriptive studies without quantitative outcomes; (2) studies with only qualitative outcomes; (3) studies that are not focused on MSM population; and (4) not original research.

Literature search and study selection

A preliminary search will be conducted in PubMed to test and refine the search keyword as well as identify amount of relevant literature. Preliminary search keywords (Mesh terms) include: ("HIV"[Mesh] OR "HIV"[tiab] OR "HIV Infections"[Mesh] OR "HIV Antibodies"[Mesh] OR HIV-1[tiab] OR HIV1[tiab] OR HIV-2[tiab] OR HIV2[tiab] OR "HIV/AIDS"[tiab] OR "Sexually Transmitted Diseases, Viral"[Mesh:NoExp] OR "human immunodeficiency virus"[tiab] OR "human immunedeficiency virus"[tiab] OR "human immune deficiency virus"[tiab] OR "AIDS"[tiab] OR "acquired immunodeficiency syndrome"[tiab] OR "acquired immunedeficiency syndrome"[tiab] OR "acquired immune deficiency syndrome"[tiab]). The following table illustrates the searching procedure. In addition, an exploration of

'related study' will be performed to retrieve additional relevant articles that are missed by keyword-searching strategy.

Comprehensive literature search

Twelve electronic databases will be searched. They are: AMED(Allied and Complementary Medicine Database, Ovid Technologies, Inc., New York), BIOSIS Previews (Biological Abstracts & Biological Abstracts/RRM, Thomson Scientific Technical Support, New York), British Nursing Index (Ovid Technologies, Inc., New York), EMBASE (Elsevier, Amsterdam, The Netherlands), EconLit (The American Economic Association, New York),ERIC (Education Resources Information Centre, Institute of Education Sciences of the U.S. Department of Education, Washington), Ovid Medline (Ovid Technologies, Inc., New York), PsycINFO (American Psychological Association, Washington), Scopus(Elsevier, Amsterdam, The Netherlands), Web of Science (Thomson Scientific Technical Support, New York). In addition, I will also employ strategies like hand searches of key journal, harvesting reference, and forward citation searching to comprehensively search available articles.

Grey literature search

Potential grey literatures will be searched through conference proceedings (e.g., APHA, IAS, AIDS-IMPACTS), governmental reports (e.g., WHO, UNAIDS), research reports, books and book chapters, libraries and archives, contacts with experts in the relevant field, explorations from organization websites, and ascertainment of relevant thesis via online resource. As supplements, I will also search databases like Cochrane

HIV/AIDS Group and Google Scholars. If anything unclear, I will contact with original authors for further information.

Management of literatures

All titles and abstracts will be reviewed by two independent reviewers (CZ and YL) to determine whether the papers are relevant to the topic. Those considered irrelevant by both of the reviewer will be excluded. Then full texts of potentially relevant articles will be downloaded for further eligibility examination. Disagreement between reviewers will be resolved by discussion. Duplicates will be identified and removed. All included studies will be managed by Endnotes X7 (Thomson Reuters, 2014).

Study selection and data extraction

Based upon inclusion and exclusion criteria (section 4.2.2), we will select all eligible studies for the following data extraction procedure.

Two reviewers will independently extract data from qualified articles using a standard screening form and developed a table containing the following information: 1) study location and time of conducting the study, 2) characteristics of participants (e.g., age, ethnicity), 3) sample size, 4) HIV infection (e.g., either self-report or lab work), 5) circumcision assessment (either self-report or genital examination), 6) sex positions if applicable (e.g., receptive vs. insertive), and 7) other information (e.g., inconsistent condom use, multiple partnership).

When information regarding any of the above information is unclear, we will contact the original authors of the included articles for further detailed information. For studies

with duplicate publications, we will report the study only once in the analyses.

Assessment of risk of bias of included studies

Although Cochrane Handbook (Higgins JPT, 2011) has provided an empirical approach for assessing both internal and external validity of included studies, the approach is more appropriately for studies with randomized control trials (RCT). As majority of studies in the current review are observational studies which may have more inflated estimates than trials, I adopt an approach developed by RTI–UNC Evidence-based Practice Center with the following criteria (ND et al., 2013) (Table 3).

Statistical analysis plan

Effect size calculation and aggregation

All calculated effect sizes (e., crude odds ratios and adjusted odds ratios) and standard errors (e.g., the square root of the variance) will be also be coded together with the above information in an EXCEL file, and will be converted to Stata file for further meta-analyses.

The major outcome of interests is the effect of VMMC on HIV infection. As all outcome variables were displayed as ORs with their 95% confidence intervals (95%CIs). For studies reporting raw data on HIV infection by their circumcision status, we calculated the OR and 95%CI directly. For studies without providing the raw data, we employed either reported crude or adjusted ORs with relevant 95%CIs from the text. For studies reported RRs, we can transfer RRs to ORs using the standard formula. For

prevalence less than 10%, RRs can be approximately equal to ORs (M. Borenstein, L. V. Hedges, J. P. T. Higgins, & H. R. Rothstein, 2009).

Choice of analytical model

In the current analysis, I will choose the random-effects model as included studies will differ in terms of characteristics of participants (e.g., older vs. younger, more educated vs. less educated) and study settings (e.g., Asian vs. non-Asian). It is possible that the true effect size varies from study to study. Random-effects model captures a distribution of true effect sizes and estimates the mean of this distribution (Borenstein, Hedges, Higgins, & Rothstein, 2010; Borenstein & Higgins, 2013; Nikolakopoulou, Mavridis, & Salanti, 2014).

Alternatively, if we can find resource of raw data from each study, we can pool all participants and employ the formula to calculate a weighted average of the estimates of the RR or OR across the strata. The weighted average provides a measure of an association that is adjusted for confounding variables (e.g., by stratification)(LaMorte & Sullivan, 2016).

Heterogeneity assessment

To quantify the heterogeneity of effect sizes over all included studies, three statistics will be calculated ('metan' command in STATA), including Tau-squared (τ^2) statistics, I^2 statistics and the Q statistics with *P*-value(Egger, Smith, & Altman, 2001; Higgins, Thompson, Deeks, & Altman, 2003).

τ^2 statistics is defined as the variance of the true effect sizes. It will give an estimate the between-study variance, representing the variability of effect sizes across the population of mean effect size values.

I^2 statistics represent a ratio of true heterogeneity to total variance across the observed effect estimates. It explains how much heterogeneity is due to true heterogeneity rather than sampling error. If I^2 is near zero, almost all observed variance is spurious (e.g., due to sampling errors); otherwise, the variance deserves explanations by subgroups analyses or meta-regression (Borenstein et al., 2010; Borenstein & Higgins, 2013; Higgins & Thompson, 2002).

Q statistics has on a Chi-squared sampling distribution with (k-1) degrees of freedom (k is the # of included studies), and it is used to test whether observed differences in effect sizes are consistent with what we would expected due to sample errors alone (The null hypothesis is: heterogeneity in ES is due to chance). A significant P-value provides that the true ES vary across studies; but a non-significant p-value could be due to low power, but not the evidence of consistent effect size across studies (Borenstein et al., 2010; Borenstein & Higgins, 2013; Brown, Upchurch, & Acton, 2003).

All these three statistics will be presented to assess the heterogeneity of the meta-analysis. In addition, I will draw a Galbaith Plot (a scatter plot of inverse standard error [X-axis] against a standardized effect size [effect size divided by its standard error, Y-axis]) to display heterogeneity (by "galbr" command in STATA). All points would lie within confidence bounds of unweighted regression if no heterogeneity exists.

Subgroup and moderator analysis

In addition to the overall assessment of the protective effect of circumcision on HIV infection, we will conduct the following subgroup analyses:

By sex positions: Previous studies suggested that MSM who had different anal sex positions or sexual roles have different levels of HIV risk (Wiysonge et al., 2011). In our review, we will perform stratified analysis by sex position (e.g., predominately receptive, predominately insertive, and predominately versatile). We anticipate that VMMC has a higher protective effect among MSM who predominantly practise insertive anal sex compared to those who prefer receptive or versatile anal sex.

By study design: Among all 33 studies, 24 employed cross-sectional study designs. A protective and significant association was noted among the 24 studies with cross-sectional design (aOR=0.92, 95% CI=0.87, 0.98). The nine studies with follow-up designs (Bartholow et al., 2006; Buchbinder et al., 2008; Buchbinder et al., 2005; Chen et al., 2011; Gust et al., 2010; Jameson, Celum, Manhart, Menza, & Golden, 2010b; Koblin et al., 2012; Sanchez et al., 2009; Templeton et al., 2009) revealed a non-significant association (aOR=1.01, 95% CI=0.86, 1.19) (Table 1).

By region: Compared to Western and African regions, HIV epidemic in Asia is featured by relatively delayed starting time of the epidemic, low-prevalence and concentrated epidemics. For instance, while other parts of the world began to deal with HI/AIDS epidemic, Asia remained unaffected (AVERT, 2015). However, by the early 1990s, HIV epidemic had emerged in this continent with a rapid increase. Although the prevalence is relatively low compared to countries in other regions, the huge population

in several countries (e.g., China, India) made the absolute number of PLWHA very significant. The epidemic among a few high-risk groups was spreading very fast, especially among MSM (AVERT, 2015). Therefore, in the current review, we will examine the circumcision effect within and outside Asia. We assume the effect may be different from Asia and the other part of the world. Therefore, we will conduct subgroup analyses by study regions (a) Asia vs. non-Asia and (b) Asian and African vs. other regions

By sample size: We will further examine studies with different sample sizes. We will compare effect size between studies with no more than 3,000 participants and studies with sample sizes larger than 3,000. The effect size may be affected by sample sizes.

By sampling strategy: We assessed studies by the reported sampling strategy. For studies employed convenience sampling, we will compare the pooled effect size with studies employing some kind of systematic sampling. We will also examine studies with probability sampling and non-probability sampling.

By assessment method: We will compare studies employing medical exams for both exposure (e.g., circumcision status) and outcome variables (e.g., HIV serostatus) with studies employing self-reported measures for both variables. The rest of the 18 studies with either, but not both measures using a medical exam had a marginally significant HIV prevention benefit suggested for circumcision (0.93, 95% CI=0.88, 0.99) (Table 1).

Publication bias assessment

The publication bias was assessed by the funnel plots (the standard error of the effect size will be plotted against the effect size). The funnel plot is based on the

assumption that in the absence of significant heterogeneity, study ESs will be normally distributed around the mean effects. Publication bias will produce asymmetry within the funnel, because studies with statistically significant effects in the desired direction will be available while those with null and contradictory results will be missing.

Then, regression tests will be performed for funnel plot asymmetry. Egger test will be used as it is the recommended test for mean or percent change effect sizes, and has more power and less inflated type I error than Begg's test does. (Moreno et al., 2009; Sutton, Duval, Tweedie, Abrams, & Jones, 2000) P-value from the global regression test, or the coefficient of 'bias' will be used make decision whether or not to reject the null hypothesis of no small study effects or possible evidence of publication bias. The last step assessing the publication bias is to perform a 'trimmed and filled' procedure to yield an 'unbiased' estimated, and compares it to the original estimate to examine if they are significantly different (Duval & Tweedie, 2000; Sutton et al., 2000).

Sensitivity analysis

Several sensitivity analyses will be conducted by removing studies with highest and lowest weight, and studies with largest and smallest sample size, respectively. In addition, I will compare the result from the sensitivity analyses with our original outcome. Meanwhile, I will assess the overall effects for studies with only crude ORs, and studies with adjusted ORs, respectively. By comparing the overall effects with unadjusted and adjusted ORs, we can evaluate if confounding is an issue to assess the intervention effect among this population.

Aim 2

Model structure

We will employ a deterministic compartmental model to predict the impacts of VMMC on HIV acquisition over the next 10 years. As being circumcised may change the risk of HIV transmission significantly among MSM (Goodreau et al., 2014; Goodreau et al., 2012; Qian et al., 2015), the study population will be divided into two mutually exclusive subgroups: 1) MSM without circumcision (S_{c-}) and 2) MSM with circumcision (S_{c+}). These two subgroups each will be further compartmentalized by HIV infection (HIV positive with circumcision vs. HIV negative without circumcision). In this model, seronegative MSM will enter the model as the susceptible population with a rate of σ; σ^+ will represent the rate entering the circumcised susceptible pool, while σ^- will represent the rate entering the uncircumcised susceptible pool. Meanwhile, MSM will leave the local transmission model by aging beyond 65 years, emigrating out of Beijing, or dying of natural causes. We will use the parameter τ to indicate rates of leaving the model among susceptible MSM, with τ^+ representing the rate of leaving the circumcised susceptible pool and τ^- representing the rate of leaving the uncircumcised susceptible pool. In this model, MSM will change from being uncircumcised to being circumcised at a rate of λ at susceptible stage.

Uncircumcised MSM will become infected and enter the compartment of HIV-infected with circumcision (I_{c-}) at an HIV transmission rate of ρ^-; and circumcised MSM will become infected (I_{c+}) at a transmission rate of ρ^+. Both circumcised and uncircumcised MSM will leave the infectious pool for the following reasons: 1) progression to AIDS, 2) death due to HIV infection, 3) having undetectable viral loads

due to either elite controller or an effective ART regime at a rate of η^- for uncircumcised and η^+ for circumcised MSM (see the schematic diagram below). This model will also consider the protective effect of VMMC on the basis of exclusively insertive, versatile, or exclusively receptive anal sex as they will affect the transmission rate of ρ^+ and ρ^-. Therefore, sexual position preference information is crucial for the model.

Transmission rate of ρ^- and ρ^+

ρ^-: we will use the actual data of HIV cases from China CDC to calculate transmission rate among uncircumcised MSM. As the prevalence of circumcision is very low among MSM in China, we can use the calculated rate as the proxy of transmission rate among uncircumcised MSM in Beijing (Table 5).

ρ^+: we will estimate the transmission rate among circumcised MSM (ρ^+) using the transmission rate among uncircumcised (ρ^-) and the pooled efficacy (OR) from Aim I.

The following table shows the actual incidence rate among uncircumcised MSM as well as the estimated transmission rate among circumcised MSM.

Relationship between odds ratio (OR), incidence, and prevalence:

- OR=odds of HIV infection among circumcised/odds of HIV infection among uncircumcised=[prev1/(1-prev1)] /[prev2/(1-prev2)]
- Prevalence = Incidence*Average Duration of HIV/AIDS

- Prev1 is the HIV prevalence among circumcised MSM
- Prev2 is the HIV prevalence among uncircumcised MSM (from China CDC data)
- OR is calculated from Aim 1

- Duration: On average, life expectancy is 14.9 years with ART treatment after the incubation time (averagely 8 years), and 1.6 years without ART treatment for a given patient(April et al., 2014; Binagwaho, Pegurri, Muita, & Bertozzi, 2010; Walensky et al., 2006). With 50% ART coverage rate in China(NHFPC, 2015), the average during of HIV/AIDS is approximately 16 years from HIV diagnosis to death considering both scenarios of ART and non-ART.

ρ^+ and ρ^- (transmission rate per year)

To find out prediction interval for ρ^- / ρ^+ using R® software. For each specific year, 100 times simulations will be conducted to assess the variability in prediction due to randomness of the transformation rate (ρ^- / ρ^+). This model is more practical to use as it captures both the trend and randomness of this parameters.

Prediction model to calculate number of HIV cases averted

To building prediction model for the next decade, we will use the 2015 data as the new initial condition to project the HIV incidence from 2016-2025. We will use the pre-scale up parameter to calculate the HIV incidence per year as the numbers of baseline cases. Based upon different VMMC coverage rates, I will compare the HIV cases at a given VMMC coverage rate with the baseline case in each year. The difference between the number of HIV cases of a given VMMC coverage rate and the number of HIV cases at the baseline will be the number of HIV cases averted per year. I will calculate the number of HIV cases averted based upon the three scenarios including predominately receptive, predominately insertive and predominately versatile (Table 8).

Aim 3

Rationale:

In this proposal, I will compare the scale up of VMMC vs. status-quo (e.g., remain at the pre-scale-up level) from the both societal and payer's perspective. Examining from the societal perspective will considers everyone affected by the intervention and counts all significant health outcomes and costs that related with it, regardless of who experience the outcomes or costs (Gold, Siegel, Russel, & Weinstein, 1996). Examining from payer's perspective, I can identify the most cost-saving strategy to curb the HIV epidemic. As economists view the maximization of the social utility function as the ultimate scheme for resource allocation, cost-minimization analysis will be used as a tool to better allocate social resources and improve general welfare.

Economic evaluation:

In order to assess the economic impact for VMMC scale-up among MSM, I will conduct the current analysis from the perspectives of budget holders and health professionals (Sullivan et al., 2014). We employed the *"numbers needed to avert"* (NNA) that defined as "the number of VMMC per new HIV case averted" as an indicator. NNA was calculated by dividing the number of HIV cases averted (compared with the baseline [λ=0.0001]) by the number of VMMC conducted at a given year. The lower the NNA, the more economically effective the VMMC campaign would be among MSM. We calculated the NNA under different annual VMMC coverage rates at each predicted year.

In addition, we further identified the breakeven point that balances the total cost of VMMC with the cost saved from averting new HIV cases. The breakeven point can be considered as the tipping point that it was economically desirable to proceed with the VMMC program among MSM in Beijing. We also calculated the total cost saved compared to the cost at baseline after expanding the VMMC program in each projected year. The cost at each scenario included the cost of VMMC and cost of HIV treatment. The cost of each individual VMMC and HIV treatment in each projected year (2016-2026) was discounted by 3% (Hunink et al., 2001)that started from the baseline cost derived from existing studies (Drabo, Hay, Vardavas, Wagner, & Sood, 2016; Farnham et al., 2013; Moon et al., 2008; Schackman et al., 2015).

Sensitivity analysis:

We conducted sensitivity analyses by setting the transmission rates for both circumcised and uncircumcised MSM at the same level as the incidence rate seen in 2015. If nothing changes from 2015 (i.e., very, very few VMMC), it represents a lower bound for the transmission rate (Supplementary Figure 1). In addition, we assessed the economic impact in terms of the NNA and breakeven points by different protective efficacies(e.g., 7%, 17%, 27%, 37%, and 47%) ranging from being very conservative 7% (Zhang, Qian, et al., Under review) to being optimistic 47%(Qian et al., 2016) incrementally in the current study.

CHAPTER IV

EFFECT OF CIRCUMCISION ON RISK OF HIV INFECTION AMONG MEN WHO HAVE SEX WITH MEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Abstract

Background: Despite the rapid increase of HIV among men who have sex with men (MSM) worldwide, the effectiveness of voluntary medical male circumcision (VMMC) as a tool for HIV prevention remains undetermined.

Purpose: We conducted a systematic review and meta-analysis to assess the association between VMMC and HIV infection among MSM.

Data sources: Following the PRISMA guidelines, we conducted a comprehensive literature search through multiple databases (PubMed/MEDLINE, Web of Science, PsycINFO, EMBASE, GOOGLE SCHOLAR) starting from February, 1 to August, 4 2016.

Study selection: From 117 suggestive titles, we identified 37 articles/abstracts from 33 studies that had a rigorous enough study design to be included in the analysis.

Data extraction: Two reviewers independently extracted data from qualified articles using a standard screening form. The risk of bias including selection, misclassification, and publication biases were assessed.

Data synthesis: We employed random-effects models and subgroup analyses based upon key study characteristics. A total of 117,293 MSM were included in the meta-analysis. The odds of being HIV positive were 7% lower among MSM who were circumcised than among MSM who were uncircumcised (aOR=0.93, 95% CI=0.88, 0.99). The evidence for the protective effect of VMMC was stronger among MSM who live in Asia and Africa (aOR= 0.62, 95% CI=0.53, 0.73).

Limitations: The limited number and scope of existing studies constrained representativeness of our findings; misclassification of circumcision status and sex positioning may lead to a bias towards the null hypothesis; the nature of cross-sectional study designs may limit the inference of the association between VMMC and HIV.

Conclusion: Our meta-analyses suggest a protective effect of VMMC against HIV infection among MSM, especially strong in Asian/African contexts.

Key words: systematic review, meta-analysis, HIV, male circumcision, sexual positioning, Africa, Asia, men who have sex with men, homosexual men

Introduction

Global HIV prevalence among men who have sex with men (MSM) ranges from 3% in the Middle East and southeast north Africa to 25% in the Caribbean countries (Beyrer et al., 2012; van Griensven, de Lind van Wijngaarden, Baral, & Grulich, 2009). HIV incidence has increased in many global settings since declines were noted in the United States and western Europe in the mid-1980s, despite available behavioral (e.g., risk reduction with condom use) and biomedical (e.g., pre-exposure prophylaxis [PrEP]) prevention tools (Vermund & Qian, 2008). Given the urgency of the global HIV

epidemic in MSM, the available tools for preventing HIV acquisition among MSM may be too limited (Vermund & Qian, 2008). Voluntary male medical circumcision (VMMC) is a single surgical procedure providing potential lifelong benefit (Vermund & Qian, 2008). Both observational studies and clinical trials demonstrate that foreskin removal via VMMC reduces a man's risk of contracting HIV through condomless heterosexual intercourses by 50-73% (Auvert et al., 2005; Bailey et al., 2007; R. Gray et al., 2012; R. H. Gray, Kigozi, et al., 2007). The global public health community would be thrilled to have an "HIV vaccine" with efficacy at this level.

Many scholars have examined the efficacy of VMMC for preventing HIV transmission among MSM, but the conclusions have been inconsistent. Two research teams conducted systematic review and meta-analyses of available observational evidence and their findings were both inconclusive (Millett et al., 2007; Wiysonge et al., 2011). Millet et al. (2008) included 15 studies revealing insufficient evidence that VMMC protected against HIV infection among MSM (Millett et al., 2007). By including six more studies, Wiysonge et al. (2011) found the same overall conclusion, but data suggested that VMMC significantly protected MSM from HIV infection in the subgroup of men who primarily practiced insertive sex (Wiysonge et al., 2011).

Since the publishing of Wiysonge's meta-analysis in 2011, twelve new epidemiological studies have been published (R. V. Barnabas et al., 2011; Chen et al., 2011; Crosby et al., 2015; Doerner et al., 2013a; Jozkowski et al., 2010; Koblin et al., 2013; Koblin et al., 2012; Oster et al., 2011; Pando et al., 2013a; Qian et al., 2016; Sanchez et al., 2011; Schneider et al., 2012a; Solomon et al., 2014; Thornton et al., 2011; Zeng et al., 2014; C. Zhou et al., 2013). For instance, a 2010-2011 study among MSM in

Beijing showed that circumcision was significantly associated with a lower odds of HIV infection among MSM predominantly practicing insertive anal sex, with a beneficial trend for other MSM as well, providing the strongest evidence to date that VMMC might be a useful biomedical tool for HIV risk reduction among MSM (Qian et al., 2016). Two other studies, both from India, similarly suggested strong protective effects of VMMC against HIV among MSM (Schneider et al., 2012a; Solomon et al., 2014).

Systematic reviews must incorporate social and contextual factors into their analyses, particularly the region of study and sexual position preferences. Compared to Western countries, the HIV epidemic in Asia differs in its later epidemic growth, comparatively low prevalence, and in the extreme social stigma faced by MSM (AVERT, 2015). As MSM in Africa may share similar behavioral patterns and social stigmas as their Asian peers (Beyrer et al., 2012; Qian et al., 2016); region-specific strata can be compared to ensure that the comparatively vast literature on VMMC and MSM from the Americas and Europe does not drown out the comparatively small literature in Asia and Africa. Assessing the efficacy of VMMC among MSM by different characteristics of individuals and settings may also be revealing, e.g., sex positioning, study sample size, measurement for exposure and outcome variables, and type of study design. By exploring different subgroups, we sought to better understand the efficacy of VMMC on HIV under different circumstances.

Following PRISMA guidelines (http://www.prisma-statement.org/), we sought to compare the odds of HIV infection between circumcised and uncircumcised MSM by including all available studies with rigorous study design (e.g., randomized controlled trials, well-designed quasi-experimental designs, and observational study designs). In

addition, stratified subgroup analyses helped examine how the effect of VMMC might differ by different characteristics of individuals and settings.

Methods

Protocol and registration

We sought to register our meta-analysis with the PROSPERO, Cochrane, and Campbell systematic review databases, but were declined by all three for different reasons. Nonetheless, we followed PRISMA guidelines.

Eligibility criteria

Inclusion: Studies were identified if they: (a) used a rigorous study design (e.g., randomized control trials, cross-sectional studies, longitudinal studies, observational studies with clear counterfactual constructs); (b) were quantitatively evaluating effects of circumcision on HIV risk among MSM; (c) provided sufficient information to calculate effect size estimates; (d) published (any language or year) either in peer-reviewed journals or in recognized conferences.

Exclusion criteria: The exclusion criteria are (a) descriptive studies that do not report outcomes or studies only report qualitative outcomes, (b) studies that do not focus on MSM (e.g., focus on heterosexual men), (c) reviews, and (d) theoretical articles without original data.

Data sources, Search Strategy and Study Selection

Following the PRISMA guidelines, we conducted comprehensive literature search through multiple databases including PubMed/MEDLINE, Web of Science, PsycINFO,

EMBASE, GOOGLE SCHOLAR by entering different combinations of a few MeSH terms ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency syndromes") AND ("circumcision" OR "foreskin surgery") AND ("men who have sex with men" OR "MSM" OR "homosexual male" OR "gay men") up to August 4, 2016 (Supplementary Table 1). We also searched through newspapers and conference proceedings, as well as references from article that met our inclusion criteria. The initial screening yielded 92 potentially relevant articles/abstracts from 117 entries identified in the search or through other sources (Figure 1). These 92 abstracts were reviewed, 53 abstracts were excluded and 39 were retained for further review. Two reviewers (CZ and YL) independently reviewed the full texts of these articles. Disagreement between reviewers was resolved by discussion, and 33 articles fulfilled the inclusion criteria and were included in the analysis. We also hand-searched all references from included studies and relevant reviews. Four abstracts were selected based upon this review of references and all four were deemed eligible and their corresponding papers were included in the analysis (Calzavara, Remis, Myers, & StudyTeam, 2007; Kumta, Setia, Jerjani, Mather, & RaoKavi, 2002; Lai, Hong, & Lan, 2004; Solomon et al., 2014). Hence, 37 articles from 33 studies were included for the systematic review and meta-analysis.

Data Extraction

Two reviewers (CZ and YL) independently extracted data from qualified articles using a standard form and developed a table containing the following information: (a) study location and time of conducting the study, (b) characteristics of participants (e.g., age, ethnicity), (c) sample size, (d) HIV assessment (e.g., either self-report or lab work),

(e) circumcision assessment (either self-report or genital examination), (f) sex positions if applicable (e.g., receptive vs. insertive), (g) numbers of HIV infection among circumcised and uncircumcised MSM, and (h) reported crude and/or adjusted odds ratios of the HIV infection and VMMC. When information regarding any of the above information was unclear, we contacted the original authors of the included articles for further detailed information (Oster et al., 2011), but no further information has been provided. For studies with duplicate publications (R. V. Barnabas et al., 2011; Buchbinder et al., 2008; Koblin et al., 2012; Mao et al., 2008; Sanchez, 2007; Sanchez et al., 2009; Templeton et al., 2009), we reported the study only once in the analyses, with the most complete data included.

Quality Assessment

Two reviewers (CZ and YL) independently assessed the risk of bias for each study. For our systematic review and meta-analysis, the selection bias may be unavoidable since we only considered articles with full-texts among widely accessible online resources. Publication bias occurred because published studies may not be representative of all studies that have ever been done. In addition, we assessed the rigor of measuring the exposure (self-report vs. genital examination) and outcome variables (self-report vs. laboratory testing) in the original studies. We also determined the quality of the sampling strategy for each study.

Statistical Analysis

Measures of effects

Most studies reported strengths of association as odds ratio (OR) with 95% confidence interval (CI). We preferred using adjusted ORs with 95% CIs from the given publication, available for 28 studies (R. V. Barnabas et al., 2011; Bartholow et al., 2006; Begley et al., 2008; Buchbinder et al., 2008; Calzavara et al., 2007; Doerner et al., 2013a; Gust et al., 2010; Jameson et al., 2010b; Jozkowski et al., 2010; Koblin et al., 2013; Koblin et al., 2012; Kreiss & Hopkins, 1993; Kumta et al., 2002; Lai et al., 2004; Lane et al., 2011; Mao et al., 2008; McDaid, Weiss, & Hart, 2010; Mor, Kent, Kohn, & Klausner, 2007; Oster et al., 2011; Qian et al., 2016; Reid, Weatherburn, Hickson, & Stephens, 2001; Reisen, Zea, Poppen, & Bianchi, 2007; Sanchez, 2007; Sanchez et al., 2009; Sanchez et al., 2011; Schneider et al., 2012a; Tabet et al., 2002; Templeton et al., 2009; Templeton et al., 2008; Thornton et al., 2011; C. Zhou et al., 2013). For five studies that did not report adjusted ORs, we used raw data to calculate the crude ORs and their 95% CIs (Chen et al., 2011; Crosby et al., 2015; Pando et al., 2013a; Solomon et al., 2014; Zeng et al., 2014).

Assessment of heterogeneity

To evaluate the extent to which studies' outcomes were consistent, we employed the I^2*-statistics* and corresponding 95% CIs to depict heterogeneity. The I^2*-statistics* describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error, and it varies from zero to 100% with higher percentages indicating higher heterogeneity (M. Borenstein, L. V. Hedges, J. Higgins, & H.

Rothstein, 2009). If the 95% CIs included zero, the included studies were considered to be reasonably homogeneous. *P*-values for I^2*-statistics* were also reported.

Assessment of publication bias

Publication bias was assessed by the funnel plots, based on the assumption that in the absence of significant heterogeneity, study effect sizes will be normally distributed around the mean effects (Michael Borenstein et al., 2009). Publication bias will produce asymmetry within the funnel, because studies with statistically significant effects in the desired direction will be published while those with null and contradictory results will be unavailable.

Data synthesis

Model selection: We employed the random-effects model, as all included studies were conducted among different populations, a feature that may influence the effects observed. Unlike the fixed effects model that assumed that all studies shared identical true effect sizes, the random effects model was designed to capture the variance of effects across studies (Michael Borenstein et al., 2009; Littell, Corcoran, & Pillai, 2008). Each study was assigned a weight directly by the calculating procedure. Forest plot of odds ratios from included studies (shaded squares, is the proportional to weights used in meta-analysis), with the summary measure (center line of diamond) and associated confidence intervals (lateral tips of diamond), and a solid vertical line of no effect was used. STATA V12 (College Station, TX); the command *metan* was used for data syntheses and analyses.

Subgroup analyses were performed to examine the effect size by sex positioning

(receptive vs. insertive), study design (cross-sectional vs. studies with follow-ups), geographical region (Asia vs. non-Asia; Asia+Africa vs. non-Asia/non-Africa), assessment method (self-report vs. genital exam), and sample size at baseline (≤3000 vs. >3000).

Sensitivity analyses were employed to examine the stability of the efficacy of circumcision by evaluating whether the overall effect size was sensitive to exclusion of any individual studies (e.g., study with highest or lowest weight, and with smallest or largest sample size).

Role of the Funding Source

The study was supported by grants from U.S. National Institutes of Health (R01AI094562 and R34AI091446). The content is solely the responsibility of the authors and does not necessarily represent the sponsor who had no role in the design or conduct of the study, the writing of this report, or its submission for publication.

Results

Overall effect size

A total of 117,293 MSM participants from 33 studies contributed to examining the association between circumcision and HIV risk. Among these studies, four studies revealed that circumcision significantly reduced the odds of HIV infection among MSM (Chen et al., 2011; Lane et al., 2011; Schneider et al., 2012a; Solomon et al., 2014), while 29 studies reported that circumcision had no statistically significant associations with HIV. The overall effect size of circumcision on HIV infection was statistically significant

(aOR, 0.93; 95% CI, 0.88-0.99) (Figure 2). In addition, details about each included study were presented in the supplementary Table 2.

Subgroup analyses

By sex positioning: Among included studies, 11 studies (Calzavara et al., 2007; Doerner et al., 2013a; Jameson et al., 2010b; McDaid et al., 2010; Qian et al., 2016; Reisen et al., 2007; Sanchez, 2007; Sanchez et al., 2009; Sanchez et al., 2011; Templeton et al., 2009; Zeng et al., 2014) have reported circumcision data for insertive anal sex, and six studies (Jameson et al., 2010b; Pando et al., 2013a; Qian et al., 2016; Reisen et al., 2007; Sanchez, 2007; Sanchez et al., 2009; Zeng et al., 2014) reported data on receptive anal sex among MSM. We performed stratified analysis by sex positioning (e.g., predominately or exclusively receptive vs. predominately or exclusively insertive anal sex). The results revealed that the odds of HIV risk among circumcised MSM who primarily/exclusively practiced insertive sex did not suggest protection (aOR, 1.16; 95% CI, 0.73-1.83), nor did the odds among circumcised MSM practicing receptive anal sex (aOR, 0.97; 95% CI, 0.74-1.28). However, the insertive sex group estimate was distorted substantially by a single study whose findings were highly disparate from other comparable studies (Zeng et al., 2014). When this one outlier study that suggested greater risk for circumcised men who primarily/exclusively practiced insertive sex was excluded, then the odds of HIV infection among circumcised MSM who primarily/exclusively practiced insertive sex (aOR, 0.51; 95% CI, 0.23-1.11) suggested a protective effective for circumcision among the insertive MSM (Table 1). While not achieving statistical significance, the protective directionality and magnitude of the point estimate of the odds

ratio for MSM primarily practicing insertive anal intercourse is both notable and biologically plausible.

By study design: Among all 33 studies, 24 employed a cross-sectional study design. A protective and significant association was noted among these studies (aOR, 0.92; 95% CI, 0.87-0.98). Nine studies with a cohort design (Bartholow et al., 2006; Buchbinder et al., 2008; Buchbinder et al., 2005; Chen et al., 2011; Gust et al., 2010; Jameson et al., 2010b; Koblin et al., 2012; Sanchez et al., 2009; Templeton et al., 2009) revealed a non-significant association (aOR, 1.01; 95% CI, 0.86-1.19) (Table 1).

By region: (a) Asia vs. non-Asia: Eight studies (Chen et al., 2011; Kumta et al., 2002; Lai et al., 2004; Qian et al., 2016; Schneider et al., 2012a; Solomon et al., 2014; Zeng et al., 2014; C. Zhou et al., 2013) were conducted in Asian countries, including five in China and three in India; the odds of being HIV infected were significantly lower among circumcised MSM compared to uncircumcised (aOR, 0.69; 95% CI, 0.58-0.81). Among non-Asian MSM, there was no protection of circumcision against HIV infection (aOR, 0.97; 95% CI, 0.91-1.03). (b) Only one African study was found. Examining Asian/African studies combined meant adding the African study to the five Chinese and three Indian, revealing an even lower odds of being HIV infected among circumcised MSM (aOR, 0.62; 95% CI; 0.53-0.73) compared to Asian MSM alone. Similarly, the odds of HIV infection among circumcised MSM outside the Asian-African continents was still non-significant (aOR, 0.99; 95% CI, 0.93-1.05) (Table 1).

By sample size: For studies with ≤3,000 participants (n=24), we found the odds of being HIV infected among circumcised MSM was significantly lower (aOR, 0.70; 95%

CI, 0.61-0.82). For studies with a sample size >3,000 (n=9) (Bartholow et al., 2006; Buchbinder et al., 2005; Gust et al., 2010; Jameson et al., 2010b; Jozkowski et al., 2010; Mor et al., 2007; Oster et al., 2011; Reid et al., 2001; Solomon et al., 2014), the odd ratio of HIV infection was close to 1 (aOR, 0.99; 95% CI, 0.93-1.05) (Table 1).

By sampling strategy: Of 17 studies using a convenience sampling strategy, the odds of being HIV infected among circumcised MSM was 5% less compared with uncircumcised MSM (aOR, 0.95; 95% CI; 0.88-1.03). For studies employing some kind of systematic sampling, the odds of being HIV infected was significantly lower among circumcised MSM (aOR, 0.92; 95% CI, 0.85-0.99). Only five studies employed probability sampling (R. V. Barnabas et al., 2011; Bartholow et al., 2006; Buchbinder et al., 2008; Gust et al., 2010; Koblin et al., 2012; Sanchez et al., 2011), and the odds of being HIV infected was slightly lower among circumcised (aOR, 0.93; 95% CI, 0.88-0.99), similar to the studies that did not use probability sampling (aOR, 0.95; 95% CI; 0.68-1.34) (Table 1).

By assessment method: For nine studies employing genital exams to measure circumcision status and laboratory testing of HIV infection (Jameson et al., 2010b; Koblin et al., 2012; Kumta et al., 2002; Mor et al., 2007; Qian et al., 2016; Sanchez, 2007; Sanchez et al., 2009; Sanchez et al., 2011; Tabet et al., 2002; Zeng et al., 2014), the odds of being HIV infected was similar between circumcised and uncircumcised MSM (aOR, 0.98; 95% CI, 0.90-1.07). For six studies employing self-report for both variables (Begley et al., 2008; Calzavara et al., 2007; Doerner et al., 2013a; Reid et al., 2001; Reisen et al., 2007; Thornton et al., 2011), the odds of getting HIV was also only slightly lower among circumcised men (aOR, 0.95; 95% CI, 0.75-1.20). The rest of the 18 studies

with either, but not both measures using a medical exam had a marginally significant HIV prevention benefit suggested for circumcision (aOR, 0.93; 95% CI, 0.88-0.99) (Table 1).

Sensitivity analyses

Sensitivity analyses were conducted by removing studies with highest and lowest weight, and studies with largest and smallest sample size, respectively. By comparing outcomes from sensitivity analyses with the original outcome, no difference has been found from the sensitivity analyses (not shown). In the subgroup analysis for men with an insertive sexual preference, a wide swing in adjusted odds ratio was noted when one study was excluded (Zeng et al., 2014).

Publication bias assessment

The publication bias was assessed by the funnel plots in which the standard error of the effect size was plotted against the effect size. By examining the funnel plot, publication bias was present as the graph showed slight asymmetry within the funnel, especially among studies with smaller odds ratios (Figure 3). We further examined the heterogeneity using I^2-statistics. The I^2-statistic was 54.0% (P <0.001), indicating moderate heterogeneity of included studies (Michael Borenstein et al., 2009).

Discussion

Our meta-analytic review included 117,293 participants from 33 studies, which had 45,600 more participants and 12 new studies compared with the one conducted by Wiysonge and colleagues in 2011 (Wiysonge et al., 2011). Our review showed that the

odds of being HIV-infected were significantly lower among MSM who were circumcised than among MSM who were uncircumcised, but the effect size was modest (7% protection, 95% CI, 1%-12%). Our meta-analysis is the first to report a statistically protective effect of VMMC against HIV infection among MSM. The evidence for the protective effect of VMMC was dramatically stronger among MSM who live in Asia or Africa. Our findings suggest that VMMC may be a protective tool against HIV infection among MSM, especially for these who living in Asia and Africa (Beyrer, 2010b; WHO, 2016).

In addition to the overall effect size, several key findings emerged from the subgroup analyses. First, the observation that VMMC may be an especially effective tool for HIV prevention among Asian and African MSM generates a hypothesis that circumcision may be more effective in MSM who have comparatively lower risk profiles (e.g., fewer sexual partners, less risky sexual activity) comparing with their Western peers (Chen et al., 2011; Qian et al., 2016; Vermund & Qian, 2008). Therefore, we speculate that VMMC could be more effective among MSM with moderate risk, but that MSM with higher risk profiles may benefit less. Second, although our findings showed increased odds of HIV infection among MSM who primarily practicing insertive sex, a counterintuitive and biologically implausible finding was noted. A strong protective effect of VMMC on HIV infection among MSM exclusively or predominantly practicing insertive anal intercourse was noted after we removed an outlier from the analytic pool. There are, however, only a limited number of available studies that reported sex positioning. Third, for studies with a sample size $\leq$ 3,000 MSM, the odds of being HIV infection was 30% significantly lower among circumcised MSM compared to their

uncircumcised peers. On the other hand, the association was non-significant among studies with a larger sample size. Perhaps studies with fewer participants can be published only if they reported significant findings, while studies with larger sample sizes are published without bias, i.e., whether the association is significant or not. Therefore, we speculate that publication bias may affect the accuracy and reliability of the efficacy of VMMC, a bias away from the null hypothesis.

Our meta-analysis has several strengths. First, it included a large number of participants. Second, we stratified the data by individual and setting characteristics to capture any potential associations in important subgroups. Third, we strictly followed the PRISMA guidelines for systematic reviews and meta-analyses.

However, a number of limitations should be considered while interpreting findings from the current study. First, the limited number and scope of existing studies constrained representativeness of our findings. Of 33 studies, 22 (67%) were conducted in the U.S., Canada, Europe, or Australia, high income regions with long-standing lesbian/gay/bisexual/transgender (LGBT) civil rights movements and high HIV prevalence among MSM. This geographic concentration may not reflect the full scope of sexual risk and HIV transmission dynamics worldwide (Beyrer, 2010b; WHO, 2016). For instance, risk profiles of MSM are far less well characterized than in other continents, and only one MSM/circumcision study was reported, a study of just 363 Black MSM in South Africa(Lane et al., 2011). Even in Latin America (three studies, some mixed with other areas) or Asia (eight MSM/circumcision studies), the data are limited. It is possible that the 22 studies from the US (n=15) (R. V. Barnabas et al., 2011; Bartholow et al., 2006; Begley et al., 2008; Buchbinder et al., 2008; Buchbinder et al., 2005; Crosby et al., 2015;

Gust et al., 2010; Jameson et al., 2010b; Jozkowski et al., 2010; Koblin et al., 2013; Koblin et al., 2012; Kreiss & Hopkins, 1993; Millett et al., 2007; Mor et al., 2007; Oster et al., 2011; Reisen et al., 2007; Sanchez et al., 2011), United Kingdom (n=4) (Doerner et al., 2013a; McDaid et al., 2010; Reid et al., 2001; Thornton et al., 2011), Australia (n=2) (R. V. Barnabas et al., 2011; Buchbinder et al., 2008; Koblin et al., 2012; Mao et al., 2008; Templeton et al., 2009), and Canada (n=1) (Calzavara et al., 2007) are underestimating the potential benefits of circumcision in other parts of the world, given their weak strength of association compared to the studies from Africa and Asia. The limited number of studies (n=13) from Asia (n=8) (Chen et al., 2011; Kumta et al., 2002; Lai et al., 2004; Qian et al., 2016; Solomon et al., 2014; Zeng et al., 2014; Zhao et al., 2016; C. Zhou et al., 2013), Africa (n=1) (Lane et al., 2011) and Latin America (n=4) (Buchbinder et al., 2008; Buchbinder et al., 2005; Koblin et al., 2012; Pando et al., 2013a; Sanchez, 2007; Sanchez et al., 2009; Tabet et al., 2002) limit our ability to generalize findings.

Second, misclassification of circumcision status and sex positioning may lead to a bias towards the null hypothesis, minimizing the ability to detect the true magnitude of association. Among all 33 included studies, only 10 studies (Jameson et al., 2010b; Koblin et al., 2012; Kumta et al., 2002; Mor et al., 2007; Qian et al., 2016; Sanchez, 2007; Sanchez et al., 2009; Schneider et al., 2012a; Tabet et al., 2002; Zeng et al., 2014) conducted genital exam of MSM's circumcision status, while the rest studies employed self-reported results. Although Templeton and colleagues have showed self-reported circumcision status was a valid measure among Anglo MSM in Australia and asserted that this can be generalized to MSM in developed countries (Templeton et al., 2008), a

Chinese study revealed the self-reported circumcision rate was higher than the rate from medical exams (Qian et al., 2016). Furthermore, for the 10 studies collecting sex positioning information (Calzavara et al., 2007; Doerner et al., 2013a; Jameson et al., 2010b; Lane et al., 2011; McDaid et al., 2010; Pando et al., 2013a; Qian et al., 2016; Reisen et al., 2007; Sanchez, 2007; Templeton et al., 2009; Zeng et al., 2014), this measure was relied on self-reporting and was usually measured with a single question. The limited assessment of circumcision status and sex positioning may lead to misclassification that would tend to underestimate VMMC benefits (Qian et al., 2016; Wiysonge et al., 2011). When reporting bias is eliminated by direct penile exam to assess circumcision status and by including detailed sexual position data, there may be more promise in VMMC as a tool to reduce HIV risk among MSM than previously assumed (Qian et al., 2016).

Third, data may be insufficient to answer the proposed question when the conclusion was derived incidentally, i.e., not through hypothesis testing. Many included studies examining the association between VMMC and HIV among MSM were generated from secondary analyses of existing data, rather than being designed specifically to address this issue (Doerner et al., 2013a; Zeng et al., 2014). This may result in residual confounding due to insufficient or incomplete measurements and/or may not address the specific research question with needed data (Boslaugh, 2007). For instance, several key studies were parts of HIV vaccine studies (R. V. Barnabas et al., 2011; Buchbinder et al., 2008; Koblin et al., 2012) whose primary goal was examining vaccine efficacy, not the association between VMMC and HIV. In secondary analyses, reported associations may be biased due to uncontrolled confounding variables.

Fourth, the nature of cross-sectional study designs may limit the inference of the association between VMMC and HIV. In our meta-analyses, two-thirds of included studies employed cross-sectional designs with convenience sampling, constraining casual inferences. Although a randomized controlled trial (RCT) could definitively determine whether VMMC reduces HIV risk among MSM, no available RCT has been conducted. Although a registered clinic trial (NCT01068015) started in 2009, we found no relevant publications regarding the effectiveness of VMMC among MSM from this trial (https://clinicaltrials.gov/ct2/show/record/NCT01068015). In addition, our subgroup analysis among all cross-sectional studies revealed a protective association between VMMC and HIV risk, while the pooled OR among cohort studies was null. Perhaps the significantly protective association was driven by uncontrolled/unadjusted confounding in these cross-sectional studies. Studies with more rigorous design are highly desired.

Fifth, no analyses for the association between HIV-1 subtypes and circumcision have been reported. Molecular epidemiology exploits the classification of HIV-1 viruses into distinct phylogenetic strains (subtypes, inter-subtypes) and several recombinants (Beloukas et al., 2016; Konou et al., 2016; Zhao et al., 2016). These subtypes were significantly different from MSM with various regions; they may change over time even within a region (Konou et al., 2016; Zhao et al., 2016). Even for MSM with the same ethnicity, the subtypes can differ based on where, and from whom, the infection was acquired (Beloukas et al., 2016; Zhao et al., 2016). However, the mechanism on how each subtype might interact with circumcision intervention remains to be determined. Future research can study subtypes of HIV-1 can provide a framework to help us to understand how circumcision benefits, if any, might vary by subtype, along with the

aforementioned factors of the magnitude of sexual risk taking and sex positioning preferences.

Although the overall effect of VMMC on HIV prevention was marginally significant, misclassification of key exposure and confounding variables may dilute the protective effect of VMMC. In turn, publication bias may exaggerate its protective effort. Research with more rigorous study designs to objectively assess HIV infection through confirmatory serological tests and evaluation of circumcision by genital exam can significantly reduce misclassification bias. In addition, future research should collect detailed data on MSM's sexual position preference at different time points in their lives (e.g., in the past 30 days, in the past six months and lifetime), as well as the degree of their sexual risk taking. We would not be surprised if we eventually learn that circumcision is highly protective for MSM, but benefits are predominantly accrued among men practicing predominantly insertive anal sex and men without highest risk behavior patterns. Subtypes may also alter the relative benefits seen, but no data exist on this point. A randomized clinical trial, if feasible, should be conducted.

Figure 1. Flow chart for study selection

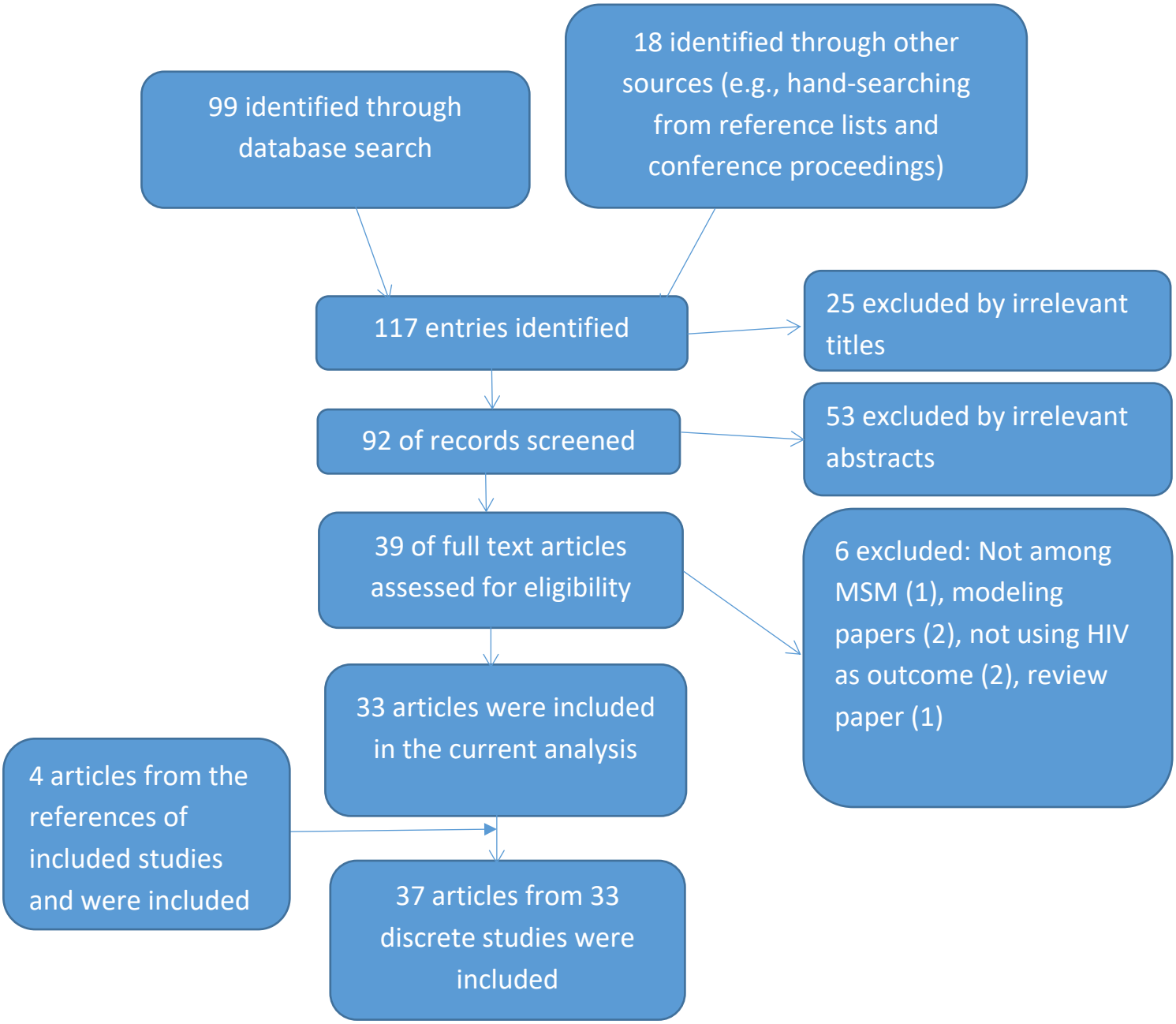


Figure 2. Overall effect size for 33 included studies of voluntary medical male circumcision and HIV risk (N=33)

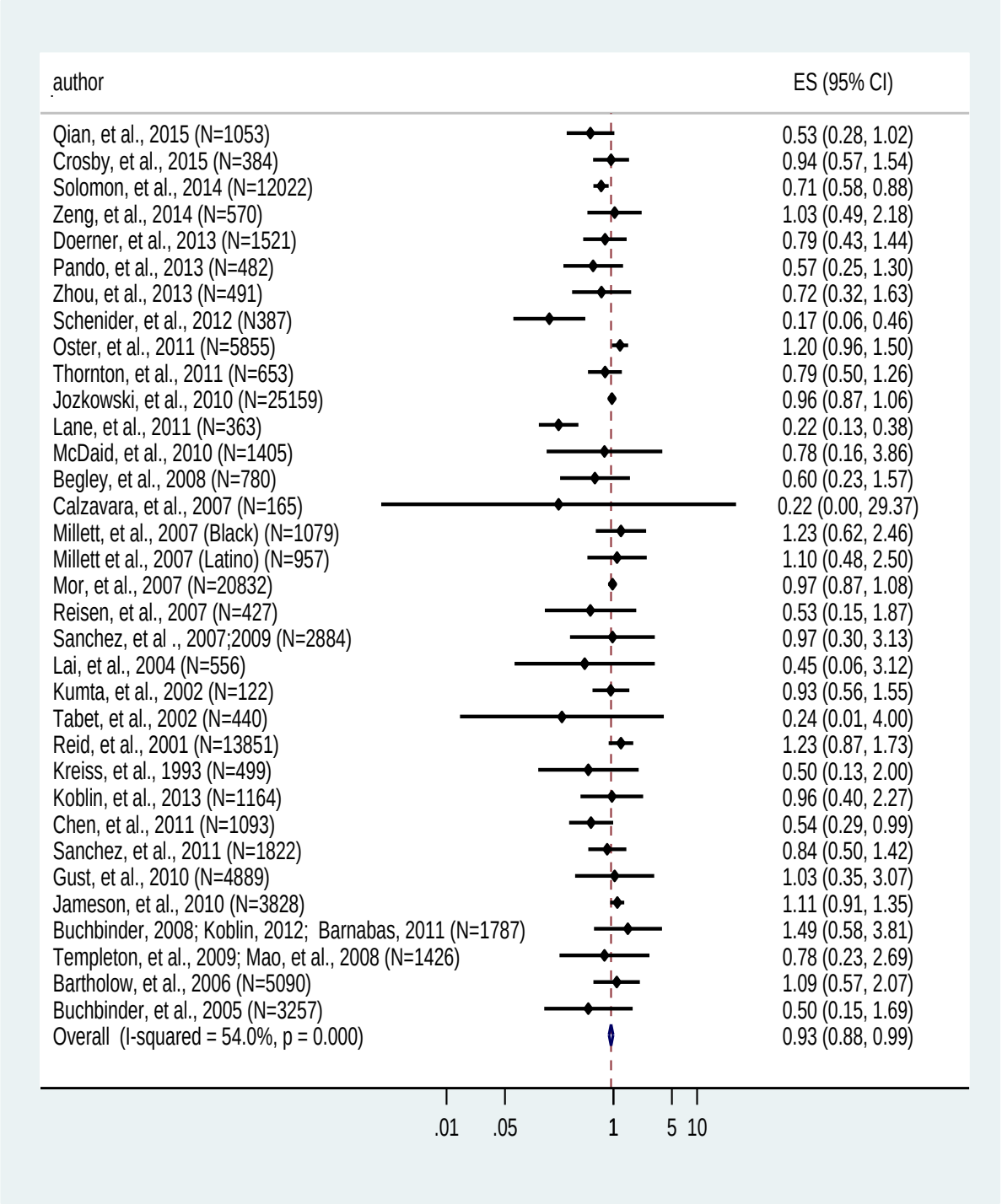


Figure 3. Funnel Plot for publication bias assessment

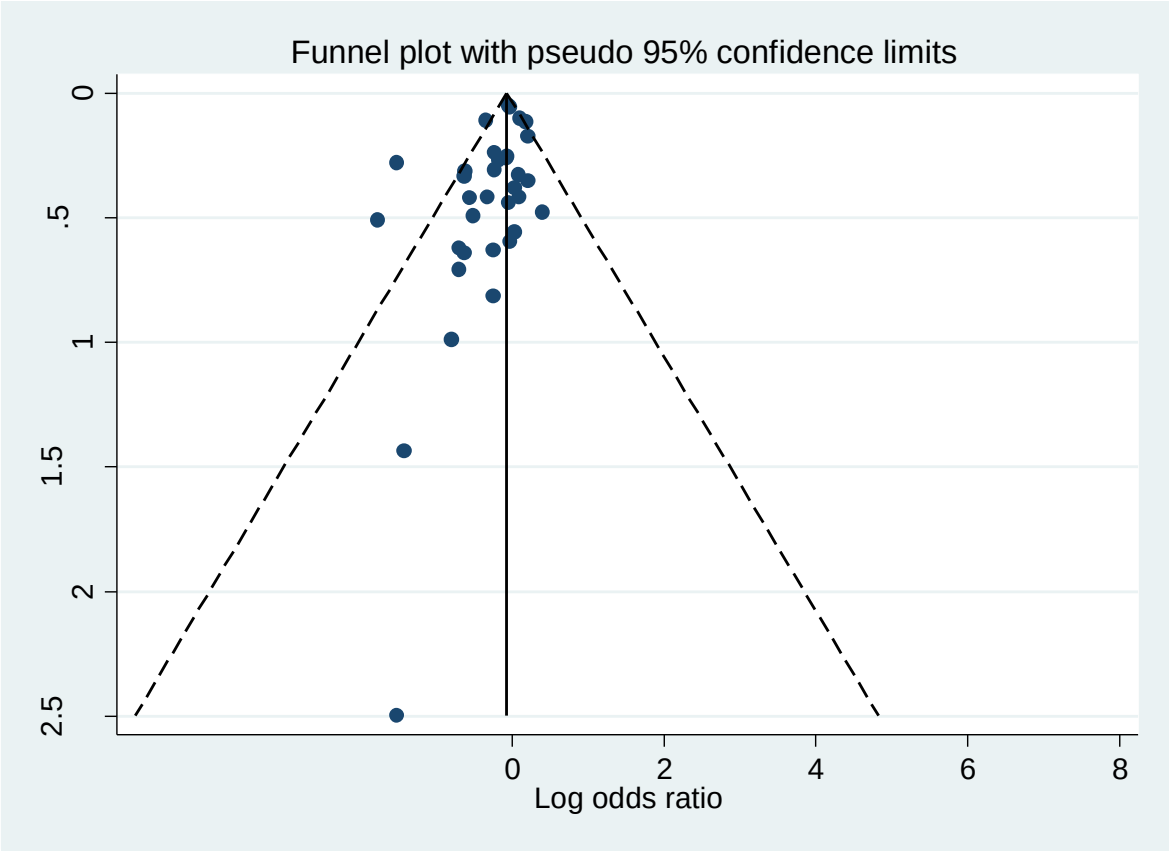


Table 1. Subgroup analyses of included studies

	# of studies	# of participants	aOR (95% CI)	I^2	*p*-value for heterogeneity chi-square
Overall	33	117,293	0.93 (0.88, 0.99)	54%	<0.0001
By sex positioning					
Insertive	11	15,946	1.16 (0.73, 1.83)	14.6%	0.31
Insertive (after delete Zeng et al., 2014)[a]	10	15,376	0.51 (0.23, 1.11)	0.00%	0.89
Receptive	6	9,244	0.97 (0.74, 1.28)	28.0%	0.23
By study regions					
Asia	8	17,458	0.69 (0.58, 0.81)	39.3%	0.12
non-Asia	25	99,835	0.97 (0.91, 1.03)	45.0%	0.007
Asia+Africa	9	17,821	0.62 (0.53, 0.73)	70.1%	0.001
non Asia/non-Africa	24	99,472	0.99 (0.93, 1.05)	0.00%	0.86
By sample size					
Smaller size (<3000)	24	22,510	0.70 (0.61, 0.82)	39.3%	0.024
Larger size (≥3000)	9	94,783	0.98 (0.92, 1.04)	52.3%	0.033
By study design					
Cross-sectional	24	92,937	0.92 (0.87, 0.98)	61.9%	<0.0001
Cohort	9	24,356	1.01 (0.86, 1.19)	0.0%	0.47
By sampling strategy					
Convenience sampling	17	54,235	0.95 (0.88, 1.03)	41.6%	0.037
Non-convenience sampling	16	63,058	0.92 (0.85, 0.99)	63.6%	0.000
Non-probability-based	28	100,448	0.95 (0.68, 1.34)	0.0%	0.67
Probability-based	5	16,845	0.93 (0.88, 0.99)	59.6	<0.0001
By HIV testing					
Lab test	27	99,896	0.93 (0.88, 0.99)	59.4%	<0.0001
Self-report	6	17,397	0.95 (0.75, 1.20)	4.0%	0.39

By VMMC					
Genital examination	9	32,715	0.98 (0.90, 1.07)	0.0%	0.61
Self-report	24	84,578	0.90 (0.84, 0.97)	62.1%	<0.0001
BY Exposure and Outcome measurement					
using genital exam and laboratory testing	9	32,715	0.98 (0.90, 1.07)	0.0%	0.61
One measured	18	67,181	0.93 (0.88, 0.99)	59.4%	<0.0001
Neither measured	6	17,397	0.95 (0.75, 1.20)	4.0%	0.39

Notes: a. The study (Zeng et al., 2014) is an outlier. After deleting, the odds of HIV risk among insertive MSM were lower compared to the odds of HIV risk among MSM who primarily practice receptive or versatile sex positioning.

Table 2: Database searching strategies using key words

Search terms		Search results
#1	"HIV"[Mesh] OR "HIV"[tiab] OR "HIV Infections"[Mesh] OR "HIV Antibodies"[Mesh] OR HIV-1[tiab] OR HIV1[tiab] OR HIV-2[tiab] OR HIV2[tiab] OR "HIV/AIDS"[tiab] OR "Sexually Transmitted Diseases, Viral"[Mesh:NoExp] OR "human immunodeficiency virus"[tiab] OR "human immunedeficiency virus"[tiab] OR "human immune deficiency virus"[tiab] OR "AIDS"[tiab] OR "acquired immunodeficiency syndrome"[tiab] OR "acquired immunedeficiency syndrome"[tiab] OR "acquired immune deficiency syndrome"[tiab]	381352
#2	"Circumcision, Male"[Mesh] OR "Foreskin/surgery"[MeSH] OR circumcision[tiab] OR circumsie*[tiab] OR circumcis*[tiab]	6693
#3	"Homosexuality, Male"[Mesh] OR "Bisexuality"[Mesh] OR "gay men"[tiab] OR "bisexual men"[tiab] OR (bisexual*[tiab] AND men[tiab]) OR MSM[tiab] OR "men who have sex with men"[tiab] OR "Transgendered Persons"[Mesh] OR "Transsexualism"[Mesh] OR transgender*[tiab] OR intersex*[tiab]	25012
#4	#1 AND #2 AND #3	108
#5	Limit #4 to: Publication date from 1980/01/01	108
#6	newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR practice guideline[pt] OR guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt]	3741476
#7	#5 NOT #6	99

Table 3: Summary of Studies of Male circumcision status and HIV risk among men who have sex with men (ABS indicates an abstract only)										
Characteristics of included studies							**Total**			
Sources	**Study time and Location**	**Race/ Ethnicity**	**Age (yrs)**	**Participants: analytical/full sample**	**HIV assessment N (%)**	**Circumcision assessment N (%)**	**Circumcised N (%) [HIV+/circ+]**	**Uncircumcised N (%) [HIV+/circ-]**	**Study design**	**Sampling strategy**
Cross-sectional studies										
[10]Qian, et al., 2016	Beijing, China, 2010-2011	Asian Chinese	Mean=31	1155	Lab: 242/1155(21.0%)	Genital exam: 79/964 (8.2%)	11/79 (13.9%)	263/885 (29.7%)	Cross-sectional	Through a local community-based organization, advertisement on a website, outreach to gay-friendly venues, snowball-sampling
[11]Crosby, et al., 2015*	A mid-size southern city, US, 2011	Black	Mean=22.6 (SD=3.13)	400 recruited, 85 declined;	Lab: 106/384 (27.6%)	Self-report: 279/384 (72.7%)	76/279 (27.2%)	30/105 (28.6%)	Cross-sectional	Convenience sampling from a HIV/STD clinic
[17]Solomon, et al., 2014(ABS)*	12 cities, India, 2012-2013	Asian Indian	Median=25	12022	Lab: 838/12022 (7.0%)	Self-report: 1963/12022 (17%)	104/1963 (5.3%)	734/10059 (7.3%)	Cross-sectional	Respondent-driven sampling
[12]Zeng, et al.,	Chengdu, China,	Asian	Median=26.5 (Range	570	Lab: 13.3%	Genital	9/66	67/504	Cross-	Stratified snowball

2014*	2009	Chinese	18-69)			examination: all MSM (18.2%)	(13.6%)	(13.3%)	sectional	sampling
[20]Doerner, et al., 2013	Britain, 2007-2008	White	Mean=36 (Range 18-75)	1521	Self-reported: 97/1097 (8.8%)	Self-report: 254/1521 (16.7%)	Not reported	Not reported	Cross-sectional	Convenience sampling via website and venues (e.g., sexual health clinics, bars, clubs and others)
[13]Pando, et al., 2013*	Buenos Aires, Argentina, Nov2007-July2009	Presumably Hispanic	Mean=30.5 (SD=11.5)	482/500 (96.4%)	Lab: 81/482 (16.8%)	Self-report: 64/482 (13.4%)	7/64 (10.9%)	74/418 (17.8%)	Cross-sectional	Respondent-driven sampling via website
[14]Zhou, et al., 2013	Chongqing, China, 2010	Asian Chinese	Median=24 (Range 18-65)	491/498 (98.6%)	Lab: All MSM (14.9%), bottom (14.9%), top (7.1%), versatile (16.7%)	Self-report: 88/498 (17.7%)	Not reported	Not reported	Cross-sectional	Respondent-driven sampling via a STD clinic
[18]Schneider, et al., 2012	South India, Aug 2008-June 2009	Asian Indian	Median=26 (Range 24-30)	387	Lab: 72/387(18.6%)	Self-report: 143/397 (36.9%)	16/143 (11.2%)	56/188 (29.8%)	Cross-sectional	Convenience sampling from drop-in centers

[22]Oster, et al., 2011	21cities, US,2008	White (61%), Black (39%)	White: Median=36, Black: Median=28	5855	Lab: White 561/3585 (45.6%), Black 619/2270 (27.3%), Overall 1180/5855(20.2%)	Self-report: 4270/5181 (82.4%)	401/4270 (9.4%)	107/911 (11.0%)	Cross-sectional	Venue-based, time-space sampling
[25]Thornton, et al., 2011	London, UK,2008	Ethnic minority (17%)	Median=39, (Range 20-87)	653 /689 (94.8%)	Self-reported: 152/653(23.4%)	Self-reported: 188/653 (28.8%)	35/188 (18.6%)	117/465 (25.2%)	Cross-sectional	Venue-based convenience sampling
[23]Jozkowski, et al., 2010	US, 2009	Black (4%), White (82.1%), Hispanic (7.4%), Asian (2.9%), Others (3.1%)	25159 (18-23yr: 14.2%, 24-29:17.6%, 30-39: 22.9%, 40-49: 27.7%, 50-59: 13.2%, 60+: 3.4%)	25159/26257 (95.8%)	Lab: 14.1%	Self-reported: 21,312 (82.1%)	3012/21312 (14.3%)	543/3847 (14.3%)	Cross-sectional	Convenience sampling via email recruitment
[40]Lane, et al., 2011	Soweto, South Africa, 2008	Black African	64% are younger than 24	363/387 (93.8%)	Lab: 69/363 (20.6%)	Self-report: 124/363 (33.6%)	Not reported	Not reported	Cross-sectional	Respondent-driven sampling

[41]McDaid, et al., 2010	Glasgow and Edinburgh, Scotland, 2008	White	Not reported	1405/1508 (93.2%)	Lab: 54/1405 (4.5%)	Self-report: 233/1405 (16.6%)	8/233 (4.2%)	46/1172 (4.6%)	Cross-sectional	Convenience sampling at gay venues
[36]Begley, et al., 2008	7 cities, US, 2006	White (55.9%), Black (25.4%), Hispanic (5.5%), Others (13.2%)	Median=32, 60% are older than 25	780/1050 (74.3%)	Self-report: 100/772 (13%)	Self-report 646/772 (84%)	81/646 (13%)	19/126 (15%)	Cross-sectional	Convenience sampling via gay pride events
[27]Calzavara, et al, 2007(ABS)	Ontario, Canada, 2001-2005	Native American (2%), Latino (4%), Others (9%), White (85%)	Not reported	165	Not reported	Self-report 11/15 (73%)	2/11 (18%)	2/4 (50%)	Cross-sectional	Convenience sampling
[8]Millett et al, 2007-Latino	3 cities, US, May 2005-Apr 2006	Latino (49%)	Median=33.1	957/1091 (87.7%)	Lab: 348/957 (36%)	Self-report: 317/957 (33%)	116/317 (37%)	232/640 (36%)	Cross-sectional	Respondent-driving sampling

[8]Millett, et al., 2007-Black	3 cities, US, May 2005-Apr 2006	Black (51%)	Median=42.5	1079/1154 (93.5%)	Lab: 563/1154 (52%)	Self-report: 794/1079 (74%)	425/794 (54%)	138/285 (48%)	Cross-sectional	Respondent-driving sampling
[42]Mor, et al., 2007	San Francisco, US, Jan1996-Dec 2005	White (66%), Latino (16%), Asian/PI (10%), Black (7%), 1% Other	Not reported	20 832	Lab: 14902 (72%)	Genital exam: 15207/20832 (73%)	8942/12 577 (71%)	5960/8255 (72%)	Cross-sectional	Electronic medical records review
[44]Reisen, et al.,2007	New York City, US	Latino (146 from Brazil, 169 from Colombia, 167 from Dominican Republic)	Brazil: Mean=37.5; Colombia: Mean=38.2; Dominican Republic: Mean=33.6	427/482 (88.6%)	Self-report: Brazilian (22.6%), Colombian (32.0%), Dominican (25.2%)	Self-report: All (25%) Brazilian (20.6%), Colombian (26.6%), Dominican (25.8%)	28/111 (25.3%)	101/336 (30.1%)	Cross-sectional	Convenience sampling
[31,32]Sanchez, et al., 2007;2009	3 cities in Peru, 1 city in Ecuador,	Presumably Hispanic	Mean=26.4 (SD=6.7)	2884	Lab: 314 (11%)	Genital exam: 123/2884 (4%)	13/123 (1%)	301/2761 (11%)	Cross-sectional	Snowball sampling from Minister of Health clinics

	Feb 2006- Jun 2006									
[28]Lai, et al., 2004 (ABS)	Taipei, Taiwan, 2003	Presumably Asian Chinese	Not reported	556	Lab: 33/556 (6%)	Self-report: 154/556 (28%)	5/154 (3%)	28/402 (7%)	Cross-sectional	Not reported
[29]Kumta, et al., 2002 (ABS)	Mumbai, India, Mar 2001- Jul 2002	Presumable Asian Indian	Not reported	122	Lab: 21/122 (17%)	Genital exam: 27/122 (22%)	2/27 (7%)	19/95 (20%)	Cross-sectional	Not reported
[45]Tabet, et al., 2002	Lima, Peru, 1996	Presumable Hispanic	Mean=24	440/451 (97.6%)	Lab: 82/444 (18.5%)	Genital exam: 36/440 (8%)	Not reported	Not reported	Cross-sectional	Convenience sampling via street-outreach
[43]Reid, et al., 2001	England and Wales, 2001	White (93%), Asian (3%), Mixed (2%), Black (1%)	Mean=32.8 (SD=10.5)	13 851/14 616 (94.8%)	Self-report: 726 /13851(5%)	Self-report: 3089/13 851 (22%)	188/3089 (6%)	538/762 (5%)	Cross-sectional	Convenience sampling via gay-focused event, booklets, and website
[39]Kreiss & Hopkins, 1993	Seattle, US, Apr 1989- 1991	White (90%), Black (4%), Latino (4%), Asian/PI	UMC: Mean=40.6, MC: Mean=34.5	499/502 (99.4%)	Lab: 313/499 (63%)	Self-report: 422/499 (85%)	254/422 (60%)	59/77 (77%)	Cross-sectional	Convenience sampling via AIDS clinics

		(1%)								
Studies with follow-up										
[19]Koblin, et al., 2013	6 cities, US, 2009-2010	Black	HIV-negative: Mean=37	1164 at baseline, 935 at 6m, 872 at 12m	Lab: 28/1162 (2.4%)	Combination of genital exam and self-report: 881/ 1162 (75.8%)	21/881(2.4%)	7/281 (2.5%)	Cohort study with follow-up at 6m and 12m	Convenience sampling at gay community and via sex networkers; part of the HPTN061
[16]Chen, et al., 2011*	Taiwan, 2001-2005	Asian Chinese	mean=32.4, sd=8.1, range 17-81	1093	Lab: -all MSM (7.4%), -2001 (3.4%), -2002 (5.1%), -2003 (8.9%), -2004(8.5), -2005 (8.3%)	Self-reported: 266/1024 (26.0%)	13/266 (4.9%)	66/758 (8.7%)	Follow-up at 6m for HIV-neg MSM for 4 years	Convenience sampling; recruit from VCT programs via 5 gay-oriented-saunas
[21]Sanchez, et al., 2011	US and Peru, 2003-2007	Presumably Hispanic and White	US: MC: Mean=30, UMC: Mean=27; Peru: MC: Mean=41, UMC: Mean=37	1822/1824 (99.9%): 1360 (74.6%) from Peru, 462(25.4%) from US	Lab: 83/1822 (4.6%)	Genital exam: All MSM: 457/1822(25.7%), US (81.8%), Peru (5.8%),	18/457 (3.9%)	67/1365 (4.9%)	Follow up for 18m at every 3m	Part of a RCT for HSV-2 suppression for HIV prevention (HPTN039)

[37]Gust, et al., 2010	57 cities in US; 3 cities in Canada; 1 city in Netherlands	White (86%), Hispanic (6%), Black (4%), Asian (2%), Other (2%)	UMC=36.9, MC=36.6	4889/5417 (90.3%)	Lab: 342/488 (7.0%)	Self-report: 4209/4889 (86.1%)	299/4209 (7.1%)	43/680 (6.3%)	Follow up for 36m at every 6m	Part of a RCT for HIV vaccine
[38]Jameson, et al., 2010	US, Oct 2001-May 2006	Whites (75%), Hispanic (8%), Black (6%), Asian/PI (5.4%), Other (4.8%)	75.7% older than 25 years	3828/4749 (80.6%)	Lab: 1142/6924 (16.5%)	Genital exam : 3241/3828 (85%)	1016/5843 (17.4%)	181/1081 (16.7%)	Follow-up with 1-6 visits	Convenience sampling via STD clinics
[15,24,30]Buchbinder,2007; Koblin et al., 2012; Barnabas, et al., 2011	North America, Caribbean, South America, Australia, 2004-2007	Black (10%), Latino (10%), Multiracial (25%), White (50%), Other (6%)	Median=30 (Range 18-45)	1787/1836 (97.3%)	Lab: 80 (5%)	Combination of self-report and genital exam: 999/ 1787 (56%)	52/999 (5%)	28/788 (4%)	Follow up at 12,30 and 52 w, and every 26w afterwards	Double-blind randomized selection (STEP study)
[33,34]Templeto	Sydney,	Anglo ethnicity	Median=35 (Range 18-	1426/ 1427	Lab:	Combination of	29/938	13/488 (3%)	Follow-up for	Convenience sampling from community-based

n, et al., 2009; Mao, et al., 2008	Australia, 2001-2004	(74%)	75)	(99.9%)	42 (3%) 0.8/100 pyr	self-report and genital exam: 938/1426 (66%)	(3%)		36m at every 6m; cohort study	venues (HIM study);
[35]Bartholow, et al., 2006	US, Canada, Netherlands Jun 1998- Nov1999	Asian/PI (2%), Other (2%), Black (4%), Latino (6%), White (86%)	Not reported	5090/5095 (99.9%)	Lab: 2.8/100 pyr , 362/5095 (7%)	Self-report: 4381/5090 (86)	315/4381 (7%)	47/709 (7%)	Follow-up for 36m	Part of a RCT
[49]Buchbinder, et al., 2005	6 cities, US, Apr 1995- May 1997	White (76%), Latino (12%), Black (7%), Asian/PI (5%)	65.4% are older than 35	3257	Lab: 1.55/100 pyr	Self-report: 2866/3257 (88%)	Not reported	Not reported	Follow-up for 18m at every 6m	Recruit from HIVNET program

Notes:

ABS: abstract; MC: male is circumcised; UMC: uncircumcised ; RCT: Randomized Control Trials; HPTN: The HIV Prevention Trials Network; VCT: Voluntary Counselling and Testing ;

HSV-2: Herpes simplex virus type 2; PI: Pacific Islander

*crude odds ratios were calculated by raw data

CHAPTER V

PREDICTING THE IMPACT OF VOLUNTARY MEDICAL MALE CIRCUMCISION ON HIV INCIDENCE AMONG MEN WHO HAVE SEX WITH MEN IN BEIJING, CHINA

Abstract

Objective: To project the number of new HIV cases over 11-year period among men who have sex with men with different assumptions of uptake of voluntary medical male circumcision (VMMC) in Beijing, China.

Methods: Using a deterministic compartmental modeling procedure to fit prevalence from 2005-2015, we projected new HIV cases during 2016-2026 under different coverage rates ranging from 0.0001 (at baseline) to 0.15 (an optimistic assumption) with simulation on varying transmission rates, model calibration to match historical data, and sensitivity analyses for several assumptions.

Results: Compared with the baseline (λ=0.0001), we found the new HIV cases would reduce with the increase of coverage rates of the VMMC among MSM. The higher the coverage rate, the lower new HIV cases would be. The number of new HIV cases would keep decreasing by 0.15%, 0.80%, 1.6%, 7.1%, 12.4% and 16.3% compared to the baseline by the end of 2026, if we increase the annual coverage rate of VMMC to 0.01, 0.005, 0.01, 0.05, 0.1 and 0.15, respectively.

Discussion: As one of the first studies to model the potential impact of VMMC among MSM in China, our model suggested a modest to significant public health impact of VMMC. Even at just 15% VMMC annual uptake rate, the reduction in new infections is substantial. Therefore, there is a strong need to determine the efficacy of VMMC among MSM, to improve the evidence base for its potential use among MSM in low circumcision settings. Only then can policymakers decide whether to incorporate VMMC into a package of HIV prevention interventions targeting MSM.

Key words: Voluntary medical male circumcision; mathematical modeling; HIV; incidence; men who have sex with men; China

Introduction

Based upon a newly released report from the Chinese government, the number of people living with HIV/AIDS (PLWHA) in China was 575,000 by the end of 2015(ChinaDaily, 2015). Although national HIV surveillance data suggest that China is a relatively low-prevalence country, the trend of increasing HIV prevalence among men who have sex with men is of concern (NHFPC, 2014, 2015).

The most common transmission route for the HIV/AIDS epidemic in China has shifted from injection drug use and contaminated plasma collection/reinfusion in the 1990s to unprotected sexual contacts in the early 21st century (Guo et al., 2011; UNAIDS & MoH, 2015). The rapid increase in male-to-male sexual transmission is of a particular concern (Chow et al., 2011a; Lu et al., 2013; J. R. Wu et al., 2013; Ye et al., 2012). Although the dominant route is still reported to be heterosexual transmission, male homosexual transmission shows a marked uptrend, representing just 2.5% of new

infections in 2006 to 25.8% in 2014 (NHFPC, 2014, 2015). In addition, homophobia and stigma against MSM is significant in China, and its MSM epidemic is very likely to be underestimated (Lou et al., 2014; Z. Wu et al., 2013; Y. Zhou et al., 2014).

Although the ever-increasing HIV epidemic explodes among Chinese MSM, few effective interventions are available and/or widely utilized (Guo et al., 2011). Condoms can effectively prevent HIV transmission, but only 20% MSM consistently use condoms during sexual activities (Guo et al., 2011; Zheng, 2009). Pre-exposure prophylaxis (PrEP) can be used by uninfected MSM, but uninfected individuals often fail to adhere to pre-exposure prophylaxis (PrEP) antiretroviral drug regimens when they do not feel ill nor perceive themselves to be at high risk. PrEP adherence is limited by drug side effects (Huang et al., 2014; Okwundu, Uthman, & Okoromah, 2012; Pretorius, Stover, Bollinger, Bacaer, & Williams, 2010). Voluntary medical male circumcision (VMMC) might serve as a biomedical tool to provide lifelong protection after a single surgical procedure for MSM, as has been demonstrated for heterosexual men (Vermund & Qian, 2008).

Circumcision is likely to protect men from acquiring HIV by eliminating the most vulnerable mucosal surface areas and HIV target cells in a minimally keratinized zone, the inner surface of the penile prepuce (Donoval et al., 2006; Vermund & Qian, 2008). Both observational studies and large randomized controlled trials (RCT) have shown that VMMC reduces the risk of HIV acquisition by over half in heterosexual men living in high prevalence areas of Africa (Auvert et al., 2005; Bailey et al., 2007; R. H. Gray, Kigozi, et al., 2007). Although the evidence on the relationship between VMMC and HIV risk among MSM has been inconclusive, protective effects have more often been observed among men who practiced insertive sex (Beyrer, 2010a; Doerner et al., 2013b;

Fankem et al., 2008; Gust et al., 2010; Jameson et al., 2010a; Jozkowski et al., 2010; Londish et al., 2010b; Sanchez et al., 2011; Schneider et al., 2012b; Wiysonge et al., 2011; C. Zhou et al., 2012). A study published in 2015 among MSM in Beijing suggested a remarkably strong protection effect among Chinese MSM who predominately practice insertive sex (adjusted odds ratio [aOR], 0.15; 95% confidence interval [CI], 0.04-0.65). This study confirmed all circumcisions by physical examination and suggested a strong beneficial trend for MSM with versatile or receptive sexual positioning as well, providing the strongest evidence to date that VMMC might be a useful biomedical tool for HIV risk reduction among MSM. Our recently conducted meta-analysis revealed a statistically significant protective effect against HIV among MSM, especially among MSM with comparatively lower risk profiles, such as MSM in Asia (Zhang, Qian, et al., Under review). Therefore, circumcision may prove to be an overlooked biomedical tool for HIV prevention among MSM.

To date, only one paper adopting a stochastic network-based model employing hypothetical sex-role preferences has been published which concluded that the roll-out of VMMC among MSM would be unlikely to reduce new HIV infection in Peru substantially (Goodreau et al., 2014). However, Goodreau et al (2014) employed older, less optimistic assumptions as to VMMC protective efficacy, not compatible with more recent literature (Goodreau et al., 2012; Qian et al., 2016; Zhang, Qian, et al., Under review). Furthermore, the Peru and China MSM epidemics are different in several epidemic and social characteristics, limiting their model's relevance for Chinese settings. Lou et al have assessed the impact of a few behavioral intervention approaches (e.g., condom use, partner reduction, HIV testing and ART) among Chinese MSM in Beijing

using mathematical modeling strategies (Lou et al., 2014; Lou, Wu, Chen, Ruan, & Shao, 2009). Neither the Peru nor China studies specifically examined the putative impact of VMMC among MSM in China.

We sought to model the extent to which VMMC could alter the MSM epidemic in Beijing, China, employing a deterministic compartmental modeling strategy to project new HIV cases from 2016 to 2026 among MSM under different assumptions, particular the uptake rates of VMMC and degree of protective efficacy of VMMC. We hypothesized that projected HIV incidence among MSM in Beijing would be reduced by greater use of VMMC. In the current study, we aimed to establish a more generic mathematical model that can be generalizable to other settings with comparable social and cultural characteristics.

Methods

Study design

We used a deterministic compartmental model for simulating and projecting the HIV epidemic among MSM in Beijing. Deterministic compartmental models can specify transmission rates between compartments (e.g., susceptible, infectious) and they fit well large populations (R. Barnabas, 2016; Trottier & Philippe, 2000). This model is usually used to describe and explain transmission patterns of certain infectious diseases at the population scale (Trottier & Philippe, 2000). In the current study, we did not employ the sex-role-preference model as the sex position was too dynamic to capture (Goodreau et al., 2014; Lou et al., 2009; Wiysonge et al., 2011). Although some MSM in Beijing have female sexual partners, they were less likely to engage risky sexual behaviors with their female partners (Lou et al., 2014; Lou et al., 2009). Therefore, we only considered the

HIV infection as the result of homosexual contacts with male partners no other route of transmission was interfered in the current study (Fan et al., 2012; Lou et al., 2014). Model parameters (e.g., demographics, behavioral and population-level) of the compartmental ordinary differential equation model were informed by key factors identified in published literature and available datasets.

In order to capture the randomness of transmission rates, we further simulated the transmission rates by 50 times using linear coefficients to capture all possible possibilities. We also assumed that the active age of sexual activities ranges from 18-65 years among MSM in Beijing (Li, Liang, & Yang, 2008; Lou et al., 2014).

Model structure

As being circumcised may change the risk of HIV transmission significantly among MSM (Goodreau et al., 2014; Goodreau et al., 2012; Qian et al., 2015), the study population was divided into two mutually exclusive subgroups: 1) uncircumcised MSM and 2) circumcised MSM. In this model, seronegative MSM were entered into the overall MSM population with a rate of σ (the susceptible population); σ^+ represented the rate entering the circumcised susceptible pool (S_{c+}), while σ^- represented the rate entering the uncircumcised susceptible pool (S_{c-}). Meanwhile, MSM could leave the transmission model by aging beyond 65 years, emigrating out of Beijing, or by dying. We used the parameter τ to indicate rates of leaving the model among susceptible MSM, with τ^+ representing the rate of leaving the circumcised susceptible pool (S_{c+}) and τ^- representing the rate of leaving the uncircumcised susceptible pool (S_{c-}). MSM would change from being uncircumcised to being circumcised at a rate of λ (Figure 1).

Uncircumcised MSM became infected and entered the compartment of HIV-infected without circumcision (I_{c-}) at an HIV transmission rate of ρ^-; and circumcised MSM became infected (I_{c+}) at a transmission rate of ρ^+. Both circumcised and uncircumcised MSM could leave the infectious pool at a rate of η^- for uncircumcised and η^+ for circumcised MSM for the following reasons: **1)** progression to AIDS, **2)** death due to HIV infection, **3)** having undetectable viral loads due to either being an elite immunologic controller (e.g., a small group of HIV-infected patients who can maintain a high level of CD4 cell counts without progressing immunologically towards AIDS over years in absence of ART (Pantaleo et al., 1995)) or adhering to an effective ART regime (Figure 1). When possible, parameters were estimated from the published literature or from available unpublished data sources (Lou et al., 2014; Lou & Smith, 2011; Lou et al., 2009); a few parameters were calculated within the model itself (Table 1).

Model calibration

In order to refine the model to provide the most valid predictions, we used data to calibrate the model parameters to enable the model to predict historical surveillance data. At the initial stage, we used 2005-2015 surveillance data for HIV prevalence in Beijing to compare trends with those predicted by our model (Figure 2). In this model calibration process, parameters were adjusted until the prediction lines best overlapped with lines that reflected the historical surveillance data. When the prediction model overlapped with the surveillance data, using plausible and defensible parameter estimations, we considered the generated model to serve well for predictions forward in time.

In Figure 2, we presented the prediction model that we used for further calculations; the predicted and historical lines among four groups of MSM (susceptible circumcised [Scm], susceptible uncircumcised [Scp], infected circumcised [Ichp], and infected uncircumcised [Ichm]) overlapped well with each other. After this initial model calibration, we used the numbers generated by the model for 2015 (e.g., ρ^{-}= 0.0099861, ρ^{+}= 0.0093921, Scm=362,476, Scp=6,970, Ichp=59, and Ichm=3,129) as the baseline initial state to predict numbers of infected and susceptible MSM from 2016 to 2026 (see Appendix 1 for detailed formulas).

Data sources and estimation

(1) Calculation of HIV incidence rates among both circumcised and uncircumcised MSM (2005-2015): To calculate incidence rates among circumcised and uncircumcised MSM for 2005-2015, we used a pooled adjusted odds ratio from a recently updated meta-analysis(Zhang, Qian, et al., Under review) as well as the HIV surveillance data from China CDC (personal communication). As these data were only available as summary statistics, no identifiers can be found to track back to individual subjects in the HIV surveillance system. We calculated the HIV incidence from 2005-2015 among circumcised and uncircumcised MSM in Beijing (Table 2; see Appendix 2 for details of these calculations).

(2) Simulation for incidence rates of HIV among both circumcised and uncircumcised MSM (2016-2025): To simulate HIV incidence from 2016 through 2025, we used existing incidence data among circumcised and uncircumcised MSM (2005-2015). We conducted a series of simulations for transmission rates of HIV among circumcised (ρ^{+}) and among uncircumcised (ρ^{-}) men. The simulation procedure is to project future transmission rates

based upon existing HIV incidence among MSM for the next 10 years (R-software, Murray Hill, NJ, USA). We assume that incidence would increase linearly. Through 50 repeated simulations, we generated the predicted transmission rates for 2016-2025 among uncircumcised and circumcised MSM (Figure 3; Table 3).

(3) Prediction of new HIV cases: Using the calibrated model as well as the simulated data, we calculated new HIV cases among MSM for each prediction year (2016-2026) by varying the annual coverage rates of VMMC from 0.0001 to 0.15. We compared the new HIV cases for each hypothetical scenario with the new HIV cases at the baseline (λ=0.0001). The reduced proportion of HIV-infected men was defined as "the (HIV cases in the predicted year minus the number of cases at baseline) divided by the baseline cases". This was used as the indicator for each hypothetical coverage rate comparing the projected date with the baseline infection rate.

(4) Sensitivity analyses: We conducted sensitivity analyses by setting the transmission rates for both circumcised and uncircumcised MSM at the same level as the incidence rate seen in 2015. If nothing changes from 2015, it represents a lower bound for the transmission rate. In addition, we calculated new HIV cases with a range of protective efficacies ranging from 0.07 (95% CI, 0.01-0.12) to 0.47 (95% CI,-0.02-0.73) as literature suggested (Qian et al., 2016; Zhang, Qian, et al., Under review).

Results

New HIV cases at each different coverage rate of VMMC

Compared with the baseline (λ=0.0001), we found the new HIV cases reduced with increasing coverage rates of the VMMC among MSM. Higher coverage rates are

associated with lower numbers of HIV new case. By the year 2026, retaining the VMMC coverage rate at the baseline 2015 rate (λ=0.0001), new HIV cases are 50,301, while a small increase of VMMC coverage to 0.0005 results in the number of HIV cases to be reduced slightly to 50,270. Similarly, by the end of 2026, the number of newly infected HIV cases decreases by 0.15%, 0.8%, 1.59%, 7.11%, 12.38% and 16.34% compared to the baseline (λ=0.0001) if we increase the annual coverage rate of VMMC to 0.01, 0.005, 0.01, 0.05, 0.1 and 0.15, respectively (Table 4).

With the increased coverage rates of VMMC, the absolute number of infected circumcised MSM increases (Figure 4a), while the number of infected uncircumcised MSM decreases over the same period of time (Figure 4b). With the increased coverage rates of VMMC, the number of susceptible circumcised MSM increases each year, given the larger pool of circumcised men (Figure 5a), while the number of susceptible uncircumcised MSM decreases over the same period of time (Figure 5b). Still, the risk of transmission is lower for the circumcised (ρ^+) than among uncircumcised (ρ^-) men, as per assumptions (see Methods).

Prevalence of VMMC among MSM

We also hypothesized the prevalence of VMMC among all MSM in Beijing. With a higher coverage rate, the prevalence of VMMC naturally increased accordingly. By the year of 2026, the prevalence increased from 1.75% when the baseline coverage rate was 0.0001 to 58.76% when the VMMC coverage rate increased to 0.15 per annum (Table 5).

Results of the sensitivity analyses

The same patterns for HIV-infected and susceptible MSM by circumcision status and proportion of circumcised men were observed when the transmission rates were set at the same incidence rate seen in 2015. In addition, a smaller magnitude of the reduction in the proportion of HIV-infected men with increasing circumcision coverage was observed (Supplementary Table 1; Supplementary Figure 2a-d).

We also assessed the HIV incidence by different protective efficacies ranging from being very conservative 7% (Zhang, Qian, et al., Under review) to being optimistic 47%(Qian et al., 2016). The transmission rate of HIV reduced among circumcised MSM with higher circumcision coverage rates (Supplementary Figure 3). Overall, fewer new HIV cases were observed with higher protective efficacies within the same circumcision coverage rate. The higher coverage rate, the fewer HIV cases would be in the projected years (Supplementary Table 2).

Discussion

We have employed a deterministic, compartmental model to predict the magnitude of the impact of VMMC on HIV acquisition over a 11-year period by estimating the reduction in proportion of HIV-infected cases (Kripke et al., 2016). By changing the coverage rates of VMMC from the very low baseline coverage (λ=0.0001) to a hypothetical scenario of an active VMMC program (λ=0.15), our model suggested a modest to significant public health impact of VMMC for MSM in China, depending on coverage assumptions, given an assumed efficacy of 7%. This low efficacy was derived from a systematic review and meta-analysis, but a 47% (95% confidence interval: -2 to

+73%) protective efficacy estimate from a Chinese study conducted in 2010-2011 suggested VMMC to be more beneficial than earlier studies suggested; our estimates of benefit are very conservative (Qian et al., 2016; Zhang, Qian, et al., Under review). The reduction in proportion of HIV-infected cases ranged from 0.06% when the VMMC coverage rate as low as 0.0001 (corresponding to the prevalence of VMMC as 1.7%) to 16.3% when the VMMC coverage rate increased to 0.15 (corresponding to the prevalence of VMMC as 58.8%) by the year of 2026. Meanwhile, we observed a big jump of the reduction in the proportion of the number of HIV cases (from 1.6% to 7.1%) when the VMMC coverage rate increased from 0.01 to 0.05. The big jump may indicate that a slight increase of the VMMC coverage rate may result in a significant reduction in new HIV cases among MSM in China, even with our use of very conservative estimates of the efficacy of VMMC in protecting MSM.

A seemingly paradoxical finding is easily explained. With the increased coverage rate of VMMC, the number of circumcised MSM increasing over time increases both the number of susceptible and infected circumcised men over time, merely because they are greater in number and we assume the very modest 7% protective efficacy. In parallel, the number of uncircumcised MSM who are either infected or are susceptible decreases over the same period of time, as they are overall reduced in number with increased circumcision coverage.

Compared with modeling estimates using data from Peru and from more resource-rich settings (Anderson et al., 2009; Goodreau et al., 2014; Njeuhmeli et al., 2011), our model suggests a more optimistic efficacy of VMMC among MSM, even when using a low protective efficacy estimate (7%) for VMMC. In the study conducted in Peruvian

MSM, authors observed less than 5-10% of HIV cases to be likely averted if VMMC coverage rate were to grow to 50% in coming years (Goodreau et al., 2014). Two other studies posited that only if a 100% coverage rate of VMMC were achieved would such an incidence reduction be observed (Anderson et al., 2009; Londish, Templeton, Regan, Kaldor, & Murray, 2010a). The proportion of MSM who have a comparatively lower-risk profile, the low baseline VMMC prevalence, and the relatively recent expansion of the HIV epidemic among MSM in China may suggest, in part, why our model is more optimistic about the VMMC role for MSM in China (Lou et al., 2014; Vermund & Qian, 2008; Zhang, Qian, et al., Under review). As a “surgical HIV vaccine" that offers lifelong protective benefits, VMMC might be embraced by the MSM community if advocated for by public health and community-based representatives. A clinical trial to estimate more precisely the protective efficacy of VMMC in men who practice predominantly insertive, versatile, or receptive anal intercourse would help refine projection models considerably.

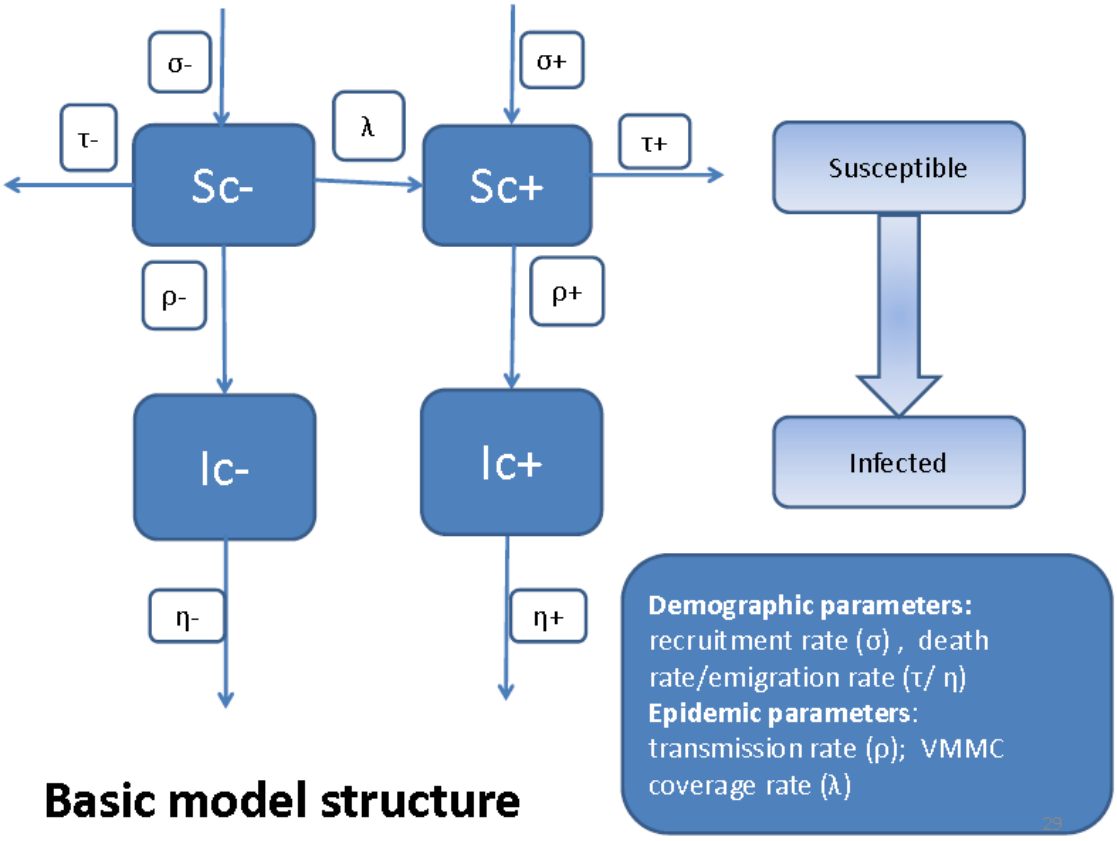
Strengths of the current study include our employment of a deterministic compartmental model for predictions. The deterministic model has advantages compared to stochastic models for predicting incidence of chronic infectious diseases such as HIV/AIDS (Lou et al., 2014). Although the output of a deterministic model was fully determined by values of included parameters and initial conditions, the simulation procedure for transmission rates can capture randomness properties better than can stochastic models (Vynnycky & White, 2010). Additionally, we used sensitivity analyses to estimate new HIV cases at their lower bound when transmission rates remained the same as seen in 2015 as well as at different protective efficacies, suggesting our findings to be robust and plausible. Our model may apply, too, to other settings with similar

epidemic characteristics. A second strength of our study is that, unlike other modeling studies using hypothetical/simulated data (Goodreau et al., 2014), we used validated data sources to calculate parameters while adjusting initial conditions for the model (Lou et al., 2014; Zhang, Qian, et al., Under review). The simulation procedure used parameters estimated from HIV surveillance data in Beijing, improving the validity of the model and likely accuracy of context-specific predictions. Third, during the model building procedure, we gradually raised the VMMC coverage rates from baseline (λ=0.0001) to multiple hypothetical situations until λ=0.15. This procedure captures the slight changes as the result of the increased VMMC coverage rate, providing a range of estimates and practical guidance for health professionals for future interventions of VMMC among MSM in China.

The major limitation of our prediction model is a simplification of the real epidemic in Beijing in our effort to balance parsimony and reality. For instance, unlike existing studies considering sexual role preferences (Goodreau et al., 2014; Lou et al., 2014), we did not stratified Chinese MSM by their sex role positioning due to the lack of population-based information as the relative frequencies of these sexual positioning preferences. However, as our prediction model was built upon average transmission rates regardless of sexual positioning, it may capture average transmission patterns among MSM as a whole in Beijing. We did not incorporate other risk factors (e.g., types of partners, multiple partnership, and condom use) in the model. With more availability of the epidemic information among this population, a more sophisticated model can emerge to assess the impact of VMMC on curbing HIV among Chinese MSM.

In conclusion, our model estimates the potential benefit of VMMC among MSM in China, using conservative to optimistic estimates of the efficacy of VMMC for HIV prevention. VMMC may serve as a new tool to reduce HIV incidence among MSM in China. Although the optimal scenario of higher VMMC coverage rates can bolster HIV incidence reduction among MSM, the lack of an efficacy trial in this population limits our ability to confidently assert the impact of VMMC on HIV, since protective efficacy of VMMC may vary greatly by epidemic context and relative frequency of predominantly insertive vs. receptive men. Without such efficacy data, widespread VMMC could be logically, ethically, and economically challenging (Sullivan et al., 2014).

Figure 4. Schematic diagram for the HIV transmission model and voluntary medical male circumcision among men who have sex with men

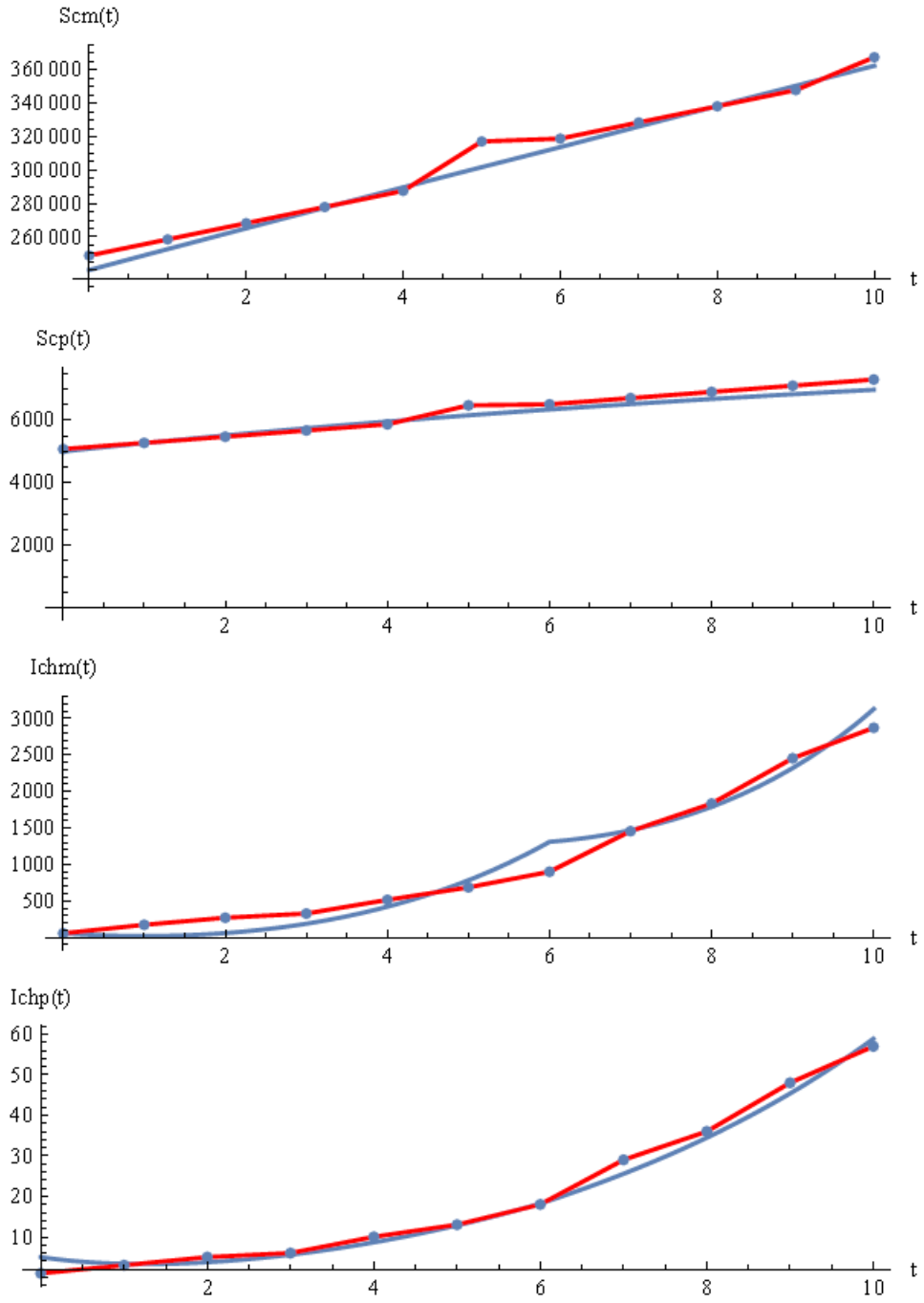


Equations from the diagram

- $S_c^-{}'(t) = \sigma^- - \rho^- * S_c^-(t) - \lambda * S_c^-(t) - \tau^- * S_c^-(t)$
- $S_c^+{}'(t) = \lambda * S_c^-(t) - \rho^+ * S_c^+(t) - \tau^+ * S_c^+(t) + \sigma^+$
- $I_c^-{}'(t) = \rho^- * S_c^-(t) - \eta^- * I_c^-(t)$
- $I_c^+{}'(t) = \rho^+ * S_c^+(t) - \eta^+ * I_c^+(t)$
-

**parameters ρ^+/ρ^- are transmission rates.*
** parameter λ will be changed based upon different coverage of VMMC*

Figure 5. Compare the model-predicted and historical trends (surveillance statistics) among four groups of men who have sex with men in China (2005-2015)



NOTE: Figure 2 compares 2005-2015 surveillance data for HIV prevalence in Beijing (red line) with data predicted by our model (blue line); Scm: susceptible circumcised, Scp: susceptible uncircumcised, Ichp: infected circumcised, Ichm: infected uncircumcised; t: in years (from the year of 2005 to the year of 2015)

Figure 6. HIV transmission rates among circumcised (circ+) and uncircumcised (circ-) men who have sex with men in China

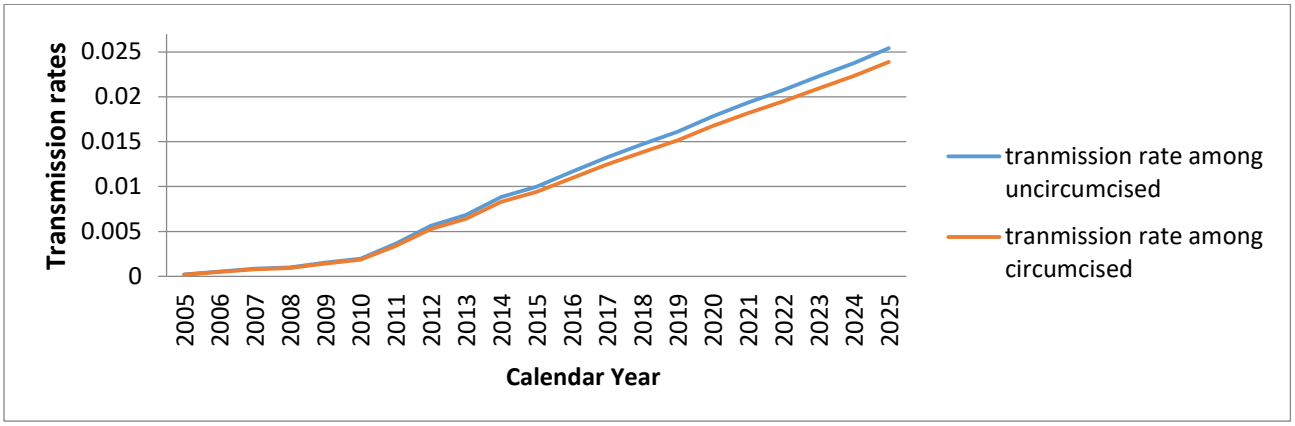


Figure 7. Number of infected circumcised men who have sex with men in Beijing by years (2016-2026)

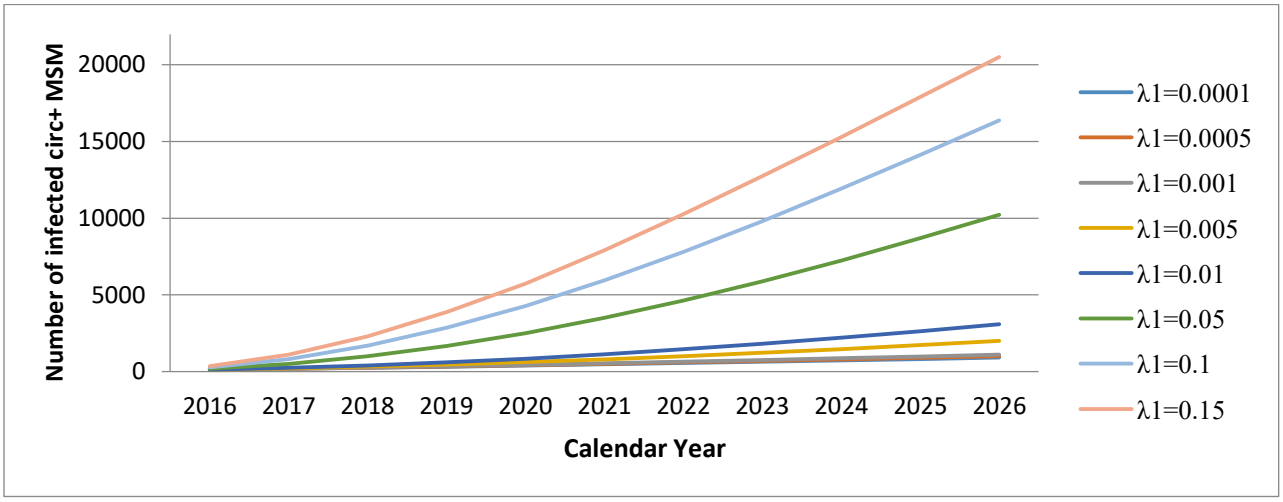


Figure 8. Number of infected uncircumcised men who have sex with men in Beijing by years (2016-2026)

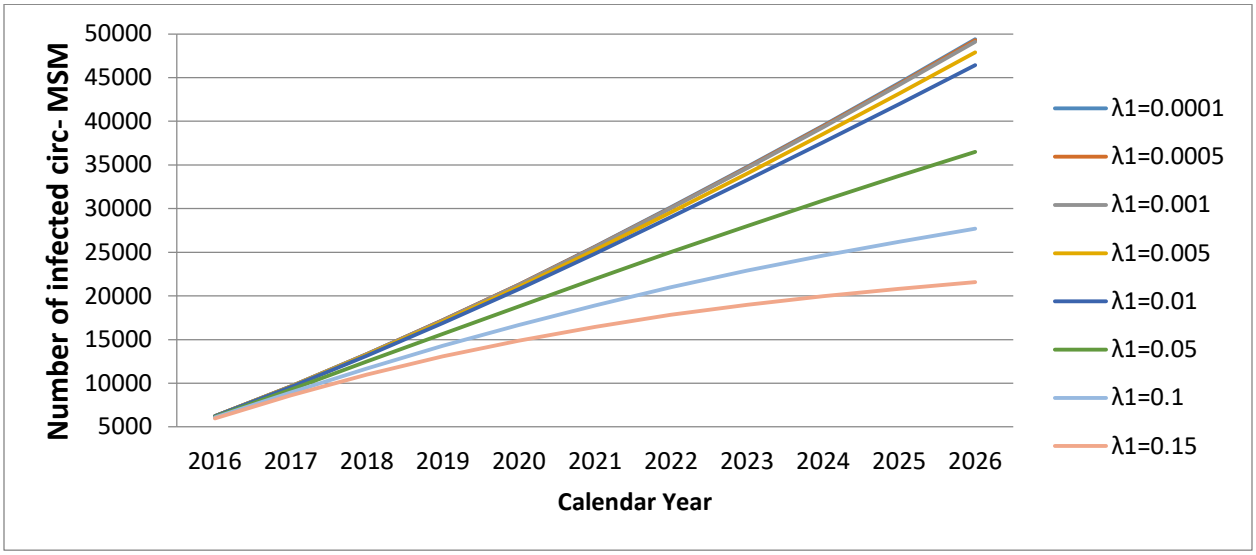


Figure 9. Number of susceptible circumcised men who have sex with men in Beijing (2016-2026)

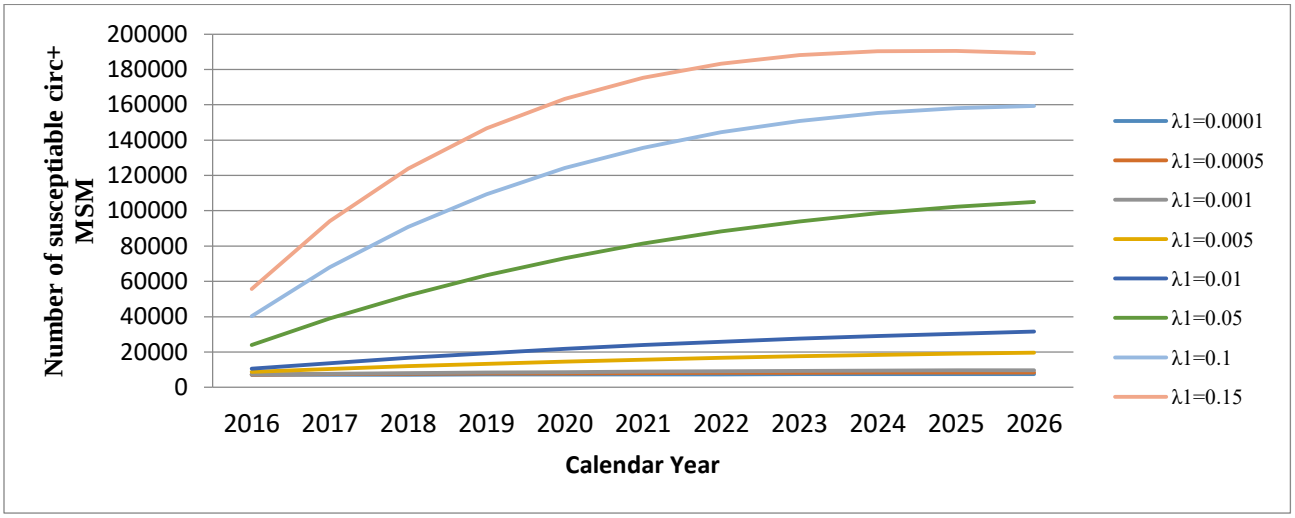


Figure 10. Number of susceptible uncircumcised men who have sex with men in Beijing (2016-2026)

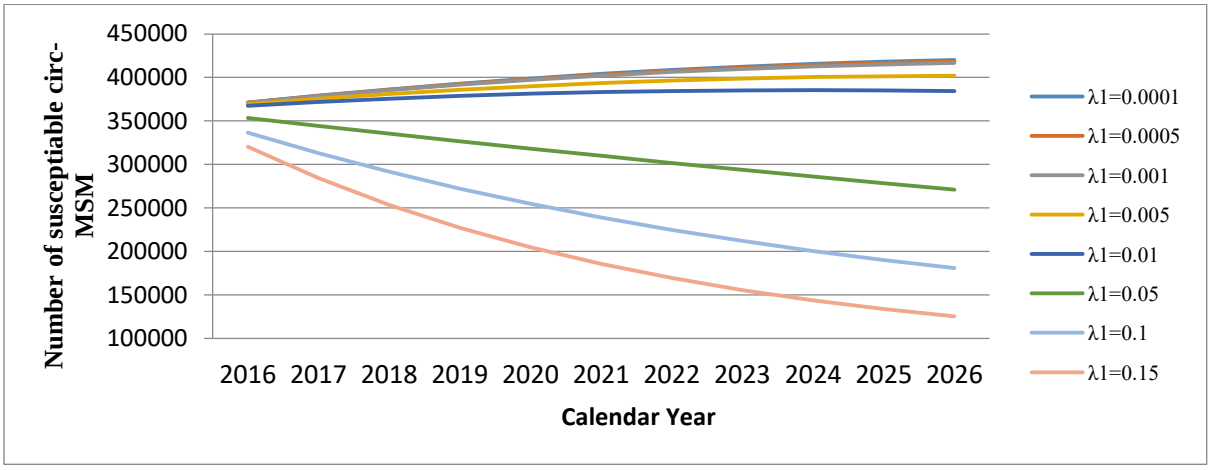


Table 4: Parameters for model building to assess HIV transmission model and the potential effect of male circumcision at varying levels of coverage among Chinese men who have sex with men

Parameters	Description	Types	Sources
σ+	Recruitment rate into circumcised per year	*actual number /year*	(Lou et al., 2014; Lou et al., 2009)
σ-	Recruitment rate into uncircumcised per year	*actual number/year*	(Lou et al., 2014; Lou et al., 2009)
τ+/τ-	Natural removal rate from susceptible circumcised MSM	*Fraction*	(Lou et al., 2014; Lou et al., 2009)
Death rate	0.01	*actual number/year*	(Lou et al., 2014; Lou et al., 2009)
emigration rate out of BJ	0.06	*actual number/year*	(Lou et al., 2014; Lou et al., 2009)
ρ+	Transmission rate from susceptible to HIV positive among circumcised MSM-overall	*Fraction*	Surveillance data from China CDC; Zhang et al., under review
ρ-	Transmission rate from susceptible to HIV positive among uncircumcised MSM-overall	*Fraction*	Surveillance data from China CDC
λ	Rate of circumcision among susceptible MSM per year	*Fraction*	Based upon different values given to λ
η+/η-	Rate of removal from the infected circumcised/uncircumcised MSM group	*Fraction*	(Lou et al., 2014; Lou et al., 2009); model adjustment*
yearly mortality rate due to AIDS	Yearly death rate	*yearly mortality rate*	(Lou et al., 2014; Lou et al., 2009); model adjustment*

undetectable rate after ART	Effective treatment that moves MSM out of the infectious pool	*undetectable rate*	(Lou et al., 2014; Lou et al., 2009); expert opinion
undetectable rate due to elite immunological control	Inherent ability of the host immune system to reduce viral load	*undetectable rate*	(Okulicz & Lambotte, 2011)
emigration rate out of BJ	Demographic factors of mobility after HIV infection	*emigration rate out of BJ*	(Lou et al., 2014; Lou et al., 2009)
Scm	Susceptible uncircumcised MSM (C-minus)	*Actual Number*	Model predictions
Scp	Susceptible circumcised MSM (C-plus)	*Actual Number*	Model predictions
Ichp	Infected circumcised MSM (C-plus)	*Actual Number*	Model predictions
Ichm	Infected uncircumcised MSM (C-minus)	*Actual Number*	Model predictions

*Parameter was adjusted in order that the model could predict historical data

Table 5: Prevalence and incidence among circumcised and uncircumcised MSM in Beijing, China (2005-2015)

	Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Uncircum-cised MSM	**Incidence**	0.00019	0.00054	0.00084	0.00099	0.00152	0.00197	0.00361	0.00563	0.00684	0.00883	0.00999
	Prevalence	0.00306	0.00868	0.0135	0.01588	0.02432	0.0315	0.05784	0.09009	0.10939	0.14134	0.15978
Circumcised MSM	**Incidence**	0.00018	0.0005	0.00079	0.00092	0.00142	0.00184	0.00338	0.00527	0.00641	0.0083	0.00939
	Prevalence	0.00294	0.00833	0.01297	0.01525	0.02337	0.03028	0.05565	0.0868	0.10548	0.13646	0.15437

Table 6: Actual and predicted HIV transmission rates among circumcised and uncircumcised men who have sex with men in China

	Year	Transmission rate for circ- (uncircumcised MSM)	Transmission rate for circ+ (circumcised MSM)
Actual transmission rates for 2005-2015	**2005**	0.0001913	0.00017795
	2006	0.0005424	0.000504712
	2007	0.0008438	0.000785447
	2008	0.0009924	0.000923922
	2009	0.0015198	0.001415785
	2010	0.0019689	0.001835104
	2011	0.0036149	0.0033755
	2012	0.0056309	0.005269953
	2013	0.006837	0.00640751
	2014	0.0088337	0.008297409
	2015	0.0099861	0.009392091
Predicted transmission rates for 2016-2025	**2016**	0.0116339	0.010932
	2017	0.0132703	0.012472
	2018	0.0147111	0.013827
	2019	0.0161193	0.015152
	2020	0.0178254	0.016758
	2021	0.0193403	0.018184
	2022	0.0207475	0.019507
	2023	0.0222659	0.020936
	2024	0.0237391	0.022322
	2025	0.0254127	0.023898

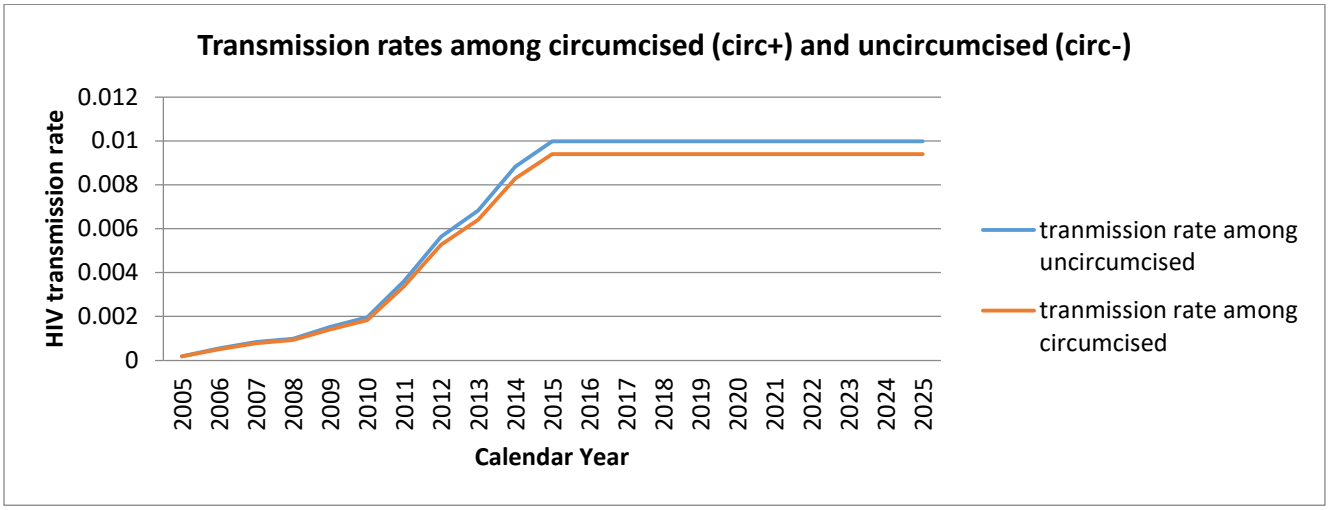
Table 7. The number of newly infected HIV cases among men who have sex with men in China with different coverage rates of voluntary medical male circumcision (2016-2026)

Year → **Circumcision coverage rate ↓**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**Reduction in proportion HIV-infected with increasing circumcision coverage (%)**
λ1=0.0001	3188	6344	9816	13581	17547	21688	26104	30694	35397	40242	45190	50301	Baseline
λ1=0.0005	3188	6344	9816	13580	17546	21685	26099	30687	35386	40225	45167	50270	0.06
λ1=0.001	3188	6344	9815	13580	17543	21679	26090	30673	35366	40199	45132	50224	0.15
λ1=0.005	3188	6343	9812	13570	17524	21644	26031	30582	35233	40013	44881	49897	0.80
λ1=0.01	3188	6343	9809	13560	17501	21603	25961	30472	35073	39788	44577	49499	1.59
λ1=0.05	3188	6337	9779	13476	17322	21279	25427	29656	33897	38170	42431	46724	7.11
λ1=0.1	3188	6330	9744	13380	17122	20923	24853	28800	32696	36553	40331	44074	12.38
λ1=0.15	3188	6324	9711	13292	16943	20614	24368	28094	31726	35279	38716	42081	16.34

Table 8. Prevalence of voluntary medical male circumcision among all men who have sex with men in Beijing by years (2016-2026) (%)

Coverage rates↓/year→	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
λ1=0.0001	1.87	1.85	1.83	1.82	1.80	1.79	1.78	1.77	1.76	1.75	1.74
λ1=0.0005	1.90	1.92	1.93	1.94	1.95	1.95	1.96	1.97	1.97	1.98	1.98
λ1=0.001	1.95	2.00	2.05	2.09	2.13	2.16	2.19	2.21	2.23	2.26	2.27
λ1=0.005	2.31	2.69	3.02	3.30	3.56	3.79	3.99	4.17	4.33	4.47	4.60
λ1=0.01	2.77	3.54	4.21	4.80	5.32	5.78	6.19	6.56	6.88	7.17	7.43
λ1=0.05	6.32	10.06	13.25	15.98	18.33	20.37	22.14	23.68	25.03	26.20	27.23
λ1=0.1	10.58	17.61	23.36	28.13	32.10	35.44	38.24	40.61	42.61	44.30	45.72
λ1=0.15	14.64	24.52	32.29	38.49	43.49	47.53	50.81	53.47	55.63	57.37	58.76

Figure 11.The extreme situation that the HIV incidence becomes stables after the year of 2015



For the second scenario, we assume the transmission rates remain stable after the year of 2015. By doing this, we can calculate the HIV prevalence in extreme situations (Figure 3b).

Table 9. Results from mathematical modeling of predicting new HIV cases at different voluntary medical male circumcision coverage rates among men who have sex with men in Beijing (Flat rates, remain the same for the next 10 years)

Year → **Circumcision coverage rate ↓**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**Reduction in proportion HIV-infected with increasing circumcision coverage (%)**
λ1=0.0001	6344	9226	11864	14284	16511	18565	20465	22228	23868	25399	26832	baseline
λ1=0.0005	6344	9226	11862	14282	16508	18561	20460	22221	23859	25388	26818	0.05
λ1=0.001	6344	9225	11862	14280	16505	18555	20452	22210	23845	25371	26797	0.13
λ1=0.005	8895	11486	13863	16048	18062	19922	21644	23242	24730	26117	27416	-2.18
λ1=0.01	6343	9220	11847	14251	16454	18477	20338	22053	23637	25103	26462	1.38
λ1=0.05	6337	9194	11781	14123	16238	18149	19870	21418	22809	24057	25174	6.18
λ1=0.1	6330	9163	11706	13979	16002	17795	19377	20765	21977	23029	23938	10.79
λ1=0.15	6324	9135	11638	13852	15797	17495	18968	20236	21319	22234	23003	14.27

Figure 12. HIV cases among circumcised men who have sex with men at different coverage rates of voluntary medical male circumcision (2016-2026)

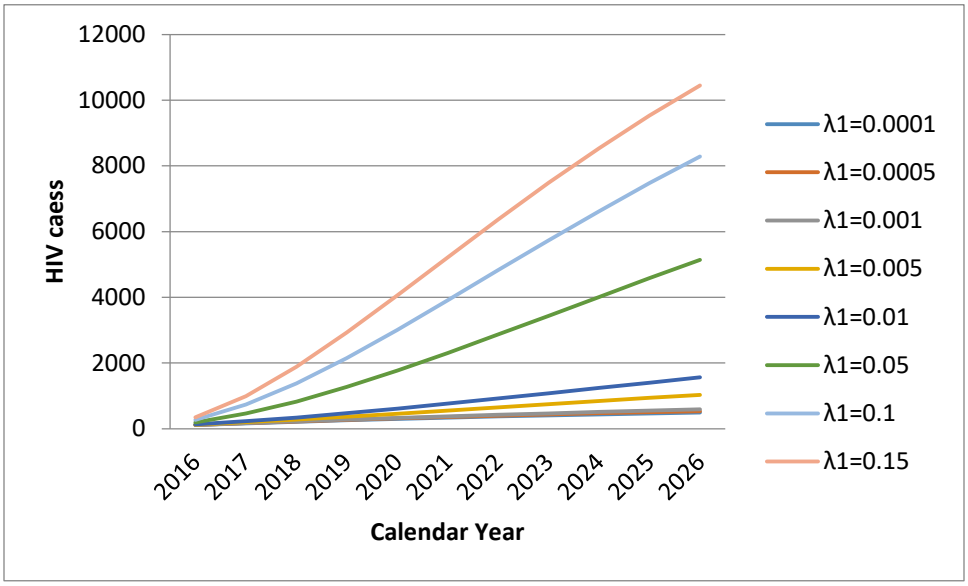


Figure 13. HIV cases among uncircumcised men who have sex with men at different coverage rates of voluntary medical male circumcision (2016-2026)

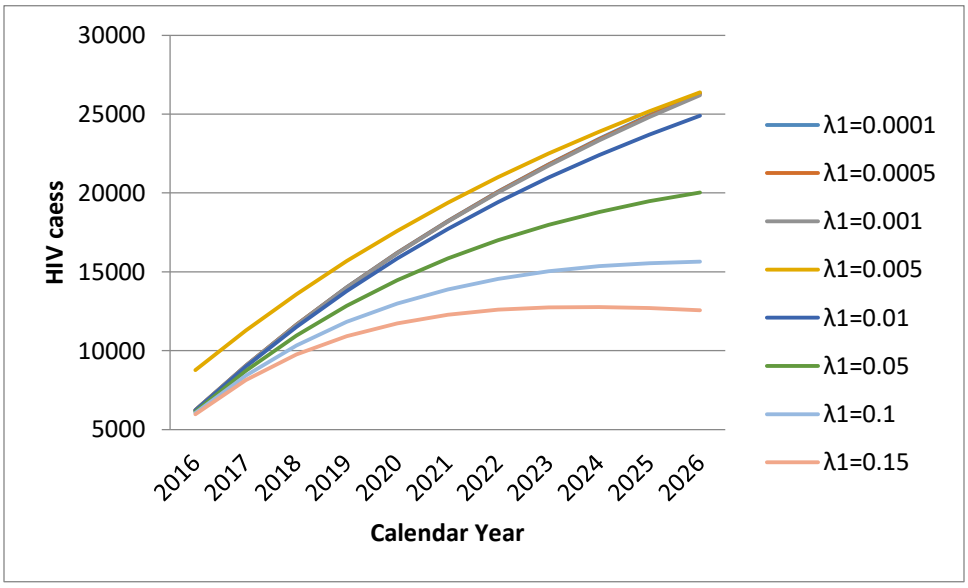


Figure 14. Susceptible circumcised men who have sex with men at different voluntary medical male circumcision coverage rates (2016-2026)

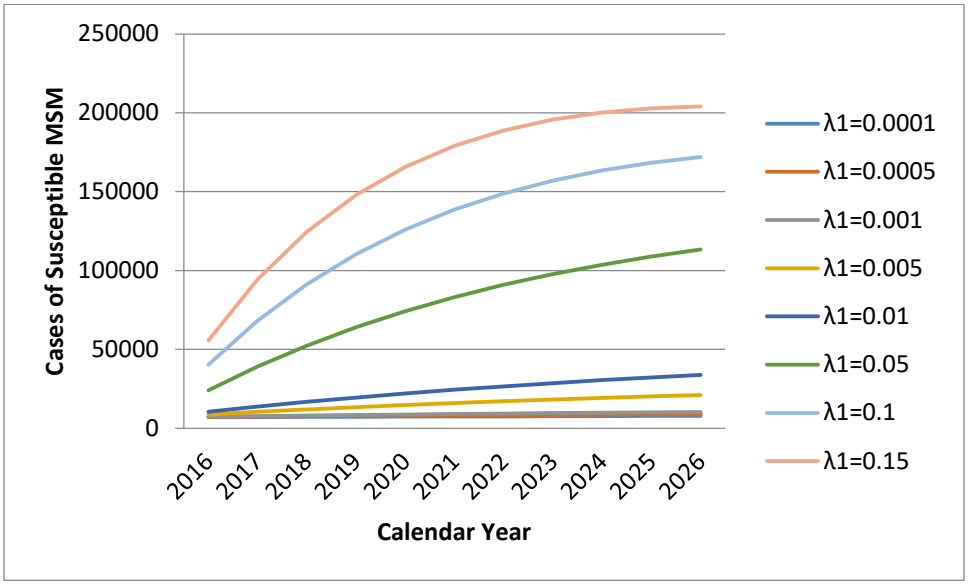


Figure 15. Susceptible uncircumcised men who have sex with men at different voluntary medical male circumcision coverage rates (2016-2026)

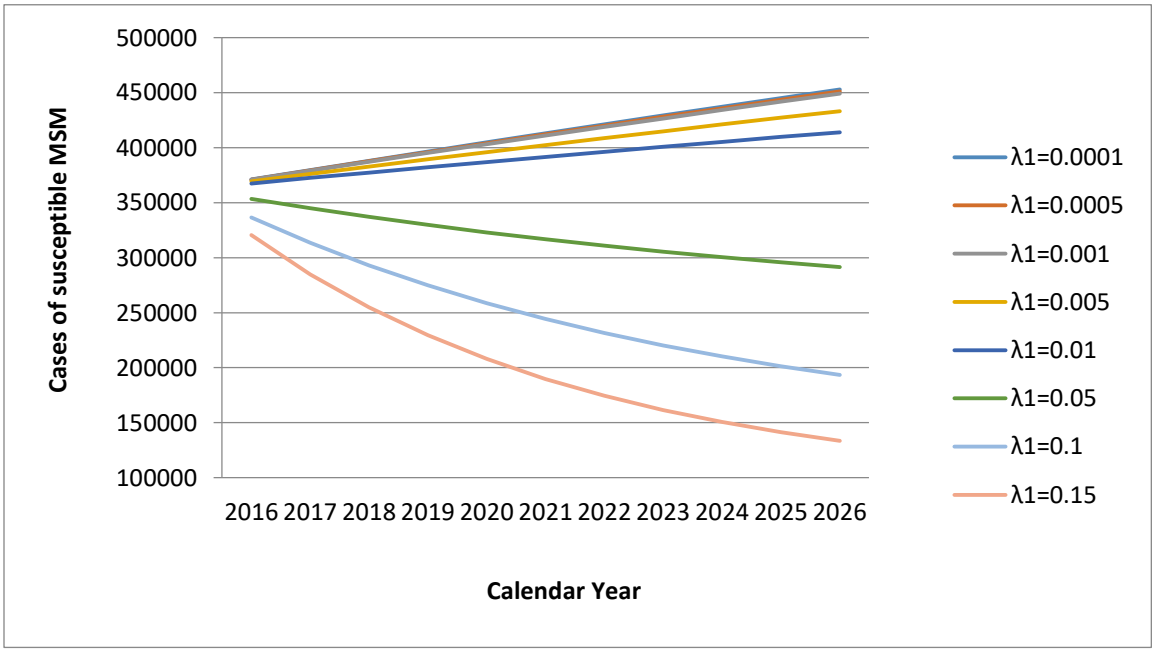


Figure 16. Transmission rates among uncircumcision and circumcised MSM by different protective efficacies (7% to 47%) (Linearly increased transmission rates)

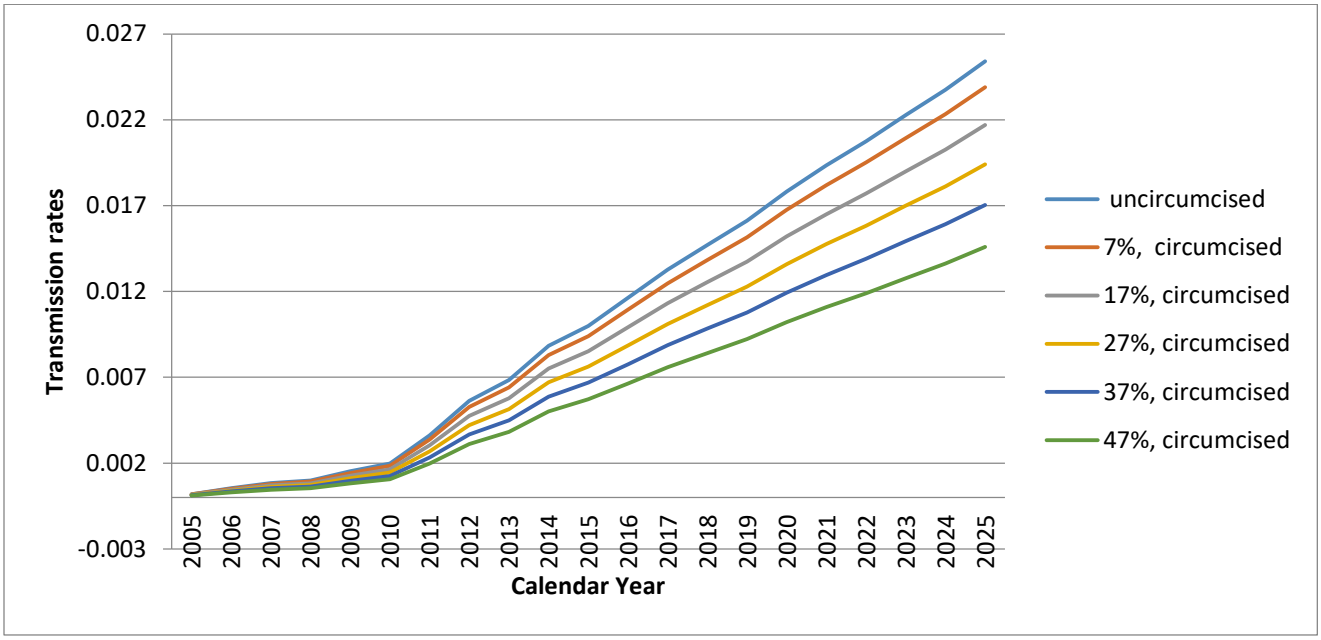


Table 10. New HIV cases with different protective efficacy of VMMC (2016-2025 projection)

λ1=0.0001	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	36	37	38	39	40	40	41	42	43	44	45	45
total # of new HIV cases	3188	6344	9816	13581	17547	21688	26104	30694	35397	40242	45190	50301
17% efficacy												
# of new VMMC per year	36	37	38	39	39	40	40	41	41	42	42	42
total # of new HIV cases	3188	6338	9804	13562	17522	21656	26065	30648	35344	40181	45121	50225
27% efficacy												
# of new VMMC per year	36	37	38	39	39	40	40	41	41	42	42	42
total # of new HIV cases	3188	6332	9791	13543	17495	21622	26023	30599	35287	40116	45048	50144
37% efficacy												
# of new VMMC per year	36	37	38	39	39	40	40	41	41	42	42	42
total # of new HIV cases	3188	6326	9778	13522	17468	21586	25979	30547	35227	40048	44972	50059
47% efficacy												
# of new VMMC per year	36	37	38	39	39	40	40	41	41	42	42	42
total # of new HIV cases	3188	6319	9765	13502	17439	21550	25935	30493	35165	39977	44892	49970
λ1=0.0005	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	181	185	189	193	196	199	202	204	206	207	208	209
total # of new HIV cases	3188	6344	9816	13580	17546	21685	26099	30687	35386	40225	45167	50270
17% efficacy												
# of new VMMC per year	181	185	189	193	196	199	202	204	206	207	208	209
total # of new HIV cases	3188	6338	9803	13561	17519	21651	26057	30635	35325	40157	45089	50183
27% efficacy												
# of new VMMC per year	181	185	189	193	196	199	202	204	206	207	208	209
total # of new HIV cases	3188	6332	9790	13541	17492	21616	26013	30584	35265	40088	45011	50096
37% efficacy												

# of new VMMC per year	181	185	189	193	196	199	202	204	206	207	208	209
total # of new HIV cases	3188	6326	9777	13521	17463	21579	25967	30529	35201	40013	44927	50002
47% efficacy												
# of new VMMC per year	181	185	189	193	196	199	202	204	206	207	208	209
total # of new HIV cases	3188	6319	9763	13499	17433	21540	25919	30471	35133	39936	44840	49904
λ1=0.001	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	362	371	378	385	392	397	402	406	410	413	415	417
total # of new HIV cases	3188	6344	9815	13580	17543	21679	26090	30673	35366	40199	45132	50224
17% efficacy												
# of new VMMC per year	362	371	378	385	392	397	402	406	410	413	415	417
total # of new HIV cases	3188	6338	9803	13559	17515	21644	26046	30619	35304	40127	45050	50132
27% efficacy												
# of new VMMC per year	362	371	378	385	392	397	402	406	410	413	415	417
total # of new HIV cases	3188	6332	9789	13538	17485	21604	25996	30560	35234	40046	44959	50031
37% efficacy												
# of new VMMC per year	362.476	371	378	385	392	397	402	406	410	413	415	417
total # of new HIV cases	3188	6325	9775	13517	17455	21566	25949	30502	35166	39967	44868	49927
47% efficacy												
# of new VMMC per year	362	371	378	385	392	397	402	406	410	413	415	417
total # of new HIV cases	3188	6319	9762	13494	17424	21526	25897	30440	35092	39882	44771	49818
λ1=0.005	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	1812	1847	1878	1905	1929	1950	1968	1982	1994	2002	2007	2009
total # of new HIV cases	3188	6343	9812	13570	17524	21644	26031	30582	35233	40013	44881	49897
17% efficacy												
# of new VMMC per year	1812	1847	1878	1905	1929	1950	1968	1982	1994	2002	2007	2009
total # of new HIV cases	3188	6337	9796	13544	17485	21592	25963	30494	35126	39885	44732	49725

27% efficacy												
# of new VMMC per year	1812.38	1847	1878	1905	192	1950	1968	1982	1994	2002	2007	2009
total # of new HIV cases	3188	6330	9781	13518	17446	21538	25891	30404	35016	39753	44576	49544
37% efficacy												
# of new VMMC per year	1812.38	1847	1878	1905	1929	1950	1968	1982	1994	2002	2007	2009
total # of new HIV cases	3188	6323	9765	13490	17403	21479	25814	30308	34897	39612	44411	49353
47% efficacy												
# of new VMMC per year	1812	1847	1878	1905	1929	1950	1968	1982	1994	2002	2007	2009
total # of new HIV cases	3188	6316	9747	13461	17360	21420	25737	30209	34776	39466	44239	49154
λ1=0.01	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	3625	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842
total # of new HIV cases	3188	6345	9814	13569	17516	21624	25990	30509	35119	39845	44646	49579
17% efficacy												
# of new VMMC per year	3624.76	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842
total # of new HIV cases	3188	6335	9791	13527	17449	21530	25862	30344	34913	39595	44350	49234
27% efficacy												
# of new VMMC per year	3624.76	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842
total # of new HIV cases	3188	6328	9771	13493	17395	21452	25758	30209	34746	39392	44108	48952
37% efficacy												
# of new VMMC per year	3624.76	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842
total # of new HIV cases	3188	6320	9751	13457	17339	21373	25651	30072	34574	39183	43860	48661
47% efficacy												
# of new VMMC per year	3625	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842
total # of new HIV cases	3188	6312	9731	13420	17283	21292	25540	29927	34393	38962	43596	48352
λ1=0.05	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**

7% efficacy												
# of new VMMC per year	18124	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561
total # of new HIV cases	3188	6341	9792	13502	17367	21346	25520	29779	34054	38362	42658	46990
17% efficacy												
# of new VMMC per year	18123.8	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561
total # of new HIV cases	3188	6324	9736	13387	17172	21054	25112	29241	33373	37530	41668	45834
27% efficacy												
# of new VMMC per year	18123.8	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561
total # of new HIV cases	3188	6310	9692	13295	17017	20820	24785	28808	32826	36860	40868	44900
37% efficacy												
# of new VMMC per year	18123.8	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561
total # of new HIV cases	3188	6296	9646	13200	16856	20578	24446	28360	32257	36161	40034	43924
47% efficacy												
# of new VMMC per year	18124	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561
total # of new HIV cases	3188	6324	9736	13387	17172	21054	25112	29241	33373	37530	41668	45834
λ1=0.1	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	36248	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18094
total # of new HIV cases	3188	6336	9765	13425	17199	21039	25014	29009	32957	36869	40703	44502
17% efficacy												
# of new VMMC per year	36247.6	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18094
total # of new HIV cases	3188	6310	9673	13228	16864	20537	24318	28101	31823	35499	39093	42650
27% efficacy												
# of new VMMC per year	36248	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18094
total # of new HIV cases	3188	6289	9599	13070	16596	20135	23760	27371	30910	34396	37795	41153
37% efficacy												

# of new VMMC per year	36247.6	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18093
total # of new HIV cases	3188	6268	9523	12908	16319	19720	23183	26615	29962	33246	36439	39587
47% efficacy												
# of new VMMC per year	36248	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18094
total # of new HIV cases	3188	6246	9444	12739	16032	19288	22582	25825	28971	32043	35018	37943
λ1=0.15	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
7% efficacy												
# of new VMMC per year	54371	48067	42665	38042	34099	30740	26264	24084	22230	20655	19316	18176
total # of new HIV cases	3188	6332	9741	13354	17049	20771	24582	28358	32035	35626	39097	42492
17% efficacy												
# of new VMMC per year	54371	48067	42665	38042	34099	30740	27873	25434	23362	21601	20107	18836
total # of new HIV cases	3188	6297	9613	13083	16591	20093	23654	27174	30593	33928	37150	40302
27% efficacy												
# of new VMMC per year	54371	48067	42665	38042	34099	30740	27873	25434	23362	21601	20107	18836
total # of new HIV cases	3188	6269	9512	12867	16225	19550	22911	26213	29407	32512	35504	38430
37% efficacy												
# of new VMMC per year	54371	48067	42665	38042	34099	30740	27873	25434	23362	21601	20107	18836
total # of new HIV cases	3188	6240	9407	12643	15848	18990	22141	25217	28174	31038	33788	36471
47% efficacy												
# of new VMMC per year	54371	48067	42665	38042	34099	30740	27873	25434	23362	21601	20107	18836
total # of new HIV cases	3188	6210	9299	12412	15455	18406	21338	24176	26886	29495	31988	34416

Appendix 1

Parameters for the model

Basic model formula for prediction

```
tmax = 10.0;

Sol = NDSolve[{Scm'[t] == σm[t] - ρm[t] * Scm[t] - λ1 * Scm[t] - τm * Scm[t],
               Scp'[t] == σp[t] - ρp[t] * Scp[t] + λ1 * Scm[t] - τp * Scp[t],
               Ichm'[t] == ρm[t] * Scm[t] - ηm[t] * Ichm[t],
               Ichp'[t] == ρp[t] * Scp[t] - ηp[t] * Ichp[t],
               Scm[0] == Scm0, Scp[0] == Scp0, Ichm[0] == Ichm0, Ichp[0] == Ichp0},
   {Scm[t], Scp[t], Ichm[t], Ichp[t]}, {t, 0, tmax}];
```

```
In[3281]:= Clear[σm, σp, ρp, ρm, λ1, τm, τp, ηm, ηp, Scm, Scp, Ichm, Ichp];
In[3282]:= σp[t_] := 700 + 5 * t; σm[t_] := 14 000.0 + 50 * t;
```

```
ρp[t_] := 0.0003 * t - 0.0001 /; t ≤ 6;
ρp[t_] := 0.0003 * t /; t > 6;

ρm[t_] := 0.0003 * t - 0.0003 /; t ≤ 6;
ρm[t_] := 0.0003 * t - 0.002 /; t > 6;

Scp0 = 5000;  Scm0 =240 000;
Ichp0 = 5;
Ichm0 = 55;
```

```
λ1 = 0.0001;

τm = 0.006; τp = 0.09;(*  ηp=0.09   ; ηm=0.003;   *)


ηp[t_] := .5 - .04 * t;
ηm[t_] := .003 - .02 * t /; t ≤ 10;
ηm[t_] := .003 - .02 * 10 /; t > 10;
```

Appendix 2. Calculation for HIV incidence and prevalence

Based upon the formula:

- Odds ratio (OR)=odds of HIV infection among circumcised/odds of HIV infection among uncircumcised=[prev1/(1-prev1)] /[prev2/(1-prev2)]
- Prevalence = Incidence*Average Duration of HIV/AIDS

✓ Prev1 is the HIV prevalence among circumcised MSM

✓ Prev2 is the HIV prevalence among uncircumcised MSM (from the HIV surveillance data)

✓ OR is calculated from Zhang et al.'s study (Zhang, Qian, et al., Under review)

✓ Duration: On average, life expectancy is 14.9 years with ART treatment after the incubation time (averagely 8 years), and 1.6 years without ART treatment for a given patient. With 50% ART coverage rate in China, the average during of HIV/AIDS is approximately 16 years from HIV diagnosis to death considering both scenarios of ART and non-ART.

CHAPTER VI

MODELING ECONOMIC AND EPIDEMIOLOGICAL IMPACT OF VOLUNTARY MEDICAL MALE CIRCUMCISION AMONG MEN WHO HAVE SEX WITH MEN IN CHINA: A DECISION ANALYSIS

Abstract

Introduction: Voluntary medical male circumcision (VMMC) among men who have sex with men (MSM) may protect against HIV acquisition. We conducted a series of analyses to assess if expanded VMMC might reduce HIV incidence among MSM effectively and economically.

Methods: We used a deterministic compartmental model to project new HIV cases (2016-2026) under annual VMMC coverage rates (λ) ranging from 0.0001 to 0.15. The "number needed to avert (NNA)" that defined as the number of VMMC per new HIV case averted was calculated. The breakeven point that balances VMMC cost with saved cost from averting HIV cases was also identified. A series sensitivity analyses were conducted with different protective efficacies.

Results: Compared with the baseline circumcision coverage rate, we projected that new HIV cases would be reduced with increasing coverage. By 2026 (last year simulated), the model generated the lowest ratio (2.29) when the annual circumcision rate was the most optimistic (λ=0.15). The breakeven point was observed at the year of 2019 with the annual VMMC coverage rate of 0.001. Sensitivity analyses showed that the higher the

protective efficacy of VMMC, a lower coverage rate and less time was required to reach the breakeven point.

Discussion: Our model suggests that acceleration in VMMC implementation among MSM could help stem the HIV/AIDS epidemic. The model is dependent upon two uncertain understudied parameters, namely the true efficacy of VMMC for HIV prevention and the likelihood that health authorities will launch, and MSM will accept, VMMC for HIV control in MSM.

Key words: Male Circumcision; HIV; Men who have Sex with Men; China; "number needed to avert" analysis

Introduction

Three randomized controlled trials (RCT) have shown voluntary medical male circumcision (VMMC) to be effective in reducing HIV acquisition among heterosexual men by over 50% (Auvert et al., 2005; Bailey et al., 2007; R. H. Gray, Kigozi, et al., 2007). However, the role of VMMC in preventing HIV infection among men who have sex with men (MSM) is controversial and circumstantial (Baral, Sifakis, Cleghorn, & Beyrer, 2007; Millett et al., 2008; Qian et al., 2015; Smith, Tapsoba, Peshu, Sanders, & Jaffe, 2009; Vermund & Qian, 2008). In a meta-analysis using published data through August 2016 assessing the efficacy of VMMC among MSM, 30 of 33 studies reported non-significant associations between VMMC and HIV although the meta-analysis suggested an overall weak, but significant protective efficacy (Zhang et al., under review)(Zhang, Qian, et al., Under review). Two studies from India suggested that

VMMC might reduce HIV risk significantly among MSM, even among males who primarily practiced receptive sex (Schneider et al., 2012a; Solomon et al., 2014). Among MSM in Beijing, a remarkably strong protection effect was noted, especially among MSM who predominately practice insertive sex (aOR=0.15, 95% CI=0.04, 0.65) vs. MSM who were uncircumcised and practicing receptive and/or versatile (both receptive and insertive) sexual positioning. These Asian studies found the strongest evidence to date that VMMC might be a useful biomedical tool for HIV risk reduction among MSM, especially for MSM with comparatively lower risk profiles, such as MSM practicing insertive anal intercourse in Asia (Zhang, Qian, et al., Under review). Circumcision is rare in Asia except among Muslims, and circumcised men have undergone the procedure in childhood or adolescence, typically, due to pre-existing medical conditions such as phimosis (Ben et al., 2009). Hence, the observational studies comparing circumcised and uncircumcised men are not likely to be biased, given the lack of association between phimosis and later sexual preference.

The willingness of VMMC uptake among Chinese males ranged from less than one-third among male miners in Guangxi (F. M. Wei et al., 2012), to more than two-thirds among general Chinese male population who received an intervention for circumcision uptake promotion (Luo et al., 2011; Ruan et al., 2009). The willingness for receiving VMMC among MSM was consistent with that among general population in China, among whom two-thirds of them expressed their willingness to accept the VMMC as a strategy to prevent HIV and other sexually transmitted infections (Lau et al., 2011; Luo et al., 2011).Well-designed interventions may facilitate increased willingness of accepting VMMC among MSM in China (Lau et al., 2012). For instance, an intervention

successfully increased the willingness to be circumcised from 8.1% to 35.1% among a group of bisexual MSM in the Southern China (Lau et al., 2012). Therefore, promoting VMMC may be beneficial for HIV prevention and is also feasible among MSM, particularly among some subgroups including youths and those who practice insertive anal sex

To assess long-term population-level impacts of expanding VMMC among MSM, we should consider the balance between investment (e.g., costs for VMMC performed) and impact (e.g., numbers of new HIV cases averted). The United States Agency for International Development (USAID) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have developed a modeling tool called "Decision Makers' Program Planning Tool" (DMPPT) to facilitate decision makers' estimates of the epidemiological impact and cost of alternative programmatic options for scaling up VMMC (Kripke & Njeuhmeli, 2016; Kripke et al., 2016; Njeuhmeli et al., 2011). However, these model-based studies only focused on heterosexual sexual men in specific settings (e.g., African nations) with generalized HIV epidemics (Bollinger et al., 2009; Kripke & Njeuhmeli, 2016; Njeuhmeli et al., 2011; Stover et al., 2016).

The DMPPT model assumes the HIV incidence rate to remain constant during the prediction period, resulting in potentially over- or underestimating the impact of VMMC (Kripke et al., 2016). To date, no analogous modeling studies have specifically addressed the potential utility of circumcision programs targeting MSM. Given the lower prevalence of VMMC among Chinese MSM (Beyrer et al., 2012; Vermund & Qian, 2008; Zhang, Qian, et al., Under review), it is conceivable that VMMC would have a

greater impact in China than in areas of high circumcision prevalence (e.g., the United States). In order to assess context-specific impacts of VMMC among MSM in China, we conducted the current analysis to assess the extent to which expanding VMMC programs might reduce HIV incidence among MSM effectively and economically.

Methods

Model Building Procedure

We employed a deterministic compartmental model to project the HIV epidemic for the period between 2016 and 2026 among MSM in Beijing (Zhang, Shephard, et al., Under review). Susceptible men are HIV-uninfected, in contrast to HIV-infected men. The fixed estimate for the protective efficacy of VMMC is derived from the meta-analysis (Zhang et al., under review)(Zhang, Qian, et al., Under review) and is set conservatively at 7%. It is plausible that efficacy for HIV prevention in MSM is much higher than this (Qian et al., 2016). The study population fell into four mutually exclusive subgroups: (1) circumcised susceptible MSM (S_{c+}); (2) circumcised infected MSM (I_{c+}); (3) uncircumcised susceptible MSM (S_{c-}); and (4) uncircumcised infected MSM (I_{c-}). With the *HIV transmission rate* of ρ^-, uncircumcised *susceptible* MSM (S_{c-}) became uncircumcised *infected* MSM (I_{c-}). Similarly, with the *HIV transmission rate* of ρ^+, circumcised *susceptible* MSM (S_{c+}) became circumcised *infected* MSM (I_{c+}). In this dynamic model, seronegative MSM entered the susceptible pool at a rate of σ. The rate of entering the circumcised *susceptible* compartment (S_{c+}) was σ^+, while σ^- represented the rate of entering the uncircumcised *susceptible* compartment (S_{c-}). Meanwhile, MSM were considered to have left the susceptible pool by aging beyond 65 years, emigrating out of

Beijing, or dying of any cause. We used the parameter τ to indicate the rate of leaving the model among *susceptible* MSM, with τ^+ representing the rate of leaving the circumcised *susceptible* pool (S_{c+}), and τ^- representing the rate of leaving the uncircumcised *susceptible* pool (S_{c-}). In this model, susceptible MSM would change from being uncircumcised to being circumcised at a rate of λ.

As very few MSM are expected to be circumcised after HIV infection (Lou et al., 2014), we did not consider the number of infected MSM who transited from being uncircumcised to being circumcised. Both circumcised and uncircumcised MSM would leave the *infectious* compartments for one reason: **1)** death due to HIV infection, or **2)** having undetectable viral loads due to either being an immunologically elite controller (e.g., the small group of HIV-infected patients who can maintain high CD4+ cell counts and low viral loads without progressing immunologically towards AIDS over years in absence of ART (Pantaleo et al., 1995)) or an effective ART regime at a rate of η^- for uncircumcised and η^+ for circumcised MSM (Figure 1). When possible, demographic and transmission parameters were estimated from the published literature (Lou et al., 2014; Lou & Smith, 2011; Lou et al., 2009) or from available unpublished data sources (personal communication); a few parameters were calculated within the model itself (Supplementary Table 1).

In order to refine the model to provide the most valid predictions, we calibrated the model parameters to enable the model to predict historical surveillance data. When the prediction model overlapped with the surveillance data, using plausible and defensible parameter estimations, we considered the generated model to serve well for predictions

forward in time. Additionally, through 50 repeated simulations, we generated the predicted transmission rates (e.g., ρ^- and ρ^+) for 2016-2025 among both uncircumcised and circumcised MSM

Economic impact analysis

In order to assess the economic impact for VMMC scale-up among MSM, we conducted the current analysis from the perspectives of budget holders and health professionals (Sullivan et al., 2014). We employed the *"numbers needed to avert"* (NNA) that defined as "the number of VMMC per new HIV case averted" as an indicator. NNA was calculated by dividing the number of HIV cases averted (compared with the baseline [λ=0.0001]) by the number of VMMC conducted at a given year. The lower the NNA, the more economically effective the VMMC campaign would be among MSM. We calculated the NNA under different annual VMMC coverage rates at each predicted year.

In addition, we further identified the breakeven point that balances the total cost of VMMC with the cost saved from averting new HIV cases. The breakeven point can be considered as the tipping point that it was economically desirable to proceed with the VMMC program among MSM in Beijing. We also calculated the total cost saved compared to the cost at baseline after expanding the VMMC program in each projected year. The cost at each scenario included the cost of VMMC and cost of HIV treatment. The cost of each individual VMMC and HIV treatment in each projected year (2016-2026) was discounted by 3% (Hunink et al., 2001)that started from the baseline cost

derived from existing studies (Drabo et al., 2016; Farnham et al., 2013; Moon et al., 2008; Schackman et al., 2015)(Supplementary Table 2).

Sensitivity analyses

We conducted sensitivity analyses by setting the transmission rates for both circumcised and uncircumcised MSM at the same level as the incidence rate seen in 2015. If nothing changes from 2015 (i.e., very, very few VMMC), it represents a lower bound for the transmission rate (Supplementary Figure 1). In addition, we assessed the economic impact in terms of the NNA and breakeven points by different protective efficacies(e.g., 7%, 17%, 27%, 37%, and 47%) ranging from being very conservative 7% (Zhang, Qian, et al., Under review) to being optimistic 47%(Qian et al., 2016) incrementally in the current study.

Results

Model predictions of the numbers of new HIV cases and averted HIV cases

We presented findings from the prediction model in Table 1, including the number of new VMMC, total number of new HIV cases, and numbers of HIV cases averted compared to baseline at each predicted year (2016-2026), varying the annual coverage rates for VMMC from λ=0.0001 to λ=0.15. With an increased VMMC coverage rate, the numbers of VMMC were increased proportionately. For example in the year 2026, under a coverage rate of 0.0001 there would be 42 new VMMC in Beijing, but under an annual coverage rate of 0.15 there would be 18,836 new VMMC. The number of susceptible MSM will have decreased over time in the latter case, but will have changed little in the

former. In the model, when a hypothetical VMMC coverage rate was no greater than 0.01, the number of new VMMC increased linearly with each year due to a minimal change in the susceptible MSM. In contrast, when a hypothetical VMMC coverage rate reached 0.05 or more, numbers of new VMMC decreased over time due to the decline in susceptible uncircumcised MSM. For instance, under an annual VMMC coverage rate of 0.1, the number of new VMMC would be 33,652 in 2016, decreasing to 18,094 in 2026. As expected given the protective estimates of VMMC for HIV prevention in MSM, new HIV cases decreased as VMMC coverage increased. By contracting the number of new HIV cases at the baseline from the number of new HIV cases under different hypothetical coverage rates of VMMC, we calculated the potential number of HIV cases averted (Table 1).

Economic impact assessment

Numbers of VMMC needed per HIV case averted under different coverage rates were presented in Table 2. Our analyses revealed that the higher the VMMC coverage rate was, the fewer numbers of VMMC was needed for one HIV case averted. For instance, under the VMMC coverage rate of 0.0005, the number of VMMC for averting one HIV case was 6.74 at 2026, and the number dropped to 5.42 when the coverage rate increased to 0.001, 4.97 under the coverage rate of 0.005, 4.79 under the coverage rate of 0.01, 3.79 under the coverage rate of 0.05, 2.91 under the coverage rate of 0.1, and 2.29 under the coverage rate of 0.15 (Table 2). We further presented the NNA for the last a few years (2021-2026) in Supplementary Figure 2.

We further calculated the prevalence of VMMC over the projected period (2016-2026). If the annual circumcision coverage rate remained at the 2015 baseline (λ=0.0001), the prevalence of VMMC would remain stable over the projected years (1.89% in 2015 vs. 1.74% in 2026), while with a high annual coverage rate (λ=0.15) in the 2016-2026 period, the coverage would rise from 1.89% in 2015 to 58.8% in 2026 (Table 3).

The analytical result for the "breakeven point" was presented in Table 4. We compared the cost spent for expanding VMMC with the cost saved from averting HIV cases. At the year of 2019 with the annual VMMC coverage rate of 0.001, the cost after scaling up VMMC was approximately equal to the cost at the baseline (costed save was approximately equal to zero), which was considered as the breakeven point of the VMMC coverage rate. Therefore, it is economically desirable to proceed with the VMMC program forward among MSM in Beijing, China beyond the breakeven point in terms of the time (e.g.,2019) and the coverage rate (e.g., 0.001). The amount of cost saved got increased with a higher coverage rate. Compared to baseline, the saved cost ranged from $2534.2 (in 1000 USD) under the coverage rate of 0.0005 to $811092.2 (in 1000 USD) under the coverage rate of 0.15.

Results from sensitivity analyses

In the sensitivity analyses, the same pattern for HIV infections and susceptibility by circumcision status was observed when the transmission rates were set at the same incidence rate seen in 2015.The higher the VMMC coverage rate, the fewer numbers of VMMC needed per HIV case averted. Similarly, the trend of a lower NNA was observed

for each given coverage rate over time. For the year of 2026, the lowest ratio was 5.23 when the annual coverage rate of VMMC was 0.15 (Supplementary Table 3).

A series of sensitivity analyses with incrementally increased protective efficacies revealed that the higher the protective efficacy of VMMC, the lower coverage rate and less time was required to reach the breakeven point. For instance, at the protective efficacy of 17%,27% and 37%, the breakeven point was achieved in the year of 2018 with the coverage rate of 0.0005; while the breakeven point was achieved earlier (e.g., 2017) with the same coverage rate (e.g., λ=0.0005) when the protective efficacy increased to 47% (Supplementary Table 4-5). The amount of cost saved increased either with a higher protective efficacy for each given coverage rate, or with a higher coverage rate for each given protective efficacy (Supplementary Figure 3).

Discussion

We employed a deterministic, compartmental model to assess epidemiologic and economic impact of expanding VMMC on HIV prevention among MSM in China. Economic impact analysis was an essential part of a comprehensive assessment of a health intervention, playing an increasingly important role in decision-making for policy makers in the current study(Sullivan et al., 2014). We found that the higher the annual coverage rate, the lower numbers of VMMC needed per HIV case averted was over time. A lower NNA can be obtained by expanding VMMC campaign significantly among MSM, which in turn, requires a higher budget cost of scaling-up the VMMC. If we achieved the greatest impact with the NNA as low as 2.29 when the annual VMMC coverage rate was 0.15, a total of 330,826 VMMC would be conducted by the year of

2026. On the other hand, if we adopted the most frugal budget to provide a low annual coverage rate (e.g., 0.0005) of VMMC, the impact would be trivial even though this coverage is five times the very low baseline. Furthermore, the analyses for "breakeven points" and total cost saved compared to baseline can assist health authorities to visualize time period and coverage rate for the tipping point of the intervention. Therefore, preventive health and decision-makers can use findings from the current modeling study for resource and budget planning.

A study conducted among heterosexual men in high HIV prevalence settings indicated that one HIV infection can be averted by every five to 15 male circumcisions performed over a 10-year time-frame with a 80% VMMC coverage (Group, 2009). Our study revealed that to avert one HIV case, 11 to 22 male circumcisions needed to be performed on average over a 10-year period with an eventual 58.7% VMMC coverage (Table 2). However, at the end of the projection time period (e.g., year of 2026), only two to seven VMMC would have to be performed in order to avert one HIV infection among MSM, even with our use of very conservative estimates of the efficacy of VMMC in protecting MSM (e.g., 7%) (Zhang et al., under review) (Zhang, Qian, et al., Under review). With a higher protective efficacy, fewer numbers of VMMC would be needed for averting one HIV case (Supplementary Table 4). Although WHO/UNAIDS guidance has stated that the VMMC would exert its greatest potential public health impact in settings where HIV prevalence exceeds 15% (Group, 2009; WHO/UNAIDS, 2007), the HIV prevalence in Chinese MSM approaches this prevalence in many cities(Vermund & Qian, 2008; Zeng et al., 2014; Zhang, Qian, et al., Under review; Zhang, Shephard, et al., Under review; C. Zhou et al., 2013). Hence, the argument for VMMC deployment among

Chinese MSM rivals that for heterosexual men in Africa, even with a lower anticipated efficacy (e.g., 7%) (Zhang et al., under review) (Zhang, Qian, et al., Under review), though this assumption may overly conservative (Qian et al., 2016).

Several strengths of our study are notable, particularly its unique contribution to the existing literature. Although the current study employed a deterministic compartmental model similar to the DMPPT of UNAIDS/UNAID (Kripke et al., 2016), we simulated transmission rates based upon the National HIV Surveillance data in order to capture possible randomness properties (Vynnycky & White, 2010). Compared to the arbitrary 15% variance strategy that employed by other published studies (Kripke & Njeuhmeli, 2016; Kripke et al., 2016), the HIV surveillance data can improve the validity of the model parameters and likely accuracy of context-specific predictions. In addition to the simulation, sensitivity analyses estimated new HIV cases at their lower bound when transmission rates remained the same as seen in 2015, suggesting our findings to be robust and plausible. Both parameter (e.g., uncertainty of transmission rates) and structural uncertainties (e.g., uncertainty of VMMC coverage rates) were assessed. The analyses based upon incrementally increased protective efficacies also comprehensively assessed the intervention impact of VMMC. Furthermore, as one of the first prediction models to evaluate VMMC from an economic perspective outside Africa (Goodreau et al., 2014), our model assists decision making and resource planning for other settings similar to China, especially for places where MSM increasingly dominated the HIV epidemic.

Limitations of other models also apply here. Our model in the current study has limited generalizability due to the context-specific parameters although we used a meta-analysis derived circumcision efficacy estimate which would presumably apply to many settings(Zhang, Qian, et al., Under review). Unlike the DMPPT model in which age-specific VMMC scaling up strategies were assessed (Kripke et al., 2016), we only assessed the overall epidemic among all MSM with an extended age range from 18 to 65 years old. In addition, we did not assess epidemiologic and economic impacts of VMMC with other concurrent behavioral (e.g., condom use), structural (e.g., microfinance for at-risk populations) or biomedical intervention strategies (e.g., pre-exposure prophylaxis) (Lou et al., 2014; Rotheram-Borus, Swendeman, & Chovnick, 2009; Vermund & Qian, 2008). The nature of these available tools depends on user-adherence, a potential disadvantage compared to VMMC (Huang et al., 2014; Lou et al., 2014; Pretorius et al., 2010; Rotheram-Borus et al., 2009; Vermund & Qian, 2008). If acceptable, if offered, and if taken up by MSM, VMMC can confer potentially lifelong protective benefits once the one-time surgical procedure is performed (Group, 2009). Future research can consider synergistic effects of other available prevention tools (Lou et al., 2014) as well as considering indirect protective effects toward women and children among bisexual men who get circumcised (Group, 2009; Kripke et al., 2016), or potential modulation of benefit due to risk compensation after the VMMC procedure was conducted (Group, 2009). Finally, due to the controversial definition of quality-adjusted life year, we did not conduct the cost-effectiveness analysis as other investigators have done (Anderson et al., 2009; Kahn, Marseille, & Auvert, 2006; Sansom et al., 2010). Nonetheless, these current analyses can provide health system and decision-makers estimates useful for deciding

when and how to deploy a VMMC scale-up strategy among MSM in settings like China (Sullivan et al., 2014).

Our model serves as one of the first studies to provide economic data (e.g., breakeven analysis, NNA, total cost saved), suggesting VMMC to be a viable prevention option for control of HIV among MSM in China and similar venues. Policy-makers would do well to consider accelerating access to VMMC targeting MSM, a neglected component in the "prevention tool box" to stem the HIV/AIDS epidemic.

Table 11. Results from mathematical modeling of predicting HIV cases at different voluntary medical male circumcision coverage rates (2016-2026)

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	Total number
λ1=0.0001 (baseline)												
# of new VMMC per year	37	38	39	39	40	40	41	41	42	42	42	441
total # of new HIV cases (baseline)	6344	9816	13581	17547	21688	26104	30694	35397	40242	45190	50301	296904
λ1=0.0005												
# of new VMMC per year	185	189	193	196	199	202	204	206	207	208	209	2198
# of new HIV cases	6344	9816	13580	17546	21685	26099	30687	35386	40225	45167	50270	296805
# HIV cases averted vs. baseline	0	0	1	1	3	5	7	11	17	23	31	99
λ1=0.001												
# of new VMMC per year	371	378	386	392	397	402	406	410	413	415	417	4387
# of new HIV cases	6344	9815	13580	17543	21679	26090	30673	35366	40199	45132	50224	296645
# HIV cases averted vs. baseline	0	0	1	4	9	14	21	31	43	58	77	259
λ1=0.005												
# of new VMMC per year	1847	1878	1905	1929	1950	1968	1982	1994	2002	2007	2009	21471
# of new HIV cases	6343	9812	13570	17524	21644	26031	30582	35233	40013	44881	49897	295530
# HIV cases averted vs. baseline	1	4	11	24	44	73	113	164	229	308	404	1374
λ1=0.01												
# of new VMMC per year	3675	3719	3756	3787	3813	3832	3845	3852	3854	3851	3842	41826

# of new HIV cases	6343	9809	13560	17501	21603	25961	30472	35073	39788	44577	49499	294186
# HIV cases averted vs. baseline	1	7	21	46	85	143	222	324	454	612	802	2718
λ1=0.05												
# of new VMMC per year	17671	17221	16776	16340	15915	15496	15086	14689	14302	13927	13561	170984
# of new HIV cases	6337	9779	13476	17322	21279	25427	29656	33897	38170	42431	46724	284498
# HIV cases averted vs. baseline	7	37	105	225	409	677	1038	1500	2071	2759	3577	12406
λ1=0.1												
# of new VMMC per year	33652	31295	29157	27226	25485	23909	22488	21211	20060	19026	18094	271603
# of new HIV cases	6330	9744	13380	17122	20923	24853	28800	32696	36553	40331	44074	274806
# HIV cases averted vs. baseline	13	72	201	425	765	1251	1894	2701	3689	4858	6227	22098
λ1=0.15												
# of new VMMC per year	48067	42665	38042	34099	30740	27873	25434	23362	21601	20107	18836	330826
# of new HIV cases	6324	9711	13292	16943	20614	24368	28094	31726	35279	38716	42081	267148
# HIV cases averted vs. baseline	20	104	290	604	1074	1736	2600	3671	4963	6474	8220	29756

Notes: ρm [ρ-]: transmission rate among uncircumcised; ρp [ρ+]: transmission rate among circumcised; Scp0: number of circumcised susceptible MSM; Scm0: number of uncircumcised susceptible MSM; Ichp0: number of circumcised infected MSM; Ichm0: number of uncircumcised infected MSM;

Table 12. Numbers of voluntary medical male circumcision needed per HIV case averted among men who have sex with men under different coverage rates (2016-2026)

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	Overall
λ1=0.0005	n/a	n/a	193.00	196.00	66.33	40.40	29.14	18.73	12.18	9.04	6.74	22.20
λ1=0.001	n/a	378.00	385.00	98.00	44.11	28.71	19.33	13.23	9.60	7.16	5.42	16.94
λ1=0.005	1847.00	469.50	173.18	80.38	44.32	26.96	17.54	12.16	8.74	6.52	4.97	15.63
λ1=0.01	3675.00	531.29	178.86	82.33	44.86	26.80	17.32	11.89	8.49	6.29	4.79	15.39
λ1=0.05	2524.43	465.43	159.77	72.62	38.91	22.89	14.53	9.79	6.91	5.05	3.79	13.78
λ1=0.1	2588.62	434.65	145.06	64.06	33.31	19.11	11.87	7.85	5.44	3.92	2.91	12.29
λ1=0.15	2403.35	410.24	131.18	56.46	28.62	16.06	9.78	6.36	4.35	3.11	2.29	11.12

Table 13. Prevalence of voluntary medical male circumcision among men who have sex with men in China under different coverage rates over the projected period (2016-2026)

Coverage rates/Year	2015 (%)	2016 (%)	2017 (%)	2018 (%)	2019 (%)	2020 (%)	2021 (%)	2022 (%)	2023 (%)	2024 (%)	2025 (%)	2026 (%)
λ1=0.0001	1.89	1.87	1.85	1.83	1.82	1.80	1.79	1.78	1.77	1.76	1.75	1.74
λ1=0.0005	1.89	1.90	1.92	1.93	1.94	1.95	1.95	1.96	1.97	1.97	1.98	1.98
λ1=0.001	1.89	1.95	2.00	2.05	2.09	2.13	2.16	2.19	2.21	2.23	2.26	2.27
λ1=0.005	1.89	2.31	2.69	3.02	3.30	3.56	3.79	3.99	4.17	4.33	4.47	4.60
λ1=0.01	1.89	2.77	3.54	4.21	4.80	5.32	5.78	6.19	6.56	6.88	7.17	7.43
λ1=0.05	1.89	6.32	10.06	13.25	15.98	18.33	20.37	22.14	23.68	25.03	26.20	27.23
λ1=0.1	1.89	10.58	17.61	23.36	28.13	32.10	35.44	38.24	40.61	42.61	44.30	45.72
λ1=0.15	1.89	14.64	24.52	32.29	38.49	43.49	47.53	50.81	53.47	55.63	57.37	58.76

Table 14. Cost saved after expanding the voluntary medical male circumcision compared to the baseline under different coverage rates [&, #]

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	Total cost
cost at baseline*	150964.0	240589.4	342848.3	456249.4	580836.7	720089.6	872089.2	1035904.8	1213026.9	1403026.6	1608538.4	8624163.3
cost saved at 0.0005	34.2	35.9	12.5	13.6	-39.0	-94.5	-153.9	-275.1	-464.3	-664.1	-939.5	-2534.2
cost saved at 0.001	77.2	56.4	59.8	-15.0[@]	-148.2	-289.2	-495.9	-802.4	-1187.8	-1688.5	-2346.1	-6779.8
cost saved at 0.005	394.3	339.9	179.5	-121.7	-681.8	-1497.0	-2646.4	-4244.8	-6330.4	-9002.1	-12309.3	-35919.9
cost saved at 0.01	816.6	704.5	380.5	-251.6	-1295.4	-2928.4	-5257.6	-8399.5	-12571.8	-17885.3	-24468.4	-71156.3
cost saved at 0.05	3906.9	3182.7	1449.9	-1742.4	-6825.9	-14532.8	-25339.2	-39737.5	-58292.4	-81479.3	-110194.4	-329604.4
cost saved at 0.1	7431.9	5674.5	2059.9	-4199.3	-13871.8	-28111.9	-47617.0	-73032.5	-105352.3	-145143.2	-193530.9	-595692.5
cost saved at 0.15	10619.0	7571.8	2015.2	-7121.5	-20780.8	-40428.3	-66862.7	-100808.7	-143304.5	-194958.7	-257033.0	-811092.2

Notes: [&] in 1,000 US dollars; [#] if the cost at any given voluntary medical male circumcision coverage rate is higher than the baseline, the number is positive, which means not economically desirable; if the cost is lower than the baseline, the number is negative, which means economically desirable; [*]total cost at the baseline when $\lambda 1=0.0001$ [@]breakeven point for the economically desirable of voluntary medical male circumcision (when $\lambda=0.001$ at the year of 2019).

Figure 17. Transmission rates of HIV among men who have sex with men during 2016-2025 (remains the same transmission rate as seen in 2015)

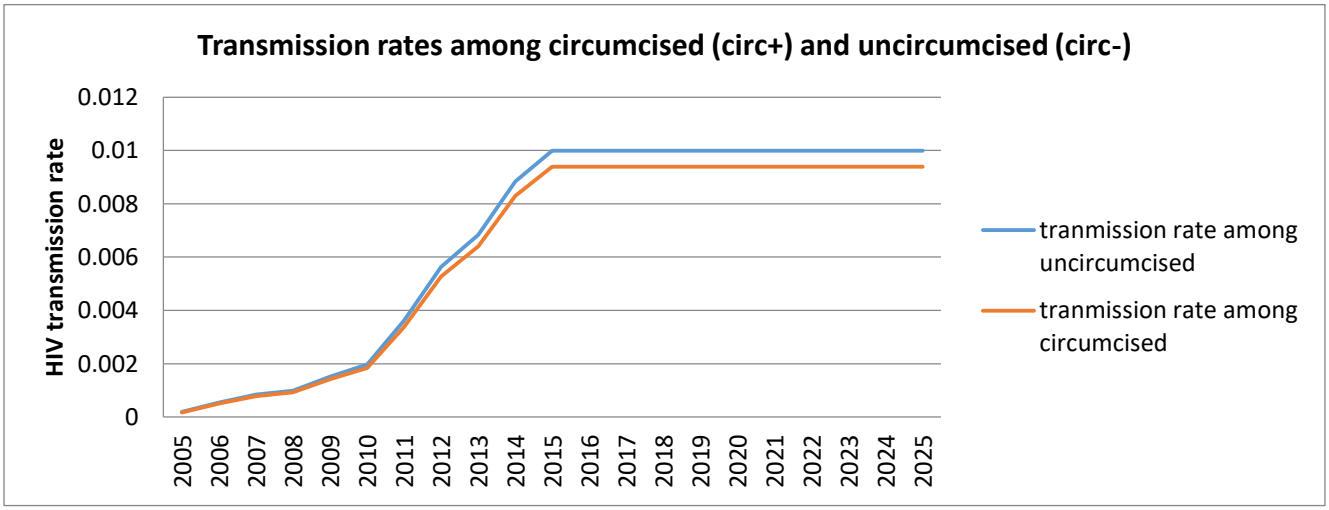


Figure 18. Numbers of VMMC needed per new HIV case averted at different coverage rates among men who have sex with men in China (2021-2026)

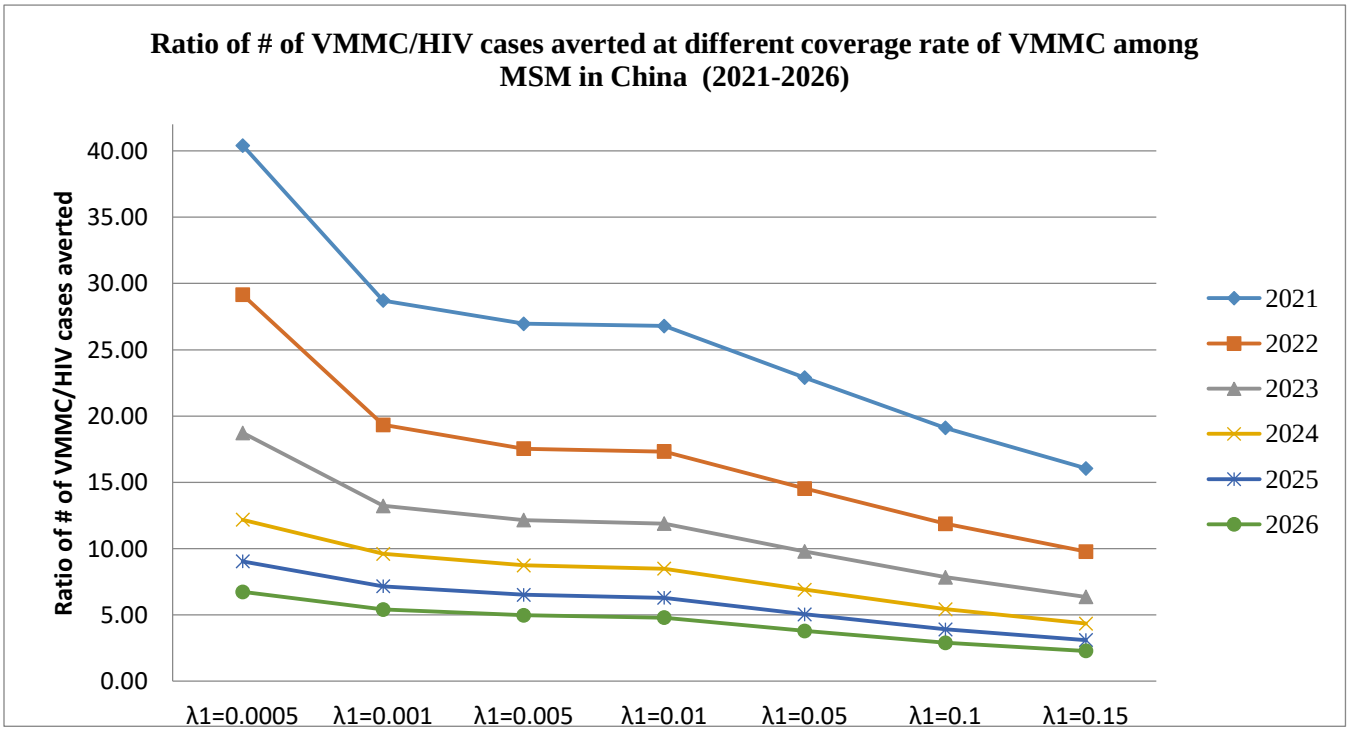


Figure 19. Saved cost from averting new HIV cases by expanding voluntary medical male circumcision among men who have sex with men in China

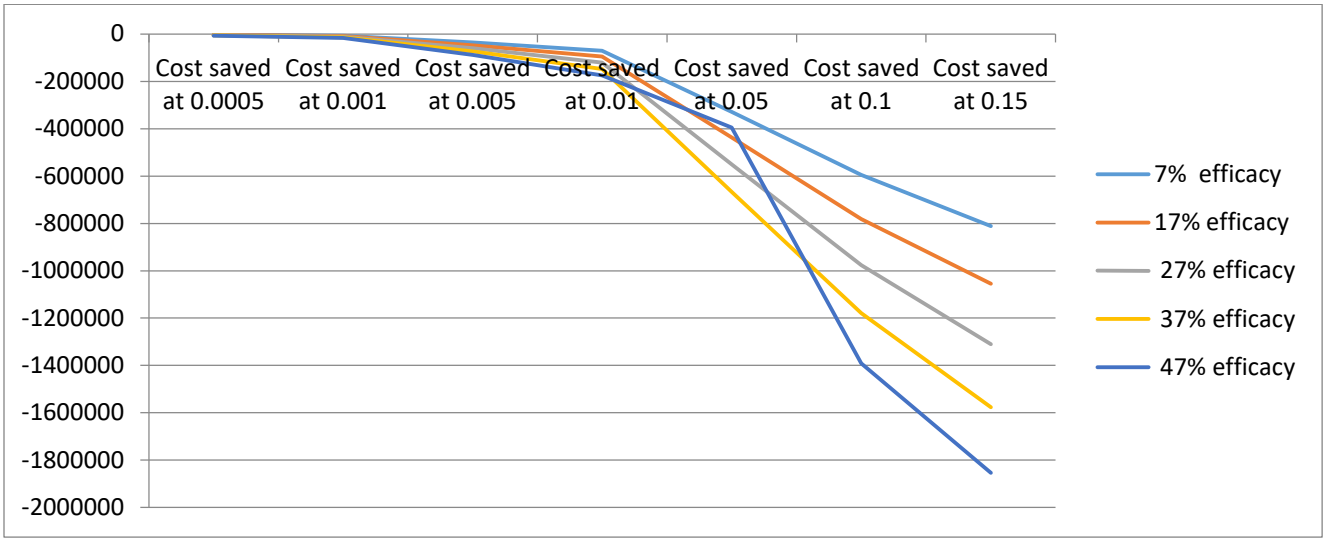


Table 15. Cost of voluntary medical male circumcision and HIV treatment after discounting at the rate of 3% (in US dollars)

Year	Cost of HIV treatment *	Cost of male circumcision &
2016	23794.83	230.77
2017	24508.67	237.69
2018	25243.94	244.82
2019	26001.25	252.17
2020	26781.29	259.73
2021	27584.73	267.53
2022	28412.27	275.55
2023	29264.64	283.82
2024	30142.58	292.33
2025	31046.86	301.10
2026	31978.26	310.14

Notes:

*The cost of HIV treatment for each given HIV infected person is calculated by summing costs of HIV testing, hospitalization and ARV medication

- **ART treatment**: (500/m*12m)/6.5*24y (average survival time after ARV)[1,2] =923*24=$22153.85 per HIV infected person in lifetime
- **Cost of test before entering free ARV program**: $150.75 [3]
- **Hospitalization**: 24.43*61=$ 1490.23[3]

Total cost for a HIV infected person on average at the year of 2016:

ARV+ Test+ Hospitalization=$22153.85+$1490.23+$150.75=$23794.83

&**Circumcision cost at the year of 2016**: 1500/6.5= $230.7692 per MSM (1 USD =6.5 RMB at the time of the current study)

References:

1.Farnham PG, Gopalappa C, Sansom SL, et al. Updates of lifetime costs of care and quality-of-life estimates for HIV-infected persons in the United States: late versus early diagnosis and entry into care. *Journal of acquired immune deficiency syndromes (1999).* Oct 01 2013;64(2):183-189.

2.Schackman BR, Fleishman JA, Su AE, et al. The lifetime medical cost savings from preventing HIV in the United States. *Medical care.* Apr 2015;53(4):293-301.

3.Moon S, Van Leemput L, Durier N, et al. Out-of-pocket costs of AIDS care in China: are free antiretroviral drugs enough? *AIDS care.* Sep 2008;20(8):984-994.

Table 16. Results from sensitivity analyses when remaining the same transmission rates as seen in 2015 (2016-2026)

Coverage rates	Items/Years	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
λ1=0.0001	**# of new VMMC per year**	37	38	39	40	40	41	42	43	44	45	45
	total # of new HIV cases	6344	9226	11864	14284	16511	18565	20465	22228	23868	25399	26832
λ1=0.0005	**# of new VMMC per year**	185	190	194	198	202	206	210	214	218	222	226
	total # of new HIV cases	6344	9226	11862	14282	16508	18561	20460	22221	23859	25388	26818
	# of HIV averted	0	0	1	3	3	4	6	7	9	11	14
	# of VMMC/HIV case averted			145.54	76.65	69.75	48.15	37.43	30.61	23.41	20.39	15.90
λ1=0.001	**# of new VMMC per year**	371	379	387	395	403	411	419	427	434	442	449
	total # of new HIV cases	6344	9225	11862	14280	16505	18555	20452	22210	23845	25371	26797
	# of HIV averted	0	0	2	4	6	10	14	18	23	28	35
	# of VMMC/HIV case averted			201.34	90.69	66.69	42.06	30.97	23.33	18.84	15.71	12.88
λ1=0.005	**# of new VMMC per year**	1847	1881	1914	1947	1980	2012	2043	2075	2106	2136	2166
	total # of new HIV cases	8895	11486	13863	16048	18062	19922	21644	23242	24730	26117	27416
	# of HIV averted	-2551	-2260	-1999	-1764	-1551	-1357	-1179	-1014	-862	-719	-584
	# of VMMC/HIV case averted	-0.72	-0.83	-0.96	-1.10	-1.28	-1.48	-1.73	-2.05	-2.44	-2.97	-3.71
λ1=0.01	**# of new VMMC per year**	3675	3725	3774	3823	3870	3917	3963	4009	4053	4097	4141
	total # of new HIV cases	6343	9220	11847	14251	16454	18477	20338	22053	23637	25103	26462

	# of HIV averted	1	6	17	34	57	88	127	175	231	296	370
	# of VMMC/HIV case averted	2696.56	602.40	219.27	113.94	68.32	44.38	31.10	22.92	17.52	13.84	11.20
λ1=0.05	**# of new VMMC per year**	17671	17249	16856	16491	16152	15836	15544	15272	15020	14787	14571
	total # of new HIV cases	6337	9194	11781	14123	16238	18149	19870	21418	22809	24057	25174
	# of HIV averted	7	32	83	162	273	417	596	810	1059	1342	1658
	# of VMMC/HIV case averted	2607.04	534.47	203.59	101.97	59.23	38.00	26.10	18.86	14.18	11.02	8.79
λ1=0.1	**# of new VMMC per year**	33652	31345	29296	27475	25859	24425	23152	22023	21023	20137	19353
	total # of new HIV cases	6330	9163	11706	13979	16002	17795	19377	20765	21977	23029	23938
	# of HIV averted	13	63	158	305	508	770	1089	1463	1891	2370	2894
	# of VMMC/HIV case averted	2516.96	498.05	185.75	90.02	50.86	31.71	21.26	15.06	11.12	8.50	6.69
λ1=0.15	**# of new VMMC per year**	48067	42733	38222	34408	31184	28461	26160	24219	22581	21200	20038
	total # of new HIV cases	6324	9135	11638	13852	15797	17495	18968	20236	21319	22234	23003
	# of HIV averted	20	91	226	433	714	1070	1497	1992	2550	3165	3829
	# of VMMC/HIV case averted	2433.51	468.97	168.93	79.51	43.68	26.59	17.47	12.16	8.86	6.70	5.23

Table 17. Numbers of voluntary medical male circumcision needed per HIV case averted among men who have sex with men (2016-2026) with protective efficacies ranging from 7% to 47%

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
7% efficacy											
λ1=0.0005	n/a	n/a	193.00	196.00	66.33	40.40	29.14	18.73	12.18	9.04	6.74
λ1=0.001	n/a	378.00	385.00	98.00	44.11	28.71	19.33	13.23	9.60	7.16	5.42
λ1=0.005	1847.00	469.50	173.18	80.38	44.32	26.96	17.54	12.16	8.74	6.52	4.97
λ1=0.01	3675.00	531.29	178.86	82.33	44.86	26.80	17.32	11.89	8.49	6.29	4.79
λ1=0.05	2524.43	465.43	159.77	72.62	38.91	22.89	14.53	9.79	6.91	5.05	3.79
λ1=0.1	2588.62	434.65	145.06	64.06	33.31	19.11	11.87	7.85	5.44	3.92	2.91
λ1=0.15	2403.35	410.24	131.18	56.46	28.62	16.06	9.78	6.36	4.35	3.11	2.29
17% efficacy											
λ1=0.0005	n/a	n/a	96.50	65.33	39.80	25.25	17.00	11.44	8.63	6.50	5.10
λ1=0.001		378.00	128.33	56.00	33.08	21.16	14.50	10.25	7.51	5.76	4.48
λ1=0.005	1847.00	268.29	105.83	52.14	30.47	19.29	12.95	9.19	6.76	5.16	4.02
λ1=0.01	1225.00	286.08	107.31	51.88	30.26	18.97	12.65	8.96	6.58	4.99	3.88
λ1=0.05	1262.21	257.03	95.86	46.69	26.44	16.26	10.72	7.45	5.39	4.03	3.09
λ1=0.1	1201.86	238.89	87.30	41.38	22.77	13.69	8.83	6.03	4.28	3.16	2.39
λ1=0.15	1172.37	224.55	79.25	36.59	19.67	11.57	7.32	4.92	3.45	2.52	1.90
27% efficacy											
λ1=0.0005	n/a	189.00	193.00	65.33	33.17	20.20	13.60	9.81	7.14	5.62	4.35
λ1=0.001	n/a	189.00	77.00	39.20	23.35	14.89	10.41	7.74	5.90	4.66	3.69
λ1=0.005	923.50	187.80	79.38	39.37	23.21	14.91	10.16	7.36	5.52	4.25	3.35
λ1=0.01	918.75	185.95	75.12	37.87	22.43	14.46	9.86	7.12	5.32	4.10	3.22
λ1=0.05	803.23	173.95	67.92	34.11	19.84	12.52	8.42	5.97	4.39	3.33	2.59
λ1=0.1	782.60	162.99	61.77	30.28	17.14	10.57	6.97	4.85	3.51	2.62	2.01
λ1=0.15	762.97	152.92	56.28	26.85	14.84	8.96	5.80	3.97	2.84	2.11	1.61

37% efficacy											
λ1=0.0005	n/a	189.00	96.50	39.20	24.88	16.83	11.33	7.92	5.91	4.62	3.67
λ1=0.001	371.00	126.00	64.17	30.15	19.85	12.97	9.02	6.72	5.10	3.99	3.16
λ1=0.005	615.67	144.46	57.73	29.68	18.22	11.93	8.29	6.06	4.59	3.58	2.85
λ1=0.01	612.50	137.74	56.91	29.59	17.90	11.68	8.09	5.90	4.46	3.46	2.75
λ1=0.05	609.34	130.46	52.10	26.70	15.77	10.11	6.90	4.95	3.68	2.82	2.21
λ1=0.1	580.21	122.73	47.49	23.70	13.65	8.55	5.72	4.03	2.95	2.23	1.73
λ1=0.15	558.92	115.00	43.28	21.05	11.84	7.26	4.77	3.31	2.40	1.80	1.39
47% efficacy											
λ1=0.0005	n/a	94.50	64.33	32.67	19.90	12.63	9.27	6.44	5.05	4.00	3.17
λ1=0.001	371.00	126.00	55.00	26.13	16.54	10.58	7.52	5.62	4.30	3.40	2.73
λ1=0.005	461.75	104.33	46.46	24.42	15.00	9.94	6.95	5.13	3.91	3.07	2.46
λ1=0.01	459.38	109.38	45.80	24.28	14.72	9.70	6.79	4.99	3.79	2.97	2.37
λ1=0.05	1262.21	257.03	95.86	46.69	26.44	16.26	10.72	7.45	5.39	4.03	3.09
λ1=0.1	454.76	97.19	38.21	19.35	11.27	7.13	4.82	3.42	2.53	1.93	1.50
λ1=0.15	440.98	91.56	34.90	17.19	9.78	6.06	4.03	2.82	2.06	1.56	1.21

Table 18. Cost saved after expanding the voluntary medical male circumcision compared to the baseline [&, #]

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	Total cost
7% efficacy												
Cost at baseline	150964.0	240589.4	342848.3	456249.4	580836.7	720089.6	872089.2	1035904.8	1213026.9	1403026.6	1608538.4	8624163.3
Cost saved at 0.0005	34.2	35.9	12.5	13.6	-39.0	-94.5	-153.9	-275.1	-464.3	-664.1	-939.5	-2534.2
Cost saved at 0.001	77.2	56.4	59.8	-15.0[@]	-148.2	-289.2	-495.9	-802.4	-1187.8	-1688.5	-2346.1	-6779.8
Cost saved at 0.005	394.3	339.9	179.5	-121.7	-681.8	-1497.0	-2646.4	-4244.8	-6330.4	-9002.1	-12309.3	-35919.9
Cost saved at 0.01	816.6	704.5	380.5	-251.6	-1295.4	-2928.4	-5257.6	-8399.5	-12571.8	-17885.3	-24468.4	-71156.3
Cost saved at 0.05	3906.9	3182.7	1449.9	-1742.4	-6825.9	-14532.8	-25339.2	-39737.5	-58292.4	-81479.3	-110194.4	-329604.4
Cost saved at 0.1	7431.9	5674.5	2059.9	-4199.3	-13871.8	-28111.9	-47617.0	-73032.5	-105352.3	-145143.2	-193530.9	-595692.5
Cost saved at 0.15	10619.0	7571.8	2015.2	-7121.5	-20780.8	-40428.3	-66862.7	-100808.7	-143304.5	-194958.7	-257033.0	-811092.2
17% efficacy												
Cost at baseline	150822.8	240284.0	342379.6	455604.3	579979.5	719006.5	870774.2	1034342.3	1211192.3	1400888.7	1606092.6	8611366.8
Cost saved at 0.0005	31.6	25.2	-11.0[@]	-50.4	-99.1	-181.6	-302.7	-486.1	-688.4	-939.8	-1266.7	-3969.1
Cost saved at 0.001	71.2	56.2	7.3	-103.2	-228.4	-429.1	-703.4	-1063.0	-1534.6	-2110.7	-2850.9	-8888.6
Cost saved at 0.005	384.8	258.2	-0.1	-493.3	-1219.0	-2301.4	-3819.5	-5806.9	-8353.2	-11501.0	-15379.7	-48231.2
Cost saved at 0.01	773.1	558.4	17.1	-946.3	-2401.2	-4567.8	-7573.7	-11510.6	-16555.7	-22806.9	-30502.4	-95516.0
Cost saved at 0.05	3738.4	2439.2	-325.5	-4990.1	-11993.1	-22139.2	-35825.0	-53507.2	-75757.4	-103045.8	-136202.1	-437608.0
Cost saved at 0.1	7104.9	4228.8	-1305.2	-10260.3	-23354.4	-41782.0	-66158.2	-97010.5	-135291.3	-181441.4	-236631.5	-781901.2
Cost saved at 0.15	10120.2	5483.8	-2797.5	-15640.6	-33887.1	-59029.1	-91682.3	-132397.6	-182193.0	-241456.0	-311482.6	-1054962.0

27% efficacy												
Cost at baseline	150680.0	239977.0	341878.1	454900.3	579062.3	717859.5	869388.0	1032679.9	1209237.1	1398626.2	1603503.6	8597792081
Cost saved at 0.0005	30.3	20.2	2.5[@]	-41.2	-119.2	-233.2	-387.5	-579.6	-818.6	5299.5	-1476.0	-4710.5
Cost saved at 0.001	67.9	22.7	-36.7	-182.7	-370.2	-638.6	-1009.5	-1445.3	-1997.5	-2658.3	-3489.0	-11737.2
Cost saved at 0.005	30.3	20.2	2.5	-41.2	-119.2	-233.2	-387.5	-579.6	-818.6	-1108.1	-1476.0	-60663.1
Cost saved at 0.01	737.0	389.5	-351.4	-1650.8	-3564.7	-6306.4	-10018.0	-14756.8	-20733.4	-28048.2	-36932.1	-121235.3
Cost saved at 0.05	3558.8	1653.6	-2142.2	-8335.2	-17350.5	-30010.8	-46721.7	-67846.9	-94002.3	-125597.4	-163480.2	-550274.8
Cost saved at 0.1	6751.3	2724.7	-4783.4	-16514.7	-33194.4	-56023.5	-85513.3	-122064.1	-166592.9	-219493.5	-281900.7	-976604.6
Cost saved at 0.15	9598.3	3303.8	-7750.5	-24434.5	-47500.3	-78387.4	-117600.1	-165452.2	-222917.3	-290272.0	-368766.0	-1310178.2
37% efficacy												
Cost at baseline	150532.3	239664.7	341369.9	454188.2	578110.7	716650.3	867910.8	1030922.0	1207181.6	1396258.5	1600803.6	8583592.628
Cost saved at 0.0005	28.7	15.0	-7.3[@]	-79.9	-164.2	-285.8	-474.0	-701.8	-1006.1	-1336.6	-1777.1	-5789.0
Cost saved at 0.001	64.5	11.2	-58.5	-240.0	-441.3	-750.7	-1165.3	-1673.4	-2330.3	-3129.4	-4107.5	-13820.9
Cost saved at 0.005	348.3	110.5	-371.2	-1203.3	-2367.8	-4030.1	-6263.2	-9084.4	-12572.0	-16823.2	-21962.8	-74219.3
Cost saved at 0.01	699.6	217.1	-750.3	-2391.3	-4721.7	-8045.4	-12447.7	-18020.5	-24965.2	-33383.2	-43527.9	-147336.3
Cost saved at 0.05	3373.0	850.4	-4039.8	-11806.9	-22885.0	-38151.3	-57995.1	-82739.3	-112989.9	-149120.7	-192007.4	-667512.1
Cost saved at 0.1	6385.5	1186.7	-8373.6	-23013.4	-43372.7	-70735.6	-105530.0	-148060.3	-199193.2	-259216.2	-329275.2	-1179197.8
Cost saved at 0.15	9058.4	1052.6	-12887.9	-33534.9	-61550.6	-98430.2	-144436.2	-199773.9	-265310.7	-341205.8	-428682.2	-1575701.5
47% efficacy												
Cost at baseline	150379.3	239345.6	340853.1	453441.9	577146.8	715426.2	866389.8	1029116.7	1205047.4	1393778.6	1597955.9	8568881.3

Cost saved at 0.0005	27.2	-12.6[@]	-40.4	-118.9	-234.1	-389.5	-587.2	-878.6	-1195.6	-1567.3	-2051.8	-7048.7
Cost saved at 0.001	60.9	-1.2	-104.4	-298.6	-562.5	-940.1	-1426.5	-2037.5	-2776.4	-3662.1	-4761.2	-16509.5
Cost saved at 0.005	329.1	0.0	-586.5	-1580.7	-2993.5	-4952.8	-7550.7	-10837.0	-14847.0	-19677.2	-25491.8	-88188.1
Cost saved at 0.01	661.0	39.7	-1158.3	-3122.3	-5947.4	-9887.3	-15042.7	-21515.4	-29499.4	-39097.0	-50555.2	-175124.3
Cost saved at 0.05	4181.9	3377.5	1200.9	-2827.7	-9160.4	-18558.8	-31440.7	-48281.6	-69612.5	-95935.8	-128065.4	-395122.5
Cost saved at 0.1	6006.8	-441.2	-12116.5	-29732.8	-53966.9	-86103.5	-126454.6	-175256.3	-233306.2	-300840.5	-378996.0	-1391207.6
Cost saved at 0.15	8499.5	-1288.2	-18213.1	-42998.7	-76224.0	-119355.7	-172474.8	-235661.1	-309684.1	-394582.6	-491562.0	-1853544.9

Notes: [&] in 1,000 US dollars; [#] if the cost at any given voluntary medical male circumcision coverage rate is higher than the baseline, the number is positive, which means not economically desirable; if the cost is lower than the baseline, the number is negative, which means economically desirable; [*]total cost at the baseline when $\lambda 1=0.0001$; [@]breakeven point for the economically desirable coverage rate of voluntary medical male circumcision

CHAPTER VII

SYNOPSIS

In this dissertation, I conducted a systematic review and meta-analysis to evaluate the protective efficacy of the association between male circumcision and HIV infection among MSM with a series of sensitivity analyses, employed a transmission model to assess the epidemiological impact of VMMC by projecting the HIV incidence for the next decade among MSM in Beijing; and determined the budget-impact of VMMC program by a decision-modeling strategy.

Our meta-analytic review included 117,293 participants from 33 studies, which had 45,600 more participants and 12 new studies compared with the one conducted by Wiysonge and colleagues in 2011 (Wiysonge et al., 2011). Our review showed that the odds of being HIV-infected were significantly lower among MSM who were circumcised than among MSM who were uncircumcised, but the effect size was modest (7% protection, 95% CI, 1%-12%). Our meta-analysis is the first to report a statistically protective effect of VMMC against HIV infection among MSM. The evidence for the protective effect of VMMC was dramatically stronger among MSM who live in Asia or Africa. Our findings suggest that VMMC may be a protective tool against HIV infection among MSM, especially for these who living in Asia and Africa (WHO, 2016; Beyrer et al., 2016).

Our model predicts the magnitude of the impact of VMMC on HIV acquisition over a 11-year period by estimating the reduction in proportion of HIV-infected cases [45]. By changing the coverage rates of VMMC from the very low baseline coverage (λ=0.0001) to a hypothetical scenario of an active VMMC program (λ=0.15), our model suggested a worthwhile potential public health impact of VMMC for MSM in China, depending on coverage assumptions, given an assumed efficacy of 7%. This low efficacy was derived from a systematic review and meta-analysis, but a 47% (95% confidence interval: -2 to +73%) protective efficacy estimate from a Chinese study conducted in 2010-2011 suggested VMMC to be more beneficial than earlier studies suggested; our estimates of benefit are therefore very conservative [33,34]. The reduction in the proportion of HIV-infected cases ranged from 0.06% when the VMMC coverage rate was low at 0.0001 (corresponding to the prevalence of VMMC as 1.7%) to 16.3% when the VMMC coverage rate increased to 0.15 (corresponding to the VMMC prevalence of 58.8%) by the year of 2026. Meanwhile, we observed a big jump of the reduction in the proportion of the number of HIV cases (from 0.92% to 4.18%) when the VMMC coverage rate increased from 0.01 to 0.05. The big jump may indicate that a slight increase of the VMMC coverage rate may result in a significant reduction in new HIV cases among MSM in China, even with our use of very conservative estimates of the efficacy of VMMC in protecting MSM.

Economic impact analysis was an essential part of a comprehensive assessment of a health intervention, playing an increasingly important role in decision-making for policy makers in the current study (Sullivan et al., 2014). We found that the higher the annual coverage rate, the lower numbers of VMMC needed per HIV case averted was over time.

A lower NNA can be obtained by expanding VMMC campaign significantly among MSM, which in turn, requires a higher budget cost of scaling-up the VMMC. If we achieved the greatest impact with the NNA as low as 2.29 when the annual VMMC coverage rate was 0.15, a total of 330,826 VMMC would be conducted by the year of 2026. On the other hand, if we adopted the most frugal budget to provide a low annual coverage rate (e.g., 0.0005) of VMMC, the impact would be trivial even though this coverage is five times the very low baseline. Furthermore, the analyses for "breakeven points" and total cost saved compared to baseline can assist health authorities to visualize time period and coverage rate for the tipping point of the intervention. Therefore, preventive health and decision-makers can use findings from the current modeling study for resource and budget planning.

In conclusion, although the overall effect of VMMC on HIV prevention was marginally significant, misclassification of key exposure and confounding variables may dilute the protective effect of VMMC. In turn, publication bias may exaggerate its protective effort. Research with more rigorous study designs to objectively assess HIV infection through confirmatory serological tests and evaluation of circumcision by genital exam can significantly reduce misclassification bias. In addition, future research should collect detailed data on MSM's sexual position preference at different time points in their lives (e.g., in the past 30 days, in the past six months and lifetime), as well as the degree of their sexual risk taking. We would not be surprised if we eventually learn that circumcision is highly protective for MSM, but benefits are predominantly accrued among men practicing predominantly insertive anal sex and men without highest risk behavior patterns. Subtypes may also alter the relative benefits seen, but no data exist on

this point. Our transmission model serves as one of the first studies to provide economic data (e.g., breakeven analysis, NNA, total cost saved), suggesting VMMC to be a viable prevention option for control of HIV among MSM in China and similar venues. Policy-makers would do well to consider accelerating access to VMMC targeting MSM, a neglected component in the "prevention tool box" to stem the HIV/AIDS epidemic. A randomized clinical trial, if feasible, should be conducted.

REFERENCES

Anderson, J., Wilson, D., Templeton, D. J., Grulich, A., Carter, R., & Kaldor, J. (2009). Cost effectiveness of adult circumcision in a resource-rich setting for HIV prevention among men who have sex with men. *J Infect Dis, 200*(12), 1803-1812. doi: 10.1086/648472

April, M. D., Wood, R., Berkowitz, B. K., Paltiel, A. D., Anglaret, X., Losina, E., . . . Walensky, R. P. (2014). The survival benefits of antiretroviral therapy in South Africa. *J Infect Dis, 209*(4), 491-499. doi: 10.1093/infdis/jit584

Auvert, B., Taljaard, D., Lagarde, E., Sobngwi-Tambekou, J., Sitta, R., & Puren, A. (2005). Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med, 2*(11), e298. doi: 10.1371/journal.pmed.0020298

AVERT. (2015). HIV and AIDS in Asia. Retrieved Feburary 18 2015, from http://www.avert.org/hiv-and-aids-asia.htm

Bailey, R. C., Moses, S., Parker, C. B., Agot, K., Maclean, I., Krieger, J. N., . . . Ndinya-Achola, J. O. (2007). Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet, 369*(9562), 643-656. doi: 10.1016/s0140-6736(07)60312-2

Baral, S., Sifakis, F., Cleghorn, F., & Beyrer, C. (2007). Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000-2006: a systematic review. *PLoS Med, 4*(12), e339. doi: 10.1371/journal.pmed.0040339

Barnabas, R. (2016). Deterministic Compartmental Models: Application: Modeling the Potential Benefit of HPV Vaccines.

Barnabas, R. V., Wasserheit, J. N., Huang, Y., Janes, H., Morrow, R., Fuchs, J., . . . Corey, L. (2011). Impact of herpes simplex virus type 2 on HIV-1 acquisition and progression in an HIV vaccine trial (the Step study). *J Acquir Immune Defic Syndr, 57*(3), 238-244. doi: 10.1097/QAI.0b013e31821acb5

Bartholow, B. N., Goli, V., Ackers, M., McLellan, E., Gurwith, M., Durham, M., & Greenberg, A. E. (2006). Demographic and behavioral contextual risk groups among men who have sex with men participating in a phase 3 HIV vaccine efficacy trial: implications for HIV prevention and behavioral/biomedical intervention trials. *J Acquir Immune Defic Syndr, 43*(5), 594-602. doi: 10.1097/01.qai.0000243107.26136.82

Begley, E. B., Jafa, K., Voetsch, A. C., Heffelfinger, J. D., Borkowf, C. B., & Sullivan, P. S. (2008). Willingness of men who have sex with men (MSM) in the United States to be circumcised as adults to reduce the risk of HIV infection. *PLoS One, 3*(7), e2731. doi: 10.1371/journal.pone.0002731

Beloukas, A., Psarris, A., Giannelou, P., Kostaki, E., Hatzakis, A., & Paraskevis, D. (2016). Molecular epidemiology of HIV-1 infection in Europe: An overview. *Infect Genet Evol*. doi: 10.1016/j.meegid.2016.06.033

Ben, K. L., Xu, J. C., Lu, L., Lu, N. Q., Cheng, Y., Tao, J., . . . Li, P. S. (2009). [Male circumcision is an effective "surgical vaccine" for HIV prevention and reproductive health]. *Zhonghua Nan Ke Xue, 15*(5), 395-402.

Beyrer, C. (2010a). Global prevention of HIV infection for neglected populations: men who have sex with men. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 50 Suppl 3*, S108-113. doi: 10.1086/651481

Beyrer, C. (2010b). Global prevention of HIV infection for neglected populations: men who have sex with men. *Clin Infect Dis, 50 Suppl 3*, S108-113. doi: 10.1086/651481

Beyrer, C., Baral, S. D., van Griensven, F., Goodreau, S. M., Chariyalertsak, S., Wirtz, A. L., & Brookmeyer, R. (2012). Global epidemiology of HIV infection in men who have sex with men. *Lancet, 380*(9839), 367-377. doi: 10.1016/s0140-6736(12)60821-6

Binagwaho, A., Pegurri, E., Muita, J., & Bertozzi, S. (2010). Male circumcision at different ages in Rwanda: a cost-effectiveness study. *PLoS Med, 7*(1), e1000211. doi: 10.1371/journal.pmed.1000211

Bollinger, L. A., Stover, J., Musuka, G., Fidzani, B., Moeti, T., & Busang, L. (2009). The cost and impact of male circumcision on HIV/AIDS in Botswana. *J Int AIDS Soc, 12*, 7. doi: 10.1371/journal.pmed.100113210.1186/1758-2652-12-7

Borenstein, M., Hedges, L. V., Higgins, J., & Rothstein, H. (2009). *Introduction to Meta-Analysis*. Hoboken, New Jersey, USA: Wiley.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods, 1*(2), 97-111. doi: 10.1002/jrsm.12

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to meta-analysis.* . West Sussex, United Kingdom: Wiley.

Borenstein, M., & Higgins, J. P. (2013). Meta-analysis and subgroups. *Prev Sci, 14*(2), 134-143. doi: 10.1007/s11121-013-0377-7

Boslaugh, S. (2007). An Introduction to Secondary Data Analysis *Secondary Data Sources for Public Health: A Practical Guide* (pp. 1-10). New York, US: Cambridge University Press.

Brown, S. A., Upchurch, S. L., & Acton, G. J. (2003). A framework for developing a coding scheme for meta-analysis. *West J Nurs Res, 25*(2), 205-222.

Buchbinder, S. P., Mehrotra, D. V., Duerr, A., Fitzgerald, D. W., Mogg, R., Li, D., . . . Robertson, M. N. (2008). Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet, 372*(9653), 1881-1893. doi: 10.1016/s0140-6736(08)61591-3

Buchbinder, S. P., Vittinghoff, E., Heagerty, P. J., Celum, C. L., Seage, G. R., 3rd, Judson, F. N., . . . Koblin, B. A. (2005). Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Defic Syndr, 39*(1), 82-89.

Calzavara, L. M., Remis, R., Myers, T., & StudyTeam, P. (2007, April 24-27,2007). *Circumcision and HIV/STI among MSM in the Polaris HIV seroconversion study [abstract 0100]*. Paper presented at the 16th Annual Candadian Association For HIV Research Toronto, Ontario, Canada.

Chen, Y. J., Lin, Y. T., Chen, M., Huang, S. W., Lai, S. F., Wong, W. W., . . . Chen, Y. M. (2011). Risk factors for HIV-1 seroconversion among Taiwanese men visiting gay saunas who have sex with men. *BMC Infect Dis, 11*, 334. doi: 10.1186/1471-2334-11-334

Cheng, W., Tang, W., Zhong, F., Babu, G. R., Han, Z., Qin, F., . . . Wang, M. (2014). Consistently High Unprotected Anal Intercourse (UAI) and factors correlated with UAI among men who have sex with men: implication of a serial cross-sectional study in Guangzhou, China. *BMC Infect Dis, 14*(1), 696. doi: 10.1186/s12879-014-0696-8

ChinaDaily. (2015). China has 575,000 people with HIV/AIDS. Retrieved Oct 1, 2016, from http://www.chinadaily.com.cn/china/2015-12/01/content_22595361.htm

Chow, E. P., Jing, J., Feng, Y., Min, D., Zhang, J., Wilson, D. P., . . . Zhang, L. (2013). Pattern of HIV testing and multiple sexual partnerships among men who have sex with men in China. *BMC Infect Dis, 13*, 549. doi: 10.1186/1471-2334-13-549

Chow, E. P., Wilson, D. P., & Zhang, L. (2011a). HIV and syphilis co-infection increasing among men who have sex with men in China: a systematic review and meta-analysis. *PLoS One, 6*(8), e22768. doi: 10.1371/journal.pone.0022768

Chow, E. P., Wilson, D. P., & Zhang, L. (2011b). What is the potential for bisexual men in China to act as a bridge of HIV transmission to the female population? Behavioural evidence from a systematic review and meta-analysis. *BMC Infect Dis, 11*, 242. doi: 10.1186/1471-2334-11-242

Crosby, R. A., Graham, C. A., Mena, L., Yarber, W. L., Sanders, S. A., Milhausen, R. R., & Geter, A. (2015). Circumcision Status is Not Associated with Condom Use and Prevalence of Sexually Transmitted Infections Among Young Black MSM. *AIDS Behav*. doi: 10.1007/s10461-015-1212-x

Doerner, R., McKeown, E., Nelson, S., Anderson, J., Low, N., & Elford, J. (2013a). Circumcision and HIV infection among men who have sex with men in Britain: the insertive sexual role. *Arch Sex Behav, 42*(7), 1319-1326. doi: 10.1007/s10508-012-0061-1

Donoval, B. A., Landay, A. L., Moses, S., Agot, K., Ndinya-Achola, J. O., Nyagaya, E. A., . . . Bailey, R. C. (2006). HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections. *Am J Clin Pathol, 125*(3), 386-391. doi: 10.1097/QAI.0b013e31829b6298

Drabo, E. F., Hay, J. W., Vardavas, R., Wagner, Z. R., & Sood, N. (2016). A Cost-effectiveness Analysis of Preexposure Prophylaxis for the Prevention of HIV Among Los Angeles County Men Who Have Sex With Men. *Clin Infect Dis, 63*(11), 1495-1504. doi: 10.1093/cid/ciw578

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

Egger, M., Smith, G. D., & Altman, D. G. (2001). *Systematic reviews in health care : meta-analysis in context* (2nd ed.). London: BMJ.

Fan, S., Lu, H., Ma, X., Sun, Y., He, X., Li, C., . . . Ruan, Y. (2012). Behavioral and serologic survey of men who have sex with men in Beijing, China: implication for HIV intervention. *AIDS Patient Care STDS, 26*(3), 148-155. doi: 10.1089/apc.2011.0277

Fankem, S. L., Wiysonge, C. S., & Hankins, C. A. (2008). Male circumcision and the risk of HIV infection in men who have sex with men. *International journal of epidemiology, 37*(2), 353-355. doi: 10.1093/ije/dym203

Farnham, P. G., Gopalappa, C., Sansom, S. L., Hutchinson, A. B., Brooks, J. T., Weidle, P. J., . . . Rimland, D. (2013). Updates of lifetime costs of care and quality-of-life estimates for HIV-infected persons in the United States: late versus early diagnosis and entry into care. *J Acquir Immune Defic Syndr, 64*(2), 183-189. doi: 10.1097/QAI.0b013e3182973966

Gold, M., Siegel, J., Russel, L., & Weinstein, M. (1996). *Cost-Effectiveness in Health and Medicine*. *Report of the Panel on Cost-effectiveness in Health and Medicine*. New York: Oxford University Press

Goodreau, S. M., Carnegie, N. B., Vittinghoff, E., Lama, J. R., Fuchs, J. D., Sanchez, J., & Buchbinder, S. P. (2014). Can male circumcision have an impact on the HIV epidemic in men who have sex with men? *PLoS One, 9*(7), e102960. doi: 10.1371/journal.pone.0102960

Goodreau, S. M., Carnegie, N. B., Vittinghoff, E., Lama, J. R., Sanchez, J., Grinsztejn, B., . . . Buchbinder, S. P. (2012). What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PLoS One, 7*(11), e50522. doi: 10.1371/journal.pone.0050522

Gray, R., Kigozi, G., Kong, X., Ssempiija, V., Makumbi, F., Wattya, S., . . . Wawer, M. J. (2012). The effectiveness of male circumcision for HIV prevention and effects on risk behaviors in a posttrial follow-up study. *AIDS, 26*(5), 609-615. doi: 10.1097/QAD.0b013e3283504a3f

Gray, R. H., Kigozi, G., Serwadda, D., Makumbi, F., Watya, S., Nalugoda, F., . . . Wawer, M. J. (2007). Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet, 369*(9562), 657-666. doi: 10.1016/s0140-6736(07)60313-4

Gray, R. H., Li, X., Kigozi, G., Serwadda, D., Nalugoda, F., Watya, S., . . . Wawer, M. (2007). The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. *AIDS, 21*(7), 845-850. doi: 10.1097/QAD.0b013e3280187544

Group, U. W. S. (2009). Male circumcision for HIV prevention in high HIV prevalence settings: what can mathematical modelling contribute to informed decision making? *PLoS Med, 6*(9), e1000109. doi: 10.1371/journal.pmed.1000109

Guo, Y., Li, X., & Stanton, B. (2011). HIV-related behavioral studies of men who have sex with men in China: a systematic review and recommendations for future research. *AIDS Behav, 15*(3), 521-534. doi: 10.1007/s10461-010-9808-7

Gust, D. A., Wiegand, R. E., Kretsinger, K., Sansom, S., Kilmarx, P. H., Bartholow, B. N., & Chen, R. T. (2010). Circumcision status and HIV infection among MSM: reanalysis of a Phase III HIV vaccine clinical trial. *AIDS, 24*(8), 1135-1143. doi: 10.1097/QAD.0b013e328337b8bd

Hallett, T. B., Singh, K., Smith, J. A., White, R. G., Abu-Raddad, L. J., & Garnett, G. P. (2008). Understanding the impact of male circumcision interventions on the spread of HIV in southern Africa. *PLoS One, 3*(5), e2212. doi: 10.1371/journal.pone.0002212

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med, 21*(11), 1539-1558. doi: 10.1002/sim.1186

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi: 10.1136/bmj.327.7414.557327/7414/557 [pii]

Higgins JPT, G. S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* The Cochrane Collaboration.

Huang, W., Du, S., Xu, J., Zhou, J., Liang, S., Yu, F., . . . Salazar, L. F. (2014). Acceptability of Condoms, Circumcision and PrEP among Young Black Men Who Have Sex with Men: A Descriptive Study Based on Effectiveness and Cost. *Biomed Res Int, 2*(1), 129-137. doi: 10.1155/2014/49898710.3390/vaccines2010129

Hunink, M., Glasziou, P., Siegel, J., Weeks, J. C., Pliskin, J. S., Elstein, A. S., & Milton, C. W. (2001). *Decision Making in Health and Medicine: Integrating Evidence and Values*: Cambridge University Press.

Jameson, D. R., Celum, C. L., Manhart, L., Menza, T. W., & Golden, M. R. (2010a). The association between lack of circumcision and HIV, HSV-2, and other sexually transmitted infections among men who have sex with men. *Sexually transmitted diseases, 37*(3), 147-152. doi: 10.1097/OLQ.0b013e3181bd0ff0

Jameson, D. R., Celum, C. L., Manhart, L., Menza, T. W., & Golden, M. R. (2010b). The association between lack of circumcision and HIV, HSV-2, and other sexually transmitted infections among men who have sex with men. *Sex Transm Dis, 37*(3), 147-152. doi: 10.1097/OLQ.0b013e3181bd0ff0

Jiang, T., Cai, G., Pan, X., & Ma, Q. (2014). [Psychosocial factors related to the practice of high risk sexual behavior among men who have sex with men: a review]. *Zhonghua Liu Xing Bing Xue Za Zhi, 35*(10), 1177-1180.

Jin, F., Jansson, J., Law, M., Prestage, G. P., Zablotska, I., Imrie, J. C., . . . Wilson, D. P. (2010). Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. *AIDS, 24*(6), 907-913. doi: 10.1097/QAD.0b013e3283372d90

Jozkowski, K., Rosenberger, J. G., Schick, V., Herbenick, D., Novak, D. S., & Reece, M. (2010). Relations between circumcision status, sexually transmitted infection history, and HIV serostatus among a national sample of men who have sex with men in the United States. *AIDS Patient Care STDS, 24*(8), 465-470. doi: 10.1089/apc.2010.0082

Kahn, J. G., Marseille, E., & Auvert, B. (2006). Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med, 3*(12), e517. doi: 10.1371/journal.pmed.0030517

Koblin, B. A., Mayer, K. H., Eshleman, S. H., Wang, L., Mannheimer, S., del Rio, C., . . . Wheeler, D. (2013). Correlates of HIV acquisition in a cohort of Black men who have sex with men in the United States: HIV prevention trials network (HPTN) 061. *PLoS One, 8*(7), e70413. doi: 10.1371/journal.pone.0070413

Koblin, B. A., Mayer, K. H., Noonan, E., Wang, C. Y., Marmor, M., Sanchez, J., . . . Buchbinder, S. P. (2012). Sexual risk behaviors, circumcision status, and preexisting immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: step study. *J Acquir Immune Defic Syndr, 60*(4), 405-413. doi: 10.1097/QAI.0b013e31825325aa

Konou, A. A., Vidal, N., Salou, M., Anato, S., Singo-Tokofai, A., Ekouevi, D. K., . . . Dagnra, A. Y. (2016). Genetic diversity and transmission networks of HIV-1 strains among men having sex with men (MSM) in Lome, Togo. *Infect Genet Evol*. doi: 10.1016/j.meegid.2016.05.030

Kreiss, J. K., & Hopkins, S. G. (1993). The association between circumcision status and human immunodeficiency virus infection among homosexual men. *J Infect Dis, 168*(6), 1404-1408.

Kripke, K., & Njeuhmeli, E. (2016). Assessing Progress, Impact, and Next Steps in Rolling Out Voluntary Medical Male Circumcision for HIV Prevention in 14 Priority Countries in Eastern and Southern Africa through 2014. *PLoS One, 11*(7), e0158767. doi: 10.1371/journal.pone.015869310.1371/journal.pone.0158767

Kripke, K., Opuni, M., Schnure, M., Sgaier, S., Castor, D., Reed, J., & Njeuhmeli, E. (2016). Age Targeting of Voluntary Medical Male Circumcision Programs Using the Decision Makers' Program Planning Toolkit (DMPPT) 2.0. *11*(7), e0156909. doi: 10.1371/journal.pone.0156909

Kumta, S., Setia, M., Jerjani, H. R., Mather, M. S., & RaoKavi, A. (2002, July 7-12, 2002). *Men who have sex with men and male to female transgender in Mumbai: a critical emerging risk group for HIV and sexually transmitted infections in India [Abstract TuOrCI 149]*. Paper presented at the 14th International AIDS Conference, Barcelona, Spain.

Lai, S. F., Hong, C. P., & Lan, Y. C. (2004, July 11-16, 2004). *Molecular Epidemiology of HIV-1 in men who have sex with men from gay saunas in Taiwan From 2000 to 2003 [abstract WePeC6097]*. Paper presented at the 15th International AIDS Conference Bangkok, Thailand.

LaMorte, W. W., & Sullivan, L. (2016). The Cochran-Mantel-Haenszel Method. Retrieved Feburary 15 2016, from http://sphweb.bumc.bu.edu/otlt/MPH-Modules/BS/BS704-EP713_Confounding-EM/BS704-EP713_Confounding-EM7.html#cochran-mantel-haenszelequations

Lane, T., Raymond, H. F., Dladla, S., Rasethe, J., Struthers, H., McFarland, W., & McIntyre, J. (2011). High HIV prevalence among men who have sex with men in Soweto, South

Africa: results from the Soweto Men's Study. *AIDS Behav, 15*(3), 626-634. doi: 10.1007/s10461-009-9598-y

Lau, J. T., Yan, H., Lin, C., Zhang, J., Choi, K. C., Wang, Z., . . . Yang, H. (2012). How willing are men who have sex with men in China to be circumcised for the sake of protecting his female sex partner? *J Sex Med, 9*(7), 1904-1912. doi: 10.1111/j.1743-6109.2010.02050.x

Lau, J. T., Zhang, J., Yan, H., Lin, C., Choi, K. C., Wang, Z., . . . Yang, H. (2011). Acceptability of circumcision as a means of HIV prevention among men who have sex with men in China. *AIDS Care, 23*(11), 1472-1482. doi: 10.1080/09540121.2011.565018

Li, D.-I., Liang, H.-Y., & Yang, Y. (2008). A Survey of Initial and Factors of Homosexual Intercourse Among Men Who Have Sex With Men. *Journal of Preventive Medicine Information, 6*, 008.

Littell, J. H., Corcoran, J., & Pillai, V. (2008). *Systematic Reviews and Meta-analysis*. New York, USA: Oxford University Press.

Liu H, L. Y., Xiao Y. . (2001). A survey on knowledge, attitude, belief and practice related to HIV/AIDS among MSM. *J China AIDS/STD Prevent Control 7*, 289 –291.

Londish, G. J., Templeton, D. J., Regan, D. G., Kaldor, J. M., & Murray, J. M. (2010a). Minimal impact of circumcision on HIV acquisition in men who have sex with men. *Sex Health, 7*(4), 463-470. doi: 10.1071/sh09080

Londish, G. J., Templeton, D. J., Regan, D. G., Kaldor, J. M., & Murray, J. M. (2010b). Minimal impact of circumcision on HIV acquisition in men who have sex with men. *Sexual health, 7*(4), 463-470. doi: 10.1071/SH09080

Lou, J., Blevins, M., Ruan, Y., Vermund, S. H., Tang, S., Webb, G. F., . . . Qian, H. Z. (2014). Modeling the impact on HIV incidence of combination prevention strategies among men who have sex with men in Beijing, China. *PLoS One, 9*(3), e90985. doi: 10.1371/journal.pone.0090985

Lou, J., & Smith, R. J. (2011). Modelling the effects of adherence to the HIV fusion inhibitor enfuvirtide. *J Theor Biol, 268*(1), 1-13. doi: 10.1016/j.jtbi.2010.09.039

Lou, J., Wu, J., Chen, L., Ruan, Y., & Shao, Y. (2009). A sex-role-preference model for HIV transmission among men who have sex with men in China. *BMC Public Health, 9 Suppl 1*, S10. doi: 10.1186/1471-2458-9-s1-s10

Lu, H., Liu, Y., Dahiya, K., Qian, H. Z., Fan, W., Zhang, L., . . . Yin, L. (2013). Effectiveness of HIV risk reduction interventions among men who have sex with men in China: a systematic review and meta-analysis. *PLoS One, 8*(8), e72747. doi: 10.1371/journal.pone.0072747

Luo, H., Liang, X., Chen, J., Yang, X. B., Jiang, J. J., Deng, W., . . . Liang, H. (2011). [Acceptability of male circumcision among male miners in Baise of Guangxi]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao, 33*(3), 313-317. doi: 10.3881/j.issn.1000-503X.2011.03.020

Mao, L., Templeton, D. J., Crawford, J., Imrie, J., Prestage, G. P., Grulich, A. E., . . . Kippax, S. C. (2008). Does circumcision make a difference to the sexual experience of gay men? Findings from the Health in Men (HIM) cohort. *J Sex Med, 5*(11), 2557-2561. doi: 10.1111/j.1743-6109.2008.00845.x

Matar, L., Zhu, J., Chen, R. T., & Gust, D. A. (2015). Medical risks and benefits of newborn male circumcision in the United States: physician perspectives. *J Int Assoc Provid AIDS Care, 14*(1), 33-39. doi: 10.1177/2325957414535975

McDaid, L. M., Weiss, H. A., & Hart, G. J. (2010). Circumcision among men who have sex with men in Scotland: limited potential for HIV prevention. *Sex Transm Infect, 86*(5), 404-406. doi: 10.1136/sti.2010.042895

Millett, G. A., Ding, H., Lauby, J., Flores, S., Stueve, A., Bingham, T., . . . Marks, G. (2007). Circumcision status and HIV infection among Black and Latino men who have sex with men in 3 US cities. *J Acquir Immune Defic Syndr, 46*(5), 643-650. doi: 10.1097/QAI.0b013e31815b834d

Millett, G. A., Flores, S. A., Marks, G., Reed, J. B., & Herbst, J. H. (2008). Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. *Jama, 300*(14), 1674-1684. doi: 10.1001/jama.300.14.1674

Mills, E., Cooper, C., Anema, A., & Guyatt, G. (2008). Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11,050 men. *HIV Med, 9*(6), 332-335. doi: 10.1111/j.1468-1293.2008.00596.x

Moon, S., Van Leemput, L., Durier, N., Jambert, E., Dahmane, A., Jie, Y., . . . Saranchuk, P. (2008). Out-of-pocket costs of AIDS care in China: are free antiretroviral drugs enough? *AIDS Care, 20*(8), 984-994. doi: 10.1080/09540120701768446

Mor, Z., Kent, C. K., Kohn, R. P., & Klausner, J. D. (2007). Declining rates in male circumcision amidst increasing evidence of its public health benefit. *PLoS One, 2*(9), e861. doi: 10.1371/journal.pone.0000861

Moreno, S. G., Sutton, A. J., Ades, A. E., Stanley, T. D., Abrams, K. R., Peters, J. L., & Cooper, N. J. (2009). Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study. *BMC Med Res Methodol, 9*, 2. doi: 10.1186/1471-2288-9-21471-2288-9-2 [pii]

Nagelkerke, N. J., Moses, S., de Vlas, S. J., & Bailey, R. C. (2007). Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. *BMC Infect Dis, 7*, 16. doi: 10.1186/1471-2334-7-16

ND, B., KN, L., M, A., M, M., E, B., E, W., . . . S, C. (2013). *Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Comparative Effectiveness Reviews* . Rockville, MD.Agency for Healthcare Research and Quality: Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

NHFPC. (2014). *2014 China AIDS Response Progress Report*. Retrieved from http://www.unaids.org/sites/default/files/documents/CHN_narrative_report_2014.pdf.

NHFPC. (2015). 2015 China AIDS Response Progress Report.

Nikolakopoulou, A., Mavridis, D., & Salanti, G. (2014). Demystifying fixed and random effects meta-analysis. *Evid Based Ment Health, 17*(2), 53-57. doi: 10.1136/eb-2014-101795

Njeuhmeli, E., Forsythe, S., Reed, J., Opuni, M., Bollinger, L., Heard, N., . . . Hankins, C. (2011). Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. *PLoS One, 8*(11), e1001132. doi: 10.1371/journal.pone.015336310.1371/journal.pmed.1001132

Okulicz, J. F., & Lambotte, O. (2011). Epidemiology and clinical characteristics of elite controllers. *Curr Opin HIV AIDS, 6*(3), 163-168. doi: 10.1097/COH.0b013e328344f35e

Okwundu, C. I., Uthman, O. A., & Okoromah, C. A. (2012). Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database Syst Rev, 7*, CD007189. doi: 10.1002/14651858.CD007189.pub3

Oster, A. M., Wiegand, R. E., Sionean, C., Miles, I. J., Thomas, P. E., Melendez-Morales, L., . . . Millett, G. A. (2011). Understanding disparities in HIV infection between black and white MSM in the United States. *AIDS, 25*(8), 1103-1112. doi: 10.1097/QAD.0b013e3283471efa

Pando, M. A., Balan, I. C., Dolezal, C., Marone, R., Barreda, V., Carballo-Dieguez, A., & Avila, M. M. (2013a). Low frequency of male circumcision and unwillingness to be circumcised among MSM in Buenos Aires, Argentina: association with sexually transmitted infections. *J Int AIDS Soc, 16*, 18500. doi: 10.1371/journal.pone.007004310.7448/ias.16.1.18500

Pando, M. A., Balan, I. C., Dolezal, C., Marone, R., Barreda, V., Carballo-Dieguez, A., & Avila, M. M. (2013b). Low frequency of male circumcision and unwillingness to be circumcised among MSM in Buenos Aires, Argentina: association with sexually transmitted infections. *J Int AIDS Soc, 16*(1), 18500. doi: 10.7448/ias.16.1.18500

Pantaleo, G., Menzo, S., Vaccarezza, M., Graziosi, C., Cohen, O. J., Demarest, J. F., . . . et al. (1995). Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. *N Engl J Med, 332*(4), 209-216. doi: 10.1056/nejm199501263320402

Pretorius, C., Stover, J., Bollinger, L., Bacaer, N., & Williams, B. (2010). Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. *PLoS One, 5*(11), e13646. doi: 10.1371/journal.pone.0013646

Qian, H. Z., Ruan, Y., Liu, Y., Milam, D. F., HM, L. S., Yin, L., . . . Vermund, S. H. (2015). Lower HIV risk among circumcised men who have sex with men in China: Interaction with anal sex role in a cross-sectional study. *J Acquir Immune Defic Syndr*. doi: 10.1097/qai.0000000000000856

Qian, H. Z., Ruan, Y., Liu, Y., Milam, D. F., Spiegel, H. M., Yin, L., . . . Vermund, S. H. (2016). Lower HIV Risk Among Circumcised Men Who Have Sex With Men in China: Interaction With Anal Sex Role in a Cross-Sectional Study. *J Acquir Immune Defic Syndr, 71*(4), 444-451. doi: 10.1097/qai.0000000000000856

Reid, D., Weatherburn, P., Hickson, F., & Stephens, M. (2001). Know the score: Findings from the National Gay Men's Sex Survey 2001 *Stigma Research*. London, UK: University of Portsmouth.

Reisen, C. A., Zea, M. C., Poppen, P. J., & Bianchi, F. T. (2007). Male circumcision and HIV status among Latino immigrant MSM in New York City. *J LGBT Health Res, 3*(4), 29-36. doi: 10.1080/15574090802263421

Reynolds, S. J., Shepherd, M. E., Risbud, A. R., Gangakhedkar, R. R., Brookmeyer, R. S., Divekar, A. D., . . . Bollinger, R. C. (2004). Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet, 363*(9414), 1039-1040. doi: 10.1016/s0140-6736(04)15840-6

Rotheram-Borus, M. J., Swendeman, D., & Chovnick, G. (2009). The past, present, and future of HIV prevention: integrating behavioral, biomedical, and structural intervention strategies for the next generation of HIV prevention. *Annu Rev Clin Psychol, 5*, 143-167. doi: 10.1146/annurev.clinpsy.032408.153530

Ruan, Y., Qian, H. Z., Li, D., Shi, W., Li, Q., Liang, H., . . . Shao, Y. (2009). Willingness to be circumcised for preventing HIV among Chinese men who have sex with men. *AIDS Patient Care STDS, 23*(5), 315-321. doi: 10.1089/apc.2008.0199

Sabido, M., Kerr, L. R., Mota, R. S., Benzaken, A. S., de, A. P. A., Guimaraes, M. D., . . . Kendall, C. (2015). Sexual Violence Against Men Who Have Sex with Men in Brazil: A Respondent-Driven Sampling Survey. *AIDS Behav*. doi: 10.1007/s10461-015-1016-z

Sanchez, J. (2007). *Cutting the edge of teh HIV epidemic among MSM.* Paper presented at the The Center for HIV Identification, Prevention, and Treatment Services. The Future Direction of Male Circumcision in HIV Prevention working conference., Los Angeles, CA.

Sanchez, J., Lama, J. R., Peinado, J., Paredes, A., Lucchetti, A., Russell, K., . . . Sebastian, J. L. (2009). High HIV and ulcerative sexually transmitted infection incidence estimates among men who have sex with men in Peru: awaiting for an effective preventive intervention. *J Acquir Immune Defic Syndr, 51 Suppl 1*, S47-51. doi: 10.1097/QAI.0b013e3181a2671d

Sanchez, J., Sal, Y. R. V. G., Hughes, J. P., Baeten, J. M., Fuchs, J., Buchbinder, S. P., . . . Celum, C. (2011). Male circumcision and risk of HIV acquisition among MSM. *AIDS, 25*(4), 519-523. doi: 10.1097/QAD.0b013e328340fd81

Sansom, S. L., Prabhu, V. S., Hutchinson, A. B., An, Q., Hall, H. I., Shrestha, R. K., . . . Taylor, A. W. (2010). Cost-effectiveness of newborn circumcision in reducing lifetime HIV risk among U.S. males. *PLoS One, 5*(1), e8723. doi: 10.1371/journal.pone.0008723

Schackman, B. R., Fleishman, J. A., Su, A. E., Berkowitz, B. K., Moore, R. D., Walensky, R. P., . . . Losina, E. (2015). The lifetime medical cost savings from preventing HIV in the United States. *Med Care, 53*(4), 293-301. doi: 10.1097/mlr.000000000000030

Schneider, J. A., Michaels, S., Gandham, S. R., McFadden, R., Liao, C., Yeldandi, V. V., Oruganti, G. (2012a). A protective effect of circumcision among receptive male sex

partners of Indian men who have sex with men. *AIDS Behav, 16*(2), 350-359. doi: 10.1007/s10461-011-9982-2

Schneider, J. A., Michaels, S., Gandham, S. R., McFadden, R., Liao, C., Yeldandi, V. V., & Oruganti, G. (2012b). A protective effect of circumcision among receptive male sex partners of Indian men who have sex with men. *AIDS and behavior, 16*(2), 350-359. doi: 10.1007/s10461-011-9982-2

Smith, A. D., Tapsoba, P., Peshu, N., Sanders, E. J., & Jaffe, H. W. (2009). Men who have sex with men and HIV/AIDS in sub-Saharan Africa. *Lancet, 374*(9687), 416-422. doi: 10.1016/s0140-6736(09)61118-1

Solomon, S. S., Mehta, S., Srikrishnan, A. K., McFall, A., Balakrishman, P., Anand, S., . . . GROUP, N. S. (2014). *Circumcision is associated with lower HIV prevalence among men who have sex with men in India.* Paper presented at the 2014 International Conference Melbourne, Australia.

Steward, W. T., Miege, P., & Choi, K. H. (2013). Charting a moral life: the influence of stigma and filial duties on marital decisions among Chinese men who have sex with men. *PLoS One, 8*(8), e71778. doi: 10.1371/journal.pone.0071778

Stover, J., Kripke, K., Perales, N., Lija, J., Fimbo, B., Mlanga, E., . . . Njeuhmeli, E. (2016). The Economic and Epidemiological Impact of Focusing Voluntary Medical Male Circumcision for HIV Prevention on Specific Age Groups and Regions in Tanzania. *PLoS One, 11*(7), e0153363. doi: 10.1371/journal.pone.015690910.1371/journal.pone.0153363

Sullivan, S. D., Mauskopf, J. A., Augustovski, F., Jaime Caro, J., Lee, K. M., Minchin, M., . . . Shau, W. Y. (2014). Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health, 17*(1), 5-14. doi: 10.1016/j.jval.2013.08.2291

Sutton, A. J., Duval, S. J., Tweedie, R. L., Abrams, K. R., & Jones, D. R. (2000). Empirical assessment of effect of publication bias on meta-analyses. *BMJ, 320*(7249), 1574-1577.

Tabet, S., Sanchez, J., Lama, J., Goicochea, P., Campos, P., Rouillon, M., . . . Holmes, K. K. (2002). HIV, syphilis and heterosexual bridging among Peruvian men who have sex with men. *AIDS, 16*(9), 1271-1277.

Templeton, D. J., Jin, F., Mao, L., Prestage, G. P., Donovan, B., Imrie, J., . . . Grulich, A. E. (2009). Circumcision and risk of HIV infection in Australian homosexual men. *AIDS, 23*(17), 2347-2351. doi: 10.1097/QAD.0b013e32833202b8

Templeton, D. J., Mao, L., Prestage, G. P., Jin, F., Kaldor, J. M., & Grulich, A. E. (2008). Self-report is a valid measure of circumcision status in homosexual men. *Sex Transm Infect, 84*(3), 187-188. doi: 10.1136/sti.2007.029645

Templeton, D. J., Millett, G. A., & Grulich, A. E. (2010). Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men. *Curr Opin Infect Dis, 23*(1), 45-52. doi: 10.1097/QCO.0b013e328334e54d

Thornton, A. C., Lattimore, S., Delpech, V., Weiss, H. A., & Elford, J. (2011). Circumcision among men who have sex with men in London, United Kingdom: an unlikely strategy for HIV prevention. *Sex Transm Dis, 38*(10), 928-931. doi: 10.1097/OLQ.0b013e318221562a

Trottier, H., & Philippe, P. (2000). Deterministic Modeling Of Infectious Diseases: Theory And Methods. *The Internet Journal of Infectious Diseases, 1*(2).

UNAIDS, & MoH. (2015). *2015 China AIDS Response Progress Report*. Retrieved from http://www.unaids.org/sites/default/files/country/documents/CHN_narrative_report_2015.pdf.

van Griensven, F., de Lind van Wijngaarden, J. W., Baral, S., & Grulich, A. (2009). The global epidemic of HIV infection among men who have sex with men. *Curr Opin HIV AIDS, 4*(4), 300-307. doi: 10.1097/COH.0b013e32832c3bb3

Vermund, S. H., & Qian, H. Z. (2008). Circumcision and HIV prevention among men who have sex with men: no final word. *Jama, 300*(14), 1698-1700. doi: 10.1001/jama.300.14.1698

Vutthikraivit, P., Lertnimitr, B., Chalardsakul, P., Imjaijitt, W., & Piyaraj, P. (2014). Prevalence of HIV testing and associated factors among young men who have sex with men (MSM) in Bangkok, Thailand. *J Med Assoc Thai, 97 Suppl 2*, S207-214.

Vynnycky, E., & White, R. G. (2010). *An introductory book on infectious disease modelling and its applications*. New York: Oxford University Press.

Walensky, R. P., Paltiel, A. D., Losina, E., Mercincavage, L. M., Schackman, B. R., Sax, P. E., . . . Freedberg, K. A. (2006). The survival benefits of AIDS treatment in the United States. *J Infect Dis, 194*(1), 11-19. doi: 10.1086/505147

Wei, C., Yan, H., Yang, C., Raymond, H. F., Li, J., Yang, H., . . . Stall, R. (2013). Accessing HIV testing and treatment among men who have sex with men in China: A qualitative study. *AIDS Care*. doi: 10.1080/09540121.2013.824538

Wei, F. M., Yang, X. B., Jiang, J. J., Yuan, X. Y., Chen, Y. H., Lin, Z. S., . . . Liang, H. (2012). [Benefits of promoting male circumcision among the general population in the high HIV prevalence areas of Guangxi Province]. *Zhonghua Nan Ke Xue, 18*(5), 391-396.

Weiss, H. A., Halperin, D., Bailey, R. C., Hayes, R. J., Schmid, G., & Hankins, C. A. (2008). Male circumcision for HIV prevention: from evidence to action? *AIDS, 22*(5), 567-574. doi: 10.1097/QAD.0b013e3282f3f406

Weiss, H. A., Quigley, M. A., & Hayes, R. J. (2000). Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *Aids, 14*(15), 2361-2370.

White, R. G., Glynn, J. R., Orroth, K. K., Freeman, E. E., Bakker, R., Weiss, H. A., . . . Hayes, R. J. (2008). Male circumcision for HIV prevention in sub-Saharan Africa: who, what and when? *AIDS, 22*(14), 1841-1850. doi: 10.1097/QAD.0b013e32830e0137

WHO. (2016). Men who have sex with men. Retrieved August 1, 2016, from http://www.who.int/hiv/topics/msm/about/en/

WHO/UNAIDS. (2007). New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications from http://www.unaids.org/sites/default/files/media_asset/mc_recommendations_en_0.pdf

Williams, B. G., Lloyd-Smith, J. O., Gouws, E., Hankins, C., Getz, W. M., Hargrove, J., . . . Auvert, B. (2006). The potential impact of male circumcision on HIV in Sub-Saharan Africa. *PLoS Med, 3*(7), e262. doi: 10.1371/journal.pmed.0030262

Wiysonge, C. S., Kongnyuy, E. J., Shey, M., Muula, A. S., Navti, O. B., Akl, E. A., & Lo, Y. R. (2011). Male circumcision for prevention of homosexual acquisition of HIV in men. *Cochrane Database Syst Rev*(6), Cd007496. doi: 10.1002/14651858.CD007496.pub2

Wu, J. R., Wang, B., Chen, L. S., Yang, T., Zhou, L. J., Xie, Y. X., . . . Huan, X. P. (2013). Alarming incidence of genital mycoplasmas among HIV-1-infected MSM in Jiangsu, China. *Eur J Clin Microbiol Infect Dis*. doi: 10.1007/s10096-013-1942-5

Wu, Z., Xu, J., Liu, E., Mao, Y., Xiao, Y., Sun, X., . . . Wang, Y. (2013). HIV and syphilis prevalence among men who have sex with men: a cross-sectional survey of 61 cities in China. *Clin Infect Dis, 57*(2), 298-309. doi: 10.1093/cid/cit210

Xu, J. J., Zhang, C., Hu, Q. H., Chu, Z. X., Zhang, J., Li, Y. Z., . . . Shang, H. (2014). Recreational drug use and risks of HIV and sexually transmitted infections among Chinese men who have sex with men: Mediation through multiple sexual partnerships. *BMC Infect Dis, 14*(1), 642. doi: 10.1186/s12879-014-0642-9

Ye, S., Xiao, Y., Jin, C., Cassell, H., Blevins, M., Sun, J., . . . Qian, H. Z. (2012). Effectiveness of integrated HIV prevention interventions among Chinese men who have sex with men: evaluation of a 16-city public health program. *PLoS One, 7*(12), e50873. doi: 10.1371/journal.pone.0050873

Young, M. R., Odoyo-June, E., Nordstrom, S. K., Irwin, T. E., Ongong'a, D. O., Ochomo, B., . . . Bailey, R. C. (2012). Factors associated with uptake of infant male circumcision for HIV prevention in western Kenya. *Pediatrics, 130*(1), e175-182. doi: 10.1542/peds.2011-2290

Zeng, Y., Zhang, L., Li, T., Lai, W., Jia, Y., Aliyu, M. H., . . . Zhang, Y. (2014). Risk Factors for HIV/Syphilis Infection and Male Circumcision Practices and Preferences among Men Who Have Sex with Men in China. *Biomed Res Int, 2014*, 498987. doi: 10.1155/2014/498987

Zhang, C., Qian, H. Z., Liu, Y., & Vermund, S. H. (Under review). Effect of circumcision on risk of HIV infection among men who have sex with men: a systematic review and meta-analysis. *Journal of Acquired Immune Difficiency Syndrome*.

Zhang, C., Shephard, B. E., Lou, J., Vermund, S. H., Qian, H. Z., Penson, D. F., & Webb, G. F. (Under review). Predicting the impact of voluntary medical male circumcision on HIV incidence among men who have sex with men in Beijing, China. *PLoS One*.

Zhao, J., Chen, L., Chaillon, A., Zheng, C., Cai, W., Yang, Z., . . . Smith, D. M. (2016). The dynamics of the HIV epidemic among men who have sex with men (MSM) from 2005 to 2012 in Shenzhen, China. *Sci Rep, 6*, 28703. doi: 10.1038/srep28703

Zheng, T. (2009). *Red Lights: The Lives of Sex Workers in Postsocialist China*. Minneapolis: Universityof Minnesota Press.

Zhou, C., Raymond, H. F., Ding, X., Lu, R., Xu, J., Wu, G., . . . Shao, Y. (2012). Anal Sex Role, Circumcision Status, and HIV Infection Among Men Who Have Sex with Men in Chongqing, China. *Archives of sexual behavior*. doi: 10.1007/s10508-012-0008-6

Zhou, C., Raymond, H. F., Ding, X., Lu, R., Xu, J., Wu, G., . . . Shao, Y. (2013). Anal sex role, circumcision status, and HIV infection among men who have sex with men in Chongqing, China. *Arch Sex Behav, 42*(7), 1275-1283. doi: 10.1007/s10508-012-0008-6

Zhou, Y., Li, D., Lu, D., Ruan, Y., Qi, X., & Gao, G. (2014). Prevalence of HIV and syphilis infection among men who have sex with men in China: a meta-analysis. *2014*, 620431. doi: 10.1155/2014/620431