The incremental role of male circumcision on a generalised HIV epidemic through its protective effect against other sexually transmitted infections: from efficacy to effectiveness to population-level impact

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Abstract:

Background: Male circumcision(MC) can reduce HIV acquisition. However, a better understanding of the indirect protective effect of MC on sexually transmitted infections (STIs) is required.

Objective: To assess the incremental benefits conferred by MC on HIV infection at the individual-level in circumcision trials (no herd immunity effect) and at the population-level (with herd immunity effect) due to its protective effect against other STIs.

Methods: A dynamical stochastic model of HIV and STI infections in a Kenyan population was used to simulate the impact of circumcision offered to a minority of trials participants or to a large fraction of men in order to study the protective role of MC on HIV infection at the individual-level and at the population-level, respectively.

Results: Less than 20% of the HIV infections prevented in the circumcised arm of the circumcision trials (individual-level) could be attributable to MC efficacy against STIs rather than MC efficacy against HIV. At the population-level, MC can significantly reduce HIV prevalence especially among males and among females in the longer term. However, even at the population-level, the long-term incremental impact of MC on HIV due to the protection against STI is modest (even if MC efficacy against the STI and STI prevalence was high).

Discussion: The protection of MC against STI contributes little to the overall effect of MC on HIV in the trials. Additional work is needed to identify if the protective effect of MC efficacy against STIs can have a significant incremental benefit on the HIV epidemic.

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List of abbreviations

UNIM = Universities of Nairobi, Illinois and Manitoba

MC = Male circumcision

RCT = randomised control trial

E_S^{HIV} = Efficacy due to a reduction in *susceptibility* to HIV infection

E_S^{STI} = Efficacy due to a reduction in *susceptibility* to STI infection

E_I^{HIV} = Efficacy due to a reduction in HIV infectiousness of HIV positive circumcised men

E_I^{STI} = Efficacy due to a reduction in STI infectiousness of STI positive circumcised men

E_{nh}^{STI} = Efficacy due to a change in the STI natural history among circumcised men

GUD= Genital ulcer diseases

RR_s= Relative risk of HIV due to STI

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Authors' contribution:

All authors have contributed to the planning, the interpretation of the results and the redaction of the manuscript. In addition, MCB and KD have performed written he first version of the manuscript, designed the study and performed the analysis.

Key Messages:

- It is important to distinguish between the overall effectiveness of MC and the efficacies of male circumcision (MC) against HIV and STIs in order to assess the population-level impact of MC on HIV

- Only a small fraction of the observed MC effectiveness against HIV in the three MC RCT could be due to the indirect efficacy against STIs, rather than the direct efficacy against HIV

- The direct protection of MC against HIV has the potential to help curb the HIV epidemic, in the long term, in population where MC prevalence is low and in absence of associated sexual disinhibition. If enough men are circumcised, females will benefit from long-term herd immunity effects.

- However, the incremental population-level benefit of MC on HIV due to a reduction in the acquisition of STIs(E_s^{STI}) among male is predicted to be modest in mature HIV epidemics, unless MC efficacy against STI is very high.

- More research is needed to better understand the potential protective mechanisms of MC against STI at both the individual and population-level.

Introduction

There is compelling evidence that male circumcision(MC) reduces susceptibility to HIV infection. Early evidence was based on ecological and observational studies(1-9). Results from a meta-analysis of observational studies showed a 50% and 70% reduction in HIV risk amongst circumcised men from the general population and higher-risk groups, respectively(6). The most compelling evidence comes from three recent unblinded randomised control trials(RCT) conducted among adult men in Kenya, Uganda and South Africa(10-12) which suggested a 50% to 60% reduction in HIV risk among circumcised men across the three trials(Table 1).

Given the overwhelming evidence and the limited preventive options available, WHO/UNAIDS have published recommendations for countries to consider scaling up access to MC in seronegative men, in areas of high HIV prevalence where MC is rare(13). However, a number of important issues such as the safety, cost, feasibility, acceptability, ethics, and potential increase in risky behaviour following circumcision should be considered ideally before the large scale implementation of MC(13). A better understanding of the potential population-level impact of MC is needed in order to identify who should be circumcised. Further research is needed to guide programme implementation and to better understand additional benefits or risks of MC, including the protective effects of MC on other sexually transmitted infections(STIs)(13). Without conducting community based randomised trials, the impact of circumcision at the population-level can be addressed with mathematical modelling if we have a clear understanding of the protective biological mechanisms of MC at the individual-level. To achieve this, it is useful to clearly understand the results of the circumcision trials and to make a distinction between *efficacy* and *effectiveness* of MC.

In this paper, we first review and discuss the efficacy and effectiveness of MC on HIV, in particular the incremental benefit of MC on HIV infection due to its indirect protection against cofactor STIs in the context of the three aforementioned randomised trials(10-12).

In addition, we present new results on the incremental benefit of MC at the population-level due to its efficacy against other STIs.

Methods

The population-level impact of MC on HIV prevalence was assessed using a previously validated stochastic compartmental model which simulates transmission of HIV and one STI in the heterosexual population in the Kisumu district of Kenya(12,14). The modelled population was stratified into six sexual activity classes with specific rates of sexual partner acquisition. In absence of specific data, the mixing between activity classes was assumed to be proportionate. The STI was modelled with two compartments representing infected or not infected individuals. Infecteds could recover from the STI and be reinfected. Without loss of generalisability, the modelled STI should be thought of as 'generic', rather than representing any one specific STI. HIV infection has been modelled with 5 stages representing susceptible, acute, asymptomatic, pre-AIDS, AIDS. The progression of individuals between states was based on specific disease stage parameters or on the force of infection(for susceptible), which depended on the sexual activity, the HIV or STI infection status, HIV and STI prevalence in the pool of partners, the strength of the HIV-STI interaction and the efficacies of MC against HIV(E_S^{HIV}) and STI(E_S^{STI}). Upon commencement of the circumcision intervention, a fixed number of susceptible men were recruited from the uncircumcised to the circumcised susceptible compartment. The model structure, the equations and the Monte-Carlo simulation process are fully described in Supplement material.

High(scenario A) and low(scenario B) STI prevalence scenarios were modelled. The distribution by sexual activity classes and rates of sexual partner acquisition for scenario B were selected to agree with infection rates in the Kisumu UNIM male circumcision trial population(12,14-17) and the 2003 Kenyan Demographic and Health Survey(15) corresponding to years 15-17 of the simulated epidemic. Remaining parameters for HIV(14,18-23) and STI(27-29) transmission probabilities, duration of the different HIV

states(14,18-24-26) and duration of STI infection(27-29) were based on published studies(Table 2).

The presence of STI in the HIV-infected sexual partner was assumed to increase HIV per-partner infectivity by 4-fold, while STI in the HIV-susceptible increased per- HIV susceptibility by 3-fold. This reflected the results from a meta-analytic review of observational studies where the relative risk of HIV due to STI(RR_s) in men was less than 4.4 for genital ulcer disease(GUD), 3.1 for all STIs, 2.7 for herpes, 2.5 for syphilis, 3.9 for gonorrhoea and 0.8 for Chlamydia(30-33). HIV infection was also assumed to increase susceptibility to and infectivity with STI by 1.5-fold(30-32). Scenario A was obtained from scenario B by increasing the average duration of STI infection from 6 months to 1.3 years. Because this change also increased HIV infection rates, due to the STI and HIV interaction, we simultaneously decreased HIV transmission probabilities during the early stage and slightly modified the rates of sexual partner change in order to hold HIV infection rates to reasonable levels. The parameter values used for both scenarios and the key characteristics of the simulated STI and HIV epidemics are summarised in Table 2. In both scenarios, the male HIV prevalence was 28% at year 15 and declined as the epidemic progressed due to a strong dependence on STI prevalence which declined due to AIDS differential mortality. In scenario A, the overall STI and HIV prevalence, and HIV incidence averaged 22.3%, 29.8%, and 5.9 per 100 person-years over the 20 years following the intervention (introduced at year 15), respectively compared to 3.7%, 16.4% and 1.9 per 100 person-years respectively for scenario B(1-3,12,14-17).

To assess the individual-level impact of MC, Desai et al(14) simulated the Kisumu MC trial by recruiting and following-up 2750 initially uncircumcised seronegative men from the overall simulated population and randomly assigning them to the circumcision or control arm. The simulated follow-up was 24 months, HIV incidence rate was 2.5% per year in control subjects, STI prevalence averaged 8.2% in controls over the 2 years, which compares with the overall prevalence of bacterial infections observed in the UNIM trial participants at baseline.

To assess the population-level impact of MC, new simulations were performed where a large scale mass circumcision programme was initiated in a mature HIV epidemic in low and high STI prevalence settings(scenarios A and B). Low to high values of MC efficacy against STI (6 scenarios in all) were assumed in MC interventions offered to 75% of HIV susceptible males(either STI positive or STI negative) instead of offering it to a minority of men (as in the simulated trials) where coverage was too small to generate herd immunity.

Theoretical context

Individual-level effect of MC: Efficacy vs Effectiveness

In the clinical trial literature, "efficacy" is typically defined as the individual-level clinical/biological benefit of the intervention used under ideal conditions(e.g. with 100% compliance and adherence) – reflecting the maximal effect it can have. Individual-level "effectiveness", often termed 'real world' effectiveness, (not to be confounded with the population-level effectiveness) refers to the effect of the intervention achieved under more realistic conditions of use(e.g., imperfect adherence) and relates more closely to the potential benefit of the intervention to individuals when widely used in practice(33-34).

Determining the efficacy of MC is more complex because MC can have different individual-level efficacies, reflecting different biological/clinical protective mechanisms conferred to individuals directly against HIV or indirectly against other STIs(14,34), such as:

(i) Reduction in *susceptibility* to HIV infection(E_s^{HIV}) or to other cofactors STI(E_s^{STI});

(ii) Reduction of the *infectiousness* of HIV infected(E_I^{HIV}) or STI infected(E_I^{STI}) circumcised men for their sexual partners;

(iii) Modification of the *natural history* of STI infection by reducing the frequency of ulcers or by accelerating the natural clearance(E_{nh}^{STI}).

In RCTs, where HIV negative individuals are randomized and follow-up, it is only possible to estimate a reduction in acquisition to HIV(E_s^{HIV}) and STIs(E_s^{STI}) independently(34).

Because cofactors STI were on the causal pathway to HIV infection, the primary outcome of the three circumcision trials was the overall effectiveness of MC on HIV acquisition, rather than the independent efficacies against HIV and STIs(11). Thus, the overall effectiveness(i.e. the overall reduction in HIV incidence) measured in the trials could have been the result of a combination of direct protection(efficacies) against HIV acquisition(E_s^{HIV}) and/or against acquisition of cofactor STI(E_s^{STI}). For example, in the South African MC trial, the overall effectiveness of 60% could be due to an efficacy against HIV only ($E_s^{HIV}=60\%, E_s^{STI} = 0\%$) or to some degree of protection against both HIV and STI($0\% < E_s^{HIV} < 60\%, 0\% < E_s^{STI} < 60\%$).

Population-level and long term: impact

MC has direct effects on HIV at the individual-level and additional indirect effects at the population-level due to herd immunity(i.e a reduced exposure to infection among non circumcised men or women due reduced STIs or HIV prevalence)(31). The total population-level impact is function of the different individual-level efficacies(E_s^{HIV}, E_s^{STI} ,$E_I^{HIV}, E_I^{STI}, E_{nh}^{STI}$), thus justifying the need to quantify each of them when possible.

It is also important to evaluate the incremental role played by MC on reducing the incidence of new STI infections and indirectly preventing new HIV infections. Knowledge of E_s^{HIV} and E_s^{STI} can help interpret the MC effectiveness results on HIV and to extrapolate results to other communities. If most of the protection against HIV was obtained indirectly via the protection against STIs, then the trial results would depend more strongly on the epidemiology of STIs and the trial population and would therefore have a poorer external validity. The potential impact of MC at the population-level would also depend on the prevalence of the different STIs and the associated synergetic impact with HIV.

Biologically, MC may reduce susceptibility to HIV infection because the underside of the foreskin is rich in HIV target cells(CD4+ T cells). It may also reduce the risk of abrasion, micro tearing and inflammatory conditions suffered by the inner mucosa of the foreskin in uncircumcised men(10-13,35-36). Only one observational study in Rakai suggested a reduction in infectiousness of HIV positive circumcised men for their female partners(8). However, in a very recent clinical trial in Rakai, higher(but not statistically significant) HIV incidence was observed among the wives of circumcised HIV positive men, which was attributed to premature resumption of sexual activity following the surgical procedure, rather than behavioural disinhibition(37).The protective effect of MC against STIs is more uncertain(37-45). A meta-analysis suggested a 33% and 12% reduction in the risk of syphilis and HSV-2 among circumcised men, respectively(38). The estimates across different observational studies varied between -10% to 88% for chancroid. Evidence on the protective effect against gonorrhoea is unclear and mostly based on early studies(9,39,41-44). One study suggested a reduced rate of Chlamydia transmission to their female partners by circumcised compared to uncircumcised men(45). Thus, in the results presented below, the MC efficacies were modelled as a reduction in males' susceptibility to HIV infection which was fixed to 60%(E_s^{HIV}). The efficacy against STI(E_s^{STI}) was varied between 0% and 70%. Low E_s^{STI}(~0-20%) reflected the efficacy of MC on chlamydia and HSV-2 while high E_s^{STI}(~60-80%) reflects efficacy against chancroid and syphilis(11,38,40). We assumed that male-to-female HIV transmission was unchanged by circumcision status(Table 2).

Results

Insights from previous clinical trial simulations

The protective role of MC against cofactor STI on the risk of HIV infection at the individual-level was assessed in Desai et al(14 study, where a small fraction of men were follow-up for two years in the simulated UNIM MC trial in Kisumu(Table 1). Under the UNIM simulated conditions, if MC did not protect against HIV(E_s^{HIV}=0%) but strongly protected circumcised men (HIV+ or HIV-) against the STI only(E_s^{STI}=80%), the overall

effectiveness against HIV would be only 13%. If the trial duration was prolonged to 5 years and MC efficacy against STI was increased to 100%, the overall effectiveness against HIV, due to the protection against STI alone, increased to 21%. The effectiveness reached 25% or 30% only when the STI prevalence was increased to 19% or when the RR_S was increased to six-fold respectively. As these assumptions, especially the 100% efficacy against the STI appeared unrealistically high, the authors concluded that the effectiveness above 50%, as observed in the field RCT, could not have been due solely to the protection against cofactor STI. MC needed to strongly protect directly against HIV(14). In addition, under the STI conditions, MC needed to have an HIV efficacy of at least 40% and 50% to generate the observed overall effectiveness of 50% or 60% against HIV, respectively, even if the efficacy against STI was as high as 60%(14). This also meant that if the MC efficacy against HIV was 40%, not more than 20% of the HIV infections prevented in the circumcised arm of the trial could be attributable to the efficacy against the STI(rather than efficacy against HIV). This proportion decreased as the efficacy against HIV increased(Figure 1A).

Insight from the three MC circumcision trials

The effect of circumcision on STI incidence was not reported in the South African trial(10). The baseline STI prevalence only was reported in the Kenyan trial. Gray et al(11) reported a baseline prevalence of 7% and a 47%(95% CI: 36%-57%) reduction in self-reported GUD in the circumcised arm during part of the trial(Table 1). In subgroup analysis, an effectiveness of 40%(95% CI: 8%, 66%) against HIV was reported in the GUD negative group compared to an effectiveness of 51%(95% CI: 16%, 72%) for the whole cohort. In line with the meta-analysis results for high-risk individuals(6), the Rakai sub-group analyses reported an effectiveness of 71%(95% CI -29%, 97%) and 70%(95% CI: 15%, 91%) in men reporting more than 2 partners and with self-reported GUD, respectively. Based on our simulation results, the difference between an effectiveness of 70% and an effectiveness of 50%-60% among high-risk individuals compared to general population, respectively, could partly be explained by the additional protection of MC against STIs if the STI prevalence(>>20%) or the recurrence of ulcers among high-risk

individuals is high. In addition, under the UNIM trial conditions, MC efficacy against HIV is predicted to be at least 40%-50% given that the observed individual-level MC effectiveness in the three trials was 50%-60%.

Insights from new simulation results: Population-level and long term impact

Because the trials were of short duration and only captured the reduction in susceptibility to HIV infection(at the individual-level), the field and the simulated trials do not necessarily reflect adequately the incremental impact of MC on HIV at the population-level due to its protective impact against cofactors STI. The full incremental impact due to MC efficacy against STIs may be larger at the population-level and over a longer time scale when coverage increases. To understand the extent of the impact of MC efficacy against STI, we simulated a high(A) and low(B) STI scenario, with a strong STI-HIV interaction.

Figure 1B shows the impact of MC on HIV prevalence over time for scenario A. The figure shows that MC can reduce the long term male HIV prevalence and that females would somewhat benefit from herd immunity effect but not noticeably until five to ten years following the intervention. Importantly, the figure also highlights the small incremental impact of MC due to MC efficacy against STI in the long term, even if E_s^{STI} was as high as 70% and if STI prevalence was high. The incremental benefit of MC E_s^{STI} was slightly greater for women than men because STI prevalence declines faster than HIV prevalence in men, and females benefit from the reduced HIV infectivity of men who avoid STIs. Figure 2 summarises the percentage reduction in HIV prevalence 5 and 15 years after the introduction the circumcision intervention. MC efficacy against the STI has a limited impact even in the long term, unless STI prevalence is high (scenario A) and E_s^{STI} is higher (>70%) than currently suggested by data. In the long term, females could benefit substantially from the herd immunity effect of MC (20% reduction in HIV prevalence). Even at the population-level, MC efficacy against HIV produced most of the benefit on HIV in both men and women. Only under specific conditions of very high

STI prevalence, high synergetic interaction or large E_s^{STI}, could MC efficacy against STI produce a noticeable incremental benefit for men and women.

Discussion

In this paper, we distinguished between the overall effectiveness of MC and the efficacies of MC against HIV and STIs in order to assess the population-level impact of MC on HIV. Together, the field and simulated trial results suggested that only a small fraction of the observed MC effectiveness against HIV in the RCT could be due to the indirect efficacy against STIs, rather than the efficacy against HIV. The fact that E_s^{STI} contributed little to the overall individual-level effectiveness, may explain the consistency of the estimates, which varied by less than 10% across trials, despite differences in STI prevalence. Thus, the three circumcision trials have good external validity and the results can be extrapolated to settings with different STI epidemiology. To generalise trial results, to settings outside sub-Saharan Africa, the mechanism of protection against HIV-in particular the relative role of hygiene compared to biological mechanisms - remains to be clarified.

Our results support previous modelling studies suggesting that MC has the potential to help curb the HIV epidemic in the long term, in population where MC prevalence is low and in absence of associated sexual disinhibition(46-51). If enough men are circumcised, females will benefit from long-term herd immunity effects. In our model, men were circumcised in a short window period. In practice such high coverage would be reached over a longer term period. It is therefore important to determine who should be circumcised first(e.g., younger and more sexually active men) in order to scale-up circumcision programme to achieve maximum impact very rapidly(51). The population-level impact of MC would even be larger, especially for females if it also reduced the infectiousness of HIV positive circumcised men. However, it could also have detrimental effects if men were more infectious to their female partners immediately after the procedure(37,46). This has obvious implications for the roll-out of mass circumcision.

In the long term, our analysis suggested that the incremental population-level impact of MC on HIV due to a reduction in the acquisition of STIs(E_s^{STI}) among male is also likely to be small. Although we only modelled one generic STI, our conclusions remained valid under extreme assumptions of high MC efficacy against STI (higher than what has been observed), strong STI and HIV association, and very high STI prevalence(Figure 2). The incremental benefit of E_s^{STI} was marginally better for women than men simply because their protection was mediated by herd immunity effects through the rapid decline in STI prevalence among men. Based on current knowledge, we assumed that MC reduced acquisition of new STIs. However, if MC also reduced the frequency or duration of ulcers during the course of infection(11,40), this may provide additional incremental benefits. Considerable uncertainty remains regarding MC efficacy against STIs. The Rakai circumcision trial on HIV acquisition reported a 50% reduction on self-reported GUD(40). However, results from a complementary trial observed a 25% reduction in acquisition of HSV-2 among HIV negative circumcised male, and a 25% reduction in GUD(40). These estimates of MC efficacy against HSV-2 were greater than those suggested in Weiss's meta-analysis(35,38). The incremental effect of MC on HIV among females would be larger if MC also reduces bacterial vaginosis and trichomonias in the wives of circumcised men(40).

Our results do not demonstrate that MC does not protect against STIs. They only predict that the incremental impact of MC against HIV due to a reduction in males' susceptibility(E_s^{STI}) to STI is likely to be relatively small in generalized HIV epidemics. Additional work is needed to identify if MC efficacy against STIs can produce more significant benefits under different epidemic characteristics(e.g. concentrated, rising) and to better understand how MC protect against STIs. Even if MC efficacy against STIs did not play an important role in preventing HIV, it would still be beneficial to reduce the burden of STIs.

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Figure legend:

Figure 1

A: Individual-level effectiveness: Fraction of new HIV infections prevented over 2-yers follow-up in the circumcised arm of the simulated Kisumu trial that is due to the indirect protection of male circumcision(MC) against the STI, rather than to a direct protection against HIV(y-axis). In these simulations, both E_s^{STI} and E_s^{HIV} were varied. The maximum HIV infection prevented is 100%. Thus, is the STI efficacy(E_s^{STI}) component prevented 20% of new infections, the remaining 80% prevented was due to the efficacy against HIV(E_s^{HIV}). As E_s^{HIV} , the contribution of E_s^{STI} to the total infections prevented declined.

B: Population-level effectiveness: Overall male and female HIV prevalence over time without and with the circumcision intervention in scenario A when E_s^{HIV} =60% and E_s^{STI} varied from 0% to 70%. 75% of uninfected men are reached and circumcised at the beginning of the intervention introduced in a mature epidemic. Scenario A: STI prevalence averaged 24.3% and 20.2% in female and male, respectively.

Figure 2: Percentage reduction in overall male and female HIV prevalence between an uncircumcised and circumcised population A) 5 and B) 15 years after a circumcision intervention. 75% of uninfected men are reached and circumcised at the beginning of the intervention which is delivered 15 years after the beginning of the HIV epidemic in scenario A and B . Scenario A: STI prevalence averaged 24.3% and 20.2% in female and male, respectively. Scenario B: STI prevalence averaged 2.9% and 4.5% in female and male, respectively.
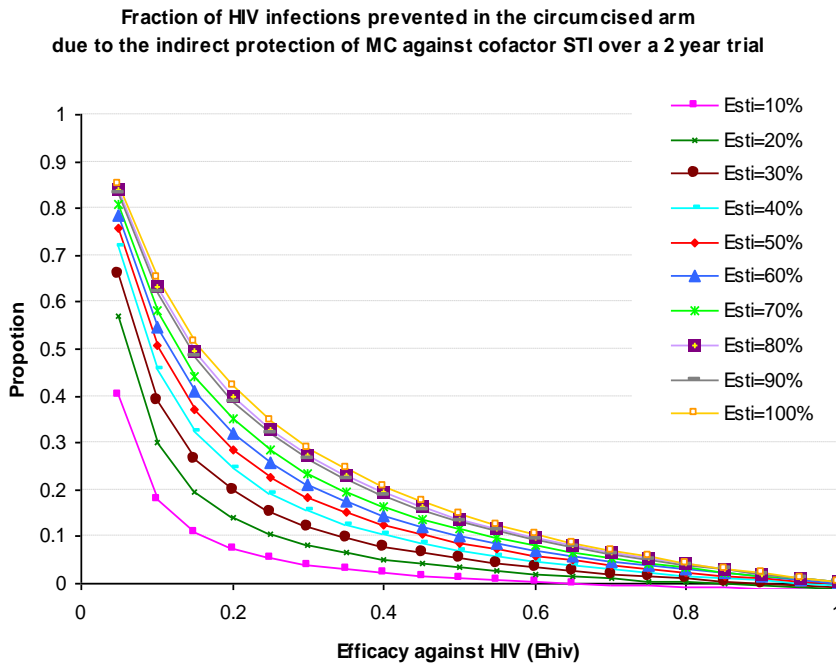
Table 1: Summary of the three randomised circumcision control trials

	South Africa (Orange Farm, Gauteng) Auvert et al(2005)	Uganda (Rakai) Gray et al(2007)	Kenya (Kisumu) Bailey et al(2007)
Community Characteristics			
Population	Semi-urban	Rural	Urban
MC rate	20%	16%	10%
HIV incidence(per year)	~1.7%	~1.8%	~1.8%
Study Characteristics			
Age	18-24	15-49	18-24
Sample size	3274	4996	2784
Mean follow-up	18 months	< 24 months	24 months[1]
Overall effectiveness (Intention-to-treat)	60% 95%CI=32-76%	51% 95%CI= 16-72%	53% 95%CI=22-72%
STI- at baseline	NR -Patients with potential GUD were excluded until successful treatment	-Self reported: 7% GUD, 3.5% urethral discharge, 6% Dysuria -Patients with potential GUD were excluded until successful treatment	28% HSV-2, 1% Syphilis, 2% Trichomonas vaginalis, 2% gonorrhoeae, 5% chlamydia, 0% Heamophilus ducreyi -Patients with STI were deferred until treatment
Protection of male circumcision against STI	-The proportion of participants attending a clinic for a GU problem in the 12 months prior to the visit at month 12 was 4.7% in the intervention group compared to the control group(7.2%).	Self-reported STI: GUD: 47%(36%-57%) Genital discharge: 16%(-11%, 37%) Dysuria: 3%(-21%-23%)	NR
Protection of male circumcision against HIV after controlling for acquisition of other STI during the trial	NR	No GUD: 40% 95%CI=-8%-67% Self reported GUD: 71%(-29%-97%)	NR
	These trials were not designed to provide evidence on the potential mechanisms of protection of male circumcision on HIV acquisition		

NR: Not Reported, [1]median

Figure 1

A)

**Fraction of HIV infections prevented in the circumcised arm
due to the indirect protection of MC against cofactor STI over a 2 year trial**

B)

Scenario A: High STI prevalence

Figure 2:

A)

**Population-level impact
at 5 years post intervention**
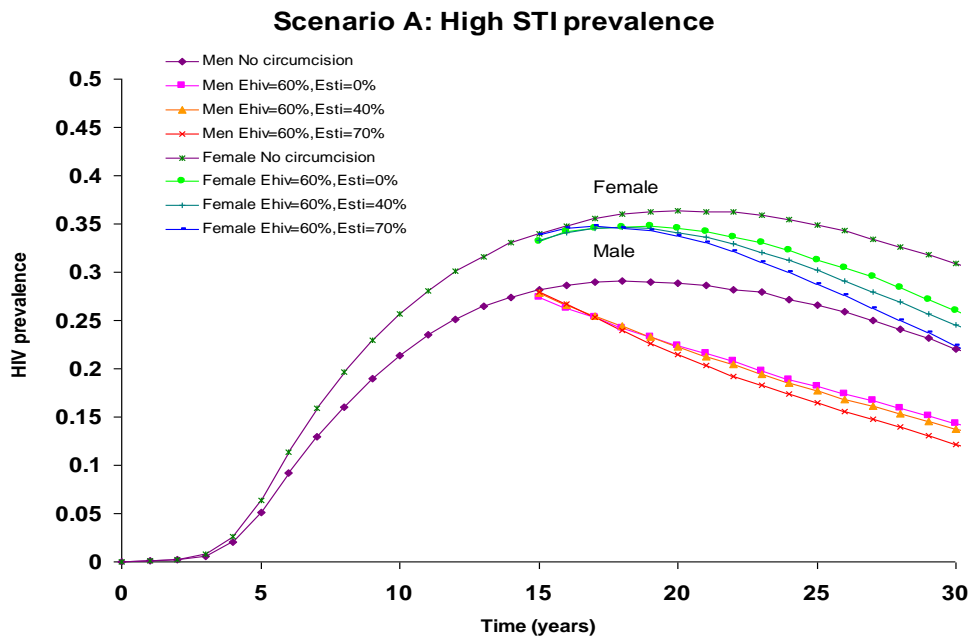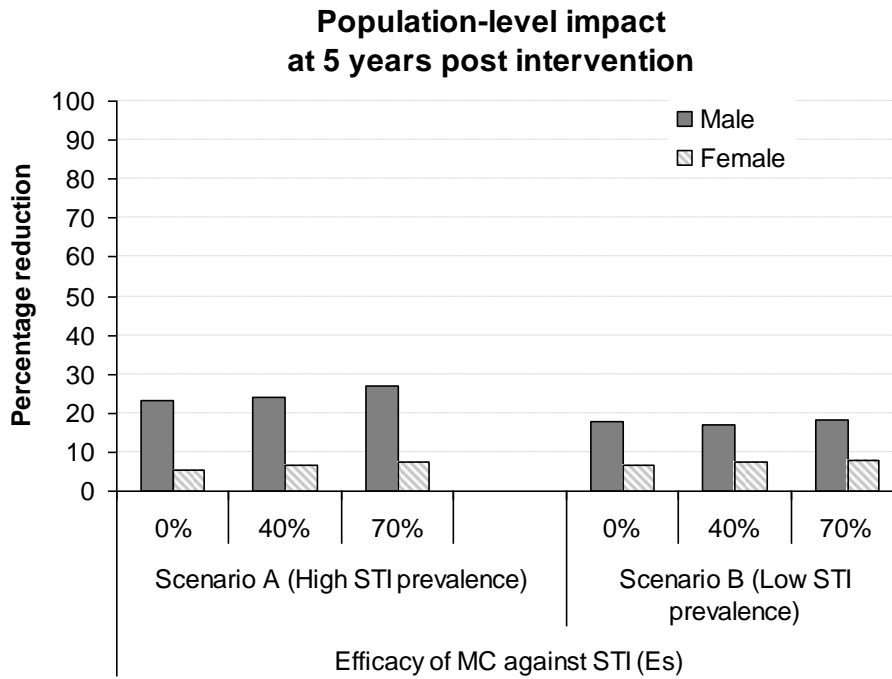
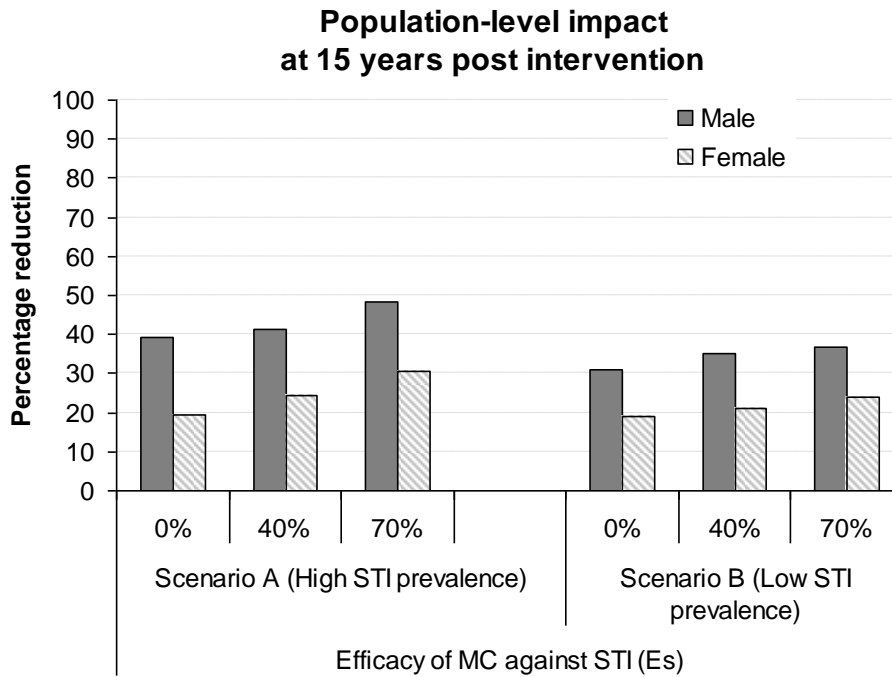

B)

**Population-level impact
at 15 years post intervention**

Table 2: Parameter input values used in model simulations for the low baseline (B) and high (A) STI prevalence scenarios (additional model details are provided in supplement material)

Description of epidemiological parameters	Parameter value with Symbols[1]			References
Duration of HIV stages:	$1/\gamma_1$ = 4.4 months, stage 2: $1/\gamma_2$ =6.5 yrs, stage 3: $1/\gamma_3$ = 2 yrs.			14,18,24-26
$\beta^h_{k*,j,i}$: **HIV transmission probabilities per partnership** from individual of sex k*, sexual activity class j and infection phase h(h=2,3,4) to partner of opposite sex k and class i. Values for females(k*=1) of low activity class(j= 1,2 = lowf) or high activity class(j=3,...,6 = highf) to males of low activity class(i= 1,2 = lowm) or high activity class(i=3,...,6 = highm). Transmission probabilities for male to female are doubled.	Scenario A			14, 18-23
	$\beta^2_{1,lowf,lowm} = 0.048$	$\beta^3_{1,lowf,lowm} = 0.0032$	$\beta^4_{1,lowf,lowm} = 0.051$	
	$\beta^2_{1,lowf,highm} = 0.026$	$\beta^3_{1,lowf,highm} = 0.0017$	$\beta^4_{1,lowf,highm} = 0.026$	
	$\beta^2_{1,highf,lowm} = 0.015$	$\beta^3_{1,highf,lowm} = 0.001$	$\beta^4_{1,highf,lowm} = 0.0071$	
	$\beta^2_{1,highf,highm} = 0.015$	$\beta^3_{1,highf,highm} = 0.001$	$\beta^4_{1,highf,highm} = 0.0071$	
	Scenario B			
	$\beta^2_{1,lowf,lowm} = 0.048$	$\beta^3_{1,lowf,lowm} = 0.0032$	$\beta^4_{1,lowf,lowm} = 0.051$	
	$\beta^2_{1,lowf,highm} = 0.026$	$\beta^3_{1,lowf,highm} = 0.0017$	$\beta^4_{1,lowf,highm} = 0.026$	
	$\beta^2_{1,highf,lowm} = 0.015$	$\beta^3_{1,highf,lowm} = 0.001$	$\beta^4_{1,highf,lowm} = 0.0071$	
	$\beta^2_{1,highf,highm} = 0.015$	$\beta^3_{1,highf,highm} = 0.001$	$\beta^4_{1,highf,highm} = 0.0071$	
Duration with STI infection for all sexes k and activity classes i.	Scenario B: $1/\sigma_{k,i}$ = 6 months Scenario A: $1/\sigma_{k,i}$ =1.33 years			27-29
Per partnership STI transmission probability: from infected individual of sex k and sexual activity class j to partner of opposite sex k* and class i.	$\xi_{k,i,j}$ = 0.15 for all k,i,j			27-29
HIV cofactors: relative risk(multiplicative factor) for: a_1 = increased infectivity with HIV given partner co-infected with STI; a_2 = increased susceptibility to HIV given STI infection in the self **STI cofactors:** relative risk(multiplicative factor) for: b1= increased infectivity with STI given partner co-infected with HIV; b_2= increased	$a_1 = 4$ $a_2 = 3$ $b_1=1.5$ $b_2 =1.5$			30-32

susceptibility to STI given HIV infection in the self.			
Mortality rate due to AIDS (α)	$1/\alpha$ = 1 year		24-26
Annual rate of sexual partner change: $m_{k,i}$ is the number of new sexual partners per year for person of sex k and sexual activity class i. k=1 represents females; k=2 males.	Scenario B: $m_{k=1,i=1\ldots6}$ = 1.0 3.5 5 10 50 75	Scenario A: $m_{k=1,i=1\ldots6}$ = 1.5 4.0 6 12 35 40	Assumed
	$m_{k=2,i=1\ldots6}$ = 1.5 5.0 10 15 20 25	$m_{k=2,i=1\ldots6}$ = 1.0 3.5 5 10 25 35	
Percentage of population by activity class i for class k at start of HIV epidemic: $pp_{k,I}$ (%)	$pp_{k=1,=1\ldots6}$= 55 20 10 10 2.5 2.5 $pp_{k=2,=1\ldots6}$= 50 30 5 5 5 5		Assumed
Rate of departure from sexually active population	μ = 0.029 ($1/\mu$ = 35 yrs)		Assumed
Size of population	100 000		Assumed
Coverage =Percentage of HIV-negative males recruited for circumcision	75%		Assumed
Efficacy of circumcision against HIV	E_s^{HIV} = 60%		10-13
Efficacy of circumcision against STI	E_s^{STI} = 0%, 40%, 70%		11,37-45
Model output			
Average HIV prevalence in general population over 20 yers	Scenario A: 29.8%	Scenario B: 16.4%	1-3,12,14-17
Average STI prevalence in general population over 20 years	Scenario A: 22.3%	Scenario B: 3.7%	
Average HIV incidence in general population over 20 years	Scenario A: 5.9 per 100 person-years	Scenario B: 1.9/100 p-yr	

[1] Symbols relate to equations in Appendix