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Financial Implications of Male Circumcision Scale-Up for the Prevention of HIV and Other Sexually Transmitted Infections in a Sub-Saharan African Community

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Abstract

Background—The financial implications of male circumcision (MC) scale-up in sub-Saharan Africa associated with reduced HIV have been evaluated. However, no analysis has incorporated reduction in a comprehensive set of other sexually transmitted infections (STIs), including human papillomavirus, herpes simplex virus type 2, genital ulcer disease, bacterial vaginosis and trichomoniasis.

Methods—A Markov model tracked a dynamic population undergoing potential MC scale-up, as individuals experienced MC procedures, procedure-related adverse events, MC-reduced STIs, and accrued any associated costs. Rakai, Uganda was used as a prototypical rural sub-Saharan African community. Monte Carlo microsimulations evaluated outcomes under four alternative scale-up strategies to reach 80% MC coverage among men 15-49, in addition to a baseline strategy defined by current MC rates in central Uganda. Financial outcomes included direct medical expenses only, and were evaluated over 5 and 25 years. Costs were discounted to the beginning of each time period, coinciding with the start of MC scale-up, and expressed in US\$2012.

Results—Cost savings from infections averted by MC vary from \$197,531 after 5 years of a scale-up program focusing on adolescent/adult procedures to over \$13 million after 25 years, under a strategy incorporating increased infant MCs. Over a 5-year period, reduction in HIV contributes to 50% of cost savings, and over 25 years, this contribution rises to nearly 90%.

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Conflict of interest statement

All authors declare that there is no potential conflict of interest relevant to this article.

Author contributions

All authors contributed to the study design, data collection, data analysis, writing and reviewing the paper.

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Conclusions—STIs other than HIV contribute to cost savings associated with MC scale-up. Previous analyses, focusing exclusively on the financial impact through averted HIV, may have underestimated true cost savings by 10-50%.

Keywords

male circumcision; HIV; HPV; sexually transmitted infections; herpes simplex virus type 2 (HSV-2); bacterial vaginosis; trichomoniasis; cost-effectiveness; Markov; Monte Carlo; Africa; Uganda

Introduction

Three randomized trials demonstrated that male circumcision(MC) reduces HIV acquisition by 51-60%.¹⁻³ The World Health Organization(WHO) and the Joint United Nations Programme on HIV/AIDS(UNAIDS) recommend encouraging voluntary MC as part of a comprehensive strategy for reducing sexual transmission of HIV in regions with HIV epidemics and low MC prevalence.⁴ Furthermore, ministries of health in several sub-Saharan African countries have proposed reaching 80% MC coverage among men 15-49 years-old by 2015.⁵

The MC trials demonstrated that MC is associated with reduced HIV as well as reduced low-risk and high-risk human papillomavirus (LR-HPV and HR-HPV), herpes simplex virus type-2 (HSV-2), and genital ulcer disease (GUD).⁶ Additionally, female partners of circumcised men have reduced rates of LR-HPV, HR-HPV, trichomoniasis, bacterial vaginosis(BV), and GUD.⁶⁻⁸

While mathematical models have shown that MC scale-up may avert substantial costs by reducing HIV,^{9,10} no study has analyzed the comprehensive impact of MC in sub-Saharan Africa, incorporating MC's effects on other sexually transmitted infections(STIs). With recently proposed PEPFAR funding cuts and increasing obligations of donor agencies, rigorous cost and effectiveness evaluations of programs to reduce HIV/AIDS and other STIs are needed to guide global health policy.

This study analyzes the healthcare costs associated with all MC-reduced infections, evaluating outcomes under alternative potential MC scale-up plans. It focuses on the Rakai District, Uganda, a prototypical rural sub-Saharan African community, to assess short and long-term financial implications of MC scale-up.

Methods

A dynamic Markov model was constructed using TreeAge Pro (Williamstown, MA) to assess changes in STI-related healthcare costs associated with MC scale-up, accounting for impact on men and women in the Rakai District, Uganda. Monte Carlo microsimulations were used to compare four strategies, varying by the scope and rate of MC scale-up, to a baseline scenario, defined by a continuation of current prevalence and trends of MC (23.6% of 15-49 year old men circumcised)¹¹.

MC Procedures and MC-Reduced Infections

This model tracked infant (0-1) and adolescent/adult (15-49) MC procedures, and accounted for potential procedure-related adverse events. In addition, it included all STIs among men and women demonstrated through randomized trials to be reduced by MC.^{3,6-8,12} Risk of acquiring each STI was assumed to be independent of prior infection history (individuals who had previously acquired particular STIs did not face an elevated risk from other

infections). The model did not incorporate potential secondary transmission events following initial infections, and MC-protection among females paralleled MC-status among males; the proportion of females experiencing protective benefits was similar to the proportion of circumcised males. STIs rates and direct medical expenses associated with MC procedures, procedure-related adverse events and STIs were tracked.

MC-reduced infections modeled among men included heterosexually-transmitted HIV (excluding mother-to-child transmission), GUD, and HR-HPV. Although the Ugandan MC trial also found reduced HSV-2 among circumcised men, most etiologically-defined GUD was attributed to HSV-2¹³. Thus, HSV-2 was not incorporated as a separate STI. MC-reduced infections modeled among women included GUD, HR-HPV, trichomoniasis, and BV. LR-HPV was not incorporated because its primary symptomatic presentation, genital warts, is not often treated in sub-Saharan Africa.

The Model – Population

Individual microsimulations followed individuals through the model in a series of 1-year cycles, tracking MC procedures and MC-reduced infections. The model (illustrated in Figure 1A) simulated an “initial population”, defined by current age and sex profiles, supplemented annually by a birth cohort, defined by birth rate¹⁴ and gender distribution at birth.¹⁵ These background parameters were assumed to remain constant. A dynamic population was explicitly generated by assigning individuals to either the initial population or to a birth cohort, based on the ratio of the current population size to the total number of individuals expected to be part of the population during the period of simulation and assuming that the size of each annual birth cohort remained constant. Further specification on how the dynamic population was explicitly generated is provided in the supplemental text. National age and sex-specific mortality¹⁶ was also incorporated through a terminal Markov state to account for death due to background or STI causes.

Individuals assigned to a birth cohort were not initiated into the model until an individual-specific birth year. Individuals of the initial population were assessed at the beginning of the simulation for existing infections and MC-protection status, using infection prevalence estimates^{11,17} and current MC rates in central Uganda.¹¹

Each potential health condition (1 or more STIs) was modeled as a gender-specific Markov state, with associated costs incorporated as incremental rewards - accrued each time an individual experienced a particular state - or as transition rewards, accrued each time an individual passed between particular states (Figure 1B). Transition probabilities between states were defined by incidence and MC efficacy, such that individuals protected by MC faced a reduced risk of transitioning to particular STI Markov states. Individuals with initial infections populated the corresponding Markov states at the start of the simulation.

The simulation was analyzed separately over 5 and 25 years to assess short and long-term impact of potential MC scale-up. Only costs incurred during these time periods were incorporated. Furthermore, input parameters (described below) were assumed to remain constant. Costs were discounted to the beginning of the analysis period, corresponding to the start of scale-up, and adjusted to US\$2012 using the medical care component of the Consumer Price Index.¹⁸

MC-Protection Status

Each MC scale-up strategy was defined by two components: one targeting uncircumcised males of the initial population (“catch-up MC”), and another targeting males of future birth cohorts.^{9,19} MCs under each program were performed among infants (ages 0-1) or among adolescents/adults (ages 15-49). Evaluated strategies (Table 1) varied by the ages of males

becoming circumcised, as well as by the rate of scale-up (rapid or gradual). While Strategy 1 reflected a continuation of baseline MC rates, without “catch-up MCs” or any change in MC trends among future birth cohorts, Strategies 2-5 defined alternative MC scale-up plans.

Under Strategies 2-5, “catch-up MCs” were conducted until 80% coverage was achieved among men aged 15-49, but the rate of scale-up (rapid or gradual) varied. Under Strategies 2 and 4, 10 years of scale-up were needed to reach 80% coverage, while under strategies 3 and 5, this level of coverage was achieved after only 5 years. Further details on identifying individuals who would gain MC protection through this “catch-up” program component are provided in the supplemental text.

Among annual birth cohorts, MC rates differed by scale-up strategy and birth year, with men born later experiencing greater MC rates than those born earlier. For simplicity, the simulation period was divided into five stages, where each stage consisted of a five-year period of scale-up. Among the men born during these stages, MC procedures were assumed to be conducted as infants (age 0-1), adolescents (age 15) or as adults (age 25). Under Strategy 1 (baseline), 23.6% of males were circumcised, with 13.6% obtaining infant MCs, 5% obtaining adolescent MCs, and 5% obtaining adult MCs. These rates persisted through stage five of the simulation. However, under Strategies 2-5, the MC rate increased through the course of the simulation, such that 80% of males born during stage five would ultimately become circumcised. Under Strategies 2 and 3, infant MCs occurred at the same rate as under the baseline strategy (13.6%), but adolescent and adult MCs were scaled up, with the adolescent MC rate ultimately reaching 40% and the adult MC rate ultimately reaching 26.4%. Strategies 4 and 5 focused on the scale-up of infant MCs (in addition to scaling up adolescent and adult MCs), such that 80% of men born during stage five were circumcised as infants. Strategy 2 characterized a more gradual scale-up than Strategy 3, and Strategy 4 characterized a more gradual scale-up than Strategy 5.^{4,5}

Input Parameters

Input parameters (Table 2) describe the costs, prevalence, and incidence of MC procedures and MC-reduced infections, and were drawn from existing literature, demographic surveys, and global databases. Efficacy estimates were drawn from the incidence rate ratios (IRR) and prevalence risk ratios (PRR) reported in randomized trials in Rakai, Uganda, which evaluated the impact of MC on male participants and their female partners. These efficacy parameters described the explicit effect of MC on an individual's acquisition, but did not explicitly describe the extent to which transmission itself was reduced. Trials in South Africa and Kenya found similar efficacy results.^{1,2,20,21}

Infection prevalence and incidence were age-specific, whenever possible. Declines in these rates were modeled for the ages below or beyond the age range of the group studied in the original data source (i.e. HIV rates were 0 at birth and declined to 0 by age 75). Where age-specific parameters were unavailable, rates were assumed to be constant over the age range reported. Incidence and prevalence rates specific to MC-protection status were derived from published incidence and prevalence rates to account for an existing portion of the current population who is already experiencing protective effects from MC. Details are provided in the supplemental text.

GUD incidence, for men and women, was assumed to be equivalent to annual GUD prevalence, as reported in the Ugandan 2006 Demographic and Health Survey.²²

Because BV is a transient state²³ and incidence estimates were unavailable, BV was modeled as a potentially prevalent infection, and not as a Markov health state. A parameter defining age at infection was drawn from a triangular distribution (mode=24.7, min=15,

max=59). A female with BV infection accumulated associated costs if she became infected during the period of analysis.

Only HR-HPV cases that led to cervical cancer (among females) or penile cancer (among males) were modeled, since these cases drive costs associated with HR-HPV. Because both of these cancers develop at least 5-10 years after HR-HPV infection²⁴, when evaluating individuals for incidence, reduced risk was only incorporated if MC-protection had been acquired before HR-HPV infection.

Because data on costs associated with HPV-induced penile cancer in Uganda were unavailable, the cost parameter associated with penile cancer was extrapolated from a cost estimate from the United States,²⁵ using a ratio of inter-country costs for cervical cancer.^{26,27} This extrapolation assumed that the ratio of costs for cervical cancer between Uganda and the United States is roughly equivalent to the inter-country ratio of costs for penile cancer.

Costs associated with GUD, BV, and trichomoniasis were incorporated in a piece-wise method, gathering individual components from the World Health Organization's "CHOICE" database,²⁸ published literature, and the International Drug Price Indicator Guide²⁹. Each infection was associated with costs from care conducted according to the Ugandan Clinical Treatment Guidelines for STIs³⁰, including expenses for a visit to a primary health center, as well as costs for the appropriate medical treatment (Acyclovir, Metronidazole and Clotrimazole, or Metronidazole, respectively). Additional model parameters accounted for the portion of infections that would not cause symptoms or cause treatment-seeking. Potential recurrence of BV (but none of the other STIs) was incorporated. For HIV, potential patient loss to follow-up was also incorporated. Furthermore, HIV-associated expenses incurred before initiating antiretroviral treatment (ART) were distinguished from post-ART expenses. Similarly, costs associated with HPV-induced cervical cancer incorporated separate values for Stages I-II and for advanced stages. Non-oncogenic or pre-cancerous effects of HPV were not incorporated.

Analysis

Under the base-case scenario, strategies were analyzed over each time period running 500,000 individual microsimulations (simulating 500,000 individuals). Cost and health outcomes for the district were extrapolated by calculating the total population present during the analysis period (from the initial population and each annual birth cohort). Cost outcomes were also separated by attributable infection to identify primary components of financial impact. Probabilistic sensitivity analysis, using 1,000 samples of 10,000 trials each, was conducted to evaluate the impact of uncertainty in sample-level input parameters. Table 2 shows the ranges and/or distributions characterizing each varied input parameter. Costs were varied by 25% in either direction using an adjustment factor sampled from a triangular distribution (mode=1, min=0.75, max=1.25). Efficacy estimates and other rates were drawn from beta distributions, using the 95%CI reported by the original data source.

Results

Under the base-case scenario, cost savings from averted MC-reduced infections vary from \$0.20 million (\$197,531) after 5 years of scale-up focusing on adolescent and adult procedures to \$13.71 million after 25 years, under a strategy incorporating increased infant MCs (Table 3). Under the strategies evaluated, net savings, accounting for scale-up costs and reduced STIs, is not expected to occur until after 10 years.

For all time periods evaluated, changes in infection costs are more substantial under strategies incorporating infant MC (Strategies 4 and 5) than those focusing exclusively on adolescent and adult procedures (Strategies 2 and 3), and differences in cost savings increase over time. Furthermore, while under the 5-year analysis period, the net change in costs is positive and strategies incorporating infant MCs are more costly than those focusing only on adolescent and adult procedures, MC scale-up becomes cost-saving over a longer period of analysis, and savings under strategies including infant MCs are ultimately more substantial.

Comparing outcomes between strategies of gradual and accelerated scale-up strategies demonstrates that accelerated strategies are associated with greater cost savings from averted MC-reduced infections. In the short-term, accelerated scale-up is associated with a greater (positive) net cost, but would result in greater net cost savings in the long-term.

Further analysis of cost savings associated with averted MC-reduced infections, shown in Table 4, shows the portion of the total infection cost attributable to each MC-reduced infection, as well as the portion of the total change in infection cost attributable to reductions in each infection. The portion of total costs attributable to each infection is reported as an average across all strategies (Strategies 1-5), and the portion of the change in costs is reported as an average across all scale-up strategies (Strategies 2-5). Attributable fractions specified for each strategy, under the base-case scenario, is provided in Supplemental Table-1. In the short-term, over 5 years, reduced HIV contributes 46.24% of MC-reduced infection costs and 50.04% of cost savings. Over 25 years, HIV contributes 78.77% of costs and 89.77% of cost savings. In addition to HIV, GUD among males and females, HPV-associated cervical cancer, and trichomoniasis contribute significantly to MC-reduced infection costs.

The cost to avert a single HIV infection was calculated for each time period evaluated, using the difference in costs of MC scale-up and prevalence of HIV infections between scale-up strategies and the baseline strategy. Over 5 years, the cost to avert a single HIV infection is \$5500-9200, but over 25 years, this cost is <\$500.

Financial outcomes from probabilistic sensitivity analysis are described in Table 5. Variation of input parameters does not substantially alter results. Cost savings from averted MC-reduced infections varies from \$0.30 million (\$295,514) after 5 years under Strategy 2, a gradual scale-up focusing on adolescent and adult MCs, to \$14.73 million after 25 years under Strategy 5, an accelerated scale-up incorporating infant MCs.

Discussion

MC has been demonstrated to be an effective preventative intervention for reducing HIV incidence^{1-3,31}. As a result, the WHO, UNAIDS, and other health agencies have promoted plans for MC scale-up⁴. However, additional medical benefits of MC exist – reduced HPV, HSV-2, and GUD among men^{6,12,20,21}, and reduced HPV, BV, trichomoniasis, and GUD among female partners⁶⁻⁸. This model suggests that previous cost analyses of MC considering only averted HIV have underestimated financial savings by 10-50%. While these findings are unlikely to dramatically alter policy, in a context of tightened budgets, financial assessment of MC-related programs which incorporates a comprehensive set of effects is essential.

This analysis is the first to evaluate the health and financial impact of MC in sub-Saharan Africa, incorporating all STIs among males and females shown through randomized controlled trials to be associated with MC. Results suggest that accelerated scale-up may lead to cost savings from averted infections earlier than gradual scale-up, and that programs

increasing infant MC procedures are associated with greater savings and fewer infections in the long-term than programs incorporating only adolescent or adult MC procedures.

The model used in this analysis allowed for substantial flexibility in the scenarios evaluated, particularly because strategy-related parameters varied both by the age of an individual at the time of MC and the stage of the scale-up program. Strategies were defined in consideration of recent MC scale-up proposals and trends among existing MC programs in sub-Saharan Africa. Although rapid scale-up incorporating increased infant MC procedures over time have been advocated, gradual scale-up, focusing on adolescent/adult MC procedures may be more practical in some settings^{4,31}. While infant MC is less costly and circumvents the possibility of sexual activity before the procedure, it may be difficult to implement because many births in sub-Saharan Africa occur outside of formal health facilities. Further, while adolescent or adult males may obtain the procedure on their own, infants rely on parents or caretakers. The additional costs or burden associated with implementing infant MC procedures has not been incorporated in this analysis.

A prior analysis suggested that a rapid scale-up of MC in 14 target African countries which reached 80% coverage among newborns and males 15-49 within 6 years of scale-up would ultimately result in 19% fewer cases of HIV and a comprehensive net savings of \$20.2 billion over 26 years.³² It is difficult to effectively compare these results with those reported here because of slight variations in context, scale, and evaluated scale-up strategies. However, these data support our findings that investment in infant MCs as a component of scale-up proposals can have substantial health and financial impact in the long-run.

This study has several limitations. Since input parameters used in the model characterized Rakai, Uganda, it may not be appropriate to extrapolate results to other regions in sub-Saharan Africa. Furthermore, the model likely underestimates the impact of MC scale-up. First, while all STIs associated with MC were incorporated, the transmission dynamics between men and women leading to infection were not explicitly modeled. Incidence rates did not vary by infection prevalence, and were held constant throughout the time period analyzed. If incidence increased from initial rates due to increased prevalence, health and financial outcomes may be underestimated.

The presented outcomes assume a continuation of the cost levels, incidence rates, and MC efficacy estimates used as input parameters. Because these input parameters may vary over time, the long-term health and financial outcomes estimated by this model may be less certain than short-term estimates. Furthermore, because MC preventative efficacy increases over time⁶, long-term averted infections and associated costs may be underestimated. Potential behavioral changes associated with MC were not incorporated in this model, because several studies have suggested that MC is not associated with any adverse post-procedural behavioral modifications^{2,3,33}.

The only MC-reduced infections incorporated were those shown by the Ugandan randomized trials to be associated with MC. However, other studies have suggested that MC is also associated with reduced infant urinary tract infections³⁴, syphilis, chlamydia, chancroid, and *Mycoplasma genitalium*³⁴⁻³⁶. Potential averted costs from these infections or from additional transmission events were not included. Although the Ugandan trial did not demonstrate reduced HIV among female partners of male MC participants³⁷, this finding is likely due to resumption of sexual activity before full healing from the MC procedure. Other studies suggest that with proper post-operative care, reduced HIV among men will indirectly affect women (and subsequently, other men) through reduced transmission^{4,38}. Incorporating potential transmission events would likely increase the portion of costs attributable to HIV.

Efficacy estimates for STIs other than HIV were based on a study of HIV-negative men and their female partners. Because it is not clear how preexisting male HIV infection affects MC protective efficacy for all other STIs evaluated, and because transmission dynamics were not explicitly modeled, this analysis did not incorporate potential effects of male HIV status on MC efficacy estimates.

Efficacy input parameters were drawn exclusively from randomized trials in Rakai, Uganda, although trials in Kenya and South Africa demonstrated similar results^{1,2,21}. Although the Kenyan trial did not show reduced HSV-2 among male MC participants, it did find similar reduction in GUD³⁹, which was assumed to incorporate symptomatic HSV-2 in this model.

Finally, this analysis included direct medical costs only, excluding indirect and non-medical costs from productivity loss, transportation, infrastructure, and caregiver or patient time. These other costs may be substantially higher than the direct medical costs considered.

This analysis suggests that short and long-term health and financial impact of MC may be more substantial than previously reported. Furthermore, strategies achieving target MC rates at an accelerated rate may become cost-saving earlier than more gradual scale-up strategies, and increasing rates of infant MC procedures may have greater long-term impact than focusing on adolescent and adult procedures. In an environment of increasingly tightened healthcare budgets, this assessment of the comprehensive impact of MC further supports the health and financial benefit of MC scale-up as a component of STI-related programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

A comprehensive evaluation of the financial implications of male circumcision scale-up in sub-Saharan Africa found that previous cost analyses focusing only on HIV have underestimated impact.

Figure 1.

(A) Simulation Design. Five distinct strategies of MC scale-up were compared in a decision-tree model. A decision node (D) led to five strategies, where Strategy 1 was considered the baseline and described a continuation of current MC levels. Strategies 2-5 described plans for MC scale-up, which differed by the rate of scale-up and the ages of the males obtaining MC. Under each strategy, simulated individuals traversed an identical Markov model (M). The model accommodated individuals of an "Initial Population" and individuals arising through annual birth cohorts during the period of analysis. At the start of the simulation, individuals of the "Initial Population" populated a temporary Markov state, and prevalent infections and initial MC-protection status were determined using input parameters (dashed

gray arrows). These individuals then transitioned to corresponding health states in the next cycle of the simulation. Individuals arising through future annual birth cohorts initially populated a “birth state,” which initialized individual-level parameters, before transitioning to health states (dotted black arrows). During each 1-year cycle, all individuals were susceptible to incident MC-reduced infections, and changes to MC-protection status. Revised time-dependent system-level parameters (including strategy-specific MC rates) and individual-level parameters were incorporated between cycles (solid black arrows). (B) Markov bubble diagram. The Markov process included gender-specific health states corresponding to having no infections, acquisition of a single infection, acquisition of multiple concurrent infections, and death. The infections modeled for each gender are consistent with results of preventative efficacy data from MC trials.

Table 1

Model Strategy Parameters

	MC Scale-up				
	Baseline ^e	Adolescent/Adult Only (15-49) ^f			Including Infants (0-1, 15-49) ^g
		1: Current MC	2: Gradual	3: Rapid	
Initial Population - MC Catch-Up Program (ages 15-49) ^a					
Prior MC (%) ^b	23.6	23.6	23.6	23.6	23.6
MC Rate After Catch-up (%) ^c	23.6	80 (after 10 years)	80 (after 5 years)	80 (after 10 years)	80 (after 5 years)
Annual Birth Cohorts ^d					
Initial Stage (years 1-5)					
No MC (%)	76.4	60	40	60	40
Infant MC (% , age 0)	13.6	13.6	13.6	20	40
Adolescent MC (% , age 15)	5	13.2	23.2	10	10
Adult MC (% , age 25)	5	13.2	23.2	10	10
2nd Stage (years 6-10)					
No MC (%)	76.4	50	30	50	30
Infant MC (% , age 0)	13.6	13.6	13.6	35	50
Adolescent MC (% , age 15)	5	18.2	28.2	7.5	10
Adult MC (% , age 25)	5	18.2	28.2	7.5	10
3rd Stage (years 11-15)					
No MC (%)	76.4	40	25	40	25
Infant MC (% , age 0)	13.6	13.6	13.6	50	60
Adolescent MC (% , age 15)	5	20	40	5	7.5
Adult MC (% , age 25)	5	26.4	21.4	5	7.5
4th Stage (years 16-20)					
No MC (%)	76.4	30	20	30	20
Infant MC (% , age 0)	13.6	13.6	13.6	65	75
Adolescent MC (% , age 15)	5	30	45	2.5	2.5

	Baseline ^e	MC Scale-up				
		Adolescent/Adult Only (15-49) ^f		Including Infants (0-1, 15-49) ^g		
		1: Current MC	2: Gradual	3: Rapid	4: Gradual	5: Rapid
Adult MC (% , age 25)	5	26.4	21.4	2.5	2.5	
5th Stage (years 21+)						
No MC (%)	76.4	20	20	20	20	20
Infant MC (% , age 0)	13.6	13.6	13.6	80	80	80
Adolescent MC (% , age 15)	5	40	40	0	0	0
Adult MC (% , age 25)	5	26.4	26.4	0	0	0

^aMC catch-up involves only individuals of the "Initial Population" not initially with MC protection.

^bPrior MC rate reflects the initial rate among males ages 15-49. Without scale-up (Strategy 1), this rate persists.

^cThe catch-up MC program increases MC among individuals in the "Initial Population" without prior MC-protection. Across scale-up strategies, the ultimate MC rate among this population rises to 80%. However, under Strategies 2 and 4, this catch-up period lasts 10 years, while under Strategies 3 and 5 this period lasts only 5 years.

^dMC scale-420 up rates among annual birth cohorts arising during the period of program analysis are time-dependent, as rates change through the course of scale-up program implementation. Rates are distinguished by program stage, where the initial stage includes years 1-5, the 2nd stage includes years 6-10, the 3rd stage includes years 11-15, the 4th stage includes years 16-20, and the 5th stage includes any years after year 20. Furthermore, MC rates are specified for three values of "Age at Circumcision": 0 (reflecting infant MC), 15 (reflecting adolescent MC), and 25 (reflecting adult MC).

^eThe baseline strategy reflects a scenario where individuals of the "Initial Population" who are not experiencing MC-protective benefits may not obtain a catch-up MC procedure. Further, the prior MC rate persists for the annual birth cohorts. Most of the MCs conducted among the annual birth cohorts are infant MC procedures.

^fScale-up strategies 2 and 3 focus only on men 15-49 (adolescent and adult procedures only). Under these scenarios, only men aged 15-49 may obtain a catch-up MC, and the scale-up for future birth cohorts reflects an increase in MC rates only among older individuals, up to 80% coverage. The MC rates among infants remain at the same level reflected in the baseline strategy.

^gScale-up strategies 4 and 5 involve MCs among individuals aged 0-1 and 15-49, and trend toward increased infant MC procedures. Under these scenarios, as the MC scale-up program for future birth cohorts progresses, the percentage of infant MC procedures increases, up to 80% coverage.

Table 2
Model Input Parameters - Base-Case Values and Ranges used in Sensitivity Analysis

Input Parameter	Base-Case (Range)	Reference
Circumcision		
Current rate (%)	23.6	s1
Increased rate (%)	See Table 1	Defined by Strategy
Procedure cost (\$, includes adverse events, adolescent/adult)	41.57	s2
Procedure cost (\$, includes adverse events, infant)	16.85	s3
<u>Adult Male (ages 13-100)</u>		
HIV		
Prevalence, ages 15-59 (% , varies by age)	0.3-9.3%	s1,4
Incidence, ages 15-19 (%)	0.558	s5
Incidence, ages 20-24 (%)	1.350	s5
Incidence, ages 25-29 (%)	1.583	s5
Incidence, ages 30-49 (%)	1.011	s5
Portion due to heterosexual transmission (%)	76 (75-85)	s6,7
Years infected before initiating treatment	8	s8
Initial portion in treatment (pre-ART, %)	56.5	s9
Initial portion in treatment (post-ART, %)	46	s10
Portion of patients lost to follow-up	Varies by time	s10
Cost per case – Pre-ART (annual, clinical, medication, and lab costs only)	123.25	s11
Cost per case – Post-ART (annual, clinical, medication, and lab costs only)	945.29	s11
MC Efficacy –IRR	0.49 (0.29-0.81)	s12
HPV		
Penile Cancer Incidence, ages 15-65 (per 100,000, varies by age) ^c	0.2-27.9	s13
Time between HPV infection and Cancer	10 (5-15)	s14,15
Portion of Penile Cancer due to HR-HPV (%)	46	s16
Cost per case – Treatment of Penile Cancer	1087.99	s17
MC Efficacy -IRR	0.65 (0.46-0.90)	s18
Genital Ulcer Disease		
Incidence, ages 15-49 (%)	6.2-11.0	s19
Prevalence, ages 15-49 (% , varies by age)	6.2-11.0	s19
Probability of Seeking Treatment (%)	12.4	s20
Cost per case – Acyclovir Treatment ^a	1.68	s21,22
Cost per case – Visit to Primary Health Center (\$) ^a	10.43	s23
Percent of cases requiring follow-up visit (%) ^a	20	s24
MC Efficacy –IRR	0.53 (0.43-0.64)	s12
<u>Adult Female (ages 15-100)</u>		
HPV		
Cervical Cancer Incidence (per 100,000, varies by age) ^b	0.1-209.7	s25,26
Time between HPV Infection and Cancer	10 (5-15)	s15

Input Parameter	Base-Case (Range)	Reference
Portion of Cervical Cancer due to HR-HPV	76.7	s26
Portion of cases progressing to Stages II-IV	73	s27
Cost per case – Treatment of Cervical Cancer: Stage I(\$)	1996.97	s26
Cost per case – Treatment of Cervical Cancer: Stages II-IV (\$)	2476.69	s26
MC Efficacy –IRR	0.77 (0.62-0.93)	s28
Bacterial vaginosis		
Prevalence among ages 15-59 (%)	50.60 (48-51)	s29,30
Portion symptomatic (%)	60.3 (19-65)	s31,32
Median age at infection	24.7 (15-59)	s33,34
Cost per case – Metronidazole and Clotrimazole Treatment (\$) ^d	0.53	s22,23
Cost per case – Visit to Primary Health Center (\$)	10.43	s23
Portion of recurrent cases (%)	60 (40-70)	s30,35
MC Efficacy – PRR ^e	0.60 (0.38-0.94)	s29
Trichomoniasis		
Incidence among ages 15-59 (%)	9.1	s36
Prevalence among ages 15-59 (%)	11.19 (10-25)	s29,31
Portion symptomatic (%)	19.9 (15-70)	s29,31,32
Cost per case – Metronidazole(\$)	0.41	s22-s23
Cost per case – Visit to Primary Health Center (\$)	10.43	s23
MC Efficacy – PRR ^e	0.52 (0.05-0.98)	s29
Genital Ulcer Disease ^a		
Incidence among ages 15-49 (% , varies by age)	16.2-20.9	s19
Prevalence among ages 15-49 (% , varies by age)	16.2-20.9	s19
Probability of Seeking Treatment (%)	12.4	s20
Cost per case – Acyclovir Treatment	1.68	s21,22
Cost per case – Visit to Primary Health Center (\$)	10.43	s23
Percent of cases requiring follow-up visit (%)	20	s24
MC Efficacy –IRR	0.78 (0.63-0.97)	s29
<u>Background</u>		
Birth Rate (per 1,000)	45	s37
Sex Ratio at Birth (Male: Female)	(102.6:100)	s38
Age-specific Mortality Rates	Varies by age	s39
Population size	562,228	s38,40

Note: All cost parameters include direct medical costs only, and have been converted to 2012 US Dollars. Incidence parameters are reported as annual rates. Where no upper age limit was provided, an upper limit was assumed, after which the incidence was modeled as a decreasing function towards zero. Efficacy estimates are expressed as incidence rate ratios (IRR) or prevalence rate ratios (PRR) and based on an intention-to-treat analysis.

^aCost associated with GUD among those seeking treatment assumed to include treatment with Acyclovir (200 mg, 5 times daily for 10 days) and a visit to a primary health center. The cost of an additional visit was only included for the specified portion of cases requiring follow-up. Individuals with GUD who did not seek treatment were assumed to accumulate no associated costs.

^bIncidence and prevalence estimates for HR-HPV among women include cases of cervical cancer due to HR-HPV.

Incidence and prevalence estimates for HR-HPV among men include cases of penile cancer due to HR-HPV.

^dCost for symptomatic BV cases included standard regimens of Metronizadole (500 mg 2 times daily for 7 days) and Clotrimazole (intravaginal cream, 3 days), and a visit to the primary health center.

^eEfficacy parameters for BV and Trichomoniasis were not available as incident rate ratios, but since these are acute, treatable infections, prevalence rate ratios were used in the model.

Table 3
Base-Case Analysis: Discounted Costs of MC Procedures and MC-Reduced Infections

Time Period	Baseline	MC Scale-up Strategies				
		Adolescent/Adult		Including Infants		
		Only (15-49) ^c	0-1, 15-49) ^d			
5 years						
<u>Discounted Cost of MC-Reduced Infections (\$) ^a</u>						
Average Male	17.24	16.87	16.23	16.86	16.22	
Average Female	13.53	13.33	13.12	13.31	13.04	
Entire Population (millions)	10.59	10.39	10.11	10.39	10.07	
Change (millions)	0.00	-0.20	-0.49	-0.21	-0.52	
<u>Discounted Cost of MC Procedures and MC-Reduced Infections (\$) ^{a,b}</u>						
Average Male	17.63	20.99	23.65	21.16	24.40	
Entire Population (millions)	10.72	11.81	12.65	11.86	12.88	
Net Change (millions)	0.00	1.08	1.93	1.14	2.15	
25 years						
<u>Discounted Cost of MC-Reduced Infections (\$) ^a</u>						
Average Male	124.73	109.77	106.53	107.37	103.37	
Average Female	23.06	21.90	21.70	21.59	21.28	
Entire Population (millions)	87.68	78.14	76.10	76.53	73.97	
Change (millions)	0.00	-9.54	-11.58	-11.15	-13.71	
<u>Discounted Cost of MC Procedures and MC-Reduced Infections (\$) ^{a,b}</u>						
Average Male	125.96	120.21	118.35	118.47	115.73	
Entire Population (millions)	88.41	84.31	83.09	83.09	81.28	
Net Change (millions)	0.00	-4.10	-5.32	-5.31	-7.13	

Note: Negative values for changes in MC-reduced infection cost or net costs indicate a cost savings, as compared to the baseline scenario.

^aMC-reduced infections among males include HIV, HR-HPV, and GUD. MC-reduced infections among females include HR-HPV, GUD, trichomoniasis, and BV. The expected cost associated with MC-reduced infections (for an average male, average female, or for the entire population) is discounted to the beginning of the time period evaluated.

^bMC procedures include those among infants, adolescents, or adults, and costs incorporate the procedure itself and potential procedure-related adverse events. MC procedures apply only to males.

^c Strategies 2 and 3 reflect potential MC scale-up plans incorporating MC procedures only among adolescent and adult men, ages 15-49.

^d Strategies 4 and 5 reflect potential MC scale-up plans which include MC procedures among infant males, as well as adolescents and adults, ages 0-1 and 15-49.

Table 4
Distribution of MC-Reduced Infection Costs Attributable to each MC-Reduced Infection, Averages Across Strategies

Time Period	Male MC-Reduced Infections			Female MC-Reduced Infections					
	HIV	HR-HPV ^b	GUD	Total	HR-HPV ^c	GUD	Trich	BV	Total
5 years									
Portion of Total Infection Costs (%) - Average Across Strategies									
Base-Case	46.24	0.03	9.24	55.52	11.10	17.95	13.18	2.25	44.48
Sensitivity Analysis	45.48	0.06	9.33	54.88	11.77	18.03	13.08	2.24	45.12
Portion of Total Infection Cost Change (%) - Average Across Scale-up Strategies ^a									
Base-Case	50.04	-0.95	17.69	66.79	1.77	9.45	15.88	6.11	33.21
Sensitivity Analysis	61.09	0.08	12.00	73.17	3.70	7.52	11.83	3.79	26.83
25 years									
Portion of Total Infection Costs (%) - Average Across Strategies									
Base-Case	78.77	0.03	4.33	83.13	4.05	6.41	4.95	1.46	16.87
Sensitivity Analysis	78.89	0.04	4.35	83.28	4.07	6.37	4.82	1.46	16.72
Portion of Total Infection Cost Change (%) - Average Across Scale-up Strategies ^a									
Base-Case	89.77	0.09	2.62	92.48	2.78	0.65	2.13	1.96	7.52
Sensitivity Analysis	90.37	0.04	2.43	92.84	2.63	0.57	2.13	1.82	7.16

^aTotal Infection Cost Change calculated in comparison to the Baseline strategy.

^bHR-HPV among males included only cases resulting in penile cancer.

^cHR-HPV among females included only cases resulting in cervical cancer.

Table 5
Probabilistic Sensitivity Analysis: Discounted Costs of MC Procedures and MC-Reduced Infections

Time Period	Baseline		MC Scale-up Strategies			
	1: Current MC	2: Gradual	Adolescent/Adult Only (15-49) ^c	3: Rapid	4: Gradual	5: Rapid
5 years - Discounted Cost of MC-Reduced Infections (\$^a; Mean (95% CI))						
Average Male	17.16 (11.73, 23.24)	16.54 (11.18, 22.70)	15.86 (10.61, 21.93)	15.85 (10.6, 21.92)	15.85 (10.6, 21.92)	15.85 (10.6, 21.92)
Average Female	13.69 (9.05, 19.18)	13.45 (9.03, 18.95)	13.28 (8.9, 18.76)	13.43 (9.02, 18.92)	13.43 (9.02, 18.92)	13.19 (8.8, 18.68)
Entire Population (millions)	10.62 (7.15, 14.60)	10.32 (6.96, 14.34)	10.03 (6.72, 14.01)	10.32 (6.96, 14.33)	10.32 (6.96, 14.33)	10. (6.68, 13.98)
Change in STI Costs (millions)	0.00	-0.30	-0.59	-0.30	-0.30	-0.62
5 years - Discounted Cost of MC Procedures and MC-Reduced Infections (\$^{a,b}; Mean (95% CI))						
Average Male	17.55 (12.02, 23.73)	20.66 (14.42, 27.73)	23.26 (16.5, 30.80)	20.83 (14.56, 27.94)	20.83 (14.56, 27.94)	24. (17.09, 31.64)
Entire Population (millions)	10.75 (7.25, 14.77)	11.74 (8.07, 16.07)	12.58 (8.74, 17.06)	11.79 (8.11, 16.13)	11.79 (8.11, 16.13)	12.8 (8.91, 17.32)
Net Change (millions)	0.00	0.99	1.82	1.04	1.04	2.05
25 years - Discounted Cost of MC-Reduced Infections (\$^a; Mean (95% CI))						
Average Male	126.75 (87.14, 170.93)	110.28 (74.91, 151.44)	106.81 (72.5, 147.28)	107.88 (72.97, 147.3)	107.88 (72.97, 147.3)	103.77 (70.11, 144.19)
Average Female	23.01 (16.02, 30.93)	21.85 (15.12, 29.75)	21.61 (15.00, 29.43)	21.51 (14.76, 29.48)	21.51 (14.76, 29.48)	21.13 (14.36, 29.13)
Entire Population (millions)	88.86 (61.21, 119.77)	78.42 (53.44, 107.53)	76.22 (51.93, 104.88)	76.79 (52.07, 104.92)	76.79 (52.07, 104.92)	74.13 (50.14, 102.87)
Change in STI Costs (millions)	0.00	-10.44	-12.64	-12.07	-12.07	-14.73
25 years - Discounted Cost of MC Procedures and MC-Reduced Infections (\$^{a,b}; Mean (95% CI))						
Average Male	127.97 (88.03, 172.52)	120.73 (82.83, 164.73)	118.68 (81.53, 162.32)	118.97 (81.54, 161.28)	118.97 (81.54, 161.28)	116.14 (79.71, 159.68)
Entire Population (millions)	89.59 (61.74, 120.72)	84.6 (58.12, 115.39)	83.24 (57.28, 113.78)	83.35 (57.14, 113.19)	83.35 (57.14, 113.19)	81.45 (55.81, 112.03)
Net Change (millions)	0.00	-4.98	-6.35	-6.23	-6.23	-8.13

Note: Negative values of change in costs reflect cost savings.

^aMC-reduced infections among males include HIV, HR-HPV, and GUD. MC-reduced infections among females include HR-HPV, GUD, trichomoniasis, and BV.

^bMC procedures include those among infants, adolescents, or adults, and costs incorporate the procedure itself and potential procedure-related adverse events. MC procedures apply only to males.

^cStrategies 2 and 3 reflect potential MC scale-up plans incorporating MC procedures only among adolescent and adult men, ages 15-49.

^dStrategies 4 and 5 reflect potential MC scale-up plans which include MC procedures among infant males, as well as adolescents and adults, ages 0-1 and 15-49.