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Modeling the Impact of Voluntary Medical Male Circumcision on Cervical Cancer in Uganda

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Background: In addition to providing millions of men with lifelong lower risk for HIV infection, voluntary medical male circumcision (VMMC) also provides female partners with health benefits including decreased risk for human papillomavirus (HPV) and resultant cervical cancer (CC).

Setting: We modeled potential impacts of VMMC on CC incidence and mortality in Uganda as an additional benefit beyond HIV prevention.

Methods: HPV and CC outcomes were modeled using the CC model from the Spectrum policy tool suite, calibrated for Uganda, to estimate HPV infection incidence and progression to CC, using a 50-year (2018–2067) time horizon. 2016 Demographic Health Survey data provided baseline VMMC coverage. The baseline (no VMMC scale-up beyond current coverage, minimal HPV vaccination coverage) was compared with multiple scenarios to assess the varying impact of VMMC according to different implementations of HPV vaccination and HPV screening programs.

Results: Without further intervention, annual CC incidence was projected to rise from 16.9 to 31.2 per 100,000 women in 2067. VMMC scale-up alone decreased 2067 annual CC incidence to 25.3, averting 13,000 deaths between 2018 and 2067. With rapidly-achieved 90% HPV9 vaccination coverage for adolescent girls and young women, 2067 incidence dropped below 10 per 100,000 with or without a VMMC program. With 45% vaccine coverage, the addition of VMMC scaleup decreased incidence by 2.9 per 100,000 and averted 8000 additional deaths. Similarly, with HPV screen-and-treat without vaccination, the addition of VMMC scaleup decreased incidence by 5.1 per 100,000 and averted 10,000 additional deaths.

Conclusions: Planned VMMC scale-up to 90% coverage from current levels could prevent a substantial number of CC cases and deaths in the absence of rapid scale-up of HPV vaccination to 90% coverage.

Key Words: voluntary medical male circumcision, human papillomavirus, cervical cancer, STI, modeling, HIV prevention

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INTRODUCTION

Voluntary medical male circumcision (VMMC) is an HIV prevention intervention in 15 southern and eastern African countries, with nearly 23 million circumcisions performed by end 2018 following WHO and UNAIDS recommendations for VMMC in 2007.[1–3] Although VMMC has provided millions of men with a lifelong 60% lower risk of HIV infection, it also provides their female partners with protection from other diseases, which should be considered in quantifications of its overall impact.

The most important such benefit is decreased risk for human papillomavirus (HPV) and resultant cervical cancer (CC),[4] because of its lethality. In sub-Saharan Africa, HPV-associated diseases, and in particular CC, are major causes of morbidity and mortality in women.[5] CC is the region's most common cause of cancer death among women, particularly in Eastern and Western Africa. Introduction of prevention services such as CC screening programs, HPV DNA diagnostic tests, and HPV vaccination programs has been slow in these resource-limited settings. Thus, CC incidence has remained high[5] and is expected to rise, along with associated mortality.[5] Risk for CC is even higher among women living with HIV,[6] for whom invasive CC is also an AIDS-defining illness.[7]

The mechanisms and efficacy of male circumcision against HPV and CC are sufficiently well-understood to support modeling around its impact for program and policy use. One of the initial randomized controlled trials[8] (RCTs) establishing the efficacy of male circumcision (MC) for HIV prevention, conducted in Uganda, also reported that MC both reduced acquisition of new high-risk (HR) HPV infections and, in HIV-negative men, increased clearance of HR-HPV infection, decreasing prevalence. Reduced risk of cervical neoplasia was also found in HIV-uninfected female partners

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of circumcised men.[9] Another RCT found in women whose partners were circumcised a lower incidence of HR-HPV infection over a 2-year follow-up period (incidence rate ratio = 0·77).[10] These trials are consistent with others[11] demonstrating lower rates of CC in women associated with male partner circumcision.[12,13]

However, the potential population-level impact of MC on CC is not well-quantified. Modeling this benefit could substantially increase estimated public health impacts of VMMC. Uganda is a priority country for quantification: it had the seventh highest incidence of CC globally in 2018 at 54.8 per 100,000,[14] and CC is its most common cancer among women aged 15–44 years. CC is also Uganda's leading cause of female cancer deaths,[15] accounting for nearly one-third in the most recent World Health Organization estimates (2008).[16] Uganda also has a long history with VMMC: after hosting the RCT discussed above,[8] Uganda launched a VMMC program in 2008, and circumcised over 4 million men through 2018, the highest national total of all 15 priority countries.[3] Despite these achievements, Uganda's HIV prevalence remains high and its VMMC scale-up plan is unfinished: the Uganda Population-based HIV Impact Assessment 2016–2017 reported an HIV prevalence of 4.7% among men aged 15–64 years; only 42% of those men were circumcised, and under 22% medically circumcised, vs. circumcised by nonmedical providers for cultural or religious reasons, potentially leaving some foreskin in place and reducing protective effects.[17]

Uganda is, therefore, an ideal setting to assess whether further VMMC scale-up could meaningfully reduce HPV-associated mortality in women. We sought to model the potential impact of VMMC on CC incidence and mortality, both with and without concurrent directed CC interventions.

METHODS

Inputs and sources are in Table 1, including: key parameters in the basic CC model and calibration to Uganda; impacts of VMMC, HPV vaccination, and CC screening and treatment; and baseline and various scale-up scenarios. Scale-up interventions for screening and treatment, and for the more optimistic vaccination scenario, are expert consensus scenarios

TABLE 1. Summary of Key Parameters and Values for the Model

	Key Assumptions	
Parameter	**Value**	**Source**
Basic CC model, demographics, and epidemiology		
Ugandan demographics (age structure)	Multiple	UN World Population Prospects, 2017[34]
2018 Uganda CC crude rate	28.8 per 100,000	WHO-affiliated HPV Information Centre[15]
2018 Uganda HPV 16/18 prevalence	3.6%	WHO-affiliated HPV Information Centre[15]
Intervention impacts		
Impact of VMMC on HPV acquisition by HIV-negative men	53% reduction	Published literature[35–37]
Impact of VMMC on HPV clearance by HIV-negative men	56% increase	Published literature[36,38]
Impact of VMMC on HPV acquisition and clearance by HIV-positive men	None	Published literature[10]
Impact of HPV9 vaccine on acquisition and CC	100% efficacy against 16/18 and other HR HPV, ie, against CC	Idealized theoretical—WHO modeling meeting[20]
Impact of HPV screen-and-treat	88% sensitivity; CC mortality reduction by stage: 99% at 0, 87% at 1, 74% at 2, 46% at 3, 0% at 4	Details in basic CC model,[22] primary data in published literature[39]
Intervention coverage (baseline and scale-up scenario)		
HPV vaccination coverage	Baseline: 5% among all women "substantial control" scale-up: Immediate, sustained 90% coverage of 9–24-year-old adolescent girls and young women	2018 UNICEF reported HPV coverage: 15-year-olds[27] Idealized theoretical—WHO modeling meeting[18]
	"Moderate aggressive" scaleup: same structure, 45% coverage	Author conjecture, bounded by ranges of HPV coverage elsewhere in East Africa (17%–85%)[27] and Ugandan girl primary school attendance (84%)[24]
HPV screen-and-treat coverage	Baseline: 9%	WHO modeling meeting[20]
	Scale-up: 25% coverage by 2029, 35% by 2044, 60% thereafter (among the 90% of women ever possibly accessing screening)	
VMMC coverage	Baseline: coverage by 5-year age band ranging: 45.5% in 15–19 through 33.7% in 50–54; overall 15–49 years 45.9%	2016 Demographic health survey for baseline[24]; idealized target for final
	Scale-up: linear to 90% of 15–49 years-old males by 2023 (consistent with current WHO/UNAIDS guidance)	

used at the 2018 meeting of the World Health Organization's Cervical Cancer Elimination Modelling Consortium,[18,19] convened to define and test service packages as potential pathways to eliminate CC as a public health problem. This used potential elimination thresholds of 4 and 10 cases per 100,000 woman-years; the current public draft strategy adopted the former.[20]

Basic CC Model, Calibration to Uganda, and Time Horizon

HPV and CC outcomes were estimated using the CC model within the Spectrum policy tool suite.[21] A detailed description of the CC model is elsewhere.[22,23] These sources provide the expanded set of assumption values and primary data references for the basic model (eg, transition probabilities between cervical dysplasia stages including regression and immunity acquisition; absolute mortality rates with treatment; etc.). Briefly, it is a deterministic compartmental model with health states corresponding to infection with high- and low-risk strains, disease stages, and immunity conferred by vaccination. The CC submodel is based on a model calibrated for East Africa's basic epidemiological transition rates, and was further fitted to Uganda-specific HPV epidemiologic estimates for 2018. Thus, all scenarios begin with the same data-based 2018 CC incidence. A 50-year horizon (2018–2067) was to capture the full effects of circumcision and HPV vaccination, given the gradual nature of CC progression. Key outputs include clinically identified (thus treatable) CC cases, and total female population deaths (selected over CC-specific deaths, because of inconsistent cause-of-death data availability). Thus, CC confers a stage-specific mortality risk increase, but deaths are not explicitly attributed to CC or any cause.

Incorporating VMMC, HPV Vaccination, and CC Screening/Treatment Interventions

Baseline Coverage and Impact

We adapted the model to incorporate HIV prevalence by sex and VMMC coverage by age based on coverage survey data, by modifying existing parameter values rather than explicitly creating HIV or circumcision states. As in the baseline circumcision coverage data source, the 2016 Uganda Demographic and Health Survey,[24] no distinction was made between medical and nonmedical circumcision. The baseline MC coverage value was 45.9% among 15–49-year-old men overall, varying by age. Estimated impacts of VMMC on HPV transmission to women and clearance were based on trial data in HIV-positive and negative men.

Because Uganda has had a school-based national HPV vaccination program for 9–14-year-olds since 2015[25,26] baseline HPV vaccine coverage was also included at 5% for 9–24-year-olds (upper age limit chosen in the original WHO CC modeling meeting), an optimistic extrapolation from the 2018 reported 3-dose series coverage of 3% among 15-year-olds.[27] Population vaccination coverage at base year was determined intrinsically by letting the baseline model run to a time horizon where it reached steady state, during which vaccinated cohorts of 9–24-year-olds rise to older age categories, yielding an even more optimistic baseline vaccination assumption. Uganda's HPV program currently uses the quadrivalent vaccine (HPV4), but in our model, taken from the 2018 WHO modeling work, assumed vaccine efficacy against CC reflected more optimistically the adoption of the nonavalent HPV9 vaccine (Table 1). In addition, because HPV strains in the model are categorized as (1) 16/18, (2) other HR (including strains not covered by HPV9), and (3) LR, vaccination was specified to confer immunity to both 16/18 and other HR strains. Vaccinated individuals thus have 100% lifelong immunity to all oncogenic strains, and unvaccinated individuals are not immune. This assumption generates extreme high impact values for vaccination at any coverage, and thus extreme conservative values for VMMC impact.

HPV screen-and-treat programming was modeled on the WHO-recommended cervical swab HPV-DNA-based screen-and-treat approach,[28] at 10% baseline coverage in only the 30–40 years age band. This approach includes treatment for all women testing positive without exam for lesions, based on the favorable expected risk–benefit balance of this approach in women aged above 30 years. Existing reports that Uganda's lifetime CC screening coverage rate lies between 4.8% and 30% support this assumption.[29,30] Treatment confers a modeled expected survival benefit, although treatment type is not specified. Its mechanism of impact was to link women with cervical intraepithelial neoplasia (CIN) and CC into treatment at earlier average dysplasia/disease stages than in the absence of screen-and-treat. This averts both cases (by enhancing regression from CIN) and deaths (via specified percent mortality reductions at each stage—Table 1).

Scenarios

We generated a baseline scenario, with no scale-up of VMMC or HPV/CC interventions beyond 2018 levels; and 3 other scenarios, representing scale-up of one of the 2 directed CC interventions: expanding HPV vaccination to adolescent girls and young women at 2 different coverage levels, and HPV screen-and-treat. Finally, all 4 of these scenarios were modeled in 2 versions each, one with and one without VMMC scale-up, to assess VMMC's marginal contribution in each case, for a total of 8 scenario versions (Table 2).

In scenarios with HPV vaccination scale-up, the target population was adolescent girls and young women. We created 2 scenarios. First, "substantial control," with highly idealized immediate coverage of 90% in 9–24-year-olds in the first year via routine plus "catch-up" vaccination, and routine coverage of 90% of 9-year-olds annually thereafter, following a policy goal of sharply driving down HPV incidence. We chose the term "control" because the empiric incidence threshold for true elimination is not known. This maximally optimistic scale-up assumption was chosen by the WHO modeling meeting group as an example of the speed of coverage scale-up necessary to eliminate CC as a public health problem (annual incidence <10 cases per 100,000 women) over the time horizon. Second, "moderate

TABLE 2. Summary of the Impact of VMMC on HPV and CC, With or Without Large-Scale HPV Vaccination or Screening Programs

	Scenario							
	Baseline: No VMMC Scale-up, No VAX AGYW, No HPV Screen	**VMMC Scale-up Only**	**"Substantial Control" VAX AGYW**	**"Substantial Control" VAX AGYW + VMMC Scale-up**	**"Moderate Aggressive" VAX AGYW**	**"Moderate Aggressive" VAX AGYW + VMMC Scale-up**	**HPV Screen Only**	**HPV Screen + VMMC Scale-up**
Epidemiology, female population								
Initial CC incidence: new clinically identified cases per 100,000 women in 2018	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9
End CC incidence: new clinically identified CC cases per 100,000 women in 2067	31.2	25.3	5.7	5.2	17.9	15.0	21.8	16.7
Cumulative outcomes and intervention impacts over the 2018–2067 period (50 years)								
Clinically identified CC cases (stage 1–4) (in 1000's)	602	554	339	332	472	445	546	495
Clinically identified CC cases averted (in 1000's)	N/A (ref)	48	263	270	130	157	56	107
Female deaths averted (in 1000's)	N/A (ref)	13	87	89	42	50	53	63

HPV screen, scale-up of HPV screen-and-treat; VAX AGYW, vaccination of adolescent girls and young women.

aggressive," with the same structure but with immediate and routine vaccination coverage values of 45%. This scenario could also be viewed as an approximation, only, for a model with higher coverage but lower than 100% efficacy.

In scenarios with CC screening and treatment scale-up, coverage was scaled-up in a stepwise pattern to 60% by 2045 (Table 1), still among 30–40-year-olds. This age range and coverage was chosen by the WHO modeling meeting group to reflect an achievable scale-up rate given health system constraints in developing countries. The conservatism of this approach is reflected in both the gradual scale-up and the narrow target age band (compared with current WHO recommendations to target women aged 30–49).[31]

In scenarios with VMMC scale-up, VMMC coverage was increased to 90% in all age groups 15–49 years by 2023 and maintained at 90% thereafter. This is the VMMC target coverage level widely modeled to achieve the national impact on HIV used in the original Fast Track Strategy developed by UNAIDS.[32] No scale-up of VMMC for 0–14 years was modeled, because this is not a priority age group under WHO/UNAIDS guidance.

RESULTS

Under the baseline scenario (Table 2), the crude CC annual incidence was projected to increase to 31.2 per 100,000 women by 2067, and cumulative all-cause deaths in women over 2018–2067 were projected to total 11,627,000 (not shown).

In the absence of CC-focused interventions, VMMC scale-up decreased annual CC incidence to 25.3 per 100,000 by 2067. It averted approximately 48,000 clinically identified CC cases (8%) and 13,000 deaths in women between 2018 and 2067 compared with the baseline scenario.

In a scenario where only HPV screen-and-treat was scaled up, annual CC incidence was 21.8 per 100,000 by 2067, and 56,000 clinically identified CC cases (9% reduction) and 53,000 deaths were averted compared with the baseline. If VMMC scaleup was added to screen-and-treat alone, an additional 51,000 clinically identified CC cases (91% more) and 10,000 deaths (63,000 in total, 19% more) were averted.

Under the "substantial control" vaccination scenario, annual CC incidence dropped to 5.7 per 100,000 by 2067, and approximately 263,000 clinically identified CC cases (44% reduction) and 87,000 deaths were averted compared with baseline. If VMMC scaleup was added, annual CC incidence dropped to 5.2 per 100,000 by 2067, and another 7000 clinically identified CC cases (270,000 total; 3% more) and 2000 deaths (89,000 in total, 3% more) were averted than with vaccination alone. Thus, with "substantial control" vaccination, annual CC incidence was less than 6 per 100,000 women with or without a VMMC program.

Under the more realistic "moderate aggressive" vaccination scenario, with vaccination alone, annual CC incidence dropped to 17.9 per 100,000 by 2067, and 130,000 clinically identified CC cases (22% decrease) and 42,000 deaths were averted compared with baseline. If VMMC scaleup was added, annual CC incidence dropped to 15.0 per 100,000 by 2067, and an additional 27,000 clinically identified cases (157,000 total; 21% more) and 8000 deaths (50,000 in total, 20% more) were averted than with vaccination alone.

DISCUSSION

Scale-up of VMMC alone to 90% coverage from current levels could prevent approximately 48,000 CC cases and 13,000 deaths between 2018 and 2067. Its marginal impact is more moderate in the setting of plausible vaccination prospects ("moderate aggressive") or modest screen-and-treat scale-up, and small in the setting of optimal vaccination ("substantial control") scaleup potentially consistent with an elimination goal. VMMC impact findings in the vaccination scenarios are very conservative given the high vaccination efficacy assumptions.

Notably, the baseline scenario projects a near-doubling of clinically identified HPV incidence by 2067. The 2 scenarios with plausible vaccination and screen-and-treat scaleup only resulted in falling annual CC incidence if combined with VMMC scaleup.

Combined impacts of VMMC and other interventions were generally subadditive. This is consistent with the intuition that VMMC has no mechanistic synergies with the other interventions, and some CC cases would be prevented by either intervention alone, so that their impacts "overlap." However, one apparent synergistic interaction was seen. Adding VMMC to screen-and-treat led to 51,000 additional clinically identified CC cases averted, whereas adding VMMC to the baseline scenario led to only 48,000 additional clinically identified CC cases averted. This does not necessarily imply more actual (including unidentified) cases averted. Screen-and-treat not only decreases progression of precancerous lesions to CC, but also increases the proportion of CC cases that would be clinically identified, and thus "countable" as being prevented by the addition of VMMC.

Intervention scenarios' effectiveness in preventing deaths during the 50-year time horizon was not linearly related to their effectiveness in preventing cases (*vis*., VMMC only prevented about ¼ as many deaths as cases, whereas HPV screening prevented nearly the same number of deaths and cases.) This is consistent with the expected variations in delay to death depending on what step of the process of developing malignancy is blocked by an intervention; VMMC intervenes earlier by preventing HPV infection, and thus a greater proportion of deaths prevented would occur after 2067.

In conclusion, the marginal impact of VMMC is minimal in the presence of a highly successful vaccination program (100% efficacy and near-maximal scale-up); this is consistent with the WHO modeling findings that adolescent girls and young women-targeted vaccination is sufficient to drive annual incidence in nearly all countries below 10 per 100,000. But the impact of VMMC is substantial in the setting of less idealized vaccination scale-up or of screen-and-treat scaleup alone. As long as both these interventions remain slow to scale up as currently is the case—and even more so until and unless a program switch from HPV4 to HPV9 becomes feasible—VMMC will continue to prevent tens of thousands of CC deaths as an incidental health benefit for women.

Similar models could be valuable for other VMMC priority countries with substantial CC burden. These should include both formal uncertainty bound assessment and more nuanced scenarios, which particular should capture the expected persistence of oncogenic HPV types not covered by HPV9. Such real-world scenarios should produce even more substantial impact findings for VMMC by reducing the impact of vaccination, as does the only other attempt we are aware of, done for Tanzania,[33] using different methodologies.

The benefits and costs of VMMC scaleup and coverage maintenance need to be regularly reviewed, especially if HIV incidence continues to decline in VMMC priority countries. Quantifying the incidental impact of VMMC on health outcomes outside the HIV realm will inform national priority-setting among public health interventions.

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