Global Variation in the Impact of Male Circumcision in Preventing HIV among MSM

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Background

The effectiveness of voluntary medical male circumcision (VMMC) as an HIV prevention measure among heterosexual men has been demonstrated in clinical trials (1). However, the efficacy and population-level effectiveness of VMMC among men who have sex with men (MSM) remains uncertain, and is likely to depend on the behavioral and demographic characteristics of specific MSM populations, such as:

- sexual role segregation
- current coverage of circumcision
- willingness to undergo VMMC
- condom use.

Observational studies have found differing results. A meta-analysis did not reveal sufficient evidence that male circumcision protects against HIV in MSM, but concluded that the measurable protective effect observed in studies conducted before the era of highly active antiretroviral therapy warranted further investigation (2). A systematic review concluded that while no statistically significant population-level effect has been measured, a measurable protective effect was observed among predominantly insertive MSM (3).

We used mathematical modelling to assess the potential impact of VMMC among MSM in different settings worldwide and to help determine the settings in which it could be an effective HIV prevention measure for MSM.

Methods

We developed a deterministic compartmental model of HIV transmission among MSM (figure 1) and simulated the HIV epidemic in nine selected countries (see table 1). The MSM were divided by: HIV status, with HIV positive MSM split between three stages of HIV infection: acute, chronic and pre-AIDS; sexual role preference: either 'Top', defined as being the insertive partner in more than 50% of their relationships, or 'Bottom', defined conversely, as well as being circumcision status.

The model incorporates infectivity by type of sex act (receptive/insertive), sexual mixing by role preference, condom use, three stages of HIV with varying infectivity, and assumes a 40%-67% VMMC efficacy during insertive anal sex (0% efficacy for receptive anal sex) (1).

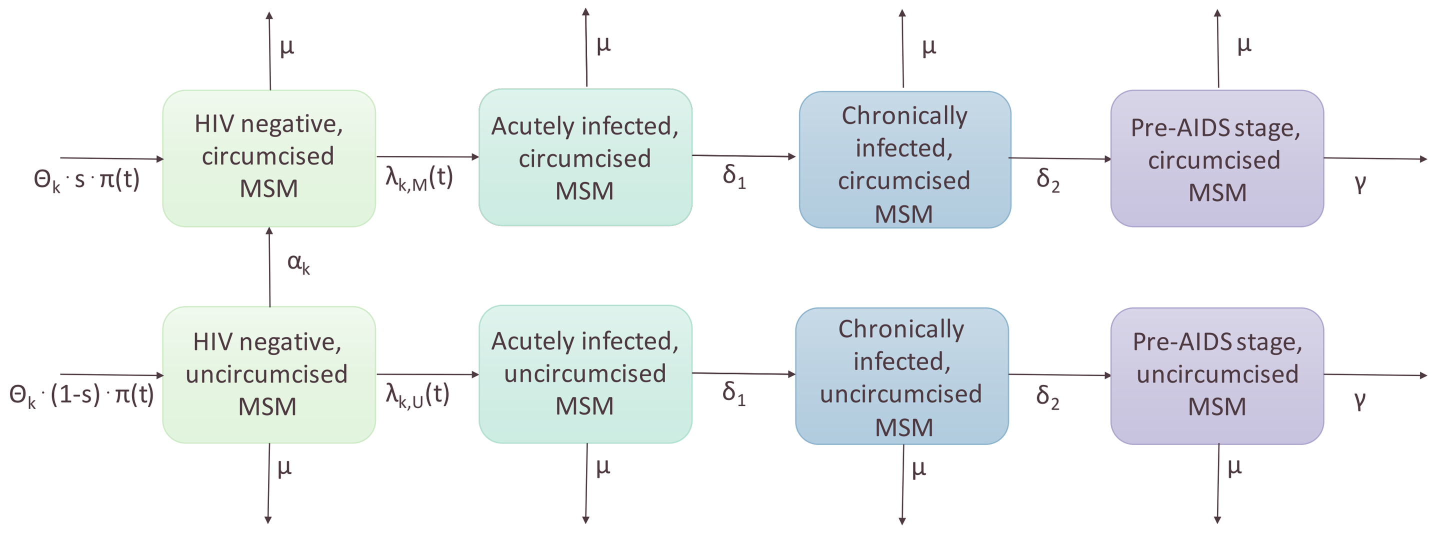

Figure 1: Uninfected MSM enter the population at rate *π(t)* per year. The population is divided by role preference (a fraction,Θ, are Tops), and circumcision status (a fraction, s, are already circumcised at birth). Uninfected, uncircumcised Tops can undergo VMMC as part of the intervention (at rate α per year). Uninfected MSM can contract acute HIV, at a rate depending on whether they are circumcised; the number (c_k), positioning (x_k) and infection stage of their partners (acute/chronic/pre-AIDS); and whether a condom was used (p), and how efficacious it was (e). Acutely infected MSM become chronically infected (at rate δ_1 per year). Chronically infected MSM develop pre-AIDS (at rate δ_2 per year). MSM with pre-AIDS develop AIDS (at rate γ per year). MSM can exit the population for non-AIDS reasons at any time (at rate μ per year).

Plan of Analysis:

We conducted two types of analysis, a worldwide and a country-specific analysis, as follows:

- We first reviewed the literature to define plausible ranges of biological and sexual behaviour parameters, HIV prevalence among MSM and pre-intervention coverage of male circumcision across countries –i.e. the worldwide range used in the worldwide analysis. We then identified countries with data on sexual role segregation (i.e. % Top or % Bottom) and condom use – to conduct country specific analyses (Table 1).
- ***Worldwide analysis*** consisted of a sensitivity analysis to identify the most influential parameters on VMMC HIV impact and inform the country-specific analysis. To do so, the parameters were sampled from within their worldwide ranges (shown in Fig 2) 200,000 times using Latin Hypercube sampling. Here, we used wide ranges assuming that nothing is known about condom use (p) and role segregation (Θ, x_T) since this information is rarely available. The model was run to equilibrium and the 5,391 parameter sets that reproduced plausible mixing scenarios and with HIV prevalence falling within our plausible worldwide range (1.8% - 35%) were retained (4). These worldwide parameter sets were used to estimate VMMC impact.
- ***Country specific analyses*** *were done in 3 steps: i)* the model was first calibrated (as described above) to available country-specific HIV prevalence among MSM and pre-intervention coverage of male circumcision, using the worldwide ranges for the remaining parameters values. Each of the country-specific fitting parameter sets were used to estimate VMMC impact in each country, ii) we stratified the impact estimates by level of role segregation, iii) we repeated the analysis in i) for countries where additional data on condom use and role segregation was available (Table 1). These series of steps allowed us to produce country-specific impact estimate and to evaluate the influence of missing information on key parameters.

Pre-intervention %	USA	Canada	Mexico	Peru	Ghana	South Africa	India	China	Australia
HIV prevalence	[14, 24]	[11, 23]	[21, 31]	[15, 22]	[20, 30]	[21, 35]	[9, 19]	[6, 26]	[6, 16]
Male circumcision coverage	[66, 86]	[22, 42]	[1, 21]	[0, 16]	[77, 97]	[36, 56]	[0, 20]	[2, 22]	[50, 70]
Tops in population (Θ)	no data	[8, 100]	no data	[60, 98]	no data	no data	[16, 66]	[18, 87]	no data
Tops in insertive partnership (x_T)	no data	no data	no data	[66, 100]	no data	[65, 90]	[68, 100]	[60, 100]	no data
Acts using condom (p)	no data	[18, 100]	no data	[36, 80]	no data	[50, 93]	[8, 97]	[28, 80]	no data

Table 1: Pre-intervention HIV prevalence among MSM and coverage of male circumcision were used to differentiate country settings in step i of the analysis (Fig 4A). Fits were then refined based on % Tops forming insertive partnerships (*Θ)*, % of Tops in population (x_T) and % of sex acts protected by a condom (p) in step iii of the analysis (Fig 4C).

VMMC Intervention scenarios

We compared intervention strategies of VMMC scale-up where 25%, 50% and 100% of uncircumcised, uninfected Tops were circumcised over the course of 5 years. Impact was measured as the cumulative fraction of new HIV infections averted over 5, 10 and 25 years (e.g. 2015-2025).

Results

Worldwide sensitivity analysis

Sensitivity analysis revealed that pre-intervention coverage of male circumcision, the proportion of Tops in the population and the level of role segregation were the most influential parameters (Fig 2). Even more so than the relative risk attributable to receptive over insertive intercourse, and the efficacy of VMMC. Greater impact was seen when MSM had a strong preference for either insertive (high x_T) or receptive intercourse (low x_B) (Fig. 2).

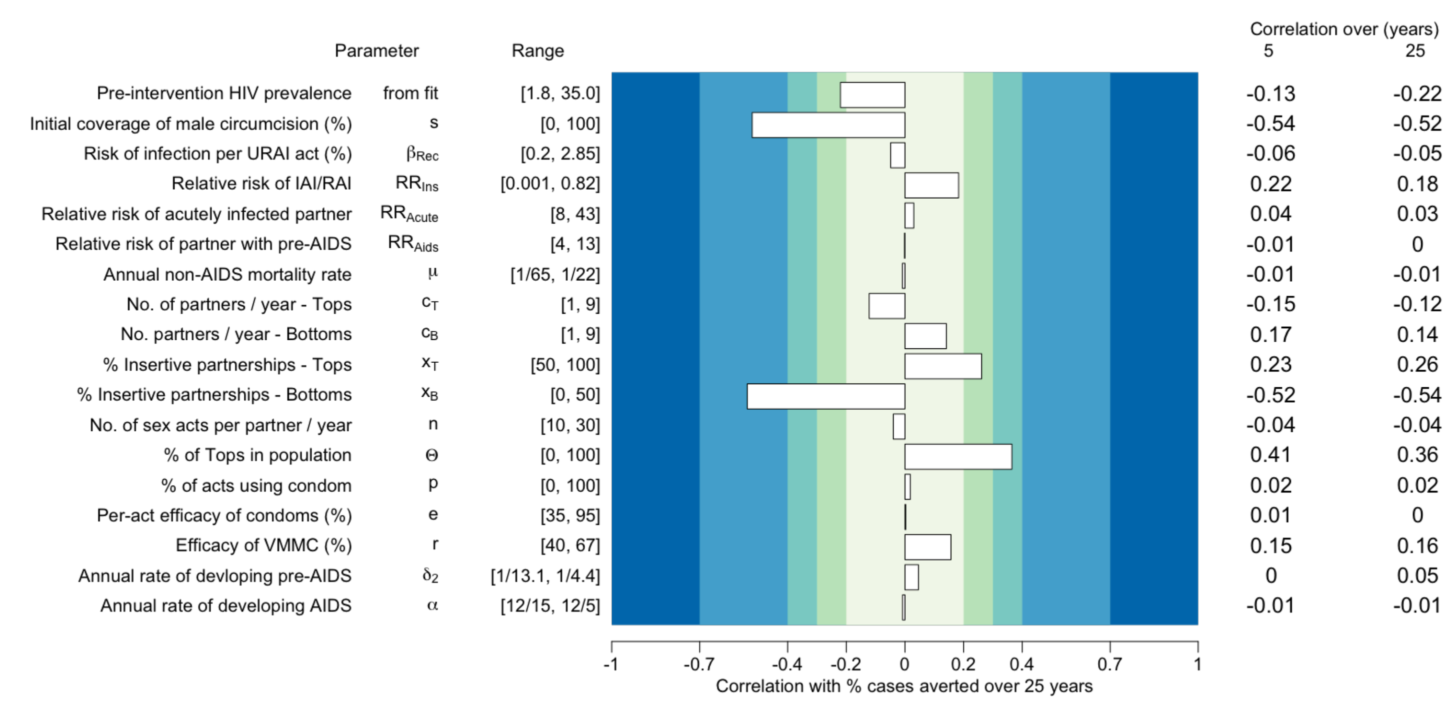

Figure 2: Tornado plot showing correlations between key model parameters and fraction of HIV infections averted over 25 years under 100% coverage scenario across all worldwide simulations. The range gives the full range of values explored for each parameter. Shaded bands denote increasing significance, from light to dark.

Country specific analysis - South African example

(fitted to South African pre-intervention HIV prevalence among MSM and pre-intervention coverage of male circumcision as in step i) The cumulative fraction of infections averted overall, and among Tops and Bottoms individually, increases as more MSM undergo VMMC (Figure 3). The impact was most pronounced among MSM receiving VMMC (Tops), although herd effects were also observed among their partners.

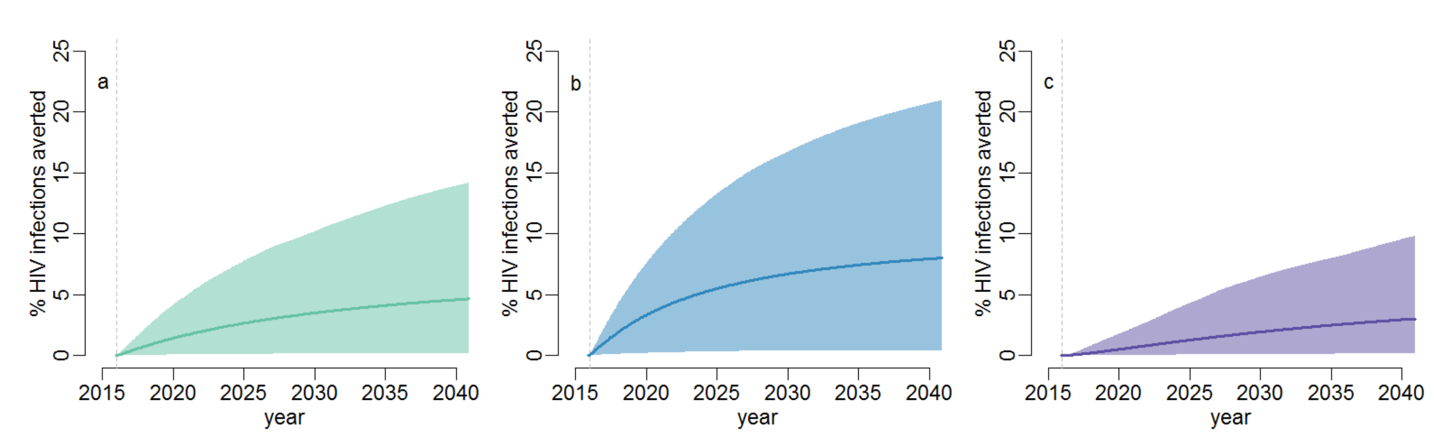

Figure 3: Predicted cumulative fraction of HIV infections averted over time by circumcising 50% of uninfected Tops by 2020 among **(a)** all MSM, **(b)** Tops, **(c)** Bottoms. Mean is shown in darker coloured lines, 95th percentile ranges are shown as a shaded area, produced from all 517 model fits to the South Africa data.

Based on the uncertainty analysis (Fig. 2) the model fits in each country setting were further refined taking into account estimates of the sexual role preferences and condom use in each of the settings, as determined by literature review (Table 1).

Country specific analysis – step i)

The map in Figure 4 shows that the range of pre-intervention coverage of male circumcision across the countries modelled varies between 1%-97%. The predicted impact of VMMC varied substantially across settings from 0% to 17% of all new infections averted over 10 years (Fig. 4A). Countries with high pre-intervention levels of male circumcision (>70%), such as the USA or Ghana, would see a minimal impact (<1% [95% CI 0%-3%] and 2% [95% CI 0%-6%] when circumcising 25% and 50% of Tops over 5 years, respectively.) The larger impact of 3% [95% CI 0%-8%] and 6% [95% CI 1%-16%] when circumcising 25% and 50% of Tops, respectively, was observed in countries with low pre-intervention levels of male circumcision (<20%), such as Peru and India. The maximum impact observed across all the countries considered was 13% [95% CI 1% - 38%], predicted using the 100% coverage intervention in the India setting.

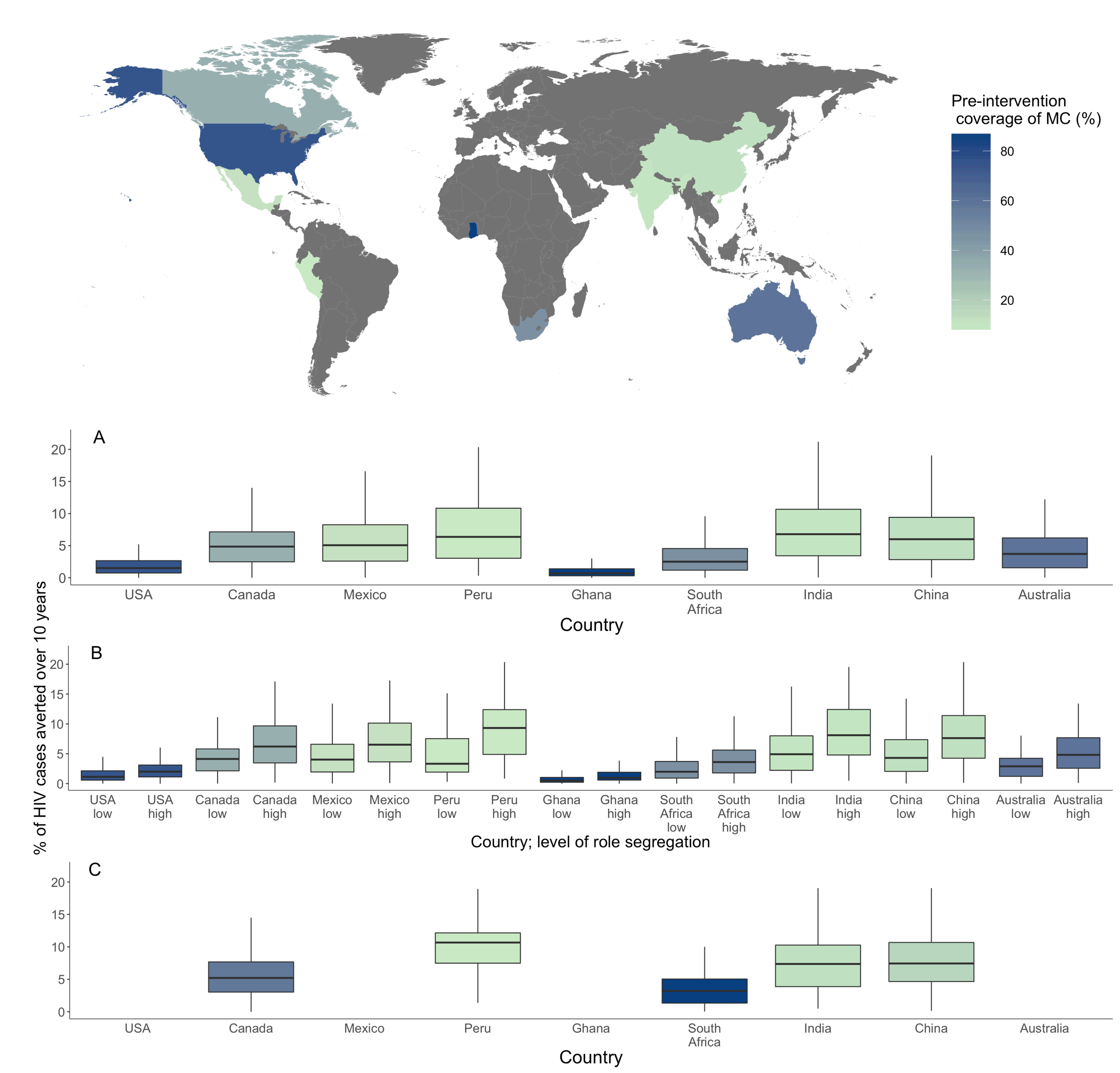

Figure 4: World map showing the pre-intervention coverage of male circumcision in each country modelled Panels A-C) show the % of new HIV cases averted over 10 years among all MSM achieved by circumcising 50% of uninfected Tops over the course of five years. Results are shown for step i) ii) and iii) of our analysis. **Boxplots:** (medians, quartiles and 95-percentile ranges) are colour-coded by pre-intervention coverage or male circumcision as indicated on the map, where model is fitted to country-specific data for A): Pre-intervention prevalence of HIV and coverage of male circumcision (step i); B): as above, but stratified by level of role segregation (where low/high refers to Tops taking preferred role in </> 80% of partnerships) (step ii); C): Country-specific estimates achieved by fitting to sexual role preference and condom use) step iii).

Country specific analysis – step ii)

When each of the country-specific estimates was stratified by role segregation, the difference in the predicted impact of VMMC was negligible in countries with a high pre-intervention level of male circumcision. However, in countries with lower levels of pre-intervention circumcision (<70%) the impact of VMMC was increased if a high level of role segregation was assumed (Tops taking an insertive role in >80% of partnerships), compared to a low level of role segregation (Tops taking an insertive role in 50%-80% of partnerships). The difference in impact was most pronounced in countries with the lowest level of pre-intervention male circumcision (e.g. Peru and India) where circumcising 50% of Tops if there is low role segregation saw impact of 3% [95% CI 0%-14%] compared to 9% [95% CI 1%-19%] if there is a high level of role segregation.

Country specific analysis – step iii)

The countries where additional data on condom use and role segregation was available were Canada, Peru, South Africa, India and China. The additional information resulted in a revision of the impact of VMMC in Peru where the impact of circumcising 50% of Tops was revised from 6% to 11% [95% CI 2%-19%], and in China, where equivalent impact estimates were increased from 6% to 8% [95% CI 1%-17%]. The impact estimates for the other countries for which additional data was available remained broadly unchanged from the analysis in step i.

Conclusions

VMMC among MSM is likely to have the greatest impact in highly role-segregated settings with low circumcision coverage, such as Peru or India. However, the public health benefits among MSM would likely be modest and slow to accumulate. The intervention is unlikely to avert more than 19% of infections even in the most favorable settings under realistically achievable intervention coverage of 50%, given that not all men would be willing to undergo VMMC.

The level of uncertainty around role segregation in MSM populations worldwide, and the lack of information available for the countries we considered is a major problem when assessing the impact of a VMMC intervention, as can be seen by comparing the difference in results between Figures 4A and 4C. Further work to determine this information is necessary to inform conclusions.

References

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