Replication research proposal

Original paper selected for replication:

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

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Abstract

There is an urgent and continuing need to identify cost-effective and practical interventions to prevent HIV transmission. Three recent studies have found that male circumcision can significantly reduce HIV incidence in men. These results opened an enormous potential intervention for HIV prevention in African countries. We propose to replicate one of the studies conducted in Kisumu, Kenya, to shed additional light on the relationship between circumcision status and HIV infection, and influence the policy trajectory. We will use the raw data and replicate methods used to produce the results presented in the published report, as well as employing methodologic modifications to include additional epidemiologic approaches and econometric approaches.

1. Reasons for replication

HIV/AIDS poses an unprecedented development and human challenge, especially in sub-Saharan Africa. In many countries, the epidemic has cut life expectancy and robbed society of millions of people in their prime working years. It has dimmed the hope of living full and productive lives for unimaginable numbers of people. 34.0 million [31.4 million–35.9 million] people were living with HIV at the end of 2011. An estimated 23.46 million people (69% of the total global seropositive population) are living with the disease in sub-Saharan Africa (UNAIDS, 2012).

The impact of HIV prevention methods is mixed. Although behavioral interventions including social and behavior change communication, HIV testing and counseling (HTC), and HIV care and treatment & ART have led to declines in HIV prevalence and incidence in several African countries, HIV prevalence remains extremely high in many parts of African countries ((((Cohen et al., 2011); (Granich et al., 2010); (Buchbinder & Liu, 2011); (UNAIDS, 2012)). Therefore there is an urgent continuing need to identify cost-effective and practical interventions to prevent HIV transmission. During the last decade, three studies found that medical male circumcision (MMC) was effective in reducing HIV acquisition ((Auvert et al., 2005); (Bailey et al., 2007); (Gray et al., 2007)). These three studies were so influential that they led WHO and UNAIDS in March 2007 to recommend male circumcision as an efficacious intervention for the prevention of heterosexually acquired HIV infection in men (WHO & UNAIDS, 2007). WHO and UNAIDS justified their recommendation by the existence of compelling evidence that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%. In addition, WHO/UNAIDS emphasized that male circumcision should be considered an

efficacious intervention for HIV prevention in countries and regions with heterosexual epidemics, high HIV and low male circumcision prevalence. Consequently, 13 countries where male circumcision should be promoted and scaled up were selected as priority countries. These countries include Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, the United Republic of Tanzania, Zambia, and Zimbabwe. Although the goal is to circumcise 20.34 million men by 2015 in order to have a high epidemiologic impact and avert 3.36 million new HIV infections through 2025 (Njeuhmeli et al., 2011), as of March 2012, only 1,535,577 men had been circumcised in 14 priority countries (AVAC, NEPHAK, & SONKE).[1] (Njeuhmeli et al., 2011) found that the scale-up of male circumcision would cost a total of US$2 billion between 2011 and 2025, and would result a net savings (due to averted treatment and care costs) amounting to US$16.51 billion. The intervention of medical male circumcision therefore shows clear potential for a major impact in reducing HIV transmission and the associated human and economic costs. The importance of the effort to prevent HIV/AIDS, and the magnitude of effort required to scale up any evidence-based intervention, underscore the importance of carefully reviewing, understanding, and confirming the study results.

Two main reasons motivate the replication of one of three studies. First, it appears clear that the three studies showing the impact of male circumcision on HIV acquisition have been and continue to be influential. These studies have significantly shaped HIV prevention in Africa, given that male circumcision is the only intervention that can be entirely completed at a single timepoint and that significantly reduces HIV acquisition for men. Second, given that the original analysis of the three studies was based on epidemiological approaches, we can make a valuable

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[1] In addition to the 13 priority countries identified by WHO and UNAIDS, The Gambella National Regional State in Ethiopia was included later in the list of priority country because The United States President's Emergency Plan for AIDS Relief (PEPFAR) is supporting activities to implement VMMC program there, where MC prevalence is low and HIV prevalence is three times the national average. Thus, to date, there are 14 priority countries.

contribution to understanding by examining the same data using an econometric approach. By replicating one of the three studies we will be able to shed additional light on the relationship between male circumcision and HIV acquisition among men, and influence the policy trajectory of the role of male circumcision in HIV prevention. The choice of one of the three studies that we will replicate was based on the fact that we were able to have access to data for this study.

2. Study presentation and remarks

(Bailey et al., 2007) evaluated the impact of male circumcision on HIV-1 acquisition. The authors randomly assigned 2784 men aged 18-24 years in an intervention group (circumcision; n=1391) and a control group (delayed circumcision, n=1393). The enrollment of participants in the study went from Feb 4, 2002 to Sept 6, 2005. Since the study was stopped early (on December 12, 2006), some participants (both intervention and control) completed less than the expected 24 month follow-up period. While the level of exposure to the treatment might affect its impact on HIV-1 acquisition, the early stopping of the study would be expected to balance this effect between intervention and control groups. Participants in both the intervention and control groups were assessed by HIV testing, medical examinations and behavioral interviews during follow-ups at 1, 3, 6, 12, 18 and 24 months. Follow-up was identical for both intervention arms, with the exception of postcircumcision visits for the circumcised men at 3, 8, and 30 days to check the wound. During these visits, clinicians recorded any complications, asked about sexual activity, level of pain, resumption of normal activities, satisfaction with the procedure, and counseled participants to not have sexual activities for at least 30 days after the circumcision. Participants in the control group were not exposed to these activities.

Three interim analyses were done. The first analysis was conducted with about 37% of the follow-up experience accrued, the second with 74% of the follow-up experience accrued and the

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third with about 87% of the follow-up experience accrued. The final analyses were done by intention-to-treat where participants were included in the analysis in the group to which they were randomly assigned, and all participants with follow-up for HIV status were included in the analysis. The primary analysis to determine the impact of male circumcision on HIV seroincidence was an unadjusted Kaplan Meier analysis. Furthermore, in an as-treated analysis, the impact of male circumcision was estimated through Cox regression models where a time-dependent covariate for the circumcision status of each participant at each follow-up visit was included as a time-dependent predictor variable in the model. The estimated impact of male circumcision through Cox regression was adjusted for baseline variables for which there were a difference between the two study groups and other features of the study. The baseline variables which were unbalanced include ethnic group, occupation, infection with herpes simplex virus type 2, and infection with *Chlamydia trachomatis*. The authors did not present any formal assessment of the proportional hazards assumption for Cox models (i.e. the assumption that the hazard ratio, comparing intervention to control group, is constant throughout study follow-up time), although Figure 2 seems supportive of this assumption.

In addition to these analyses, the authors used the generalized estimating equations (GEEs) extension of generalized linear models proposed by Liang and Zeger to estimate the impact of male circumcision on behavioral outcomes including unprotected sexual intercourse with any partner in previous 6 months, last time had sexual relations with a casual partner, sexual abstinence in previous 6 months, consistent condom use in previous 6 months, and two or more partners in previous 6 months. GEE models are able to accommodate correlated data, in which variables measured repeatedly through time are expected to be correlated with each other in some way within individuals. GEE models can obtain a consistent and unbiased estimation of

parameters' standard errors even when the correlation structure (i.e. the strength of correlations that are assumed to exist between various specific measurements) is misspecified. Nevertheless, the choice of correlation structure to specify between measurements at any two follow-up times should be based on substantive reasons whenever possible, and sensitivity analyses are recommended to compare the results obtained when specifying different correlation structures (Wang & Carey, 2003; Zorn, 2001). The authors specified the working correlation between measurements at any two follow-up times as constant. The selection criterion for this choice was not discussed, and an important element of our reanalysis will be to assess robustness of results by considering different working correlation structures.

3. Main results and remarks

The authors found that the treatment group and the control group were much the same in most of the baseline variables. The treatment groups were also similar in terms of the timing of the follow-ups visits. HIV status was incomplete for 240 participants: 126 in the treatment group and 114 in the control group. The authors found that these 240 participants were different from the rest of the 2544 participants in terms of secondary education and were much the same for other observables. However, the authors did not present an assessment of baseline differences between the 126 participants in the treatment group and 114 in the control group with incomplete HIV status. Indeed, it is not very clear how the authors dealt with missing data in applying the ITT analysis. When performing an ITT analysis, primary outcome data should be available for as many trial participants as possible (Sainani, 2010). In this replication, we propose to conduct a sensitivity analysis by using several different approaches for handling missing data and compare the results.

The authors found that the 2-year HIV incidence was 2.1% in the circumcision group and 4.2% in the control group. Thus, the risk ratio (RR) of HIV acquisition in the circumcision group compared with the control group was 0.47. This corresponds to a reduction in the risk of acquiring an HIV infection in the circumcision group of 53%. Excluding from the analysis three participants who were originally judged to be HIV positive at month 1 but were found to be positive at baseline and one participant who were originally judged to be HIV negative at month 6 but was found to be HIV positive at baseline, the 2-year HIV incidence in the circumcision group was 1.9% versus 4.1%. This corresponds to a reduction in the risk of HIV among circumcised men of 59%. Furthermore, in the as-treated analysis which adjusted for individuals who did not adhere to the randomization assignment, the authors found that the RR for male circumcision was 0.40, corresponding to a 60% protective effect of circumcision. The authors evaluated heterogeneous treatment effects by age group (ages 18-20 and 21-24 years). They found that the results were consistent with the overall results and there were no significant differences between the age groups in 2-year HIV incidence.

The authors did not present results for analyses of heterogeneous treatment effects for other individual characteristics at baseline. However, risky sexual behavior (possibly related to risk compensation among men in the group receiving circumcision) may be an important modifier of the treatment effect, and in our analysis we will therefore evaluate heterogeneous treatment effects by risky sexual behavior. Potential risk compensation due to male circumcision was one of the barriers mentioned by participants in acceptability studies undertaken in nine countries. The main reason is that if men and their partners believe that circumcision offers protection from HIV infection, they may be more likely to engage in behaviors with higher risk for HIV infection, thereby mitigating a partially protective effect of male circumcision

(Westercamp & Bailey, 2007; Herman-Roloff et al. 2011). Consequently, it is plausible that individuals having high risk sexual behavior at baseline may be more likely to exhibit risk compensation behavior, possibly mitigating a stronger protective impact of male circumcision in this subgroup.

Therefore, one important aspect of our reanalysis will be to assess the impact of male circumcision in individuals who do or do not engage in risky sexual behaviors at baseline. Following Chinkhumba et al. (2012) and using baseline data, we will construct a dichotomous risky sexual behavior variable. Individuals who practice safe sex and who have low risk sexual behavior (sexual abstinence in previous 6 months or consistent condom use in previous 6 months) will be coded 0, and other individuals who practice risky sex (unprotected sexual intercourse with any partner in previous 6 months or last time had sexual relations with a casual partner, or two or more partners in previous 6 months) will be coded 1.

The authors analyzed the impact of male circumcision on behavioral variables by treatment at baseline, month 6, month 12, month 18, and month 24. They found that in general, there were decreasing proportions of men reporting risky sexual behaviors over time in both the treatment group and the control group. Although this reduction of risky sexual behaviors was significantly greater for the control group than the treatment group, the authors claimed that there was no risk compensation associated with male circumcision by arguing that the difference between the two groups were attributable to an increase in safer sexual practices in the control group rather to a change in risky sexual behaviors patterns in the circumcision group. In fact, there is strong evidence of risk compensation. Specially, for four of five behavioral outcomes, the proportion of men engaging in risky sexual behaviors was significantly higher for treatment group than the control group. Although the reduction of risky sexual behaviors in the treatment

groups indicate that the initial behavioral counseling and voluntary HIV testing offered to the participants were effective as mentioned by the authors, the fact that this reduction was higher in the control group than the treatment group suggests that in this study male circumcision may lead to risk compensation. Thus, given the potential existence of risk compensation, it will be important to check robustness of the impact of male circumcision on behavioral outcomes using different methods of estimation.

4. Replication plan

We are aiming to conduct a pure replication of the original study and then move on to measurement and estimation analysis by mainly applying the econometric approach for analyses.[2] We will make every effort to resolve any discrepancies that arise, through analysis and communication with the original authors; and in the event that discrepancies persist in our results, we will make every effort to understand the sources of the discrepancies.

4.1 Pure replication

The aim of the pure replication is to re-conduct the original analyses, using data provided by the authors. The rationale for doing this is that discrepancies can arise in statistical analyses, stemming from different decisions made in regard to construction of variables needed for the

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[2]3ie Replication Typology describes three types of replication: pure replication (PR), measurement and estimation analysis (MEA), and theory of change analysis (TCA). . " PR includes reconstructing the estimation variables, writing and running new programs for the estimations, and auditing the original data manipulation and estimation code, particularly when the new estimation results differ substantively from the originals" and "MEA beyond PR to further test the robustness of the original findings beyond the robustness checks employed in the original article. In MEA, replication researchers examine the empirical methods by redefining the variables of interest, introducing additional control variables, using alternative estimation techniques, and/or implementing other redefinition strategies within the research"(3ie Replication Typology, 2013).

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analysis including case definition, follow-up time, inclusion and exclusion criteria. We have obtained the raw data from the completed study, and will conduct a new analysis using the raw data in order to make a direct comparison with the published study results. We will construct all variables required for the pure replication using the raw data obtained from the authors. For the pure replication, we will conduct analyses mirroring the analyses the authors conducted to produce the results presented in the study. In addition to this work, we will conduct additional analyses detailed in Section 4.2, Measurement and Estimation Analysis. Specifically, for the pure replication, we will reproduce Table 1 (Baseline characteristics), Table 2 (Incidence rates for intervals of follow-up), Table 3 (Adverse events recorded by severity and relatedness to the surgery), and Table 4 (Sexual history with women reported at baseline and follow-up visits). Furthermore, we will reproduce Figure 2 (cumulative HIV seroincidence across follow-up visits by treatment). Figure 1 is the trial profile presenting the number of men registered at the clinic, the number of men assigned in the treatment group and the control group, the number of loss of follow-up at month 1, month 3, month 6, month 12, month 18, and month 24. In addition to reproducing tables presented in the paper, we will replicate the authors' secondary analysis, using a Kaplan Meier analysis taking into account noncompliance, false inclusions, crossover, and nonadherence. We will also conduct the as-treated analysis to adjust for individuals who did not adhere to the randomization assignment. In the same vein, using the as-treated analysis and Cox regression models, we will adjust for baseline variables for which there were differences between the two study groups at baseline. The aim of these analyses is to obtain the other results presented in the paper. Lastly, we will estimate the heterogeneous treatment effects within age strata (ages 18–20 and 21–24 years).

4.2 Measurement and Estimation Analysis

For the measurement and estimation analysis, we will take an approach differing in several respects from the approach described in the published manuscript. The main differences between our planned analyses and those presented in the published manuscript are summarized in the following table.

Table 1. Summary of changes in proposed **measurement and estimation analysis**

	Approach presented in published manuscript	Our planned approach
Intent-to-treat analysis	The authors employed the Kaplan-Meier method to conduct intent-to-treat analyses.	We will fit generalized estimating equation (GEE) models for intent-to-treat analyses, in order to incorporate time-varying behavioral covariates (risky sexual behavior)
Correlation structure for GEE models	The authors employed a constant working correlation between measurements at any two follow-up points.	We will test several different correlation structures to evaluate model fit. Possible working correlation structures include unstructured, independent, compound symmetry, and autoregressive.
Proportional hazards assumption	The authors did not specify whether they evaluated the proportional hazards assumption in the Cox regression model.	We will employ Cox regression models to conduct an as-treated analysis, and we will evaluate the proportional hazards assumption to test whether the hazard ratio varies during follow-up time. If so, we will include an (intervention group x time) interaction term in the model.
Econometric analysis	The authors did not conduct any econometric analysis.	We will estimate fixed effects models for our main outcome and behavioral variables in order to control for invariant individual unobserved heterogeneity. Furthermore, we will conduct the treatment

		on the treated analysis using an instrumental variables approach. Specially, we will instrument the variable surgery (the surgery is 1 for those who got the surgery and 0 otherwise) by the random assignment of participants to the trial.
Heterogeneous treatment effects by age	The authors evaluated heterogeneous treatment effects by age (18-20 versus 21-24 years) by intent-to-treat analysis	We will evaluate heterogeneous treatment effects by age using an econometric approach (least squares estimation and fixed effects model).

In Cox proportional hazards models to conduct time-to-event analyses of HIV seroconversion, a major assumption of the model is that the hazard ratio is constant across follow-up time. We will evaluate this proportional hazard assumption by testing the intervention*time interaction term, which will be statistically significant if the hazard ratio (comparing hazard of HIV seroconversion in intervention versus control group) is not constant over follow-up time. If the assumption of the proportional hazard is not verified, we will retain the intervention*time interaction term in the model. As noted above, some variables were imbalanced at baseline, and the authors adjusted for this in the as-treated analyses. In our reanalysis, we will adjust for this imbalance in intent-to-treat analyses in addition to the as-treated analysis. Thus, in our intent to treat analysis, we will use Cox regression models and we will include in the model variables which were imbalanced at the baseline. In addition, as described above, an ITT analysis should include as many participants as possible with primary outcome data. We will use methods including Cox models and GEE models which are able to include

participants with partially missing data. In addition, we will conduct a sensitivity analysis to evaluate how different the missing participants would have to be, in order to have introduced bias producing the observed results. To accomplish this sensitivity analysis, we will begin with the actual study results, which showed a significant benefit in the circumcised group. By making progressively more extreme hypothetical assumptions about opposing results that theoretically could have been found in individuals with missing data, we will determine 1) whether different unobserved results in this group could be mathematically capable of attenuating the observed hazard ratios to a non-significant association, and 2) if so, how different the group with missing data would need to be for this to occur. These analyses will provide important information regarding the robustness of our results.

Despite the limitations of the original study raised above and the indication of how this will be addressed in this replication, it is important to emphasize that the approach adopted by the authors is a standard approach used in epidemiology. Thus, the application of the econometric approach for analyses in this statistical replication aims only to assess the robustness of results using a different approach. The application of the econometric approach is not meant to imply that the approach used by the authors is not appropriate. Therefore, in the second part of the statistical replication, we will apply the econometric approach for analyses.

Given that men were followed at month 1, month 3, month 6, month 12, month 18, and month 24, we will arrange data for month 6, month 12, month 18 and month 24 in order to have panel data structure with two dimensions, namely time and individual. Taking advantage of this panel structure of data, we will be able to control for individual fixed effects. Since participants were randomly assigned to the treatment or control group, we do not expect group differences at baseline. However, the panel structure of data provides us the possibility to control for individual

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fixed effects to see whether results are robust. We will conduct intent to treat analysis by using a fixed effects model and the treatment on the treated analysis using instrumental variables approach. Specially, we will instrument the variable surgery (the surgery is 1 for those who got the surgery and 0 otherwise) by the random assignment of participants to the trial. In addition, we will conduct intent to treat analysis and the treatment on the treated analysis using instrumental variables approach by adjusting for variables which were imbalanced at the baseline.

For the behavioral outcomes, we will use a different perspective to evaluate risk compensation. Instead of comparing differences in risky behaviors between treatment and control groups at different follow-up visit timepoints, we will take advantage of the panel structure of the data to control for individual fixed effects in order to analyze the impact of male circumcision on risk behaviors for the whole trial.

4.3 Additional analyses

Study participants in the treatment group were advised to abstain from sexual activity for at least 30 days post circumcision; in addition, they interacted with clinicians during post-circumcision visits. These could be considered a different treatment in addition to male circumcision. Thus, we will conduct the same analyses as those mentioned above for the statistical replication, with additional control for this "additional treatment". Since postcircumcision visits were scheduled for 3, 8, and 30 days to check the wound, all circumcision men should normally have carried out three visits 30 days after circumcision; however, not all circumcised men complied with this requirement. For "additional treatment", we will construct a variable which gives the number of visits carried out for each circumcised men. This variable will capture all interactions that circumcised men had with the clinician, and that can impact the outcomes of the study. Furthermore, given that enrollment of study participants occurred from

Feb 4, 2002 to Sept 6, 2005, we will construct a variable measuring the months of exposure to the treatment, in order to assess the impact of male circumcision for each additional month of exposure, and more importantly whether this has changed over time. Lastly, we will estimate heterogeneous treatment effects of male circumcision for individuals with high risk sexual behaviors and individuals with low risk sexual behaviors. For the heterogeneous treatment effects, we will conduct ITT analysis and the as-treated analysis using an epidemiologic approach, and ITT analysis and the treatment on the treated analysis using an econometric approach, with adjustment and without adjustment for variables which were imbalanced between the two groups at baseline.

5. Conclusion

In this study, we propose to replicate one of the three studies that led to the scale up of male circumcision in Eastern and Southern Africa. We propose to conduct a pure replication with the aim to reproduce and reconcile the findings published in the original study. In addition to a pure replication, we will conduct measurement and estimation analysis. In our measurement and estimation analysis, after testing the proportional hazard assumption; we will conduct ITT analysis and the as-treated analysis with adjustment and without adjustment for variables which were imbalanced between the two groups at baseline. We will also conduct sensitivity analysis for our ITT analysis. Moreover, taking advantage of the panel structure of the data, we will apply an econometric approach to assess the robustness of the main study results. Lastly, we will estimate heterogeneous treatment effects of male circumcision for individuals with high risk versus low risk sexual behaviors using an ITT analysis, an as-treated analysis, and an econometric approach.

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