Male Circumcision and HIV Prevention
Insufficient Evidence and Neglected External Validity

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Background

Recent editorials have asked the global health community to scale up male circumcision for HIV prevention in regions with HIV epidemics following the publication of three randomized controlled clinical trials (RCCTs) in Africa (in South Africa, Uganda, and Kenya).[1–5] One editorial concluded: "The proven efficacy of MC [male circumcision] and its high cost-effectiveness in the face of a persistent heterosexual HIV epidemic argues overwhelmingly for its immediate and rapid adoption."[6] This "Current Issue" review questions not the internal validity of the studies, but their external validity, an issue that has been discussed more generally in two commentaries,[7,8] an editorial,[9] and a systematic review of research on prevention trials[10] in this journal. External validity is the issue that questions the generalization from the RCCT results to a policy of "immediate and rapid adoption" of circumcision of men across Africa.

Five dimensions of external validity should be weighed before the global health community can determine that male circumcision is a widely effective, cost-effective, or cost-beneficial use of resources, as well as an effective and safe method for controlling the HIV epidemic in Africa. These trials provide a case illustration of how a policy might be adopted without due consideration of external validity in experimental trials that appear to have established internal validity for a short-term reduced risk of infection.

General Population Correlates

Effectiveness in real-world settings rarely achieves the efficacy levels found in controlled trials, making predictions of subsequent cost-effectiveness and population-health benefits less reliable. The following related concerns deserve further scrutiny:

1. The three RCCTs were terminated early because results had reached significance showing reduced HIV infections in experimental compared with control groups; however, it was too soon to gauge long-term effectiveness.
2. The results have no relevance for women or for men who have sex with men.
3. Far more participants were lost to follow-up than were reported to have contracted HIV.
4. A substantial number of participants appeared to have contracted HIV from nonsexual sources: 23 of the 69 infections reported in the South African trial and 16 of the 67 in the Ugandan study.[11]
5. Participants received continuous counseling, free condoms, and monitoring for infection, which was unlikely in real-world campaigns.
6. The sanitary conditions of the surgeries would be difficult to replicate on a mass scale in many parts of Africa where HIV infection rates and prevalence are highest.

Correlation between HIV prevalence and male circumcision prevalence in observational studies[12,13] is inconclusive. Substantial evidence contradicts the RCCTs' results and suggests that real-world population benefits from male circumcision might be minimal:

1. An analysis[14] of HIV prevalence compared to circumcision status in sub-Saharan Africa concluded that male circumcision is *not* associated with reduced HIV prevalence.
2. Another study[15] on circumcision prevalence compared to HIV in the general South African population concluded: "Circumcision had no protective effect on HIV transmission."
3. When commercial sex worker patterns are controlled, male circumcision is not significantly associated with lower HIV prevalence.[16]
4. Mathematical impact modeling of circumcision, antiretroviral therapy (ART), and condom use for South Africa concluded: "Male circumcision was found to have considerably lower impact than condom use or anti-retroviral therapy on HIV infection rates and death rates."[17]
5. Both the U.S. and sub-Saharan Africa have relatively high incidence rates of HIV infection, considering that

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about 75% of U.S. men and about 70% of sub-Saharan African men are circumcised—higher percentages than in most other regions or countries with lower prevalence of HIV (Demographic and Health Surveys, www.measuredhs.com).

Therefore, although the *efficacy* of using male circumcision in reducing HIV infections was significant within the strict circumstances of the three trials, taken to scale under the very different prevailing circumstances of Africa, their *effectiveness* cannot be generalized.

Follow-up data from the Kenyan RCCT[18] reported the protective effect of male circumcision as extending at least 3.5 years. More comprehensive follow-up of any of these RCCTs is impossible. Study participants agreed to be circumcised when joining the study and were randomized into "circumcise now" and "circumcise later" groups. When the studies were halted early, the uncircumcised men were offered circumcision. In the Kenyan study, during follow-up, 38% of the control group asked to be circumcised, but some of them, and others, were lost to follow-up.

Increased Risk to Women

A recent prospective study[19] showed that male circumcision offered no protection to women, and an RCCT[20] found that male circumcision actually increased the risk to women, presumably because they resumed sex before their circumcised male partner's open wound had healed. A 2008 WHO study[21] found that 24% of ritual circumcisions and 19% of clinical circumcisions had not healed 60 days postsurgery.

Women also are placed at greater risk from unsafe sex practices when they, or their circumcised male partners, wrongly believe that with circumcision they are immune to HIV and therefore they choose not to use condoms.[22,23] An underlying issue is that male circumcision programs do not reduce the risk of infection among women or men who have receptive sex with men. Public health officials must take into consideration the often high levels of sexual abuse of women and children where male circumcision is being advocated.[24,25] Hence, there are legitimate concerns about: (1) how male circumcision programs, or being circumcised, will influence human behavior; (2) the sidelining of women when considering male circumcision as a prevention method; and (3) the tendency of both men and women to ascribe undue power to a technical fix for what must remain a matter of human control, as in the use of condoms and other safe sex practices.

Substantial Complications of Male Circumcision

Traditional circumcisions increase HIV transmission risk because of contaminated equipment.[26] A 2008 WHO bulletin[21] reports that 35% of traditional male circumcisions in Africa result in complications, as do 18% of clinical circumcisions. Among all clinical neonatal circumcisions in Africa, 20.2% result in complications.[27] The RCCTs themselves reported unacceptable levels of complication, even though these trials were conducted under optimal conditions. For example, the Ugandan trial[3] reported a total of 22 HIV infections in the circumcised group, and 45 in the control group, yet it had 178 adverse events in 2328 surgeries—complications in 8%, or four times more complications than the HIV infections that *might* have been prevented or delayed through circumcision. Of these complications, 94 were judged as mild, with 79 complications considered moderate and five classified as severe. A mild case of swelling or bleeding cannot compare to the ramifications of an HIV infection, but circumcision, like all surgeries, entails the rare possibility of severe, life-threatening complications. Even a small number of severe complications must give pause to consider ramifications of mass surgical campaigns. Likely higher rates of complications with the mass circumcision campaigns could overwhelm the healthcare infrastructure and may negate any protective effect that male circumcision might have.

Cost–Benefit Considerations

Before circumcising millions of men in regions with high prevalences of HIV infection, it is important to consider alternatives. A comparison[28] of male circumcision to condom use concluded that supplying free condoms is 95 times more cost effective. This mathematical modeling analysis, presented at the 2009 International AIDS Society, revealed the cost effectiveness of male circumcision to be a distant third compared to condom use or ART. The mathematical analysis showed that increasing both condom use and ART to 50% would result in 700,000 fewer infections, whereas raising the level of circumcision from the current 51% to 90% would add only 48,000 more infections averted to this total. Condom use and ART coverage, alone or in combination, were found[17] to reduce new HIV infections by 64% to 95% by 2025 and to reduce mortality by 10% to 34%. Circumcision would bring about a 3% to 13% reduction in new HIV infections and a 2% to 4% reduction in mortality.

Ethical Issues Unresolved

Male circumcision constitutes the removal of healthy, functional, and biologically unique tissue.[29] For fully informed consent to occur, men must be educated about the risks and sensory losses from circumcision, as well as made aware that circumcision does not offer full protection. Further, any shift from condom use to reliance on circumcision for HIV prevention places men and their partners at increased risk of HIV infec-

tion. Published research[30,31] has delved into the association of microbicide use with less consistent condom use (condom migration). Evidence on the level of condom migration that has resulted from circumcision promotion is lacking; however, the content of reports[32] of African men agreeing to circumcision under the belief that they no longer need to use condoms suggest that many are consenting to surgery without being fully informed of incomplete protection. These reports raise concerns about high levels of condom migration if this intervention is adopted on a wide scale.

Any promotion of newborn circumcision for the prevention of HIV requires additional ethical consideration. Elevated cortisol levels, prolonged high-pitched crying, elevated blood pressures, changes in heart and respiratory rates, and the deep sleep (non–rapid eye movement) that many infants fall into after circumcision, are all markers of intense pain.[33–35] Although there clearly would be no HIV prevention benefit to newborns for at least 15–20 years, if at all, performing circumcisions places newborns at immediate risk of infection (including HIV), plus hemorrhage, penile damage, and even death.[36,37]

Ethical analysis of medical procedures and interventions can be weighed against four accepted bioethical criteria: (1) autonomy; (2) beneficence; (3) nonmaleficence; and (4) justice.[38] An analysis of these bioethical criteria needs to precede any mass circumcision campaign, either for adults or for children.

Because circumcision is a multibillion-dollar business and an ingrained part of American medical tradition, it is reasonable to raise the issue of cultural bias on the part of some researchers. A Cochrane Review[39] cautioned: "Circumcision practices are largely culturally determined, so there are strong beliefs and opinions surrounding them. It is important to acknowledge that researchers' personal biases and dominant circumcision practices of their respective countries may influence interpretation of findings." Ethics reviews of using male circumcision as an HIV prevention tool should be as free as possible from cultural bias regarding male circumcision.

Conclusion

Recommending mass circumcision by generalizing from the particular RCCTs to the diverse populations of Africa highlights problems of external validity identified in several areas of preventive medicine and public health research. Studies published since the RCCTs show that (1) male circumcision is not correlated with lower HIV prevalence in some sub-Saharan populations[14,15]; (2) circumcision is correlated with increased transmission of HIV to women[20]; and (3) male circumcision is not a cost-effective strategy.[17,28] This new evidence warrants caution and further study before recommending circumcision campaigns. In addition, ethical considerations, informed consent issues, and possible increase in unsafe sexual practices from a sense of immunity without condoms must be weighed.

The global health community understands that the most important modifiable factor in sexually transmissible HIV is human behavior.[40] The policy questions to be considered are not whether a link exists between male circumcision and reduced rates of HIV infection, but, rather, whether mass circumcision is (1) an ethical and safe public health choice, and (2) the most cost-effective use of limited resources.

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Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amepre.2010.07.010.

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Male Circumcision As a Component of Human Immunodeficiency Virus Prevention

To the Editor: A paper by Green et al.[1] questions the external validity of the three RCTs of medical male circumcision for HIV prevention, all of which reported 50%–60% reduction of HIV acquisition in heterosexual circumcised men. The trials differed in the age of participants, background HIV incidence, and surgical techniques, and it is very encouraging that they achieved such similar results. Here, we address the key points from that paper:

The authors note that the effectiveness of interventions in real-world settings rarely achieves the efficacy found in RCTs. However, the most comprehensive meta-analysis conducted to date of real-world observational studies concluded that male circumcision was associated with a 50%–60% reduction in HIV risk,[2] consistent with the trial data. Indeed, the majority of observational and ecologic studies support reduced risk of HIV with male circumcision.[2–4]

Green and colleagues[1] criticize the early closure of the trials, but evidence of efficacy reached predetermined stopping rules of statistical significance at interim analyses in all three studies, and continuation would have been unethical. The Kisumu[5] and Rakai[6] trials have maintained post-RCT follow-up, with evidence of continued long-term effectiveness.

Disappointingly, male circumcision of HIV-positive men did not reduce HIV transmission to women over a period of 2 years in an RCT in Rakai, and we observed a higher rate of transmission in couples who initiated intercourse before completed wound healing, but not in those who delayed until healing was complete.[7] However, if fewer men acquire HIV as a consequence of male circumcision, this will benefit women by reducing exposure to HIV-infected men. Male circumcision also reduced vaginal infections, genital ulceration, and human papillomavirus in female partners of men randomized to male circumcision,[8,9] and thus the procedure is of substantial relevance to women.

We agree, as does the WHO,[10] that male circumcision programs require resources to ensure trained providers and adequate facilities to offer safe surgery. It is misleading for Green et al.[1] to cite complication rates from traditional procedures or from earlier clinical observations: Clinicians were often inadequately trained in adult male circumcision, which was generally performed because of antecedent penile pathology, thus increasing complication rates.

Male circumcision services can and should serve as a gateway to a range of male reproductive health and HIV-prevention services, including risk-reduction counseling, condom promotion, HIV counseling and testing, and treatment of sexually transmitted infections. Operations research is ongoing to optimize feasible, replicable, and safe male circumcision programs. Male circumcision is a once-in-a-lifetime procedure, and modeling, not cited by Green et al.,[1] suggests that it will be cost effective for HIV prevention.[11]

Finally, we agree with Green et al.[1] that provision of male circumcision must adhere to the highest standards of informed consent and ethics. One can argue that it is unethical not to offer heterosexual men at risk of HIV the option of voluntary, safe circumcision.

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Author Response

The primary intent of our article[1] was not to challenge the 50%–60% results obtained by the three RCCTs conducted to evaluate the efficacy of male circumcision at reducing HIV transmission. Rather, it was to challenge the public health benefit of extrapolating these results to general populations in real-world settings. Mass circumcision campaigns, both planned and underway, involve investing billions of dollars, as well as placing millions of males at risk for surgical complications,[2] placing female partners at greater risk of HIV infection,[3] and posing a myriad of informed consent and related ethical issues surrounding mass prophylactic surgical campaigns. Compared with other prevention measures such as (1) providing sterile medical equipment and needles, (2) abstinence, (3) condoms, (4) secondary prevention with anti-retroviral treatments, and (5) aggressive surveillance and treatment of sexually transmitted infections, male circumcision is neither efficacious nor ethical.

Wawer et al.[3] point out that follow-up on the RCCT participants show continued risk reduction. However, this is a small group of individuals who received free health care, counseling, and extensive education, again, not likely to be replicated in real-world circumcision programs. Also, this follow-up group was self-selected, because many in the control group elected to be circumcised or were lost to follow-up, which, taken together, skew results. We do not see statistically significant external validity in their follow-up.

Wawer et al.[3] contend that highly trained circumcision operators will have surgical complication rates less than the 18%–33% complication rates that WHO previously reported.[2] We assert that *no* rate of complication is acceptable when other, more effective HIV prevention methods are available that have no surgical risk. Wawer et al.[3] acknowledge that male circumcision increases the risk to female partners, yet suggest that women will have a net benefit from male circumcision. This assumption is unsubstantiated. We believe it is unethical to promote an intervention known to increase the risk of transmission to females.

Although we are most concerned with the ethical issues of nonconsensual *neonatal* circumcision, which is a policy frequently suggested in both Africa and the U.S. as a result of publicity of these trials, it is ethically important for women to know of their increased risk of HIV from circumcised men[3] and for men to be fully informed about the sensory losses of circumcision.[4] We reiterate that circumcised men will have a higher tendency to avoid using condoms, a concern that is underscored in a new article[5] and reinforced by publicity in the media that make comparisons of male circumcision to a "vaccine."[6]

Enough contradictory evidence and ethical concerns exist to warrant reconsideration in the push for mass circumcision campaigns. A number of studies challenge the value of male circumcision in the real-world settings for HIV reduction.[7–9] Further, as we cited, other studies and analysis conclude that investment in other forms of HIV-reduction campaigns, such as condom promotion[10] and anti-retrovirals,[11] have far higher rates of risk reduction, lower cost, and are free of the risks and ethical conundrums inherent in mass surgical campaigns.

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Circumcision Denialism Unfounded and Unscientific

To the Editor: Although three RCTs[1–3] and dozens of observational studies have confirmed that medical male circumcision reduces the risk of HIV acquisition in men by at least 60%,[4] Green et al.[5] continue to question its effectiveness and would deny millions of men—and their female partners—a proven, permanent, and inexpensive method to reduce their lifetime risk of HIV infection. Such denialism in the face of the ongoing pandemic are unethical and immoral.

The argument that the clinical trials of medical male circumcision lack external validity because of ideal counseling conditions and condom promotion is nonsensical because both study arms were equally exposed to those noncircumcision interventions. The concern that the effect is not durable is not supported by evidence from the Kenya trial showing that the protective effect of medical male circumcision was sustained—and actually strengthened—at 54 months of follow-up.[6] Outside of study settings, a wealth of ecologic data shows that countries with widespread male circumcision consistently have low HIV prevalence. In West Africa where nearly all men are circumcised, HIV has been circulating for more than 80 years. Yet, as is true of all countries where male circumcision is nearly universal, no country in that region has an adult HIV prevalence greater than 6%.[4]

Advocates of medical male circumcision are not arguing for—as Green et al.[5] suggest—a "shift from condom use to reliance on circumcision for HIV prevention." Medical male circumcision has been integrated into the WHO's recommended prevention package of HIV testing and counseling, treatment for sexually transmitted infections, and provision and promotion of safer sex practices, including condoms.

Medical male circumcision also benefits women. In addition to protection from *Trichomonas vaginalis*, bacterial vaginosis, herpes simplex virus, and cervical cancer, a recent meta-analysis found that "circumcision may confer a 46% reduction in the rate of HIV transmission from circumcised men to their female partner."[7] Further, the population effect, or herd immunity, means that with fewer HIV-infected men, far fewer women would be at risk.

With respect to the concern that men might engage in riskier sexual behavior after circumcision, data from the three RCTs[1–3] and a prospective cohort study[8] found no overall increases in risk behavior following circumcision. Among the Kenya RCT participants, Mattson et al.[9] found that risk behavior actually decreased over the course of 12 months. While Green et al.[5] attempt to stall efforts to scale up medical male circumcision by citing debunked arguments,[10] modeling reveals that in sub-Saharan Africa alone, widespread circumcision could avert up to 2 million new HIV infections and 300,000 deaths over the next 10 years, many of those among women.[11] The urgency has never been more apparent or the evidence more clear: Further delay is counter-productive. Deliberate misrepresentation of data, broad generalizations, and poor understanding of research methodology undermine efforts to prevent millions of premature deaths annually. It is time to mobilize sufficient resources to provide safe and widespread medical male circumcision in high-HIV-burden countries.

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Author Response

The authors of the preceding letter assert that the scientific questioning of male circumcision as a public health measure is immoral and unethical. Such a position untenably ignores the public health community's responsibility to encourage open discussion of the ethics and efficacy, as well as a thorough cost–benefit analysis of any public health intervention, especially a surgical one.

A surgically based public health measure requires ensuring that those receiving the surgery have comprehensive informed consent, including an understanding of the increased iatrogenic risks to themselves and their partners. In the case of circumcision as an HIV measure, the minimal components of adequate informed consent include information about (1) alternative HIV prevention options; (2) surgical risks; (3) sensory losses; and (4) ultimate limits of effectiveness of the procedure. A 50%–60% transmission reduction in a population engaging in high-risk behaviors ultimately is not very effective, especially when it promotes a false sense of impunity for individuals in having sex without condoms. In addition, consent requires a social environment free from coercion to undergo the procedure. A 2010 *Journal of Medical Ethics* article, thoroughly reviewing the ethics of mass circumcision for HIV prevention, concluded, "it is premature to promote circumcision as a reliable strategy for HIV prevention."[1]

There is insufficient evidence that this intervention will be effective in real-world settings at the efficacy level found in the trials or would ultimately save lives. Evidence continues to suggest that the results from the randomized trials lack external validity when extrapolated to general populations in Africa. A December 2010 study in Kisumu, Kenya (where one of the RCCTs was conducted) also showed that circumcision was not associated with reduced HIV in the general population, but was associated with inconsistent condom use, confirming a lack of external validity and concerns about secondary hazards.[2] In addition to the data we cited in our original article,[3] a 2009 publication shows that circumcision status does not generally correlate with lower HIV prevalence rates in the general population. Rather, national survey data showed that HIV was higher in circumcised males for 10 of the 18 countries in which circumcision status was tracked (Cameroon, Guinea, Haiti, Lesotho, Malawi, Niger, Rwanda, Senegal, Tanzania, and Zimbabwe).[4]

Circumcision campaigns may also undermine proven public health measures for HIV prevention through risk compensation. Banerjee's letter references highly controlled studies showing no risk compensation, which may be the result of the subjects' awareness of the attention to condom use itself (a short-lived Hawthorne effect). In contrast, reports from circumcision clinics demonstrate that newly circumcised males are abandoning condoms or have a false sense of immunity from circumcision. For example, a 2009 South African National Communication Survey on HIV/AIDS found that 15% of men and women held the mistaken belief that circumcision meant they did not need a condom.[5] Reports from circumcision clinics reveal the story of men thinking that circumcision makes sex without condoms acceptable for HIV prevention[6]; men lining up to be circumcised so that they will "no longer need condoms"[7]; and newly circumcised males bragging about their new "skoon sex" (clean sex—circumcised, no condom needed).[8] This belief was further reinforced when public health officials recently distributed materials that listed "It means that men don't have [to] use condoms" as one advantage of circumcision.[6]

Current evidence also shows that circumcision increases HIV risk to female partners of infected men,[9] an effect that would amplify the harm of reduced condom usage.

Existing evidence, summarized above, suggests that HIV prevention programs targeting high-risk behaviors using social means (e.g., increasing levels of monogamy, increasing condom use), and dealing with iatrogenic infections, will ultimately be more effective, safe, and resource-effective than circumcision as a public health intervention. We are not alone in wanting more information before recommending broad policy decisions based on limited research. The 2009 Cochrane Report requested further research to "assess the feasibility, desirability, and cost-effectiveness of implementing the procedure."[10]

From a public health perspective, it is difficult to justify promoting expenditures of scarce healthcare resources on a risky surgical procedure for HIV prevention in areas of the world that continue to lack clean water, adequate food supplies, and the most basic medical care, much less sanitary surgical conditions.

In summary, the use of circumcision as a public health measure presents many concerns:

1. Ethical questions about genital surgeries, especially when children are involved
2. Evidence of poor external validity
3. High surgical complication rates
4. HIV infection spread by circumcision
5. Misunderstandings that circumcision makes one immune to HIV
6. Reduction in condom usage
7. Increased male-to-female transmission
8. Diversion of resources from other healthcare and HIV/AIDS prevention strategies

We substantiate these concerns in our original article[3] and in our response to the Wamai letter, and they remain unaddressed by the authors of the Banerjee letter. Until these

concerns are addressed, mass surgical campaigns remain unwarranted and counterproductive to the health of the public.

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