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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.