Cut to Fit

Major studies support circumcision as prevention in Africa but a small yet vocal group argues the science is flawed. Can circumcision lower U.S. HIV rates?

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The evidence appeared overwhelming. Dozens of smaller studies conducted from the late 1980s onward suggested that circumcised men in sub-Saharan Africa were at reduced risk of acquiring HIV.

Some of the research had conflicting results, but meta-analyses supported the hypothesis that removing the male foreskin protected against HIV transmission. Eventually, there was enough data to justify three randomized controlled trials—considered the gold standard of scientific research—of more than 10,000 HIV-negative uncircumcised men in Kenya, Uganda and South Africa.

In each of the three trials, half the men were randomly selected for circumcision while the others served as a control. Each trial was halted early on ethical grounds because it was so clear that circumcised men were acquiring HIV at significantly reduced rates when compared with the control group.

The results of the studies, one of which was published in 2005 and the other two in 2007, fell neatly in line with one another. Circumcision, the researchers concluded, reduces heterosexual men's risk of HIV by about 60 percent.

"We very rarely have a circumstance where we have three trials that show you almost identical effects," says Edward Mills, PhD, an associate professor at the Interdisciplinary School of Health Sciences at the University of Ottawa, who wrote a 2008 meta-analysis of the studies. "And therefore, the inferences that we can draw from these three trials are much stronger than in virtually any other circumstance."

Jason Reed, MD, MPH, an epidemiologist in the Office of the U.S. Global AIDS Coordinator (OGAC), says of the studies' findings: "It's a remarkable level of consistency that I think other scientific interventions only wish that they had."

Indeed, in 2007 the World Health Organization (WHO) put all its weight behind ramping up voluntary medical male circumcision (VMMC) in sub-Saharan Africa. The global public health agency characterized VMMC as a highly effective method of reducing female-to-male sexual transmission of HIV—"proven beyond reasonable doubt"—and as a cost-effective means of curbing the rampant epidemic in that part of the world.

WHO, along with UNAIDS, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and other global stakeholders, established 13 countries in eastern and southern regions of the continent (PEPFAR, which is the primary funder of Africa's VMMC programs, later added the Gambela region of Ethiopia), each of which had predominantly heterosexually driven epidemics, high rates of HIV and relatively low levels of male circumcision either nationally or in specific regions. This constellation of variables invited the best bang for the buck in the scale-up of VMMC programs.

The agencies set ambitious goals for the program: to work through African ministries of health to support reaching 80 percent circumcision prevalence among 15- to 49-year-old males in the priority countries by the end of 2016. Mathematical models run in 2009 projected that 3.4 million HIV transmissions could be prevented by 2025, or a 22 percent reduction of expected new cases, as a result of such an effort.

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In the search for explanations as to why the lack of a foreskin might reduce men's risk of acquiring HIV, scientists have long theorized that Langerhans cells may play a major role. Found in abundance in the foreskin, these immune cells ordinarily would absorb and destroy a pathogen such as HIV. However, recent studies have helped hone a hypothesis that anaerobic microorganisms that thrive beneath the foreskin may give rise to inflammation, which may then cause the Langerhans cells to switch their role into that of a Trojan horse: actually carrying HIV to CD4 cells and helping establish a chronic infection. The anaerobes and inflammation may also draw CD4s to the foreskin, making them more vulnerable to direct infection.

Consequently, removing the foreskin would not only reduce the number of Langerhans cell targets, but also greatly diminish the population of inflammation-causing anaerobic microorganisms on the penis, helping protect the body against HIV.

Supporting the hypothesis that the very volume of tissue influences the foreskin's role in HIV transmission, a 2009 paper published in the journal AIDS found that the larger the foreskin, the more likely men were to acquire HIV. The top 25 percent size-wise were 2.37 times as likely to contract the virus when compared with the bottom quartile.

Such biological explanations as to circumcision's apparent health benefits tend to fade into the background in an ongoing ideological war waged by a small yet highly vocal group of dissidents fighting against the VMMC movement in Africa. Sometimes referred to as "intactivists" (as in "intact foreskin"), and largely hailing from the United States and Europe, these skeptics have

sounded a steady drumbeat of protest against what they argue is a trio of deeply flawed randomized controlled trials that have supported a waste of precious resources on a procedure many of them view as barbaric.

Indeed, the principles of VMMC overlap and at times clash with religious traditions, social and cultural norms and deeply held personal beliefs. To the loose syndicate of dissidents, the flurry of excitement and activity over VMMC is anathema. Publishing numerous, forceful articles in medical journals, they've committed to an ongoing volley with the vast scientific community supporting the VMMC scale-up abroad. Over the years, VMMC backers have responded in kind, rebutting all the dissidents' arguments and calling their attempts to discredit the science strikingly misguided, if not purposefully manipulative.

Ronald H. Gray, MD, a professor of epidemiology at Johns Hopkins Bloomberg School of Public Health, who was the lead author of the Uganda trial, says of the dissidents, "What they tend to do is cherry-pick at details in these papers."

John Potterat, a former director of STD/AIDS programs in the El Paso County Health Department in Colorado Springs, Colorado, has spent much of his retirement years stirring skepticism toward the position that sexual activity is the main driving force behind HIV transmission in sub-Saharan Africa. He calls Gray's accusation malicious and untrue—"calumny," to use his exact word.

"I've done my homework for 40 years; believe me I really know my shit, OK?" says Potterat, who, though he lacks an advanced degree, was dubbed by Malcolm Gladwell as "one of the country's leading epidemiologists" in the journalist and author's 2000 best seller The Tipping Point.

"Most of what I have read coming out of Africa can be summarized as follows: first-world researchers doing second-rate science in third-world countries," Potterat says. "Circumcising all these men in Africa is based on a useless result."

Simon Collery, a blogger, development worker and HIV advocate with a master's in education and international development from the University of London, says it is the VMMC advocates who are the cherry-pickers.

"They wanted to spend a lot of money circumcising people," says Collery, who lived in Kenya but now lives in Cambodia, "and therefore they found the evidence, which is very weak evidence."

While the dissidents may have failed to sway major players in the global public health sphere enough to change actual policy, OGAC's Jason Reed says their voices have been heard on the ground by Africans themselves.

"I think they fuel this ongoing debate about 'Does this really work?'" Reed says of the intactivists' persistent attempts to chip away at the public's perception of VMMC's efficacy. "And in a number

of countries [African stakeholders] are still looking for validation to move slowly. That definitely has an impact…sometimes hamper[ing] programs by spreading misinformation and creating skeptics among those who stand to benefit the most."

The VMMC rollout has indeed proved relatively modest thus far, if steadily gaining in momentum now that the basic framework has been laid. According to Rachel Baggaley, MD, who coordinates innovative prevention policies in the HIV department at WHO, an estimated 3 million African males have been circumcised during the past five years. This figure is far out of pace from the 20 million global stakeholders initially set as a goal to circumcise by the end of 2016.

However, Baggaley says such public health goals are often aspirational targets set overly high in order to light a fire under programs that require a good deal of effort to get off the ground. Nevertheless, she acknowledges that WHO and its partners underestimated the complexities and social sensitivities required to successfully promote the program in certain populations. Two major challenges moving forward, she says, are an insufficient number of local health care providers and older African men's resistance to circumcision.

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In the United States, about 79 percent of adult males report being circumcised. According to a new analysis from the National Center for Health Statistics, 65 percent of newborns were circumcised in 1981. After dropping during the '80s and rising in the '90s, the circumcision rate then fell to 58 percent by 2010. In 2012, the American Academy of Pediatrics (AAP) revised its previously neutral policy on circumcision; it now states that the procedure's potential benefits outweigh its risks, although the AAP refrains from a full-on recommendation.

The health benefits of circumcision AAP cites include a reduction in risk for sexually transmitted infections, including herpes and human papillomavirus (HPV), as well as a reduced risk of penile cancers and lesions. The group says the risks of circumcision are typically minor but may include bleeding and infections.

While many intactivists argue circumcision reduces sexual pleasure, the AAP's position is that research does not support such a claim. A 2008 study of the members of the Uganda VMMC trial found no differences in sexual satisfaction or function between the circumcision and control arms of the study, with more than 98 percent reporting no problems in those realms.

The AAP also has declared that circumcision can reduce the risk of acquiring HIV among heterosexual men in the United States. In fact, scientists believe that the 60 percent reduction in risk found in the three African VMMC trials applies to all heterosexual men globally.

For men who have sex with men (MSM), studies have not shown that circumcision offers noticeable protection against the virus. This is likely because few MSM who engage in anal intercourse exclusively play the insertive, or top, role. Only 100-percent tops might significantly

benefit from circumcision, and one recent research study estimated that only about one in five HIV cases among gay men in the United States results from a receptive partner, or bottom, transmitting to a top.

Three quarters of all new infections in the United States are among MSM or injection drug users, while just 8.5 percent occur in the heterosexual male population. So the presence or absence of a foreskin in the male population at large is unlikely to lower HIV rates anywhere near to the extent it would in sub-Saharan Africa, where the epidemic is predominantly driven by heterosexual intercourse and where adult prevalence rates in the VMMC scale-up countries are as high as 23.6 percent in Lesotho and 26.4 percent in Swaziland, compared with the overall U.S. prevalence of 0.45 percent.

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The skeptics, however claim that the assertion that sub-Saharan Africa's epidemic is largely fueled by sexual practices is a far from settled matter. Their primary opposing theory is that unsafe medical, dental or cosmetic practices, or other puncturing exposures, may in fact be the main drivers of the HIV epidemic in that part of the world.

A particularly vocal VMMC dissident, David Gisselquist, PhD, who received his doctorate in economics from Yale and who has spent more than a decade arguing his case, says the unsafe medical practice theory of HIV transmission in Africa is supported by "outstanding evidence." He has accused WHO of enacting a "continuing cover-up of hospitals' and clinics' contribution to Africa's epidemics."

However, a 2006 epidemiological analysis published in the journal Sexually Transmitted Diseases calculated that the per-injection risk factor and the number of unsafe injections sub-Saharan Africans would need to receive each year to reach the HIV prevalence rates found in that part of the world are "unfeasibly high."

Also, a series of analyses reported in a 2011 Journal of the International AIDS Society (JIAS) paper found that, between Uganda, Kenya, Zambia, Swaziland and Lesotho, injections or blood transfusions had a negligible effect on the countries' HIV epidemics, while sexual behavior accounted for between 94.1 and 99.8 percent of transmissions. Transmission among MSM, the paper stated, makes up an estimated 15.7 percent of new HIV infections in sub-Saharan Africa.

Gisselquist dismisses the models on which such estimates are based as deriving from "made-up parameters."

Rupert Kaul, PhD, a professor in the departments of medicine and immunology at the University of Toronto, disagrees vehemently. "If we're talking about sub-Saharan Africa," he says, "there's absolutely no question that what we're talking about is sexual transmission."

Of the dissidents' long-running unsafe medical practices line of argument, he says, "This is just sort of their high horse."

The 2011 JIAS paper examined the evidence to support VMMC in sub-Saharan Africa and pointed out that only about 10 percent of the region's HIV cases are among those younger than 15, and that prevalence jumps dramatically in those 15 and older. This correlation is "clearly consistent with sexual behavior as the main mode of transmission," the authors wrote.

Gisselquist, along with Potterat and others, criticize epidemiologists for not tracing the source of individual infections when Africans test positive—in other words, for not doing the legwork in the field to see if something other than sex might have been at play. They point out that in three circumcision trials a significant proportion of men who acquired HIV did so while reporting either no sex or consistent condom usage, including 23 of the 69 transmissions in the South Africa study and 16 of the 67 new infections in the Uganda trial. (The Kenya trial did not publish such specific data.)

"I'd say, 'Look at the evidence,'" Gisselquist says, addressing the authors of those studies. "'This is the evidence you reported.' But these guys are sitting under a tree in Baltimore and saying, 'Well, we know it's all from sex in Africa anyways.'"

Ronald Gray, who headed up the Uganda trial, says that all six of the men in the study who did not report intercourse during the period when they were infected did report sex both before and after that period. He theorizes they "likely misreported their sexual behaviors."

"We know that self-reporting on sexual behavior is not good," says OGAC's Jason Reed. Stating a common point, he argues: "The fact that male circumcision was the only difference between these two groups of people across three studies, and that it still reduced their HIV incidence by the same proportion [in all three studies], would suggest that male circumcision is protecting them against whatever is putting them at risk."

In 2011, Gregory J. Boyle, PhD, a consultant from Queens-land, Australia, and George Hill, vice president for bioethics and medical science at Doctors Opposing Circumcision in Seattle, published a lengthy criticism of the randomized controlled trials of VMMC in the Journal of Law and Medicine (JLM). The next year, the same journal published a 30-page rebuttal whose nine authors, including Robert Bailey, lambasted Boyle and Hill for recycling discredited theories and relying on "outmoded evidence, outlier studies and flawed statistical analyses."

Like many dissidents, Boyle and Hill highlighted the observational studies of circumcision, some of which showed a correlation between lacking a foreskin and raised HIV risk, not the other way around. Potterat calls the overall findings of those earlier studies "a toss-up."

The JLM rebuttal, which sneered at the dissidents' "highly selective literature review," pointed to one particular meta-analysis of observational studies that found circumcision had a 61 percent protective effect, thus negating any apparent inconsistencies in the study findings.

Skeptics have expressed concern that the early termination of the controlled trials over-estimated circumcision's protective effect—a common statistical result of ending a trail prematurely. But the JLM rebuttal cited the fact that nearly five years of follow-up in two of the trials found that the reduction in risk only increased over time: to 67 percent risk reduction in the Kenyan study and 73 percent in the Uganda trial.

Recent research also is beginning to show that widespread circumcision is already having an appreciable effect on specific African communities. In Orange Farm, South Africa, the site of that country's VMMC trial, the subsequent large-scale roll-out of the program has seen an estimated 57 to 61 percent reduced HIV incidence among circumcised men as compared with uncircumcised men. And in Rakai, Uganda, VMMC rates among non-Muslim men between 15 and 49 years old jumped from 5.6 percent between 2000 and 2003 to 25.3 percent in 2009. During that time, HIV incidence among all non-Muslim men dropped 22 percent, and researchers have calculated that 37 percent of that drop can be attributed to the scale-up of circumcision.

Another argument posed by the skeptics is the notion that recently circumcised men are likely to put themselves at increased risk of infection should they engage in unprotected sex before their wounds heal.

Robert Bailey, PhD, MPH, a professor of epidemiology at the University of Illinois at Chicago, who was the principal investigator for the Kenyan VMMC trial, has completed a study showing that 35 percent of men do start having sex again before the WHO-recommended six-week waiting period, but that only 7 percent do so before the wounds heal. He argues that an approximate two-week period of increased risk for these men, when compared with the permanent risk reduction of circumcision, is relatively insignificant.

A further area of concern is the phenomenon known as "risk compensation"—the notion is that if a man believes he is more invincible with a circumcised penis, he may be more likely to have unprotected sex or increase his number of partners. Research has been mixed in this area. Time will tell how men's behavior plays out.

In the meantime, Seth Kalichman, PhD, a professor of psychology at the University of Connecticut, who published a 2007 article in PLOS Medicine questioning the VMMC trials for improperly accounting for risk compensation, says that a major challenge posed to circumcision efforts is how to communicate the practical implications of a "60 percent risk reduction" to African men without giving a false sense of security.

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All the back and forth between the VMMC supporters and the dissidents aside, the march toward widespread circumcision in sub-Saharan Africa remains a major priority in global public health, and its detractors are few in number.
Ronald Gray of Johns Hopkins says, "I've given up trying to respond to their many publications."

“It’s a circular discussion that on some levels probably won’t ever be satisfied,” says Reed of OGAC. Regarding the dissidents, he says, “It’s a group of people that largely argue, I think, from an emotional place. I think our position is that no amount of scientific data is going to satisfy the very real issues that they have with the intervention. I think they try to make the case that it’s not valuable from a scientific standpoint, when in fact the problems that they have with it aren’t the science.”

Potterat, who explains that “skepticism is part of the fabric of my mind,” says he’s open to suggestion that circumcision is a worthwhile intervention, but is still waiting for what he considers solid evidence.

“We’re not saying we know,” Potterat says. “We’re saying there’s something wrong with this picture and we don’t know what’s going on, but neither do you. And I guess that really has stepped on people’s ideological, political, academic or other agendas that they just don’t want to see.”

Rachel Baggaley at the WHO sees the argument from a different perspective: that of Africans at high risk for HIV. “The denialists are often coming from places where HIV is not a massive threat to them. Whereas, if you’re a young man in South Africa, you’ve got such a high lifetime chance of acquiring HIV, that, frankly, to deny that opportunity to something that reduces that chance by 60 percent is rather paternalistic.”

Editor’s Notes:

The print edition of this story incorrectly stated that there were two different 2011 Journal of the International AIDS Society papers that, respectively, referenced information about HIV transmissions through injections in Africa and HIV incidence by age group in Africa. Both citations actually come from the same paper.

Also, the print edition stated that the VMMC scale-up in Orange Farm, South Africa, yielded a 76 percent protective effect. A journal article released since the print edition went to press found that circumcision in Orange Farm was linked to an estimated reduction in HIV incidence among men of 57 to 61 percent.

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http://beta.docker.poz.com/article/circumcision-debate-24568-8603