Criticisms of African trials fail to withstand scrutiny: Male circumcision *does* prevent HIV infection

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A recent article in the JLM (Boyle GJ and Hill G, "Sub-Saharan African Randomised Clinical Trials into Male Circumcision and HIV Transmission: Methodological, Ethical and Legal Concerns" (2011) 19 JLM 316) criticises the large randomised controlled trials (RCTs) that scientists, clinicians and policy-makers worldwide have concluded provide compelling evidence in support of voluntary medical male circumcision (VMMC) as an effective HIV prevention strategy. The present article addresses the claims advanced by Boyle and Hill, demonstrating their reliance on outmoded evidence, outlier studies, and flawed statistical analyses. In the current authors' view, their claims portray misunderstandings of the design, execution and interpretation of findings from RCTs in general and of the epidemiology of HIV transmission in sub-Saharan Africa in particular. At the same time they ignore systematic reviews and meta-analyses using all available data arising from good-quality research studies, including RCTs. Denial of the evidence supporting lack of male circumcision as a major determinant of HIV epidemic patterns in sub-Saharan Africa is unsubstantiated and risks undermining the evidence-based, large-scale roll-out of VMMC for HIV prevention currently underway. The present article highlights the quality, consistency and robustness of the scientific evidence that underpins the public health recommendations, guidance, and tools on VMMC. Millions of HIV infections will be averted in the coming decades as VMMC services scale-up to meet demand, providing direct benefits for heterosexual men and indirect benefits for their female partners.

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BACKGROUND

The aim of the present article is to critically evaluate arguments by male circumcision opponents in a recent article in the *Journal of Law and Medicine*[1] questioning the now widely accepted evidence from several large randomised controlled (not "clinical") trials (RCTs) in sub-Saharan Africa that have shown that voluntary medical male circumcision (VMMC) protects against heterosexual acquisition of HIV.[2] The level of protection attained after almost five years of follow-up is 67-73%.[3] Most of the claims by the authors, Gregory Boyle, an Independent Research Consultant, and George Hill, the Vice-President for Bioethics and Medical Science of Doctors Opposing Circumcision, are not new, having been published previously in articles by others.[4] Importantly, such articles have all been challenged by AIDS and male circumcision experts as being seriously flawed.[5] Given that the JLM has, nevertheless, chosen to publish the article in question in spite of this, the current authors consider that an evidence-based response by leading experts is warranted, given the substantial scientific, medical, public health and policy ramifications posed by the claims in the article in question. In so doing, the current authors endeavour to "put science back at the core"[6] of the debate on VMMC for HIV prevention and to reassure the HIV/AIDS policy and implementation community that the evidence in support of male circumcision for HIV prevention is solid, consistent and beyond any reasonable doubt.

Boyle and Hill have previously expressed their opposition to male circumcision in general.[7] It is the view of the current authors that they and other critics of male circumcision tend to misrepresent the evidence and cite selective sources out of context, leading them to refute the extensive scientific support for the ability of male circumcision to reduce the risk of HIV infection and a range of other

[1] Boyle GJ and Hill G, "Sub-Saharan African Randomised Clinical Trials into Male Circumcision and HIV Transmission: Methodological, Ethical and Legal Concerns" (2011) 19 JLM 316.

[2] Auvert B, Taljaard D, Lagarde E et al, "Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial" (2005) 2(e298) PLoS Med 1112; Bailey RC, Moses S, Parker CB et al, "Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial" (2007) 369 *Lancet* 643; Gray RH, Kigozi G, Serwadda D et al, "Male Circumcision for HIV Prevention in Men in Rakai, Uganda: A Randomised Trial" (2007) 369 *Lancet* 657.

[3] Bailey RC, Moses S, Parker CB et al, "The Protective Effect of Adult Male Circumcision Against HIV Acquisition is Sustained for At Least 54 Months: Results from the Kisumu, Kenya Trial", XVIII International AIDS Conference, 18-23 July 2010, Vienna Abstract No FRLBC1; Gray R, Kigozi G, Kong X et al, "The Effectiveness of Male Circumcision for HIV Prevention and Effects on Risk Behaviors in a Post-trial Follow Up Study in Rakai, Uganda" (2012) 26 AIDS 609.

[4] Van Howe RS, "Circumcision and HIV Infection: Review of the Literature and Meta-analysis" (1999) 10 Int J STD AIDS 8; Green LW, McAllister RG, Peterson KW et al, "Male Circumcision is Not the 'Vaccine' We have been Waiting For!" (2008) 2 Future HIV Ther 193; Gisselquist D, Potterat JJ, St Lawrence JS et al, "How to Contain Generalized HIV Epidemics? A Plea for Better Evidence to Displace Speculation" (2009) 20 Int J STD AIDS 443; Green LW, Travis JW, McAllister RG et al, "Male Circumcision and HIV Prevention Insufficient Evidence and Neglected External Validity" (2010) 39 Am J Prev Med 479; Van Howe RS and Storms MR, "How the Circumcision Solution in Africa will Increase HIV Infections" (2011) 2(e4) J Public Health Africa 11.

[5] Moses S, Nagelkerke NJD and Blanchard JF, "Commentary: Analysis of the Scientific Literature on Male Circumcision and Risk for HIV Infection" (1999) 10 Int J STD AIDS 626; O'Farrell N and Egger M, "Circumcision in Men and the Prevention of HIV Infection: A 'Meta-analysis' Revisited" (2000) 11 Int J STD AIDS 137; Castellsague X, Albero G, Cleries R and Bosch FX, "HPV and Circumcision: A Biased, Inaccurate and Misleading Meta-analysis" (2007) 55 J Infect 9155; Wamai RG, Weiss HA, Hankins C et al, "Male Circumcision is an Efficacious, Lasting and Cost-effective Strategy for Combating HIV in High-prevalence AIDS Epidemics: Time to Move Beyond Debating the Science" (2008) 2 Future HIV Ther 399; Banerjee J, Klausner JD, Halperin DT et al, "Circumcision Denialism Unfounded and Unscientific [Critique of Green et al, 'Male Circumcision and HIV Prevention: Insufficient Evidence and Neglected External Validity']" (2011) 40 Am J Prevent Med e11; Morris BJ, Waskett JH, Gray RH et al, "Exposé of Misleading Claims that Male Circumcision will Increase HIV Infections" (2011) 2(e28) J Publ Health Africa 117; Wamai R and Morris BJ, "'How to Contain Generalized HIV Epidemics' Article Misconstrues the Evidence" (2011) 22 Int J STD AIDS 415; Wamai RG, Morris BJ, Bailis SA et al, "Male Circumcision for HIV Prevention – Current Evidence and Implementation in sub-Saharan Africa" (2011) 14 J Int AIDS Soc 49.

[6] Collins H, "We Cannot Live by Skepticism Alone" (2009) 458 *Nature* 30.

[7] Boyle GJ and Hill G, "Matters Arising: 'The Case for Boosting Infant Male Circumcision in the Face of Rising Heterosexual Transmission of HIV'… and Now the Case Against" (2011) 194 MJA 97 (Letter).

sexually transmitted infections (STIs) in men and their female partners without adverse effects on sexual function, sensation or satisfaction.[8]

Boyle and Hill suggest that the RCTs were conducted in ignorance of "contradictory evidence" and argue that the resultant endorsement of the intervention by the WHO and UNAIDS was ill-advised. Randomised controlled trials are the established "gold standard" of evidence in epidemiology.[9] Criticism of scientific findings is healthy when based on valid and reasonable arguments, but when criticisms are spurious, and possibly made to support a particular ideology or "cause", harm to science and society can result.[10] Not only do most of the criticisms by the authors of the article lack novelty, but the authors do not acknowledge the detailed critiques of previous articles by research experts in the field. For instance, an article by Green et al in 2008[11] engendered a thoughtful 18-point rebuttal by a coalition of 48 prominent HIV researchers from around the world.[12] That rebuttal emphasised the quality of the evidence from the RCTs supporting male circumcision and why the procedure is a critical component in the "tool box" of HIV prevention approaches. It seems that Boyle and Hill, just as other opponents of male circumcision, can be categorised among those who Collins argues cannot be convinced by "any amount of evidence".[13]

While Boyle and Hill offer little new evidence opposing male circumcision for HIV prevention, the evidence in support of the efficacy of male circumcision for HIV prevention since the RCTs' findings were published has continued to mount. The partially protective effect of male circumcision against HIV acquisition in heterosexual men has been sustained, in fact reaching 67% by 4.5 years in the Kenyan RCT,[14] and 73% by 4.8 years in the Ugandan RCT.[15] Moreover, data from a large-scale community roll-out of male circumcision for HIV prevention (in South Africa) found a protective effect of 76%.[16] Thus, while the trials found VMMC to be approximately 60% effective, the ongoing data point to rising efficacy with time.

The current article presents an overview of the research on male circumcision and HIV epidemiology. It then provides, in a sequential manner, counter-arguments to each of the claims made by Boyle and Hill, while offering concrete examples of their logical fallacies. It addresses the methodological concerns that Boyle and Hill expressed about the trials, their criticisms of the external

[8] See the following reviews: Alanis MC and Lucidi RS, "Neonatal Circumcision: A Review of the World's Oldest and Most Controversial Operation" (2004) 59 Obstet Gynecol Surv 379; Morris BJ, "Why Circumcision is a Biomedical Imperative for the 21st Century" (2007) 29 BioEssays 1147; Kigozi G, Watya S, Polis CB et al, "The Effect of Male Circumcision on Sexual Satisfaction and Function, Results from a Randomized Trial of Male Circumcision for Human Immunodeficiency Virus Prevention, Rakai, Uganda" (2008) 101 Br J Urol Int 65; Smith DK, Taylor A, Kilmarx PH et al, "Male Circumcision in the United States for the Prevention of HIV Infection and Other Adverse Health Outcomes: Report from a CDC Consultation" (2010) 125(Suppl 1) *Public Health Reports* 72; Tobian AA, Gray RH and Quinn TC, "Male Circumcision for the Prevention of Acquisition and Transmission of Sexually Transmitted Infections: The Case for Neonatal Circumcision" (2010) 164 Arch Pediatr Adolesc Med 78; Morris BJ and Castellsague X, "The Role of Circumcision in the Preventing STIs" in Gross GE and Tyring SK (eds), *Sexually Transmitted Infections and Sexually Transmitted Diseases* (Springer-Verlag, Berlin and Heidelberg, 2011) p 715; Tobian AA and Gray RH, "The Medical Benefits of Male Circumcision" (2011) 306 JAMA 1479; Morris BJ, Gray RH, Castellsague X et al, "The Strong Protection Afforded by Circumcision Against Cancer of the Penis (Invited Review)" (2011) (Article ID 812368) Adv Urol 1.

[9] Vandenbroucke JP, "Observational Research, Randomised Trials, and Two Views of Medical Science" (2008) 5 PLoS Med e67.

[10] Collins, n 6; Chigwedere P, Seage GR 3rd, Gruskin S et al, "Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa" (2008) 49 J Acquir Immune Defic Syndr 410; Timberg C and Halperin DT, *Tinderbox: How the West Sparked the AIDS Epidemic and How the World Can Finally Overcome It* (Penguin Press HC, New York, 2012).

[11] Green, McAllister, Peterson et al, n 4.

[12] Wamai, Weiss, Hankins et al, n 5.

[13] Collins, n 6.

[14] Bailey, Moses, Parker et al, n 3.

[15] Gray, Kigozi, Kong et al, n 3.

[16] Auvert B, Taljaard D, Rech D et al, "Effect of the Orange Farm (South Africa) Male Circumcision Roll-out (ANRS-12126) on the Spread of HIV", 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17-20 July 2011, Rome, Italy. WELBC02.

validity of the trials, ethical-legal concerns, the issue of non-sexual transmission, and their claims of contradictory evidence. It demonstrates that the scientific evidence does not support the claims of Boyle and Hill that male circumcision confers little risk reduction, is not cost-effective and its long-term effectiveness is unknown. These individuals reveal a misunderstanding of the literature on methodologies for, and results from, the multiple studies on the efficacy of, and cost-savings produced by, male circumcision. The current article challenges the points made in their Discussion and Conclusion sections and systematically reviews the articles they provide in their Appendix attempting to support their claims. Concluding that HIV prevention policy must be based on scientific evidence, it urges readers to reject the arguments in the article in question.

AN OVERVIEW OF THE EVIDENCE CONCERNING MALE CIRCUMCISION AND HIV PREVENTION

There is no shortage of scientific evidence on the protection against HIV conferred by male circumcision (Box 1). Extensive analyses have been conducted over the years. Any review that expects to be regarded as objective will always consider analyses arising from the full range of quality studies in which there is broad scholarly consensus.[17] Such studies are distinguished by their application of different methodologies, including observational studies, classical narrative reviews, systematic reviews and meta-analyses. Observational studies are used to determine incidence, prevalence, and to compare phenomena in groups.[18] Classical reviews have a wide focus, systematic reviews are more deliberately focused, and meta-analyses apply statistical and mathematical methods to yield relative risk (RR) estimates.[19] The latter types of studies can provide useful data and direction for translating results into policy and to guide clinical practice, especially where data are unavailable or there are conflicting results.[20] Recently, the United States Institute of Medicine has developed eight guidelines and 21 standards for systematic reviews.[21] One of these is that key clinical and/or scientific stakeholders should be included.[22]

Box 1 Studies on male circumcision for HIV prevention by type of method

- ☐ 4 ecological studies
- ☐ 35 cross-sectional studies
- ☐ 14 prospective studies
- ☐ 3 randomised control trials
- ☐ 100s of reviews, systematic reviews and meta-analyses

Sources: Siegfried, Muller, Deeks et al, n 33; Dickson and Farley, n 179; Weiss, Quigley and Hayes, n 25; Weiss, Halperin, Bailey et al, n 32. Bailey, Moses, Parker et al, n 2; Wamai, Morris, Bailis et al, n 5.

[17] Collins, n 6; Purtill R, "The Purpose of Science" (1970) 37 Phil Sci 301.

[18] Mann CJ, "Observational Research Methods. Research Design II: Cohort, Cross Sectional, and Case-control Studies" (2003) 20 Emerg Med J 54.

[19] Mann, n 18.

[20] Leibovici L and Falagas ME, "Systematic Reviews and Meta-analyses in Infectious Diseases: How Are They Done and What Are Their Strengths and Limitations?" (2009) 23 Infect Dis Clin North Am 181.

[21] Eden J, Levit L, Berg A et al, *Finding What Works in Health Care. Standards for Systematic Reviews* (Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine of the National Academies, 2011).

[22] Anonymous, "Guiding the Guidelines" (2011) 377(9772) *Lancet* 1125.

Of the numerous systematic reviews, Cochrane Reviews and meta-analyses that have examined the possible role of male circumcision in reducing female-to-male HIV transmission, only one – a single meta-analysis – has purported to find a positive correlation between male circumcision and HIV infection. This particular meta-analysis was conducted by the vocal male circumcision opponent, Robert Van Howe.[23] Critical evaluations of that article by several different experts found that the statistical analyses involved erroneous methodology and that the article contained serious discrepancies that together caused it to lack credibility.[24] Consequently, its conclusions have been rejected as fallacious.

All other reviews and meta-analyses have found that male circumcision protects men against acquisition of HIV infection during heterosexual intercourse. Soon after the Van Howe article, a systematic review and meta-analysis by Weiss et al examined data from 27 studies that had been conducted prior to 1999, and found that 21 (78%) of these had observed lower HIV in circumcised men.[25] The overall summary risk ratio for the 27 studies indicated a "highly significant" reduction in risk of HIV infection (pooled RR = 0.52, 95% CI 0.40-0.68). When the analysis was confined to the 15 studies that had adjusted for potential confounders, the protective effect of male circumcision was found to be stronger (adjusted RR = 0.42, 95% CI 0.34-0.54). The protective effect was stronger still in high-risk men (adjusted RR = 0.29, 95% CI 0.20-0.41) as compared to men who were not high-risk (adjusted RR = 0.56, 95% CI 0.44-0.70).[26] This analysis was followed in 2003 by a systematic review of 37 studies by the Cochrane collaboration.[27] It found consistent support for a protective effect of male circumcision, but recommended that RCT data were required before a recommendation in support of male circumcision for HIV prevention could be made.

The next systematic review by the principal author of the Cochrane committee, Nandi Siegfried, discussed the results of the first of the RCTs to report its findings.[28] Although it accepted the findings of this trial, conducted in South Africa, it concluded by saying, "Considering the results of all three trials together is likely to provide us with stronger evidence to guide policy". After the findings from the two other trials, in Kenya[29] and Uganda,[30] were published in the *Lancet*, several meta-analyses of the data from all three trials appeared. One meta-analysis of the RCT data reported a relative risk reduction of 56%.[31] Another review and meta-analysis of both the RCTs and all the observational studies before the trials found a protective effect of male circumcision of 58% in both types of studies (95% CI 43-69% and 95% CI 46-66%, respectively).[32] In 2009 the Cochrane committee reported its findings after conducting further extensive detailed evaluation of the trial data.[33] It concluded that

[23] Van Howe, n 4.

[24] Moses, Nagelkerke and Blanchard, n 5; O'Farrell and Egger, n 5.

[25] Weiss HA, Quigley MA and Hayes RJ, "Male Circumcision and Risk of HIV Infection in sub-Saharan Africa: A Systematic Review and Meta-analysis" (2000) 14 AIDS 2361.

[26] Weiss, Quigley and Hayes, n 25.

[27] Siegfried N, Muller M and Volmink J et al, "Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men" (2003) Cochrane Database Syst Rev CD003362.

[28] Siegfried N, Muller M, Deeks J et al, "HIV and Male Circumcision – A Systematic Review with Assessment of the Quality of Studies" (2005) 5 Lancet Inf Dis 165.

[29] Bailey, Moses, Parker et al, n 2.

[30] Gray, Kigozi, Serwadda et al, n 2.

[31] Mills E, Cooper C, Anema A et al, "Male Circumcision for the Prevention of Heterosexually Acquired HIV Infection: A Meta-analysis of Randomized Trials Involving 11,050 Men" (2008) 9 HIV Med 332.

[32] Weiss HA, Halperin D, Bailey RC et al, "Male Circumcision for HIV Prevention: From Evidence to Action? (Review)" (2008) 22 AIDS 567.

[33] Siegfried N, Muller M, Deeks JJ et al, "Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men" (2009) Cochrane Database Syst Rev CD003362.

there was "strong evidence" for male circumcision efficacy in reducing risk of infection in heterosexual men and that "inclusion of male circumcision into current HIV prevention measures [and] guidelines is warranted".[34]

Other systematic reviews have assessed epidemiological, observational and RCT studies. In 2008 Byakika-Tusiime et al conducted another meta-analysis that included 13 studies of which 85% were from sub-Saharan Africa.[35] They found 57% protection in the RCTs and 61% in the observational studies. For cohort studies it was 71%, and for case-control studies it was 46%. Additionally, their meta-analysis reported a protective effect of 45% when male circumcision status was ascertained by self-report, whereas for studies that ascertained circumcision status by clinical genital examination, the protective effect of male circumcision was 65%.[36] In 2010 a cross-sectional study of observational data from 18 countries in sub-Saharan Africa found the protective effect of male circumcision against HIV infection to be 83% (OR 4.12; 95% CI 3.85-4.42).[37] Also in 2010 a systematic review that examined 37 late-phase RCTs of multiple HIV prevention interventions found that male circumcision was the only intervention to show consistent HIV prevention efficacy.[38]

The ability of male circumcision to reduce HIV transmission to women has also been examined. A meta-analysis by Weiss and co-workers in 2009 assessed findings from 19 epidemiological studies of male circumcision and HIV prevalence in women in 11 populations.[39] The random-effects meta-analysis of the Rakai RCT in which men were HIV-positive, and six other longitudinal analyses in sero-discordant couples where the man was HIV-positive, revealed "little evidence" of a protective effect under these circumstances (summary RR = 0.80).[40] They calculated that in order to obtain definitive results for whether circumcision of HIV-positive men could reduce HIV transmission to women, a RCT involving around 10,000 couples would be required, pointing out that the feasibility of such a study was low.[41] They nevertheless concluded that benefits would likely still result if male circumcision services were integrated as part of existing prevention strategies in such sero-discordant populations. Subsequent research has noted that HIV prevalence in women with circumcised partners was 38% lower in a multinational study,[42] and was predicted to be reduced by 46% in a modelling analysis.[43]

Based on the above evidence, it is problematic that Boyle and Hill have published their highly selective literature review, ignoring so much of the wider literature on male circumcision and HIV prevention. In addition, although they refer to the 2009 Cochrane report by noting its statement of the need for localised research to assess "feasibility, desirability, and cost-effectiveness",[44] they fail to state the primary findings of that report. Furthermore, Boyle and Hill seem unaware of the numerous recent studies of the popularity and acceptability of male circumcision among men and their

[34] Siegfried, Muller, Deeks et al, n 33.

[35] Byakika-Tusiime J, "Circumcision and HIV Infection: Assessment of Causality" (2008) 12 AIDS Behav 835.

[36] Byakika-Tusiime, n 35.

[37] Gebremedhin S, "Assessment of the Protective Effect of Male Circumcision from HIV Infection and Sexually Transmitted Diseases: Evidence from 18 Demographic and Health Surveys in Sub-Saharan Africa" (2010) 14 Afr J Reprod Health 105.

[38] Padian NS, McCoy SI, Balkus JE et al, "Weighing the Gold in the Gold Standard: Challenges in HIV Prevention Research" (2010) 24 AIDS 621.

[39] Weiss HA, Hankins CA and Dickson K, "Male Circumcision and Risk of HIV Infection in Women: A Systematic Review and Meta-analysis" (2009) 9 Lancet Infect Dis 669.

[40] Weiss, Hankins and Dickson, n 39.

[41] Weiss, Hankins and Dickson, n 39.

[42] Baeten JM, Donnell D, Kapiga SH et al, "Male Circumcision and Risk of Male-to-Female HIV-1 Transmission: A Multinational Prospective Study in African HIV-1-Serodiscordant Couples" (2010) 24 AIDS 737.

[43] Hallett TB, Alsallaq RA, Baeten JM et al, "Will Circumcision Provide Even More Protection from HIV to Women and Men? New Estimates of the Population Impact of Circumcision Interventions" (2011) 87 Sex Transm Infect 88.

[44] Siegfried, Muller, Deeks et al, n 33.

partners,[45] the feasibility of implementation of VMMC programs,[46] as well as their cost-effectiveness.[47] All of these diverse findings demonstrate strong support for male circumcision. Contrary to assertions by Boyle and Hill, many such studies were conducted prior to the recommendations by WHO and UNAIDS in support of male circumcision to reduce HIV in high prevalence settings, providing added evidence underpinning the recommendations by these normative bodies.[48]

By selectively citing several outlier studies that they claim did not find higher HIV in uncircumcised men,[49] Boyle and Hill fail to acknowledge the overall support for male circumcision from the systematic reviews and meta-analyses referred to above. Nor do these authors reveal the reasons provided by authors of the outlier studies as to why their data were inconsistent with the bulk of the research findings in the literature. As pointed out in one of the systematic reviews and meta-analysis,[50] the current data on male circumcision satisfy six of the nine criteria of causality outlined by Hill,[51] namely strength of association, consistency, temporality, coherence, biological plausibility and experiment.

WHY BOYLE AND HILL'S "METHODOLOGICAL CONCERNS" CANNOT BE SUPPORTED

Factors jeopardising internal validity

Researcher expectation bias

Boyle and Hill claim that there was a lack of "equipoise" in all three RCTs and that the researchers involved were biased in favour of male circumcision. Might Boyle and Hill then consider why there was support from the funding bodies that financed these studies, the review editors of the journals that published the findings, and the policy community, including WHO and UNAIDS, which later endorsed the findings? The trials in Kenya and Uganda were funded and ethically approved by, among others, the United States National Institutes of Health (NIH). The South African trial was approved by the French National Agency for AIDS Research. In all three countries, approval was also given by

[45] Lukobo MD and Bailey RC, "Acceptability of Male Circumcision for Prevention of HIV Infection in Zambia" (2007) 19 AIDS Care 471; Westercamp N and Bailey RC, "Acceptability of Male Circumcision for Prevention of HIV/AIDS in Sub-Saharan Africa: A Review" (2007) 11 AIDS Behav 341; Yang X, Abdullah AS, Wei B et al, "Factors Influencing Chinese Males' Willingness to Undergo Circumcision: A Cross-sectional Study in Western China" (2012) 7 PLoS One e30198.

[46] Weiss, Halperin, Bailey et al, n 32; Wamai, Morris, Bailis et al, n 5; Sawires SR, Dworkin SL, Fiamma A et al, "Male Circumcision and HIV/AIDS: Challenges and Opportunities" (2007) 369 *Lancet* 708; Hankins C, Forsythe S and Njeuhmeli E, "Voluntary Medical Male Circumcision: An Introduction to the Cost, Impact, and Challenges of Accelerated Scaling Up" (2011) 8 PLoS Med e1001127; UNAIDS and PEPFAR, *Voluntary Medical Male Circumcision for HIV Prevention: The Cost, Impact, and Challenges of Accelerated Scale-Up in Southern and Eastern Africa* (2011), http://www.ploscollections.org/article/browseIssue.action?issue=info:doi/10.1371/issue.pcol.v01.i11 viewed 15 January 2012.

[47] Kahn JG, Marseille E and Auvert B, "Cost-effectiveness of Male Circumcision for HIV Prevention in a South African Setting" (2006) 3(e517) PLoS Med 2349; Gray RH, Li X, Kigozi G et al, "The Impact of Male Circumcision on HIV Incidence and Cost Per Infection Prevented: A Stochastic Simulation Model from Rakai, Uganda" (2007) 21 AIDS 845; Londish GJ and Murray JM, "Significant Reduction in HIV Prevalence According to Male Circumcision Intervention in Sub-Saharan Africa" (2008) 37 Int J Epidemiol 1246; Galarraga O, Colchero A, Wamai RG and Bertozzi S, "HIV Prevention Cost Effectiveness: A Systematic Review of the Literature 2005-2008" (2009) 9(Suppl 1) BMC Public Health S1; Njeuhmeli E, Forsythe S, Reed J et al, "The Impact and Cost of Expanding Male Circumcision for HIV Prevention in Eastern and Southern Africa" (2011) 8 PLoS Med e1001132.

[48] UNAIDS, *Safe, Voluntary, Informed Male Circumcision and Comprehensive HIV Prevention Programming: Guidance for Decision-makers on Human Rights, Ethical and Legal Considerations* (2008), http://www.data.unaids.org/pub/Report/2008/JC1552_Circumcision_en.pdf viewed 12 February 2012; WHO/UNAIDS, *New Data on Male Circumcision and HIV Prevention: Policy and Program Implications* (2007), http://www.who.int/hiv/mediacentre/MCrecommendations_en.pdf viewed 12 February 2012; UNAIDS/WHO, *Ethical Considerations in Biomedical HIV Prevention Trials* (2007), http://www.data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf viewed 10 February 2012.

[49] See in particular Boyle and Hill, n 1, Appendix, and the review of this in Table 1 (below).

[50] Byakika-Tusiime, n 35.

[51] Hill BA, "The Environment and Disease: Association or Causation?" (1965) 58 Proc Royal Soc Med 295.

national institutional review bodies. According to the NIH training protocol for conducting research in human subjects, "A state of 'equipoise' is required for conducting research that may pose risks to research participants".[52] This NIH source explains that

> for a clinical trial to be in equipoise, investigators must not know that one arm of a clinical trial provides greater efficacy over another, or *there must be genuine uncertainty among professionals about whether one treatment is superior than another*.[53]

A similar statement appears in Freedman,[54] a source Boyle and Hill cite. Based on the preponderance of evidence considered during the ethical review on this issue, the RCTs were fully justified *because* the prevailing observational evidence at the time *was* mixed.

Boyle and Hill's accusation that the lead researchers had an inherent bias in favour of male circumcision includes a statement that such bias was because they were from Western countries where circumcision is widely practised.[55] While the leaders of the RCTs in Kenya and Uganda – Robert Bailey and Ronald Gray, respectively – were from the United States, where male circumcision is common, the leader of the RCT in South Africa – Bertran Auvert – was from France, where male circumcision is not common. The purpose of science is to "explain and predict" societal phenomena.[56] Moreover, scientists adopt a meta-ethical approach in their research. Not to do so would impede the progress of science and be professionally damaging. The fact that a plethora of research by scientists has generated data to indicate that male circumcision has beneficial effects cannot be judged as biased.

To support their point, Boyle and Hill provide a Table of references that were used as citations by the lead authors of the trials, and categorise these references into pro-male circumcision, anti-male circumcision and neutral.[57] They then conduct a chi-squared analysis to show that the pro-male circumcision articles predominate. This is an exercise in futility because the majority of the observational studies *did* show a protective effect of male circumcision, as each of the trial publications acknowledged, and as Boyle and Hill themselves acknowledge. Despite the latter, they present a contradictory position based on a list of selected references in their Appendix.[58] Their suggestion of an inherent Western bias is, if anything, unjustified because there was, in fact, considerable resistance to accepting the male circumcision evidence by the major players and funders in the AIDS arena, despite the very strong observational evidence that had accumulated prior to the RCTs.[59] But as overwhelming evidence emerged, even former UNAIDS director Peter Piot could appreciate that, had male circumcision been adopted without delay, "it could have saved lives"[60]

It seems Boyle and Hill may have decided to ascribe bias automatically without regard for the height of the bar of scientific research evidence that was required to justify these trials being undertaken. They note that "[i]n none of the reports was even a single reference cited opposing male circumcision".[61] There is a very good reason for this: there are no strong credible references opposing male circumcision (see Table 1 below). Instead, one can find only specious arguments by male circumcision opponents made in the absence of support from experts in the scientific community. In cases in which such anti-male circumcision "evidence" has been published in a peer-reviewed journal,

[52] National Institutes of Health (US), *Human Subjects Protections Training* (US Department of Health & Human Services. Office of Extramural Research, National Institutes of Health, 2008), http://www.grants.nih.gov/grants/policy/hs/training.htm viewed 20 January 2012.

[53] National Institutes of Health, n 52 (emphasis added).

[54] Freedman B, "Equipoise and the Ethics of Clinical Research" (1987) 317 NEJM 141, cited by Boyle and Hill, n 1 at fn 14.

[55] Boyle and Hill, n 1 at 325.

[56] Purtill, n 17.

[57] Boyle and Hill, n 1 at 319,

[58] Boyle and Hill, n 1 at 333.

[59] Timberg and Halperin, n 10; Green EC and Ruark AH, *AIDS, Behavior, and Culture: Understanding Evidence-based Prevention* (Left Coast Press, Walnut Creek, CA, 2011).

[60] Timberg and Halperin, n 10, p 298.

[61] Boyle and Hill, n 1 at 320.

it has generally been exposed as fallacious or even apparently fraudulent in published critiques that have followed.[62] Boyle and Hill go on to say that it is "problematic" that no acknowledgment was made of "the published evidence showing no prophylactic benefit of male circumcision".[63] This claim is extraordinary given the enormous scientific evidence of the wide array of benefits as listed in the "Background" section above.

Boyle and Hill then say that the researchers knew each other well, having co-authored various academic papers. Such an assertion fails to recognise the cooperation and collaboration that are inherent in scientific endeavours. They fail to identify that these trials could not have been conducted without participation by local professionals and scholars whose names appear as co-authors of the studies. A total of 23 separate co-authors are listed in all three trials – only one name appears in common, this being for the trials in Uganda and Kenya. Contrary to their assertion that the "lead investigators … concurred",[64] in actual fact the *entire body of researchers concurred with the evidence* that led to the circumcision recommendations. The claim that because the Ugandan female-to-male trial[65] and the male-to-female trial[66] had multiple authors whose name appeared on both presents a bias and non-independence is ironic, since each of these particular trials generated differing results. In light of this, it is not clear where the supposed "bias" would be. Was it in the study showing support, or was it in the one showing less support? Co-authorship alone cannot subsequently pose an automatic bias or evidence of non-independence. In addition, these studies used different subjects and looked at a different dynamic: HIV transmission from women to men versus HIV transmission from *HIV-positive* men to their HIV-negative female sexual partners.[67] Boyle and Hill refer to the lead investigators as "documented circumcision *advocates*".[68] This is, however, an inappropriate use of the term, since it is appropriate to use strong scientific evidence as a basis for advocating change. Their claim can be contrasted with those of self-identified lobby groups, such as Doctors Opposing Circumcision, of which Hill reveals in their article he is "Vice-President for Bioethics and Medical Science".

Participant expectation bias

Here Boyle and Hill state that the men were asked "leading questions [that] may have influenced [their] decisions to participate".[69] As evidence for this they cite the South African trial[70] as having reported that 59% of men agreed to circumcision if it decreased risk of infection from HIV and other STIs. However, Auvert and co-workers were here referring to a study in 2003 of male circumcision acceptability,[71] not to the men who participated in the trial.

Boyle and Hill argue that the researchers should have informed the participants of contrary observational evidence. The supposed "evidence" they refer to is, however, flimsy at best and lacks credibility.[72] In the introduction of each article reporting the findings of each particular trial, the authors cite the established evidence that guided them in the design and commitment to undertake the trial. In inquiring whether the trial researchers misleadingly induced demand for male circumcision

[62] See "Background" section above.

[63] Boyle and Hill, n 1 at 320.

[64] Boyle and Hill, n 1 at 319.

[65] Gray, Kigozi, Serwadda et al, n 2.

[66] Wawer MJ, Makumbi F, Kigozi G et al, "Circumcision in HIV-infected Men and Its Effect on HIV Transmission to Female Partners in Rakai, Uganda: A Randomised Controlled Trial" (2009) 374 *Lancet* 229.

[67] Wawer, Makumbi, Kigozi et al, n 66.

[68] Boyle and Hill, n 1 at 319 (emphasis added).

[69] Boyle and Hill, n 1 at 320.

[70] Auvert, Taljaard, Lagarde et al, n 2.

[71] Lagarde E, Dirk T, Puren A et al, "Acceptability of Male Circumcision as a Tool for Preventing HIV Infection in a Highly Infected Community in South Africa" (2003) 17 AIDS 89.

[72] See Table 1 below for a review of the studies cited in Boyle and Hill's Appendix.

from participants, Boyle and Hill cite Dowsett and Couch.[73] However, Dowsett and Couch's review does not actually question the efficacy results of the trials. The latter authors agree that the trials provide a "significant part of the evidence base to recommend implementation of MC" and call for male circumcision to be placed within the existing broad context of HIV programming,[74] with which the current authors are in full agreement. The recruitment methods for all three RCTs are well detailed in the publications reporting the findings from each. These methods are conventional, practical and beyond reproach. Now that the trials have proven the efficacy of male circumcision for HIV prevention, it comes as no surprise that demand for male circumcision has grown, with numbers circumcised in the priority countries of eastern and southern Africa by mid-2011 exceeding half a million since roll-out in 2008.[75]

Inadequate double-blinding and experimental mortality

Boyle and Hill correctly point out that a double-blinding in the male circumcision trials was a practical impossibility. But it is not necessary that a trial be double-blinded to be valid.[76] On the other hand, since Boyle and Hill acknowledge the impracticability of blinding in these trials, it is not clear what their point is in raising the question. Ironically, for instance, they assert that because in the Kenyan trial some men disclosed their male circumcision status to the nurse who filled out the questionnaire, the *nurse's knowledge* of that fact could have somehow "influenced responses on the questionnaire".[77] To suggest that lack of such blinding undermines the veracity of participant information in the trials would have to assume dishonesty or incompetence on the part of those conducting the interviews. There is no support for such a claim and if there had been any hint of such a serious breach, the researchers would have intervened.

Another remarkable claim they make is that participants lost from the trials might have been mostly circumcised men who had become infected with HIV, so diluting the findings of a protective effect of male circumcision. Their Figure 2, a bar graph reproduced from an anti-circumcision website (http://www.circumstitions.com), portrays what they say were "significant numbers" of such losses.[78] This claim is repeated later under the subheading "Experimental mortality". Their claim and the analysis provided in their Figure are not based on evidence, nor is the statistical analysis they use in supporting their claim of "significant" loss (see Table 2 of the current article below). Contrary to their claim, in all three RCTs, use of survival analysis accounting for 15% annual loss (in both groups) indicated that such losses *did not differ statistically between groups*[79] and "reduced the potential attrition bias in each trial".[80] For instance, the South African trial reported:

> Even though some participants were lost during the follow-up, and the loss to follow-up rate was greater than the event rate, the impact of missing participants on the overall results of this study is likely to be small not only because the loss to follow-up was small for a cohort study conducted in a general population, but also because those who were late for at least one follow-up visit were protected by male circumcision just as the other participants.[81]

The fact that Boyle and Hill use as "evidence" a Figure from a non-peer-reviewed source, instead of

[73] Dowsett GW and Couch M, "Male Circumcision and HIV Prevention: Is There Really Enough of the Right Kind of Evidence?" (2007) 15 Reprod Health Matters 33, cited by Boyle and Hill, n 1 at fn 21.

[74] Dowsett and Couch, n 73.

[75] Wamai, Morris, Bailis et al, n 5; WHO/UNAIDS, *Progress in Scale-up of Male Circumcision for HIV Prevention in Eastern and Southern Africa: Focus on Service Delivery* (2011), http://www.malecircumcision.org/documents/MC_country_12sept11a.pdf viewed 31 January 2012.

[76] Smith GC and Pell JP, "Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomised Controlled Trials" (2003) 327 BMJ 1459; Vandenbroucke, n 9; Padian, McCoy, Balkus et al, n 38.

[77] Boyle and Hill, n 1 at 320.

[78] Boyle and Hill, n 1 at 321.

[79] Auvert, Taljaard, Lagarde et al, n 2; Bailey, Moses, Parker et al, n 2; Gray, Kigozi, Serwadda et al, n 2.

[80] Siegfried, Muller, Deeks et al, n 33.

[81] Auvert, Taljaard, Lagarde et al, n 2.

recognised actual trial data, leads to an impression of a willingness to use pseudo-scientific "evidence" when it supports their belief, and that they harbour an indifference towards scientific conventions.

Lead-time bias

Boyle and Hill are correct that, owing to instructions to abstain from having sexual intercourse while their circumcision wound healed, men in the intervention arm had one-to-three months less exposure time over the course of the 18-month trial period. On this basis, and by citing an unpublished manuscript by Van Howe, they argue that statistics on the protective effect of male circumcision would be diminished.[82] Van Howe's manuscript should be considered inadmissible as support unless published in a peer-reviewed journal, especially in the context of his previous statistical analyses on HIV and other conditions that have been exposed as being fallacious. In one particular example, Van Howe used false source code data in his meta-analysis of sexually transmitted urethritis,[83] Waskett et al revealed that when the true source data were subjected to a meta-analysis, rather than a higher rate of sexually transmitted urethritis in circumcised men, the prevalence was in fact lower, although not significantly so.[84] Therefore, Boyle and Hill's citation of Van Howe does not inspire confidence. The issue of "lead-time bias" of a month or so has been rendered inconsequential now that follow-up epidemiological data in two of the trial populations out to 54-57 months have shown an increase in the protective effect to 67-73%.[85] Such a level of protection is consistent with the first data from the large-scale community roll-out of male circumcision for HIV prevention, undertaken in the South African trial site, Orange Farm, and that has shown a reduction in HIV prevalence of 76% (20.0% prevalence among uncircumcised men versus 6.2% among those circumcised (P<0.001); adjusted HIV incidence rate ratio in those aged 15-34 of 0.20 (95% CI 0.00-0.55)).[86] Furthermore, all three trials included HIV testing at multiple points in time. If the protective effect could be explained by the healing period, then it would be reasonable to expect to see a protective effect only in the early part of a trial. The data show that the protective effect was sustained throughout the duration of each trial.

Selection and sampling bias

In this section of their article Boyle and Hill flag three issues: socio-economic background of the men, ethnic background, and between-group differences in risk of acquisition of HIV. The first claim is that the "samples were skewed towards men from lower socio-economic backgrounds".[87] To the contrary, the Ugandan and South African trials reported that 94% and 98% of the participants, respectively, had completed primary education or higher,[88] and in the Kenyan trial 66% had completed secondary or higher levels of education.[89] The Ugandan and South African trials did not report employment/income status, and the Kenyan trial reported an equal unemployment status of 64% in each group. These data provide no support to Boyle and Hill's claims. In reality, the evidence shows that the trial participants represented socio-economic characteristics similar to the general populations of the countries in which the trials were conducted.

Boyle and Hill claim, without evidence, that there were more "at-risk men" and that a "higher prevalence" of STIs was found in the control arm in the South African and Ugandan trials.[90] Data on STIs do not appear in the articles reporting on the results of these two trials. At enrolment, the South African trial reported that "at-risk behaviour" was 46.7% in the control group and 46.8% in the

[82] Boyle and Hill, n 1 at 322.

[83] Van Howe RS, "Genital Ulcerative Disease and Sexually Transmitted Urethritis and Circumcision: A Meta-analysis" (2007) 18 Int J STD AIDS 799.

[84] Waskett JH, Morris BJ and Weiss HA, "Errors in Meta-analysis by Van Howe" (2009) 20 Int J STD AIDS 216.

[85] Bailey, Moses, Parker et al, n 3; Gray, Kigozi, Kong et al, n 3.

[86] Auvert, Taljaard, Rech et al, n 16.

[87] Boyle and Hill, n 1 at 322.

[88] Auvert, Taljaard, Lagarde et al, n 2; Gray, Kigozi, Serwadda et al, n 2.

[89] Bailey, Moses, Parker et al, n 2.

[90] Boyle and Hill, n 1 at 322.

intervention group. In the Kenyan trial there were no differences in the reported "sexual history with women" or other variables predisposing to risky behavior such as alcohol use. Similarly, in the Ugandan trial, there were no differences between each arm of the trial in number of sexual partners, condom use, alcohol use or self-reported STIs. Boyle and Hill attempt to fault the studies on the basis of differences in other parameters such as age, religion and ethnic background. Such factors were, however, analysed in the trials and found not to influence the outcomes reported. Moreover, their assertion that there were false HIV-positive results is baseless, and their remark that mis-assignment of such cases could only influence results if the majority of these cases were in the control group is puzzling, since it renders their point meaningless.

Early termination

The claim that the early termination of the RCTs (since the protective effect of male circumcision made it apparent that continuing the study and denying the control group this potentially life-saving intervention was unethical) exaggerates "any effects" was made in 2008 by Green and colleagues,[91] and shown in the current authors' critique of that article at the time to be false.[92] As explained in that rebuttal, four factors found in all of the trials negate such a claim of compromised efficacy due to early stoppage. These are: predetermined conservative stoppage rules, consistency of results, decreased risk of overestimation because of a small number of events as enunciated by Montori and associates,[93] whom the current authors cited – as did Boyle and Hill – and an observed effect of male circumcision that was similar to existing credible observational studies.[94] As mentioned earlier, Boyle and Hill did note the follow-up findings by Bailey et al showing the effect of male circumcision to be sustained by 42 months,[95] but may have been unaware of the more recent "roll-out" data in South Africa that indicate a risk reduction of 76%. An examination of the totality of the evidence thus renders untenable the claim by Boyle and Hill repudiating the trials because of "incomplete observational data".

Factors jeopardising external validity

Despite another rebuttal made by the current authors against claims of external validity,[96] referring to them as "nonsensical",[97] Boyle and Hill continue to raise multiple similar challenges in their article. They begin by saying that the studies sampled "mostly poorly educated, impoverished African men".[98] This seemingly condescending and inaccurate generalisation based on the compensation given to the trial participants is addressed in the "Selection and sampling bias" section above.

Boyle and Hill go on to say that the trials "inadequately" investigated "confounding factors".[99] Rather than repeating an already published repudiation of this claim here, readers are directed to an article by the current authors in 2008,[100] in which they responded to the same claim by Green and co-authors.[101] Similarly, readers are referred to a previous response by trial authors[102] and to an article by Wamai et al in 2011.[103] These previous publications show that non-sexual transmission of HIV is very low in sub-Saharan Africa.

[91] Green, McAllister, Peterson et al, n 4.

[92] Wamai, Weiss, Hankins et al, n 5.

[93] Montori VM, Devereaux PJ, Adhikari NK et al, "Randomized Trials Stopped Early for Benefit: A Systematic Review" (2005) 294 JAMA 2203.

[94] Wamai, Weiss, Hankins et al, n 5.

[95] Bailey, Moses, Parker et al, n 3.

[96] Green, Travis, McAllister et al, n 4.

[97] Banerjee, Klausner, Halperin et al, n 5.

[98] Boyle and Hill, n 1 at 323.

[99] Boyle and Hill, n 1 at 323.

[100] Wamai, Weiss, Hankins et al, n 5, section entitled "Many infections appear to be from non-sexual sources".

[101] Green, McAllister, Peterson et al, n 4.

[102] Auvert B, Taljaard D, Lagarde E et al, "Authors' Reply" (2006) 3 PLoS Med e67.

[103] Wamai, Morris, Bailis et al, n 5, section entitled "What we know about the drivers of HIV infection in sub-Saharan Africa".

The next assertion by Boyle and Hill is that the trials failed to acknowledge adverse events. This claim is false since each trial reported the incidence of adverse events, as can be seen in Table 3 of the article reporting results for the Kenyan trial,[104] Table 6 in that for the South African trial,[105] and information from the Ugandan trial.[106] In all of the trials adverse event rates were low and comparable between each trial.

In support of a claim about "problems in generalising" trial results to "real-world" settings, Boyle and Hill provide several citations by male circumcision opponents.[107] We would find it surprising if Boyle and Hill are unaware that two of these articles[108] have been strongly criticised by researchers in the field,[109] and that convincing favourable cost and cost-effectiveness data have been published.[110] They claim there may be a lack of population representativeness that somehow affects real-world effectiveness.[111] This assertion is, however, negated by the persistence of population-level effectiveness for at least 4.5 to 4.8 years,[112] and by the first data from the large-scale community roll-out of male circumcision for HIV prevention.[113] The claim is also contradicted by the enormous amount of observational evidence cited as informing the trials in the first place. This kind of supportive data was evident in a cross-sectional analysis of 18 studies involving 70,554 men.[114] This analysis showed the protective effect of male circumcision against HIV infection was highly significant (OR 4.12; 95% CI 3.85-4.42), and even higher (OR 4.95; 95% CI 4.57-5.36) after adjusting for "lifetime partners, sexual behavior, age, place of residence (urban/rural), educational status, marital status, comprehensive knowledge towards HIV/AIDS and frequency of use of mass media".[115] A subsequent study similarly showed protection of 80%.[116] As noted in the previous section, the contrary assertions and references cited as support[117] are plainly untenable.

Boyle and Hill raise the important issue of implementation, namely that the services provided in the trial (medical advice and counselling) are difficult to replicate outside the trial setting, and thus might lead to diminished "real-world" male circumcision effectiveness. While it is true that implementation has been slow in the scale-up countries,[118] achievements being made in real-world settings in countries like Kenya, Swaziland, Ethiopia, Zambia and South Africa indicate considerable potential for further progress and substantial proof of success, provided availability of resources increases.[119] It is important to observe that the WHO statement that Boyle and Hill refer to by saying

[104] Bailey, Moses, Parker et al, n 2.

[105] Auvert, Taljaard, Lagarde et al, n 2.

[106] Gray, Kigozi, Serwadda et al, n 2.

[107] Boyle and Hill, n 1 at fn 43.

[108] Green, McAllister, Peterson et al, n 4; Green, Travis, McAllister et al, n 4.

[109] Wamai, Weiss, Hankins et al, n 5; Banerjee, Klausner, Halperin et al, n 5.

[110] Kahn, Marseille and Auvert, n 47; Gray, Li, Kigozi et al, n 47; Londish and Murray, n 47; Njeuhmeli, Forsythe, Reed et al, n 47.

[111] Boyle and Hill, n 1 at 324.

[112] Bailey, Moses, Parker et al, n 3; Gray, Kigozi, Kong et al, n 3.

[113] Auvert, Taljaard, Rech et al, n 16.

[114] Gebremedhin, n 37.

[115] Gebremedhin, n 37.

[116] Oluoch T, Mohammed I, Bunnell R et al, "Correlates of HIV Infection Among Sexually Active Adults in Kenya: A National Population-based Survey" (2011) 5 Open AIDS J 125.

[117] Boyle and Hill, n 1 at fnn 45 and 46.

[118] Wamai, Morris, Bailis et al, n 5.

[119] UNAIDS and PEPFAR, n 46; Wamai, Morris, Bailis et al, n 5.

"the female-to-male Kenyan and Ugandan findings might not generalize to real-world settings",[120] was made in 2006, ie, before publication of the results of all of the RCTs and commencement of implementation.

Their next claim is that "the RCTs were premised on the untested assumption that men who have sex with men are extremely rare in Africa and that the HIV epidemic is primarily heterosexual in nature" and that "[e]vidence suggests this is not the case".[121] That heterosexual transmission is the primary mode of HIV transmission in sub-Saharan Africa is well established, as the reader will find in a previous rebuttal of this assertion.[122] Boyle and Hill further claim that "[p]articipants were deemed heterosexual because they *said* they were".[123] This can only mean that Boyle and Hill are alleging that the men could have lied about their sexual preferences. In support of this hypothesis they say "[i]n sub-Saharan Africa capital punishment has been advocated for sodomy, making it unlikely that men would willingly admit to homosexual or bisexual activity"[124] and then that "[t]he American doctors conducting these trials were offering perhaps the only medical attention many of these men were ever likely to receive, making it unlikely that they would admit to homosexual activity if it meant being denied this medical attention".[125] This is conjecture that has no place in epidemiological arguments. Furthermore, non-admittance of possible cases would not make the results statistically different. As an analysis of modes of transmission has shown, although homosexuality has a small role in the sub-Saharan Africa HIV epidemic, heterosexual activity is the primary driver, a fact for which there is general agreement by major international institutions, policy-makers and researchers.[126] In addition, it is noteworthy that any homosexual men, if present in the trials, would have been distributed equally between the intervention and control groups.

Boyle and Hill state[127] that "[t]he WHO/UNAIDS recommendation to implement mass circumcision programs in Africa … failed to heed [the Cochrane Collaboration's systematic review of the RCTs that stated that] further research is required to assess the feasibility, desirability, and cost-effectiveness of male circumcision implementation within local contexts".[128] As noted earlier, each of these have in fact been done.[129] But Boyle and Hill make no reference to the literature attesting to such research, much of which has emerged after the trials were published. It is also important to distinguish between the *effectiveness of the randomised controlled trials* and the *effectiveness of male circumcision*. As noted above, RCTs cannot be the only basis for making sound public health policy decisions.[130] The efficacy of the RCTs from the rigorous methodological perspective of science is clearly not in doubt. At the same time, the plethora of evidence of the effectiveness of male circumcision from observational epidemiological studies, systematic reviews and

[120] Boyle and Hill, n 1 at fn 48.

[121] Boyle and Hill, n 1 at 324.

[122] See Wamai, Morris, Bailis et al, n 5, section entitled "What we know about the drivers of HIV infection in sub-Saharan Africa".

[123] Boyle and Hill, n 1 at 324 (emphasis in original).

[124] Boyle and Hill, n 1 at 324.

[125] Boyle and Hill, n 1 at 325.

[126] UNAIDS, *World AIDS Day Report 2011* (2011), http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf viewed 3 February 2012; Green EC, *Rethinking AIDS Prevention: Learning from Successes in Developing Countries* (Praeger, Westport, Ct, 2003); Timberg and Halperin, n 10; Green and Ruark, n 59; Wamai, Morris and Bailis et al, n 5.

[127] Boyle and Hill, n 1 at 325.

[128] Siegfried, Muller, Deeks et al, n 33.

[129] Kahn, Marseille and Auvert, n 47; Gray, Li, Kigozi et al, n 47; Londish and Murray, n 47; Lukobo and Bailey, n 45; Westercamp and Bailey, n 45; Sawires, Dworkin, Fiamma et al, n 46; Weiss, Halperin, Bailey et al, n 32; Galarraga, Colchero, Wamai and Bertozzi, n 47.

[130] Potts M, Prata N, Walsh J et al, "Parachute Approach to Evidence Based Medicine" (2006) 333 BMJ 701; Lie RK and Miller FG, "What Counts as Reliable Evidence for Public Health Policy: The Case of Circumcision for Preventing HIV Infection" (2011) 11 BMC Med Res Methodol 34; Vandenbroucke, n 9.

meta-analyses is unequivocal. Boyle and Hill choose not to be convinced by the abundance of analytical evidence in the literature. They instead seem to prefer the unsubstantiated information of fellow male circumcision opponents when arguing their case.

REBUTTAL OF "ETHICAL AND LEGAL CONCERNS"

This section of Boyle and Hill's article reveals an apparent lack of familiarity with key elements of ethics in research practice, including the conduct of institutional review boards, the process of informed consent, confidentiality, and the practice of HIV testing. Prior to approval of the male circumcision trials, the protocols used were evaluated by ethics committees devoted to evaluation of the protocol for each specific trial. Boyle and Hill acknowledge this but question the rigour of these approvals and assert that there were multiple ethical irregularities in the conduct of the trials.[131] This is a major claim and would require substantiating. It should be noted that the ethical review committees took into account the three criteria outlined by the Commissioners of the United States National Bioethics Advisory Commission, Harold Shapiro and Eric Meslin, justifying a clinical trial in developing countries as being ethically sound.[132] These criteria are: process of informed consent, research design and ethics review, and post-trial benefits. Such criteria are similar to those provided by the Nuffield Council on Bioethics in a document that involved scientific and public lay consultations from over 20 countries.[133] All three RCTs met each of these tests of ethics. Not only were the subjects well informed and voluntarily consented to participate, the study designs and the treatment of both the control and intervention groups were approved by national and foreign (United States and French) review boards. All the men recruited to the trials desired to be circumcised. When conclusive evidence of efficacy was obtained, the control participants were offered circumcision. Efficacy was closely monitored by the trial data safety monitoring boards of each RCT. As soon as a benefit was observed, the boards decreed that to avoid exposure to a preventable risk, the trial should be terminated, so that the control group could be offered circumcision. Premature termination transpired for each of the three RCTs. This was ethically appropriate, and in fact, an ethical requirement.

Soon after the first RCT was published, the primary author of the Cochrane committee stated that the decision not to inform the participants of their HIV status during the trial "is unlikely to have affected the results".[134] Primary reasons for non-disclosure, as argued by those conducting the trials, were that antiretroviral drugs were largely unavailable and that exclusion from the trial due to a positive test "would certainly lead to stigmatization".[135] In addition, the authors "considered it unethical to inform participants of their HIV status without their permission" or deter "potentially at-risk men who did not want to know their HIV status" from participating because those testing positive would benefit from the clinical care aspects of the trial, including voluntary counselling and testing and treatment of STIs.[136] While affecting participants and their partners, the non-disclosure of HIV status for those reasons may meet the Belmont test of beneficence (do no harm, maximise possible benefits, and minimise possible harms).[137] In a setting with very low HIV testing, especially in the mid-2000s, researchers provided intensive counselling on how to avoid contracting or transmitting HIV in tandem with encouragement of testing. The Ugandan trial also included HIV-positive men as did the South African one (though the positive cases in this RCT were excluded

[131] Boyle and Hill, n 1 at 326.

[132] Shapiro HT and Meslin EM, "Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries" (2001) 345 NEJM 139.

[133] Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (Nuffield Council on Bioethics, 2005), http://www.nuffieldbioethics.org/research-developing-countries viewed 12 February 2012.

[134] Siegfried N, "Does Male Circumcision Prevent HIV Infection?" (2005) 2 PLoS Med e393, section entitled "Ethical concerns".

[135] Auvert, Taljaard, Lagarde et al, n 2 at 1114.

[136] Auvert, Taljaard, Lagarde et al, n 2.

[137] United States Department of Health and Human Services, *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 18 April 1979), http://www.hhs.gov/ohrp/policy/belmont.html viewed 15 February 2012.

from the statistical analysis), but the Kenyan trial did not. While all the trials produced remarkably similar results, despite the different inclusion criteria, differing policies by the funders can result in ethical challenges.[138] Still, if one accepts the arguments by Boyle and Hill, then the trial data should have shown either no difference or higher HIV in men in the circumcised arm of the trial. Not only did the Cochrane committee state in 2009 after their analysis of all three trials that the data from the trials were so conclusive that "no further trials are required",[139] given the current evidence of its protective effect, they made it clear that a further large-scale RCT of male circumcision for HIV prevention is unlikely as it would now rightly be deemed unethical.

Circumcision as a cause of HIV infection

Boyle and Hill posit that male circumcision is a likely *cause* of HIV transmission.[140] They fail to explain, however, that the 2007 publication[141] and the earlier conference abstract they refer to,[142] are not about medical circumcisions, but rather about traditional tribal circumcisions, known to pose a HIV risk when crude instruments are used serially on several men without sterilisation between each procedure. Nonetheless, the evidence for the occurrence of such infections in traditional circumcision is mixed.[143] Boyle and Hill convey the impression of being unaware that the trials, male circumcision policies and current implementation practices promote voluntary *medical* (not traditional) male circumcision. In VMMC programs, men are counselled to delay resumption of sex until complete post-circumcision wound healing and to practise safer sex in order to reduce the risk of HIV transmission.[144] Boyle and Hill cite Gisselquist and colleagues who have speculated that other modes of transmission such as contaminated skin-piercing instruments or multidose vials of local anaesthetics are major factors for HIV transmission in sub-Saharan Africa,[145] but fail to acknowledge the criticism such speculation has received.[146]

Boyle and Hill then turn to the trial by Wawer et al of HIV transmission from HIV-positive men to women after the men had been circumcised.[147] This study found 61% higher HIV prevalence in the female sexual partners of men in the circumcised arm of the trial, although this difference did not reach statistical significance. Over the course of their article, Boyle and Hill reiterate the finding from this single outlier study 12 times. But they fail to note that a critical explanation for the higher HIV in women in the circumcision arm was a consequence of early resumption of sexual intercourse before wound healing. To quote from Wawer et al, in the intervention group "female acquisition of HIV, assessed at 6 months, occurred in a higher proportion of couples who resumed sex early [27.8%; 95%

[138] Gray RH, Sewankambo NK, Wawer MJ et al, "Disclosure of HIV Status on Informed Consent Forms Presents an Ethical Dilemma for Protection of Human Subjects" (2006) 41(2) J Acquir Immune Defic Syndr 246; Clark P, "AIDS Research in Developing Countries: Do the Ends Justify the Means?" (2002) 8 Med Sci Monit ED5.

[139] Siegfried, Muller, Deeks et al, n 33.

[140] Boyle and Hill, n 1 at 325.

[141] Brewer DD, Potterat JJ, Roberts JM Jr et al, "Male and Female Circumcision Associated with Prevalent HIV Infection in Virgins and Adolescents in Kenya, Lesotho, and Tanzania" (2007) 17 Ann Epidemiol 217.

[142] Boyle and Hill, n 1 at fn 54.

[143] Shaffer DN, Bautista CT, Sateren WB et al, "The Protective Effect of Circumcision on HIV Incidence in Rural Low-risk Men Circumcised Predominantly by Traditional Circumcisers in Kenya: Two-year Follow-up of the Kericho HIV Cohort Study" (2007) 45 J Acquir Immune Defic Syndr 371; Bailey RC, Egesah O and Rosenberg S, "Male Circumcision for HIV Prevention: A Prospective Study of Complications in Clinical and Traditional Settings in Bungoma, Kenya" (2008) 86 Bull World Health Org 669; Wilcken A, Keil T and Dick B, "Traditional Male Circumcision in Eastern and Southern Africa: A Systematic Review of Prevalence and Complications" (2010) 88 Bull World Health Org 907.

[144] Wamai, Morris, Bailis et al, n 5.

[145] Gisselquist D, Potterat JJ, St Lawrence JS et al, "How to Contain Generalized HIV Epidemics? A Plea for Better Evidence to Displace Speculation" (2009) 20 Int J STD AIDS 443.

[146] Schmid GP, Buvé A, Mugyenyi P et al, "Eliminating Unsafe Injections is Important, But Will Have Little Impact on HIV Transmission in sub-Saharan Africa" (2004) 363 *Lancet* 48; Wamai and Morris, n 5; Wamai, Morris, Bailis et al, n 5.

[147] Wawer, Makumbi, Kigozi et al, n 66.

CI 7.10-57.55] than in couples who delayed resumption of sex [9.5%; 95% CI 3.26-15.74]".[148] In fact, the rate of HIV acquisition in those who delayed resumption of sex after circumcision for six months (9.5%; 95% CI 3.26-15.74) was similar to that in the control group (7.9%; 95% CI 1.26-14.61).[149] Thus, a singular focus on this outlier study and obfuscation of its design and findings tends to undermine the objectivity of Boyle and Hill. Their arguments would have seemed more credible had they broadened their perspective by reviewing the entire literature. If they had, they should have noted the overwhelming evidence of a demonstrated efficacy, not only of male circumcision for HIV prevention in heterosexual men not infected with HIV and who adhered to advice during counselling to wait for wound to heal before resuming sexual intercourse and then practise safer sex, but also the lack of any significant increase in HIV prevalence in female sexual partners of circumcised men. Boyle and Hill also quote out of context the conclusion by Wawer and co-workers that "male circumcision programmes … confer an overall benefit to women" in HIV infection risk reduction.[150] In contrast, the entire sentence in Wawer et al reads: "male circumcision programmes are thus likely to confer an overall benefit to women".[151] Furthermore, here Wawer et al are referring to the fact that the efficacy of male circumcision in preventing "HIV in uninfected men is clear", rather than data from their own study. By misquoting the authors, Boyle and Hill then allege that the conclusion from the trial by Wawer et al was "an apparent example of irrational *motivated* reasoning".[152] Such an assertion would appear foolhardy.

Boyle and Hill's citation of the study by Wawer et al, while ignoring the meta-analysis by Weiss et al in 2009 of all studies of male circumcision and risk of HIV in women,[153] is an illustrative example of inappropriate selective citation. The meta-analysis of all data to that time, including Wawer et al, found 20% *lower* HIV prevalence in women whose partner was circumcised, even though this reduction did not achieve statistical significance. As mentioned earlier, Weiss and co-authors suggested that for definitive results a RCT involving around 10,000 sero-discordant couples would be required. Although the feasibility of such a large study is improbable, they noted that benefits would likely still result if male circumcision services were integrated as part of existing prevention strategies in sero-discordant populations.[154] If HIV-positive men delayed resumption of sex after circumcision until their circumcision wound had healed, and practised safer sex thereafter, HIV transmission to their female partner would be negligible.[155] This is pertinent, especially because it has been estimated recently that the per-coital-act HIV infectivity among African sero-discordant couples is 1 in 1,000 in each sex.[156]

Boyle and Hill ignore a subsequent study of several countries in sub-Saharan Africa that found women to be at 38% lower risk of being infected with HIV if their male partner was circumcised.[157] They also ignore a modelling study that predicted that, in a general population setting, male circumcision would confer a 46% reduction in the rate of male-to-female HIV transmission.[158] Thus, contrary to assertions by Boyle and Hill, when all of the scientific evidence – including modelling and country-specific estimates of the potential impact for women – is considered, it is clear that male

[148] Wawer, Makumbi, Kigozi et al, n 66.

[149] Wawer, Makumbi, Kigozi et al, n 66.

[150] Boyle and Hill, n 1 at 326.

[151] Wawer, Makumbi, Kigozi et al, n 66.

[152] Boyle and Hill, n 1 at 326 (emphasis in original).

[153] Weiss, Hankins and Dickson, n 39.

[154] Weiss, Hankins and Dickson, n 39.

[155] Wawer, Makumbi, Kigozi et al, n 66.

[156] Hughes JP, Baeten JM, Lingappa JR et al, "Determinants of Per-Coital-Act HIV-1 Infectivity Among African HIV-1-Serodiscordant Couples" (2012) 205 J Infect Dis 358.

[157] Baeten, Donnell, Kapiga et al, n 42.

[158] Hallett, Alsallaq, Baeten et al, n 43.

circumcision confers long-term indirect and potential direct positive impacts to women.[159] These include reduction in oncogenic types of human papillomavirus, herpes simplex virus type 2, bacterial vaginosis and possibly other STIs or sexually associated infections.[160] The reduced risk in circumcised men of contracting such infections results in less exposure for women as a result of their male partner(s) being circumcised.[161]

Since the benefits of male circumcision in HIV prevention are now proven, the question as far as ethics is concerned is not that advocating male circumcision is a violation of ethical principles or human rights, but rather that failure to advocate male circumcision to help protect against infection by HIV, or indeed the other STIs and other infections, might be deemed a dereliction of duty by any medical practitioner or health authority. Ethical analyses have emphasised that it is unethical in medical practice to not offer a proven intervention such as male circumcision for HIV prevention.[162] Such a failure to offer a beneficial procedure has previously resulted in the needless loss of thousands of lives.[163]

Non-sexual transmission of HIV

This issue has been addressed above in the section "Factors jeopardising external validity". It has also been addressed in various previous publications.[164] It is therefore curious that instead of providing a critique of these, Boyle and Hill have chosen to ignore the previous exposés of the same conjectures they repeat in their article.

To show that non-sexual transmission is not a major driver of HIV infection in sub-Saharan Africa the current authors refer to findings arising from modes of transmission analyses using consultative methodologies and other standard approaches for collection of epidemiological observational data for multiple countries in sub-Saharan Africa that they have evaluated.[165] These and other studies provide solid, unequivocal evidence in support of heterosexual exposure as the major route of HIV infection in these countries.[166] Moreover, Boyle and Hill and the other male circumcision opponents they cite such as Vines[167] and Gisselquist[168] should recognise that the available evidence in support of the efficacy of male circumcision is not just the RCT data but considerable and consistent observational data starting

[159] UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention (Corresponding author, Hankins C), "Male Circumcision for HIV Prevention in High HIV Prevalence Settings: What Can Mathematical Modelling Contribute to Informed Decision Making?" (2009) 6 PLoS Med e1000109; Wamai, Morris, Bailis et al, n 5; Njeuhmeli, Forsythe, Reed et al, n 47.

[160] Morris, n 8; Tobian, Gray and Quinn, n 8; Giuliano AR, Nyitray AG and Albero G, "Male Circumcision and HPV Transmission to Female Partners" (2011) 377 *Lancet* 183; Zetola N and Klausner JD, "Male Circumcision Reduces Human Papillomavirus Incidence and Prevalence: Clarifying the Evidence" (2012) 39 Sex Transm Dis 114; Morris, Gray, Castellsague et al, n 8; Tobian and Gray, n 8; Albero G, Castellsagué X, Giuliano AR et al, "Male Circumcision and Genital Human Papillomavirus: A Systematic Review and Meta-analysis" (2012) 39 Sex Transm Dis 104.

[161] Weiss, Halperin, Bailey et al, n 32.

[162] Lie RK, Emanuel EJ and Grady C, "Circumcision and HIV Prevention Research: An Ethical Analysis" (2006) 368 *Lancet* 522; UNAIDS, n 48.

[163] Chigwedere, Seage, Gruskin et al, n 10.

[164] Auvert, Taljaard, Lagarde et al, n 2; Wamai, Weiss, Hankins et al, n 5; Wamai, Morris, Bailis et al, n 5.

[165] Wamai, Morris, Bailis et al, n 5, Table 1.

[166] Buvé A, Caraël M, Hayes RJ et al, "Multicentre Study on Factors Determining Differences in Rate of Spread of HIV in Sub-Saharan Africa: Methods and Prevalence of HIV Infection" (2001) 15(Suppl 4) AIDS S5; Buve A, "The HIV Epidemics in Sub-Saharan Africa: Why So Severe? Why So Heterogenous? An Epidemiological Perspective" in Denis P and Becker C (eds), *The HIV/AIDS Epidemic in Sub-Saharan Africa in a Historical Perspective* (Senegalese Network, Law, Ethics, Health, Online edition, 2006) p 41; Orroth KK, White RG, Freeman EE et al, "Attempting to Explain Heterogeneous HIV Epidemics in Sub-Saharan Africa: Potential Role of Historical Changes in Risk Behaviour and Male Circumcision" (2011) 87 Sex Transm Infect 640.

[167] Vines J, "Major Potential Confounder Not Addressed" (2006) 3 PLoS Med e63, cited in Boyle and Hill, n 1 at fn 64.

[168] Gisselquist, Potterat, St Lawrence et al, n 4, cited in Boyle and Hill, n 1 at fn 65.

as early as the 1980s, as well as systematic reviews and meta-analyses referred to earlier. When all of the evidence is considered as a whole, there is ample justification for the implementation of programs to offer VMMC to millions of men.

Contradictory evidence

Boyle and Hill present a calculation from Van Howe's unpublished work (their footnote 26) leading to their claim that the trial data show that male circumcision is only able to reduce HIV infection by 1.3%.[169] However, unpublished data from an unreliable source are not credible. The authors reveal a naivety in relation to epidemiology in general and the conduct of RCTs in particular. They seem to have failed to understand the methodologies and statistical outcomes that were explained in the published trials and the supplementary materials associated with those publications. These were all quite conventional. It is incorrect to cite as insignificant the 1.3% they report as an "*absolute* decrease"[170] and use this as evidence disputing the conclusions from the RCTs. The Cochrane systematic review and meta-analysis of all three trials points out that there was a "significant *absolute risk* reduction of 0.83% at 12 months and of 1.80% at 21 or 24 months, following circumcision".[171] This led the esteemed Cochrane committee to state that the trials provided "*strong evidence* that medical male circumcision reduces the acquisition of HIV by heterosexual men by between 38% and 66% over 24 months".[172] Post-trial follow-up has shown that by 4.5 to 4.8 years the protective effect has increased to 67-73%,[173] and this is supported by initial data from the large-scale community roll-out.[174]

The trials were large and well-powered statistically in order to detect a protective effect should one truly exist or rule out a protective effect should one not exist. Indeed, each trial was stopped early because a beneficial effect was noted, allowing the intervention (male circumcision) to be offered to the control group. Not to do so would have been unethical. Had ethical considerations been put aside and the trials had run their full course or even had continued beyond the predetermined stopping date, it would have led to many more of the control group becoming infected unnecessarily.

Boyle and Hill further state that "the claimed efficacy of male circumcision in reducing HIV transmission has been contradicted by at least 17 observational studies",[175] then cite as support a number of studies including Green et al.[176] In their Figure 1 and Appendix they list countries in which studies have found higher HIV in circumcised men. Their Figure 1 is from a non-peer reviewed website (http://www.circumstitions.com) by a male circumcision opponent. The Figure shows no protection against HIV infection in seven of 12 countries in sub-Saharan Africa. However, Boyle and Hill fail to cite a published peer-reviewed meta-analysis that includes data from all of those same countries, as well as 11 others, that found a protective effect of male circumcision of 83%.[177] Usually a peer-reviewed report is regarded as having greater credibility than one that is not peer-reviewed. Furthermore, Boyle and Hill fail to mention that five countries of the 12 they depict in their Figure 1 in fact show higher prevalence of HIV infection among uncircumcised men. Indeed, the observational evidence going back around 25 years is much more extensive than the selected studies in Boyle and Hill's Figure 1. For example, a Cochrane review referred to over 30 studies in suggesting a protective effect of male circumcision,[178] while other authors refer to over 50 studies.[179] (See Box 1.)

[169] Boyle and Hill, n 1 at 326.

[170] Boyle and Hill, n 1 at 322 (emphasis in original).

[171] Siegfried, Muller, Deeks et al, n 33 (emphasis added).

[172] Siegfried, Muller, Deeks et al, n 33 (emphasis added).

[173] Bailey, Moses, Parker et al, n 3; Gray, Kigozi, Kong et al, n 3.

[174] Auvert, Taljaard, Rech et al, n 16.

[175] Boyle and Hill, n 1 at 326.

[176] Green, McAllister, Peterson et al, n 4. See also Boyle and Hill, n 1 at fn 66.

[177] Gebremedhin, n 37.

[178] Siegfried, Muller, Deeks et al, n 33.

Boyle and Hill then ask "why HIV prevalence is much higher in the United States (where most men are circumcised) than in developed countries where most men are intact".[180] The answer to that question is simple. First, the main drivers of HIV transmission in developed countries are receptive anal intercourse in men who have sex with men and injection of drugs with contaminated equipment.[181] Male circumcision is unable to prevent HIV infection via either of these modes of transmission.[182] Secondly, the United States has higher prevalent and incident HIV than other developed countries,[183] owing in part to historical reasons concerning the route and timing of the arrival of HIV in the United States,[184] and the predominant mode of transmission in the United States, namely receptive anal intercourse among men who have sex with men.[185] Thirdly, HIV incidence is proportionately higher in African-American populations,[186] which also have a lower prevalence of male circumcision,[187] and higher rates of heterosexually-acquired HIV.[188] Hence, rather than note simple correlations, proper epidemiological evaluation of disease prevalence depends on an understanding and consideration of basic differences between concentrated and generalised HIV epidemics,[189] indeed of the multifactorial nature and basic epidemiology of HIV prevalence and acquisition across different settings and population subgroups. When the single factor of male circumcision in relation to infection during heterosexual sex has been studied, male circumcision has been shown to afford similar protection against HIV infection in the United States[190] as seen in sub-Saharan Africa and elsewhere in the world, such as India.[191] Moreover, even in low-prevalence

[179] Dickson K and Farley T, "Male Circumcision Scale-up", Oral Presentation, Paper No 62, 17th Conference on Retroviruses and Opportunistic Infections (CROI), 16-19 February 2010, San Francisco, http://www.app2.capitalreach.com/esp1204/servlet/tc?c=10164&cn=retro&e=12350&m=1&s=20431&&espmt=2&mp3file=12350&m4bfile=12350 viewed 10 February 2012.

[180] Boyle and Hill, n 1 at 327.

[181] UNAIDS, n 126; Halperin DR and Bailey RC, "Male Circumcision and HIV Infection: 10 Years and Counting" (1999) 354 *Lancet* 1813.

[182] Lane T, Raymond HF, Dladla S et al, "High HIV Prevalence Among Men Who have Sex with Men in Soweto, South Africa: Results from the Soweto Men's Study" (2011) 15 AIDS Behav 626; Millett GA, Flores SA, Marks G et al, "Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who have Sex with Men: A Meta-analysis" (2008) 300 JAMA 1674; Wiysonge CS, Kongnyuy EJ, Shey M et al, "Male Circumcision for Prevention of Homosexual Acquisition of HIV in Men" (2011) 6 Cochrane Database Syst Rev CD007496.

[183] UNAIDS, n 126.

[184] Gilbert MT, Rambaut A, Wlasiuk G et al, "The Emergence of HIV/AIDS in the Americas and Beyond" (2007) 104 Proc Natl Acad Sci USA 18566.

[185] UNAIDS, n 126.

[186] Hall HI, Song R, Rhodes P et al, "Estimation of HIV Incidence in the United States" (2008) 300 JAMA 520.

[187] Xu F, Markowitz L, Sternberg M et al, "Prevalence of Circumcision in Men in the United States: Data from the National Health and Nutrition Examination Survey (NHANES), 1999-2002" (2006) XVI International AIDS Conference Abstract No TUPE0395.

[188] Centers for Disease Control, "Centers for Disease Control and Prevention. Racial/Ethnic Disparities in Diagnoses of HIV/AIDS – 33 States, 2001-2005" (2007) 56 Morb Mortal Wkly Rep 189.

[189] Green and Ruark, n 59; Wilson D, *HIV Epidemiology: A Review of Recent Trends and Lessons* (The World Bank, Washington DC, 2006).

[190] Telzak EE, Chiasson MA, Bevier PJ et al, "HIV-1 Seroconversion in Patients With and Without Genital Ulcer Disease: A Prospective Study" (1993) 119 Ann Intern Med 1181; Sullivan PS, Kilmarx PH, Peterman TA et al, "Male Circumcision for Prevention of HIV Transmission: What the New Data Mean for HIV Prevention in the United States" (2007) 4(e223) PLoS Med 1162; Warner L, Ghanem KG, Newman DR et al, "Male Circumcision and Risk of HIV Infection Among Heterosexual African American Men Attending Baltimore Sexually Transmitted Disease Clinics" (2009) 199 J Infect Dis 59.

[191] Reynolds SJ, Shepherd ME, Risbud AR et al, "Male Circumcision and Risk of HIV-1 and Other Sexually Transmitted Infections in India" (2004) 363 *Lancet* 1039; Munro HL, Pradeep BS, Jayachandran AA et al, "Prevalence and Determinants of HIV and Sexually Transmitted Infections in a General Population-based Sample in Mysore District, Karnataka State, Southern India" (2008) 22(Suppl 5) AIDS S117.

settings such as the United States, infant male circumcision has been shown to be cost-*saving*, reducing lifetime risk of HIV infection by 16%.[192]

Boyle and Hill claim that langerin, which is synthesised in Langerhans cells, "blocks transmission of HIV",[193] failing to explain that the study they cite[194] is not about transmission to other people, but to T cells in lower layers of the foreskin epithelium, and then only at low viral loads.[195] At high viral loads langerin is overwhelmed. This is why for each log10 increase in plasma HIV-1 RNA the per-coital-act risk of HIV transmission to the sexual partner is elevated 2.9-fold.[196] More importantly, Boyle and Hill do not cite the extensive biological information now available that explains why the foreskin is a risk factor for HIV acquisition and why male circumcision protects against HIV acquisition.[197] Such biological evidence extends beyond langerin and includes evidence of infection not involving Langerhans cells.

Boyle and Hill then quote[198] from an opinion piece that says "Langerhans cells occur in the clitoris, the labia, and in other parts of both male and female genitals, and no one is talking about removing these in the name of HIV prevention".[199] This statement fails to recognise the ethical, medical and biological absurdity of such an argument, considering (i) the clitoris is the female equivalent of the penis and has an important functional and sensory role during intercourse and other sexual activities;[200] and (ii) that owing to the area of vulnerable mucosal epithelium, most genital HIV infections in women occur via the cervico-vaginal epithelium, not the clitoris or labia.[201] Using Boyle and Hill's logic, lopping off the penis would also reduce HIV infections. But since (i) it is the foreskin that is the part of the penis responsible for HIV infection, (ii) the foreskin is not only redundant, but prone to disease, and (iii) based on the bulk of the current scientific literature, the foreskin has no functional or sensory importance, its removal by male circumcision is much more logical.

They next claim that a vaccine trial in Thailand was six times more effective than male circumcision,[202] when in fact the protective effect of the vaccine was at best only 31.2%, although this did span all modalities of infection, not just heterosexual sex.[203] As pointed out in editorials entitled "Mind the Spin"[204] and "Jury Still Out on HIV Vaccine Results",[205] the data from this trial have received a mixed reception. Of 39 HIV prevention RCTs, this was the only vaccine trial to report an effect, whereas all three male circumcision trials were spectacularly successful.[206]

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[192] Sansom SL, Prabhu VS, Hutchinson AB et al, "Cost-effectiveness of Newborn Circumcision in Reducing Lifetime HIV Risk Among US Males" (2010) 5 PLoS One e8723.

[193] Boyle and Hill, n 1 at 327.

[194] De Witte L, Nabatov A, Pion M et al, "Langerin is a Natural Barrier to HIV-1 Transmission by Langerhans Cells" (2007) 13 Nat Med 367.

[195] De Witte, Nabatov, Pion et al, n 194.

[196] Hughes, Baeten, Lingappa et al, n 156.

[197] Morris BJ and Wamai RG, "Biological Basis for the Protective Effect Conferred by Male Circumcision Against HIV Infection" (2012) 23 Int J STD AIDS 153; Price LB, Liu CM, Johnson KE et al, "The Effects of Circumcision on the Penis Microbiome" (2010) 5 PLoS One e8422.

[198] Boyle and Hill, n 1 at 327,

[199] Dowsett and Couch, n 73.

[200] O'Connell HE, Sanjeevan KV and Hutson JM, "Anatomy of the Clitoris" (2005) 174 J Urol 174 1189.

[201] Mingjia L and Short R, "How Oestrogen or Progesterone Might Change a Woman's Susceptibility to HIV-1 Infection" (2002) 42 ANZ J Obstet Gynaecol 472.

[202] Boyle and Hill, n 1 at 327.

[203] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al, "Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand" (2009) 361 NEJM 2209.

[204] Anonymous, "Mind the Spin" (2009) 461 *Nature* 1174.

[205] Butler D, "Jury Still Out on HIV Vaccine Results" (2009) 461 *Nature* 1187.

[206] Padian, McCoy, Balkus et al, n 38.

Boyle and Hill then refer[207] to a RCT of a microbicide gel of 1% Tenofovir which was found to reduce HIV infection in women by 39% overall and 54% in high adherers,[208] by making the curious observation that "circumcised men may not benefit from Tenofovir treatment because their preputial mucosa has been excised"! Whether Tenofovir might reduce transmission of HIV from a HIV-positive woman to a HIV-negative man of either male circumcision status has not yet been tested. Even if Tenofovir was as effective in uncircumcised men as in women, it would nevertheless be less effective than male circumcision, which reduces HIV infection by 67-73%.[209] Moreover, just as male or female condoms must be used correctly and consistently prior to every sex act, a microbicide would need to be applied consistently prior to sexual activity each and every time over decades for efficacy to be expected at these levels. While other measures for HIV prevention are well worth advocating as critical components in the "tool box" of HIV prevention approaches, they provide more limited lifetime protection than male circumcision.[210] In concluding their assertions about "contradictory evidence" Boyle and Hill selectively cite a 2006 article[211] that appeared before all of the RCTs were published. The field has moved on considerably since that time.

Lack of fully informed consent

Boyle and Hill say that the "provision of fully informed consent may have been compromised" because "[r]esearchers controlled the information available to men".[212] But they provide no evidence for the so-called control of information. Instead, they cite a statement about a false sense of security that appeared in one of Uganda's national newspapers, a statement by a health official in a Brazilian newspaper, and an off-the-cuff remark by Uganda's President Yoweri Museveni that appeared in an online newspaper article.[213] Importantly, these sources indicated that the individuals concerned were expressing their personal opposition to male circumcision rather than providing any evidence of men being misled into a false sense of security.

Boyle and Hill also cite studies on risk compensation from 1997, 2002 and 2007, arguing that men who have been circumcised will stop using condoms altogether, have sex before wound healing, and have sex with more partners.[214] This is misleading because more recent studies of the trial populations have shown no such thing.[215] In the reports emanating from the trials themselves, there was no evidence of risk compensation in either the Kenyan[216] or Ugandan[217] trials, and although there was increased frequency of sex in the South African trial, there was no increase in the numbers of sexual partners.[218] It should be noted that counselling was provided to men in each group urging them to adopt behaviours that would reduce their risk of HIV and other STIs and to always use condoms. The issue of risk compensation is actually an argument in favour of male circumcision in infancy,

[207] Boyle and Hill, n 1 at 327.

[208] Karim QA, Karim SSA, Frohlich JA et al, "Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women" (2010) 329 *Science* 1168.

[209] Bailey, Moses, Parker et al, n 3; Gray, Kigozi, Kong et al, n 3.

[210] Marrazzo JM and Cates W, "Interventions to Prevent Sexually Transmitted Infections, Including HIV Infection" (2011) 53(Suppl 3) Clin Infect Dis S64.

[211] Garenne M, "Male Circumcision and HIV Control in Africa" (2006) 3 PLoS Med e78, cited in Boyle and Hill, n 1 at fn 77.

[212] Boyle and Hill, n 1 at 328.

[213] Boyle and Hill, n 1 at 328.

[214] Boyle and Hill, n 1 at 328.

[215] Agot KE, Kiarie JN, Nguyen HQ et al, "Male Circumcision in Siaya and Bondo Districts, Kenya: Prospective Cohort Study to Assess Behavioral Disinhibition Following Circumcision" (2007) 44 J Acquir Immune Defic Syndr 66; Mehta SD, Gray RH, Auvert B et al, "Does Sex in the Early Period After Circumcision Increase HIV-seroconversion Risk? Pooled Analysis of Adult Male Circumcision Clinical Trials" (2009) 23 AIDS 1557; Mattson CL, Campbell RT, Bailey RC et al, "Risk Compensation is Not Associated with Male Circumcision in Kisumu, Kenya: A Multi-faceted Assessment of Men Enrolled in a Randomized Controlled Trial" (2008) 3 PLoS One e2443.

[216] Bailey, Moses, Parker et al, n 2.

[217] Gray, Kigozi, Serwadda et al, n 2.

[218] Auvert, Taljaard, Lagarde et al, n 2.

since by the time the male reaches sexual maturity and begins having sex, the issue of a change in his circumcision status that might lead to him behaving more recklessly is avoided.

Participant inducement

Here Boyle and Hill fail to appreciate the well-established ethical standards for clinical trials. These include informed consent and the common practice of modest compensation for study participation.[219] The NIH training protocol for research on human subjects[220] defines coercion as "implied threats", and undue influence such as "excessive compensation". This training protocol also contains a detailed consent process. In the case of the United States-led RCTs it was made clear in the publications arising that the NIH approved the studies. The claim by Boyle and Hill of participant inducement is unfounded. Each trial reported the amounts by which participants were compensated, these having been approved by the ethical review boards as being justified to cover transport and loss of work income. Furthermore, the practice of male circumcision is common in most African cultures and for both Christian and Muslim religions.[221] This has been documented in the ecological analysis of male circumcision and HIV in 118 developing countries.[222] Moreover, it is interesting that at least some African indigenous or "traditional" healers have, for decades, advocated male circumcision for prevention of HIV and other infections and conditions long before the RCTs were conducted. These authors explained that men with repeat STIs tended to come from societies where males do not circumcise, so they were led to promote male circumcision not by the scientific literature but by their own empirical observations.[223]

Boyle and Hill state that "[t]he prepuce is a highly erogenous part of the penis"[224] and cite a study funded by NOCIRC (a group opposed to male circumcision),[225] while failing to cite Waskett and Morris who showed that a proper statistical analysis of those data failed to support this assertion.[226] Of all glabrous (hairless) regions of the body, the foreskin has the lowest number and least sophisticated Meissner's corpuscles (touch receptors).[227] More important, though, is the fact that sexual sensations are mediated by genital corpuscles, not Meissner's corpuscles, and these are absent from the foreskin.[228] Moreover, a study of 70 circumcised and 11 uncircumcised men in the United States found each ranked the *ventral surface* of the penis (underside of glans and shaft) highest for degree of "sexual pleasure" and "orgasm intensity", followed by the upper surface and sides of the penis, the foreskin being less important.[229] Boyle and Hill fail to cite research in which measurements by thermal imaging found that sensation of the penis during arousal did not differ between circumcised and uncircumcised men aged 18 to 45.[230] Interestingly, more circumcised participants exhibited an increase in their level of arousal, while more uncircumcised men were found to be unaffected by the

[219] Shapiro and Meslin, n 132; Nuffield Council on Bioethics, n 133; National Institutes of Health, n 133.

[220] See National Institutes of Health, n 52.

[221] Wilcken, Keil and Dick, n 143; Wamai, Weiss, Hankins et al, n 5.

[222] Drain PK, Halperin DT, Hughes JP et al, "Male Circumcision, Religion, and Infectious Diseases: An Ecologic Analysis of 118 Developing Countries" (2006) 6 BMC Infect Dis 172.

[223] Green EC, Zokwe B and Dupree JD, "Indigenous African Healers Promote Male Circumcision for Prevention of Sexually Transmitted Diseases" (1993) 23 Trop Doctor 182.

[224] Boyle and Hill, n 1 at 328.

[225] Sorrells ML, Snyder JL, Reiss MD et al, "Fine-touch Pressure Thresholds in the Adult Penis" (2007) 99 BJU Int 864.

[226] Waskett JH and Morris BJ, "Fine-touch Pressure Thresholds in the Adult Penis" (2007) 99 BJU Int 1551 (critique of Sorrells et al, n 225).

[227] Bhat GH, Bhat MA, Kour K et al, "Density and Structural Variations of Meissner's Corpuscles at Different Sites in Human Glaborous Skin" (2008) 57 J Anat Soc India 30.

[228] Rhodin JAG, *Rhodin's Histology* (Oxford University Press, 1974).

[229] Schober JM, Meyer-Bahlburg HF and Dolezal C, "Self-ratings of Genital Anatomy, Sexual Sensitivity and Function in Men using the 'Self-Assessment of Genital Anatomy and Sexual Function, Male' Questionnaire" (2009) 103 BJU Int 1096.

[230] Payne K, Thaler L, Kukkonen T et al, "Sensation and Sexual Arousal in Circumcised and Uncircumcised Men" (2007) 4 J Sex Med 667.

erotic stimulus (a movie). In fact, in order for the erect penis to enter the vagina one might expect that sensitivity of the penis would need to be lower when aroused than when flaccid. This indeed was seen, and the measurements in this Montreal study indicated a similar reduction in the circumcised and uncircumcised penis.[231]

Other statements made by Boyle and Hill can also be disputed. These include claims that male circumcision constitutes "significant bodily injury", "irreversible amputation", that the procedure causes "adverse psychosexual effects", and that it may be "tantamount to criminal assault".[232] Boyle and Hill provide no evidence in support of these assertions, which should therefore be disregarded. The cultural and biomedically-sound preventive health practice of male circumcision is common among diverse societies around the world. It is possible that for some individuals male circumcision status may be a physical marker for broad inter-cultural tensions. In evaluating the opinions of Boyle and Hill, readers should consider the following:

- Male circumcision has been a historical, cultural and religious practice since the beginning of civilisation,[233] and there is evidence that it predates recorded history, with evidence of male circumcision in art forms from Paleolithic Europe (38,000 to 11,000 years BCE).[234] If it really did have any adverse effects, one would have expected the practice to have died out long ago. Since it may have facilitated reproduction, male circumcision could even have enhanced our success as a species.[235]
- The three RCTs received ethical clearance according to established standards. This was required for funding. Ethical approval was also given by governing bodies in the countries where the trials were undertaken. Ethical requirements included confidentiality that barred researchers from disclosing the status of the subjects to others. If, during the thorough review that the ethics committees undertook, any substantive evidence of male circumcision being inherently harmful had been identified, then the committees would not have approved the trials.
- The findings that emerged from the trials led to policy endorsement by global intergovernmental multilateral and bilateral as well as national bodies.[236]
- There is high acceptability of male circumcision worldwide, especially after the provision to people of balanced information on benefits and risks.[237] In southern Africa, where the highest HIV prevalence is found, promotion among key groups (Zulu, Tswana, Swazi) meant reintroducing a prior custom of male circumcision that had died out for a variety of reasons, including contact with European civilisation (perhaps because of missionary disapproval of rites of passage), and a Zulu king who felt that he could not afford to have men off the battle field as would happen during post-circumcision wound healing.[238]

Boyle and Hill go on to ask "does the United States medical establishment regard poor, black African men as an expendable resource to be exploited?"[239] Not only is there no evidential support for

[231] Payne, Thaler, Kukkonen et al, n 230.

[232] Boyle and Hill, n 1 at 329.

[233] Gairdner D, "The Fate of the Foreskin. A Study of Circumcision" (2009) 2 BMJ 1433; Gollaher D, *A History of the World's Most Controversial Surgery* (Basic Books, New York, 2000); Alanis and Lucidi, n 8; Kaicher DC and Swan KG, "A Cut Above: Circumcision as an Ancient Status Symbol" (2010) 76 *Urology* 18; Cox G and Morris BJ, "Why Circumcision – From Pre-history to the 21st Century" in Bolnick DA, Koyle MA and Yosha A (eds), *Surgical Guide to Circumcision* (Springer, London, 2012) p 243.

[234] Angulo JC and García-Díez M, "Male Genital Representation in Paleolithic Art: Erection and Circumcision Before History" (2009) 74 *Urology* 10.

[235] Cox and Morris, n 233. Cox G, "De Virginibus, Puerisque, The Function of the Human Foreskin Considered from an Evolutionary Perspective" (1995) 45 Med Hypoth 617.

[236] WHO/UNAIDS, n 48; UNAIDS, n 48.

[237] Lukobo and Bailey, n 45; Westercamp and Bailey, n 45; Yang, Abdullah, Wei et al, n 45.

[238] Timberg and Halperin, n 10, p 8.

[239] Boyle and Hill, n 1 at 329.

this statement, many would regard it as provocative and offensive. Participation of men in the trials was purely voluntary. The existing guidelines for male circumcision interventions are of a high standard and preclude coercion.[240]

FALLACIOUS STATEMENTS IN "DISCUSSION"

In this section of their article Boyle and Hill make assertions that are untenable when weighed against valid scientific evidence. The current authors find no credible evidence to support Boyle and Hill's claims that male circumcision has little "absolute" risk reduction, that it is not cost-effective and that its long-term effectiveness is unknown.[241] The RCTs, observational studies and reviews on male circumcision efficacy that the current authors have referred to dispute the claims of Boyle and Hill of little risk reduction. The current authors have also referred to numerous cost-effectiveness studies that contradict the claim to the contrary by Boyle and Hill. One such recent study found that "An investment of US$1.5 billion between 2011 and 2015 to achieve 80% coverage in 13 priority countries in southern and eastern Africa will result in net savings of US$16.5 billion".[242] Boyle and Hill's statement that "any long-term effectiveness in sub-Saharan Africa will not be known for many years"[243] has already been proven to be untrue in that data from the large-scale community roll-out of male circumcision in South Africa has already shown a population-level protective effect against HIV.[244]

In attempting to water down the evidence supporting male circumcision for HIV prevention, Boyle and Hill use pseudo-science rather than an evidence-based assessment. They present arguments that ignore the breadth and currency of research in the field, use selective citation of outlier studies that would suit an agenda that opposes male circumcision, and refer to poor-quality studies that have often been dismissed in published critiques. For example, Boyle and Hill cite studies reporting on the challenges of achieving mass male circumcision,[245] but fail to realise that mass male circumcision roll-out already underway is being achieved, despite the challenges, with negligible adverse effects.[246] Likewise, Boyle and Hill's assertion that HIV transmission in sub-Saharan Africa is "largely by non-sexual means"[247] can be dismissed as an unproven conjecture that contradicts high-quality and long-established conventional evidence. No credible source in the HIV research community would make such claims. The current authors posit that only researchers and other actors who follow fringe theories (eg, HIV is causally unrelated to AIDS, medical misuse of needles causes most HIV infections, war or poverty is the primary "driver" of AIDS, AIDS is an autoimmune disorder caused by the body absorbing too many toxins, etc) would make such a claim at this stage of development of AIDS science. In contrast to Boyle and Hill, supporters of male circumcision abide by the scientific method and the preponderance of evidence. As such, a meta-ethical approach used by scientists is a teleological and a utilitarian one: decide on the validity of the act (male circumcision) by weighing up the advantages against the disadvantages consequent to performing male circumcision. This approach is also more nuanced because a decision about a biomedical intervention on an individual level is not necessarily the same one as that to be taken at the population level. The present body of evidence concerning the efficacy of male circumcision for HIV prevention and the drivers of HIV transmission stands in sharp contrast to the speculative claims and weak evidence that Boyle and Hill present in opposing male circumcision.[248] (See Box 1.)

[240] UNAIDS, n 48.

[241] Boyle and Hill, n 1 at 330.

[242] Hankins, Forsythe and Njeuhmeli, n 46.

[243] Boyle and Hill, n 1 at 330.

[244] Auvert, Taljaard, Rech et al, n 16.

[245] Boyle and Hill, n 1 at fnn 102 and 103.

[246] UNAIDS and PEPFAR, n 46; Wamai, Morris, Bailis et al, n 5.

[247] Boyle and Hill, n 1 at 330.

[248] Wamai, Morris, Bailis et al, n 5. See also Box 1 above.

Overall, Boyle and Hill demonstrate a misunderstanding of the literature on methodologies for, and results from, the multiple studies on the efficacy of and cost-savings produced by male circumcision. Implementing male circumcision programs to combat the heterosexually-driven HIV epidemics in sub-Saharan Africa is not "wasting scarce resources", nor is it unethical, as Boyle and Hill claim.[249] Such arguments may be akin to those projected by critics when antiretroviral drugs became available that they could not help people in Africa because "Africans could not keep time",[250] an argument that would be scorned today. Boyle and Hill appear intent on inducing readers into thinking that there are "more effective" measures than male circumcision and that male circumcision is a risky procedure. Nothing is farther from the truth. There is no biomedical intervention currently being implemented that has been demonstrated scientifically to be more efficacious[251] or cost-effective[252] than male circumcision. The imperative for implementing accelerated male circumcision programs is not only ethical,[253] but the resultant estimated savings in cost and lives in this, the region of the world with the largest burden of heterosexually-acquired HIV,[254] are overwhelming.

REBUTTAL OF "APPENDIX"

In their Appendix, Boyle and Hill list 17 studies that they say show either "no relationship" or "higher risk" of infection for circumcision, yet they admit that 70% of the observational studies that were cited by the trials are indicative of reduced infection in circumcised men. The references Boyle and Hill cite are remarkable for perhaps one thing – all of these publications are 14 to 24 years old. Boyle and Hill fail to find even one *recent* scientific report that supports their claims. Some of these old studies failed to correct for multiple confounding factors. In a previous article,[255] researchers pointed out that although observational studies can provide valuable data, they should be treated with caution. Observational studies suffer from multiple problems.[256] Among these are problems associated with subgroups, "confounding by indication", and the "axis of multiplicity", ie, the repeated analysis of data often for aims other than the purpose for which the data were collected.[257] The latter point is especially the case for Demographic and Health Surveys which Gebremedhin[258] and, presumably, Young,[259] used. Because of this, it is imperative that researchers use multiple types of studies, not just observational, as the current authors' analysis has done, but which the one by Boyle and Hill failed to do.

In reality, these authors would have readers believe that they have presented a plethora of evidence in their Appendix to prove their point. Unfortunately, a close examination reveals that this is far from the case. In Table 1, the current authors present a systematic review of these studies. According to their review of each, seven contain either no mention of any correlation between male circumcision and HIV infection or do not say whether a significant finding was obtained. Another six articles demonstrated a positive effect of male circumcision in reducing risk of HIV infection,

[249] Boyle and Hill, n 1 at 331.

[250] Timberg and Halperin, n 10.

[251] Padian, McCoy, Balkus et al, n 38; UNAIDS/WHO, n 48; WHO/UNAIDS, n 48, p 51; Karim SS and Karim QA, "Antiretroviral Prophylaxis: A Defining Moment in HIV Control" (2011) 378 *Lancet* e23.

[252] Galarraga, Colchero, Wamai and Bertozzi, n 47.

[253] Lie, Emanuel and Grady, n 162.

[254] Hankins, Forsythe and Njeuhmeli, n 46; Wamai, Morris, Bailis et al, n 5.

[255] Wamai, Morris, Bailis et al, n 5.

[256] Vandenbroucke, n 9; Gersovitz M, "The HIV Epidemic in Four African Countries Seen Through the Demographic and Health Surveys" (2005) 14 J Afr Econ 191; Mishra V and Assche SBV, "Concurrent Sexual Partnerships and HIV Infection: Evidence from National Population Based Surveys" (DHS Working Paper 62, 2009), http://www.measuredhs.com/pubs/pdf/WP62/WP62.pdf viewed 12 February 2012; Wamai, Morris, Bailis et al, n 5.

[257] Vandenbroucke, n 9.

[258] Gebremedhin, n 37.

[259] Cited by Boyle and Hill, n 1, Figure 1 from http://www.circumstitions.com.

although found the protective effect to be small. In three studies, being circumcised or not had no significant effect on HIV prevalence. Only in one study was male circumcision reported to increase risk. In this 18-year-old article[260] partner circumcision was included in a long list of other factors comprising "history of multiple sexual partners, history of at least one sexually transmitted disease (STD), relatively high socioeconomic status (SES), being unmarried, young age at first pregnancy, and low gravidity […] women who had used oral contraceptives, [and] smoked more than one cigarette per day".[261] As pointed out above, observational studies such as this ought to be treated with extreme caution. Studies from African countries show circumcision prevalence is often higher in men with higher income and education and that such men have more sexual partners, which subsequently increases their risk of HIV infection.[262]

CONCLUSION

When self-identified opponents of male circumcision reject research results, misrepresent the literature, use selective citations and resort to misleading statements in order to assert their long-standing anti-male circumcision agenda, they also reject established scientific norms and rules, so making scientific discourse all but impossible. By rejecting heterosexual sex and lack of male circumcision as important drivers for the HIV epidemic in sub-Saharan Africa, Boyle and Hill have little choice but to construct and promote an alternative hypothesis for their cause. The arguments used to oppose male circumcision are based on a highly selective choice of fringe, and poorly designed studies, including ones that often incorporate statistics that have been subjected to damning critiques by experts due to small sample sizes and problematic methodology. Not only have the statistics and claims made by male circumcision opponents regarding male circumcision and HIV infection been shown to be fallacious,[263] but so have the arguments and statistical analyses they use to discredit other good-quality studies that have demonstrated the ability of male circumcision to protect against a wide range of medical conditions and diseases, that include genital cancers, as well as a variety of STIs, one of which is HIV.[264]

It seems the opponents and proponents of male circumcision take quite different approaches. Many in the anti-male circumcision lobby use a deontological (moral absolutist) approach that posits that the so-called natural state is intrinsically the "right" state, ergo male circumcision is fundamentally wrong, and that every avenue should be employed to end male circumcision, which has been practised by diverse peoples for thousands of years. The present article has assessed the various claims by Boyle and Hill arguing against male circumcision and has shown that they are unfounded assertions, unsupported by reliable evidence. The current authors have reiterated the credible scientific evidence for the efficacy and cost-effectiveness of male circumcision for HIV prevention in HIV epidemic settings. Their evaluation reveals that Boyle and Hill denounce male circumcision despite its numerous demonstrated benefits.[265] The current authors observe that providing patients and parents

[260] Chao A, Butlerys M, Musanganire F et al, "Risk Factors Associated with Prevalent HIV-1 Infection Among Pregnant Women in Rwanda" (1994) 23(2) Int J Epidemiol 371.

[261] Chao, Butlerys, Musanganire et al, n 260.

[262] Mishra and Assche, n 256; Lowndes CM, Alary M, Belleau M et al, *West Africa HIV/AIDS Epidemiology and Response Synthesis: Implications for Prevention* (World Bank, Washington DC, 2008); Tanzania Commission for AIDS (TACAIDS), National Bureau of Statistics (NBS), and ORC Macro, *Tanzania HIV/AIDS Indicator Survey 2003-04* (Calverton, Maryland, USA: TACAIDS, NBS and ORC Macro, 2005), http://www.tgpsh.or.tz/fileadmin/uploads/docs/THIS_FINAL_2005.pdf viewed 10 December 2011; Piot P, Greener R and Russell S, "Squaring the Circle: AIDS, Poverty, and Human Development" (2007) PLoS Med 4 e314.

[263] Moses, Nagelkerke and Blanchard, n 5; O'Farrell and Egger, n 5; Wamai, Weiss, Hankins et al, n 5; Banerjee, Klausner, Halperin et al, n 5; Morris, Waskett, Gray et al, n 5; Wamai and Morris, n 5; Wamai, Morris, Bailis et al, n 5.

[264] Castellsague, Albero, Cleries and Bosch, n 5; Morris, n 8; Waskett and Morris, n 226; Morris, Waskett, Gray et al, n 5; Waskett, Morris and Weiss, n 84.

[265] Alanis and Lucidi, n 8; Morris, n 8; Tobian, Gray and Quinn, n 8; Tobian and Gray, n 8.

with biased information in order to discourage circumcision may have legal implications.[266]

Male circumcision is a controversial subject and has its "fans and foes".[267] The foes have little evidence on which to base their claims. Boyle and Hill are in no position to offer advice about policy, especially given that their claims contravene hard-earned and now-established scientific evidence and policy norms regarding male circumcision for HIV prevention. Policy must be based on scientific evidence.[268] The present article provides a strong defence of that principle. Thus the current authors reiterate their exhortation to readers and policy-makers to be unfazed by such criticisms and support the accelerated implementation and scale-up of VMMC programs in priority countries.[269]

TABLE 1 Systematic review of observational studies on HIV and male circumcision cited by Boyle and Hill in their Appendix

Citation	Study setting, country/countries	Study design and target population	Epidemic profile*	Main results
Hira S, Kamanga J, Macuacua R et al, 1990	Zambia, Africa	This is a correspondence item; no methods available.	Generalised high level	Correspondence mentions that in Zambia, people at greatest risk of HIV are uncircumcised men and women who are frequently infected by STD pathogens.
Pepin J, Quigley M, Todd J et al, 1992	Outpatient clinic of the Medical Research Council Laboratories in Fajara, a suburb of Banjul, The Gambia (West Africa)	624 men ages 14-68, studied from 1988-1990. All male patients with genital complaints. Patients were given questionnaire to fill out and their sera were tested for antibodies to HIV-1 and HIV-2.	Generalised low level	Circumcised patients with residual foreskin were more likely to be HIV-1 infected than patients with complete circumcision.
Bollinger R, Brookmeyer R, Mehendale S et al, 1997	2 STD clinics in Pune, India	Systematic case-control study to measure of prevalent HIV-1 p 24 antigenemia for identification of risk factors for newly acquired HIV infection a method as well as to describe the signs and symptoms of acute HIV infection.	Concentrated	98% (n=50) of uncircumcised were positive of p 24 antigen compared to 2% (n=1) of circumcised men. No interpretation or analysis is made of the correlation between the results obtained and circumcision.

[266] Russell T, "Non-circumcision a Legal Risk", *Law in Practice* (August 2005), http://www.circumcision.com.au/Further_Information/newsid374/1/Non-Circumcision-a-Legal-Risk.aspx viewed 1 February 2012.

[267] Collier R, "Vital or Vestigial? The Foreskin has Its Fans and Foes" (2011) 183 CMAJ 1963.

[268] Collins, n 6; Fauci AS, "Let Science Inform Policy" (2011) 333 *Science* 13.

[269] Wamai, Morris, Bailis et al, n 5; UNAIDS/WHO, *Joint Strategic Action Framework to Accelerate the Scale-up of Voluntary Medical Male Circumcision for HIV Prevention in Eastern and Southern Africa 2012–2016* (2011), http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2251_Action_Framework_circumcision_en.pdf viewed 25 February 2012.

TABLE 1 *continued*

Citation	Study setting, country/countries	Study design and target population	Epidemic profile*	Main results
Chiasson M, Stoneburner R, Hildebrandt D et al, 1990	Clinic in the Bronx, New York City, NY, USA	Non-blinded study; data collected from 1988-1990, patients selected from individuals being evaluated for treatment of an STD.	Concentrated	Study does not mention any correlation between the results obtained and circumcision.
Carael M, Van de Perre PH, Lepage PH et al, 1988	"Centre Hospitalier de Kigali", Kigali Rwanda	Case study of 150 heterosexual sero-discordant couples.	Generalised high level	No difference due to circumcision in seronegatives and seropositives. Most powerful variables associated with seropositivity of the couples were presence of STDs, sexual contacts with prostitutes and number of previous unions.
Moss G, Clemetson D, D'Costa L et al, 1991	Nairobi CityCommission Special Treatment Clinic for STDs, Nairobi, Kenya, Africa	Persons in sexual partnerships attending clinic from Jun 1988-Feb 1989. Multivariate analysis. 69 HIV sero-positive men and 70 women (their partners; one had 2 wives).	Generalised high level	Study does not discuss the significance of male circumcision. Circumcision is listed as one of the questions asked but not discussed due to lack of any significant finding.
Allen S, Lindan C, Serufilira A et al, 1991	Outpatient pediatric and prenatal clinics at the Centre Hospitalier de Kigali, Urban Rwanda	Cross sectional survey of 1458 pregnant women aged 19-37 to determine behavioural and demographic risk factors for HIV infection in central Africa.	Generalised high level	In the groups of Muslim women (whose partners are ritually circumcised) and women who had partners with a history of "VD" (in whom circumcision was performed to relieve complications), HIV rates were higher in both groups of women whose partners were uncircumcised.
Seidlin M, Vogler M, Lee E et al, 1993	Patients from multiple sources throughout New York City, NY, USA	Cohort study of risk of HIV infection in female partners; 158 heterosexual partners of HIV infected individuals; 93% women, 54% Hispanic white, 23% Black and 65 partners of intravenous drug users.	Concentrated	Study does not mention any correlation between the results obtained and circumcision.

TABLE 1 *continued*

Citation	Study setting, country/countries	Study design and target population	Epidemic profile*	Main results
Konde-Lule J, Berkley S and Downing R, 1989	Two rural sub-counties, the Kasangati region and Nsangi region in Uganda, Africa	35,000 people in the two communities but restricted to those over the age of 15 years; chi squared statistical test; 2 year study to evaluate impact of intensive health education on the socio-behavioural aspects of AIDS.	Generalised high level	Study does not mention any correlation between the results obtained and circumcision.
Van de Perre P, Clumeck N, Steens M et al, 1987	Butare, South Rwanda, Central Africa	Sero-epidemiological study. 118 individuals.	Generalised high level	Study does not mention any correlation with the results and circumcision.
Quigley M, Munguti K, Grosskurth H et al, 1997	Mwanza Region, Tanzania, Africa	Case-control study nested with a randomised trial of improved sexually transmitted disease treatment. Objective was to examine the associating between HIV infection and patterns of sexual behaviour and other risk factors.	Generalised high level	Circumcision showed a protective effect, but this did not reach statistical significance. Main confounder of the effect of circumcision was occupation. More non-farmers vs farmers were circumcised. There was a lower prevalence in the over 15 year olds who were circumcised.
Hudson C, Hennis A, Kataaha P et al, 1988	2 Church of Uganda mission hospitals at Kisiizi and Kagando in southwest Uganda	357 patients selected from sample to reflect age and sex composition of the general population.	Generalised high level	Study does not mention any correlation between the results obtained and circumcision.
Laumann E, Masi C, Zuckerman E, 1997	USA	1410 American men aged 18-59. Comparative analyses of data from the National Health and Society Life Survey.	Concentrated	Study concludes that there is a slight benefit of circumcision, but a negligible association with most outcomes.
Barongo L, Borgdorff M, Mosha F et al, 1992	Mwanza Region, Tanzania, Africa. Divided into 3 strata: urban, roadside and rural.	Cross-sectional population survey of adults aged 15-54; 2,434 from 20 rural villages, 1,157 from 20 roadside settlements and 1,554 from 20 urban wards.	Generalised high level	No evidence of any association between HIV 1 infection and male circumcision before or after adjustment for other risk factors.
Grossfurth H, Mosha F, Todd J et al, 1995	12 communities in the Mwanza Region of Tanzania, Africa	Baseline survey of 1,000 adults aged 15-54 randomly sampled from each community.	Generalised high level	No association was found between HIV infection and lack of male circumcision.

TABLE 1 *continued*

Citation	Study setting, country/countries	Study design and target population	Epidemic profile*	Main results
Chao A, Butlerys M, Musanganire F et al, 1994	Town of Butare, southern Rwanda, Africa	Cross-sectional study of 5,690 pregnant women from one of 5 antenatal clinics.	Generalised high level	Women, who reported that the father of their baby was circumcised were significantly more likely to be infected with HIV.
Urassa M, Todd J, Boerma J et al, 1997	Northwestern Tanzania (Mwanza region) Africa.	Population-based study.	Generalised high level	Significantly lower HIV prevalence in circumcised men. This protective effect was stronger in urban areas and roadside settlements compared to rural areas.

*For "epidemic profile" see Wilson, n 189.

TABLE 2 Pertinent data from the three randomised controlled trials of male circumcision and HIV infection

	South Africa (Orange Farm)	Uganda (Rakai)	Kenya (Kisumu)
Sample size:	3,274	4,996	2,784
Control	1,654	2,522	1,393
Intervention	1,620	2,474	1,391
Age	18-24	15-49	18-24
% lost to study:*	8.0%	9.1%	8.6%
Control	9.5%	9.2%	8.2%
Intervention	6.5%	9.0%	9.1%
Sero-conversions:			
Control	49	45	47
Intervention	20	22	22
% risk reduction	61%	51%	53%**
P-value	P < 0.001	P < 0.005	P < 0.005

Data shown are taken from the published trial reports (Auvert, Taljaard, Lagarde et al, n 2; Gray, Kigozi, Serwadda et al, n 2; Bailey, Moses, Parker et al, n 2).

* % lost to trial are at 21 months for South Africa and 24 months for Uganda and Kenya.

** Using methods comparable to those applied in Orange Farm and Rakai (ie, modified intent-to-treat), the protective effect of male circumcision was 59% in the Kisumu trial (Robert Bailey, personal communication, 22 February 2012).