Background, Methods, and Synthesis of Scientific Information Used to Inform the "Recommendations for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV infection, STIs, and other Health Outcomes."

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Introduction

Male circumcision is the surgical removal of some or all of the foreskin (or prepuce) from the penis[1]. Medically attended circumcision performed by health care professsionals are voluntary, elective procedures that are preceded by an informed consent process. Male circumcision may also be performed as part of religious or cultural rites. Circumcision is a very common procedure; it has been estimated that approximately one-sixth of the world's male population is circumcised[2]. In the United States, overall rates of newborn male circumcision rose through much of the twentieth century, largely due to changing cultural norms, increased rates of childbirths in hospitals, and a perception that male circumcision was more hygienic[3]. Personal decisions about circumcision are influenced by information about the preventive health benefits, safety and risk of the procedures as well as ethical, religious, cultural, familial, and economic considerations. Until recently, prevention of human immunodeficiency virus (HIV) infection was unlikely to factor in the decision to circumcise a male newborn or boy, although other preventive health benefits of male circumcision may have been considered.

However, data now indicate that male circumcision reduces the risk of male HIV acquisition through penile-vaginal sex. Although results from randomized controlled trials (RCTs) provide the strongest level of evidence, we describe data from both RCTs and observational studies. Observational studies are often conducted due to cost or other barriers to conducting RCTs, and may in some cases be the only feasible methodology for studying particular health outcomes, such as cancer. The results of three randomized controlled trials (RCTs) of voluntary male circumcision involving more than 10,000 HIV-negative men in settings in sub-Saharan Africa with predominantly heterosexual HIV transmission demonstrated 50-60% reductions in HIV incidence[4-6] in the study population. In the two trials for which data are available, reductions in the incidence of herpes simplex virus type 2 (HSV-2) and the prevalence of high-risk oncogenic human papillomavirus (HPV) were also demonstrated[7-9]. Observational studies indicate that male circumcision is likely to be associated with other health benefits as well, such as reduced rates of other sexually transmitted infections (STIs) in men and their female partners, reduced risk of penile and cervical cancer, and reduced rates of infant urinary tract infections (UTIs). Risks potentially associated with male circumcision include surgical adverse events, the possibility of adverse effects on sexual sensation and function, and possible behavioral risk compensation (increased risk behavior because of perception of decreased risk). In February 2007, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) jointly recommended that male circumcision be recognized as an additional important intervention to reduce heterosexual acquisition of HIV infection among men in settings with high HIV prevalence and low male circumcision rates[10].

There are both inherent limitations and strengths to be considered when describing the generalizability of the results of the African RCTs to the United States. In the United States, the prevalence of HIV and the lifetime risk of HIV infection are generally much lower than that in sub-Saharan Africa; most new HIV infections in the United States are attributed to male-male sex, a population for whom male circumcision has not been proven to reduce the risk of HIV acquisition. Despite these overall differences, the results of African trials are likely to have application to HIV prevention efforts in the United States. The United States differs epidemiologically from regions targeted by the WHO/UNAIDS recommendations and the sub-Saharan African areas in which the randomized trials were conducted in that the overall prevalence of HIV infection and the risk of HIV acquisition are considerably lower. However, there exist geographic areas and subpopulations in the United States with HIV incidence comparable to that of sub-Saharan African countries. Furthermore, studies have demonstrated efficacy in preventing male acquisition of HIV only for penile-vaginal sex, the predominant mode of sexual HIV acquisition among men in Africa. Although the predominant mode of sexual HIV acquisition among men in the United States is by penile-anal sex among men who engage in male-to-male sexual contact, one in every ten estimated new HIV infections in the United States are attributed to female-to-male sexual transmission[11]. In addition, although most American men are circumcised, African-American and Hispanic men, the men with the highest rates of HIV-infection are known to be significantly less likely to be circumcised compared to white, non-Hispanic men. Thus, although similar randomized clinical trials have not been conducted in the United States, based on evidence from the African trials, uncircumcised heterosexual men living in areas with high HIV prevalence are likely to experience the most public health risk-reduction benefit from elective male circumcision. In light of recent decreases in neonatal male circumcision rates in the U.S., it remains to be seen whether men at higher risk for heterosexual acquisition of HIV would be willing to undergo circumcision, or whether parents would be willing to have their newborns circumcised to reduce possible future HIV and sexually transmitted infection (STI) risk.

This document presents a summary of data on the associated preventive health benefits, safety, and risks of the procedure and acceptability, provider attitudes, access and cost-effectiveness of male circumcision, ethical considerations, and examines these data in the context of the United States. Data from other countries are included to inform the U.S. experience, particularly where data are lacking in the U.S. or for comparison purposes. This background document was used to inform the development of recommendations for providers counseling male patients and parents regarding the role of male circumcision as a prevention strategy[1]. CDC has developed recommendations to help ensure that persons considering undergoing male circumcision or parents of newborn boys considering male circumcision for their infants have the best possible public health information to guide those decisions. Factors such as social, cultural, religious, and ethical considerations also play an important role for some people.

[1] The draft recommendations are available for public comment at www.regulations.gov. Locate document by placing docket no. "CDC-2014-0012" in search window.

Methods to gather, synthesize and interpret information

A two-day symposium to discuss medically attended male circumcision in the United States was held on April 26-27, 2007. It included a face-to-face meeting of external partners and a broad range of subject matter experts, including clinicians, academicians, and public health practitioners to obtain input on the potential role of male circumcision in preventing transmission of human immunodeficiency virus in the U.S.[12]. A systematic Medline search was conducted and relevant literature describing male circumcision for the prevention of HIV and policy statements regarding male circumcision were distributed to participants in advance of the meeting. Views on the benefits of male circumcision, as well as risks and adverse effects, were presented by meeting participants to obtain input on the potential role of male circumcision in the United States. Participants examined scientific evidence to assess the relevance of male circumcision to the HIV epidemic in the United States and explored factors such as potential cost-effectiveness, cultural, ethical and safety concerns, and integration with existing prevention methods. The questions posed to the participants, the resulting working group proposals, and names of participants in this symposium have been described[12].

For this document, a systematic literature review was conducted in order to assess quality of evidence to data on the association of male circumcision with medical benefits and adverse effects. Systematic reviews were conducted for the following outcomes related to medically attended male circumcision: HIV acquisition and transmission (female-to-male, male-to-female, and male-to-male); other STIs; penile cancer; cervical cancer; infant UTIs; risks and adverse events; sexual function and penile sensation. All studies of outcomes of male circumcision up to the end of November 2012 in Medline, Embase and Cochrane Library, as well as citation lists were included. More recent data through March 2013 were included in updating data related to the HIV epidemic in the United Statates. Studies were restricted to those published in English after 1950, presenting original data, including RCTs, cohort studies, case-control studies, cross-sectional studies, case series and case reports. Study design was classified according to guidelines used for collecting scientific data in reports published in the *Guide to Community Preventive Services (the Guide)* [13]. The evidence was assessed according to strength of association, consistency of findings across studies and the methodologic rigor of study designs[13-15]. Because they eliminate spurious causality and bias, RCTs were considered the most rigorous method for determining whether a cause-effect relationship exists between a treatment and an outcome. Our literature review through November 2012 also included a broad, non-systematic narrative review for the section *Considerations related to male circumcision in the United States,* because this section did not evaluate clinical outcomes.

In formulating the recommendations, available evidence from the literature review was considered together with suggestions made at the 2007 symposium[12] in addition to numerous comments from the public that were received and reviewed. A subcommittee of the CDC Public Health Ethics Committee (PHEC) reviewed the recommendations and provided guidance on ethical issues related to elective male circumcision. None of the primary authors of these recommendations reported a financial or other conflict of

interest. These recommendations will be updated as needed based on availability of relevant significant new information.

Summary of evidence

Effect of male circumcision on health outcomes

This section describes the evidence base about the biological plausibility; results of randomized clinical trials and observational studies, including meta-analyses; on the effect of male circumcision on acquisition of HIV and STIs. It also describes study results about the frequency of penile and prostate cancers among circumcised men, cervical cancer in female partners of circumcised men, urinary tract infections in circumcised infants, and other associated health risks, including effect on sexual function and penile sensation.

Biological plausibility

The foreskin can serve as a portal of entry for STIs (including HIV), lending biological credibility to the role of circumcision in preventing STI and HIV acquisition through insertive sexual intercourse[16]. The likely mechanism of increased susceptibility associated with an intact foreskin involves both histopathological and anatomic factors, as well as the interaction between HIV and other STIs.

Compared to the dry external skin surface of the glans penis and the penile shaft, the inner surface of the foreskin is less keratinized. This may allow easier access to the epithelial cells of the epidermis and dermis (in which STIs such as HPV and HSV-2 replicate) as well as access to target cells for HIV infection[16, 17]. In some laboratory studies, foreskin tissue has been shown to be more susceptible to HIV infection than keratinized epithelium[18, 19] although some studies have failed to show any difference in the ability of HIV to penetrate inner compared to outer foreskin surface[20]. Furthermore, the inner surface contains higher density of HIV target cells, such as Langerhans cells close to the skin surface[21-24], and in men with a history of recent STIs, the number of target cells in the prepuce is increased[22]. The fact that the size of foreskins excised from 965 men enrolled in the Rakai Community Cohort Study[25] significantly correlated with HIV incidence rates may be explained by the hypothesis that surface area would be associated with more resident HIV immune cells such as Langerhans cells, CD4+ T cells, CD8+ T cells, and macrophages and therefore greater rates of HIV transmission[26]. However, the precise role of Langerhans cells is not fully understood[27-29].

Because the inner surface of the foreskin is lightly keratinized, it may be relatively susceptible to traumatic epithelial disruptions during intercourse, providing a portal of entry for pathogens[16]. Furthermore, the foreskin retracts away from the glans and over the shaft of the penis during intercourse, which exposes this surface to the body fluids of the sex partner[21]. It has been postulated that the foreskin may serve as a reservoir for sexually transmitted pathogens, since the micro-environment in the preputial sac between the unretracted foreskin and the glans penis may be conducive to viral survival, thereby

increasing contact time of these infectious agents with penile tissues[18]. The anoxic microenvironment of the preputial sac may support pro-inflammatory anaerobes that can activate Langerhans cells to present HIV to CD4 cells in draining lymph nodes[30]. Investigators determined that uncircumcised compared to circumcised males had higher rates of 'wetness' around the glans or coronal sulcus and that higher degrees of 'wetness' were associated with higher rates of HIV infection[31]. Among male attendees at an STD clinic in Durban, South Africa, men with any level of penile wetness compared to men with no wetness had HIV seroprevalences of 66.3% and 45.9% , respectively. Langerhans cells and CD4+T cells in the inner foreskin are significantly more responsive to certain inflammatory cytokines than those in the outer foreskin. This may suggest that immune cells of the inner foreskin more easily respond to infectious and other exposures resulting in increased viral susceptibility of the inner foreskin[26, 32].

HIV infection and other STIs, which independently may be more likely in uncircumcised men, interact synergistically to increase acquisition risk[33-37]. Infection with ulcerative STIs such as HSV-2 has been associated with increased risk of HIV infection in observational studies[35, 38, 39]; this risk was 3-fold in a recent meta-analysis[40]. In the South African trial, the authors estimated that approximately 28% of incident HIV cases were attributable to HSV-2 seropositivity or acquisition[7]. Proposed mechanisms of increased susceptibility include breaches in the mucosal barrier and increased susceptibility of tissue due to inflammation, or increasing HIV target cells associated with inflammation[17]. Synergistically, HIV seropositivity may increase the risk for new STIs[35, 41], although some studies have failed to find such an association[42].

Male circumcision and the risk of HIV infection acquisition

Male acquisition of HIV infection from female partners

Three RCTs have been undertaken in sub-Saharan Africa to determine whether circumcision of adult males will reduce their risk for HIV infection (Table 1)[4-6]. The randomized, controlled follow-up in all three studies was stopped early when interim analyses demonstrated that circumcision by a clinician significantly reduced male participants' risk of HIV infection. The control group was then offered circumcision, as it was determined to be unethical not to offer them circumcision. In intent-to-treat analyses, men who had been randomly assigned to the circumcision group had a 60% (South Africa), 53% (Kenya), and 51% (Uganda) lower incidence of HIV infection compared to men assigned to the group to be circumcised at the end of the study. In all three studies, some of the men who had been assigned to be circumcised did not undergo the procedure, and vice versa. Non-compliance with assigned study group may mean that the intention-to-treat analyses underestimated the potential benefit of circumcision. When the data were reanalyzed to account for these crossovers, men who had been circumcised had 76% (South Africa), 60% (Kenya), and 55% (Uganda) reductions in risk of HIV infection compared to those who were not circumcised[4-6]. However, it should be noted that as-treated analyses may be considered biased.

The Ugandan RCT included male participants 15 years of age or older[6]. Among all men 15 – 49 years at 24 months of follow-up there was a 51% lower HIV incidence in circumcised compared to uncircumcised males. However, the reduction in HIV acquisition rate did not vary significantly by age group.

The protective effect of male circumcision appears to be durable. In a rigorous meta-analysis of the three RCTs, the overall relative risk reduction of acquiring HIV using the intent-to-treat data was 50% at 12 months and 54% at 21 or 24 months following circumcision[43]. With 42 months of follow-up, a 64% reduction in HIV infection risk was seen in circumcised men compared to uncircumcised men. As of March 2010, results of longer-term follow-up of 54 months from the Kenya RCT indicate a 63% (46, 75) reduction in HIV infection risk in circumcised men compared to uncircumcised men[44], similar to a 64% reduction at 42 months [45] and 60% reduction at 24 months[5]. Also, more recently, during 4.79 years of trial surveillance of participants in the Rakai randomized trial of male circumcision, investigators found that the overall HIV incidence was 0.50/100 person-years and 1.93/100 person-years in circumcised men and uncircumcised men, respectively (adjusted effectiveness 73% [95% confidence interval (CI) 55–84%])[46]. The HIV prevention effectiveness in the post-trial observational study was not statistically significantly different to that of the as-treated effectiveness of circumcision observed during the randomized trial.

International observational studies also indicate that male circumcision is associated with lower rates of HIV[47, 48], although some cross-sectional studies conducted in general populations have failed to find an association between circumcision status and HIV-1[49-51]. A systematic review and meta-analysis of 28 studies that focused on heterosexual transmission of HIV in Africa was published in 2000[47]. It included 19 cross-sectional studies, five case-control studies, three cohort studies, and one partner study. In the overall pooled unadjusted analysis, a substantial protective effect of male circumcision on risk for HIV infection was noted, with a 48% reduction in risk for HIV infection among circumcised compared to uncircumcised men[pooled RR = 0.52, 95% confidence interval (CI) 0.40-0.68. P <0.001]. In addition, in three of four studies which were adjusted for other factors, including history of current or previous genital ulcer disease (GUD), an additional 1-6% risk for HIV infection was noted suggesting that a greater protection against HIV transmission is associated with male circumcision in populations with more prevalent GUD. After adjusting for confounding factors in the population-based studies, the relative risk for HIV infection was 44% lower in circumcised men compared with uncircumcised men. The strongest association was seen in men who were most likely to be exposed to HIV, such as patients at sexually transmitted disease (STD) clinics, for whom the adjusted relative risk was 71% lower for circumcised men.

Prior to the completion of randomized clinical trials, another review was conducted that included stringent assessment of 10 potential confounding factors and was stratified by study type or study population[48, 52] and included 37 studies[48], including 18 studies (1 cohort, 16 cross-sectional, and 1 case-control) conducted in the general population and 19 studies (4 cohort, 12 cross-sectional, and 3 case-control) conducted in high risk populations. Most of the studies were from Africa. Of the 37 studies included in the

review[48], the 18 studies conducted in general populations had inconsistent results, whereas the 19 studies conducted in high-risk populations found a consistent, substantial protective effect, which increased with adjustment for confounding. Of the 18 studies in the general population, the single cohort study showed a benefit of male circumcision (OR=0.58, 95% CI 0.36-0.96), the case-control study found no significant difference (OR=1.90; 95% CI 0.50-7.20), and the 16 cross-sectional studies had varying results including ten studies indicating a beneficial effect of male circumcision and six indicating a harmful effect (ORs ranging from 0.21-1.73). Of the eight cross-sectional studies with statistically significant findings, six indicated a benefit and two indicated harm. The one large prospective cohort study conducted in the general population, including 5,507 HIV-negative Ugandan men, and 187 HIV-negative men in discordant relationships, showed a significant protective effect, with 42% lower odds of acquisition of HIV infection among circumcised men[53]. Among serodiscordant couples, in a substudy of this cohort, none of 50 circumcised men with HIV-infected female partners seroconverted, whereas there were 40 incident cases among 137 uncircumcised men with HIV-infected female partners[53, 54]. The 19 studies conducted in high-risk populations in this review [48]were in better agreement than the 18 studies in the general population, finding a consistent, substantial protective effect. All four cohort studies indicated a beneficial effect from male circumcision, including three with statistically significant results with point estimates from crude odds ratios (ORs) varying from 0.10 to 0.39. Eleven of the 12 cross-sectional studies indicated a benefit of male circumcision, including eight which were statistically significant with ORs of 0.10 to 0.66. Of the five cross-sectional studies reporting adjusted ORs, these ranged from 0.20-0.59. Among the three case-control studies in high risk populations, all indicated a protective effect of circumcision on HIV status, including two which were statistically significant with ORs ranging from 0.37 to 0.88.

A more recent meta-analysis of 13 studies, which included RCTs in addition to cohort and case control studies, found a 58% reduced risk for HIV infection among circumcised men (overall risk ratio [RR], 0.42; 95% confidence interval [CI] 0.33-0.53) and determined that the studies met criteria for causality between lack of circumcision and HIV-1 infection[55].

At least one study has examined the association of male circumcision in reducing HIV acquisition in the context of other STI infections. In a randomized trial studying the role of genital ulcer disease (GUD) and HSV-2 in the protection against HIV associated with male circumcision in Rakai, Uganda, male circumcision significantly reduced the risk of HIV acquisition in HSV-2 seronegative men (incidence rate ratio [IRR] = 0.34, 95% CI 0.15–0.81). There were 11.2% and 8.6% reductions in HIV acquisition mediated by reductions in symptomatic GUD (95% CI 5.0–38.0) and HSV-2 incidence, respectively. In Kenya, male medical circumcision did not affect HSV-2 incidence and GUD and HSV-2 did not impact the protective effect of male medical circumcision against HIV[56].

Ecologic studies also demonstrate a strong association between lack of male circumcision and HIV infection at the population level. Although links between male circumcision, culture, religion, and risk behavior likely account for some of the differences in HIV infection prevalence, the countries in Africa and Asia with prevalence of male circumcision of less than 20% have HIV-infection prevalence several times as high (seroprevalence range: 0.24 – 25.84) than countries in those regions where more than 80% of men are circumcised (seroprevalence range: 0.03-11.64)[57].

The question of whether resumption of sexual intercourse soon after adult male circumcision affected HIV risk was examined in a combined analysis of data from the three RCTs, limited to HIV-negative men who were randomized to and underwent circumcision[58]. Early sex (intercourse <42 days after circumcision) was reported by 3.9% of participants in Kenya, 5.4% in Uganda, and 22.5% in South Africa. In all 3 trials, early resumption of sex was reported more often among men who were married or living as married. In pooled analyses, circumcised men reporting early sex did not have higher HIV infection rates at 3 or 6 months than circumcised men who did not have early sex.

The RCTs in Africa and numerous observational studies have demonstrated that male circumcision reduces the risk for female-to-male transmission of HIV. Careful consideration is required to apply these findings to the U.S. context, given differences in HIV epidemics[59, 60]. In contrast to the sub-Saharan African countries where the clinical trials were conducted, the United States has a low population prevalence of HIV infection (0.4%)[61], with ~50,000 new cases annually since the mid-1990s and an epidemic that has been concentrated among men who have male-to-male sexual contact (men who have sex with men [MSM] and men who have sex with men and women) rather than men who have sex with women[11, 62, 63]. While no RCTs have been conducted in the United States, a similar magnitude of risk-reduction benefit of circumcision would likely apply to U.S. men engaged in penile-vaginal sex. However, the population effect would be less pronounced in the United States compared to sub-Sharan Africa due to the smaller proportion of cases among men acquired through heterosexual sex in the United States.

Few U.S. studies have evaluated the effect of male circumcision for preventing heterosexually acquired HIV infection. Two published observational studies have reported on the association between circumcision and the risk of HIV infection in the United States among male patients attending STD clinics[37, 64]. While the first study suggests that being uncircumcised might be associated with increased HIV risk, the finding was limited by small sample size and not statistically significant. The more recent study was a cross-sectional evaluation conducted among heterosexual African American men attending STD clinics in Baltimore, with an overall HIV seroprevalence of 3%[64]. Among approximately 40,000 visits by patients with unknown HIV exposure, male circumcision was not associated with reduced HIV prevalence. However, among 394 visits by men who had female sexual partners who were known to be infected with HIV, male circumcision was significantly associated with a 51% reduced relative prevalence of HIV infection (10.2% among circumcised men vs. 22.0% among uncircumcised men).

HIV infection transmissionfrom circumcised men to female partners

Studies on the effect of male circumcision on HIV transmission from male partners to female partners have shown mixed results. Some observational studies suggest a benefit, while a randomized prospective study failed to demonstrate one. In a study of serodiscordant couples in Uganda in which the male partner was HIV infected and the female partner was initially HIV-negative, the infection rates of the female partners differed by the male circumcision status and viral load of their male partners. If the HIV viral load in the blood of the male partner was <50,000 copies/mL, there was no HIV transmission if the man was circumcised, compared to a rate of 9.6 per 100 person-years if the man was uncircumcised[53]. For all male partners, regardless of viral load, the male-to-female transmission rate from circumcised men was somewhat lower than that from uncircumcised men, but this was not statistically significant. Such an effect may be due to decreased viral shedding from circumcised men or to a reduction in ulcerative STIs acquired by female partners of circumcised men[65]. In a another study of heterosexual serodiscordant couples from 7 sites in eastern Africa and 7 sites in southern Africa, in which the HIV-infected partner was also infected with HSV, 1,096 couples had a male as the HIV-infected partner. Adjusting for male partner plasma HIV-1 concentrations, female partners of circumcised men compared to those with partners of uncircumcised men retained a non-statistically significant 40% reduced risk of HIV-1 acquisition (HR 0.60, 95% CI 0.31-1.16, p=0.13, for genetically-linked events). After also excluding follow-up time occurring after male partners initiated antiretroviral therapy, the risk of HIV acquisition decreased by a non-statiscially significant 47% (HR 0.53, 95% CI 0.26-1.07, p=0.07, for genetically-linked events)[66]. Other observational studies have evaluated the effect of male circumcision on HIV risk to women without limiting the participants to serodiscordant couples. In a prospective study among 2,471 HIV-uninfected women in Tanzania, having an uncircumcised husband was associated with a significantly increased risk of HIV acquisition (age-adjusted relative risk, 3.60; 95% CI, 1.12–11.59)[67]. Similarly, in a cross-sectional case-control study of 4,404 women in Kenya, having a regular sex partner who was uncircumcised was associated with an odds ratio (OR) of 2.9 (95% CI 2.0-4.2) of being HIV infected[68]. However, another observational study from Uganda found that after adjustment for other risk factors, male circumcision of the primary sex partner was not associated with women's risk for HIV infection[69].

Finally, an RCT in Rakai, Uganda among HIV-infected men failed to demonstrate benefit to female partners. In this trial, 922 uncircumcised, HIV-infected men were randomly assigned to immediate or delayed circumcision. HIV-negative female partners were concurrently enrolled[70]. Overall, 18% of women in the intervention group and 12% of women in the control group acquired HIV during follow-up (HR 1.58; 95% CI 0.68-3.66). In a subanalysis not specified in the protocol, early resumption of sexual relations following male circumcision was significantly associated with higher risk for HIV acquisition among female participants, with a rate ratio versus control of 3.50 (95% CI 1.14-10.76). These results suggest an increased risk for HIV acquisition with early resumption of sex after male circumcision. However, among couples in the immediate male circumcision arm who delayed resumption of sex until after wound healing, there was no significant difference in HIV incidence relative to uncircumcised controls (rate ratio 1.2; 95% CI 0.39-3.73).

A systematic review and meta-analysis of the evidence for a direct effect of male circumcision on the risk of women becoming infected with HIV identified 19 epidemiological analyses, from 11 study populations[71]. The meta-analysis of data from the one RCT and six longitudinal analyses showed little evidence that male circumcision directly affects the risk of HIV in women (RR 0.80, 95% CI 0.53-1.36).

More recent estimates of the effect of male circumcision on male-to-female transmission were calculated using two mathematical models representing the HIV epidemics in Zimbabwe and Kisumu, Kenya, based on four trials of circumcision among adults and new observational data of HIV transmission in stable partnerships from men circumcised at younger ages. According to these models, it is estimated that male circumcision may confer a 46% reduction in the rate of male-to-female HIV transmission[72].

Whether or not circumcision of HIV-infected men directly reduces HIV risk for their female partners, male circumcision of HIV-negative men offers benefit to women to the extent that it contributes to a decline in the overall prevalence of HIV in the male population, and thus fewer HIV-infected sexual partners[73].

Male acquisition of of HIV and other STIs from male partners

HIV transmission. The RCTs demonstrating HIV risk reduction associated with male circumcision were conducted in settings in which most HIV transmission is through heterosexual sex and apply to men engaging mainly in insertive penile-vaginal sex[74-76]. Only 6 (0.2%) trial participants reported having had male-to-male sexual relations in the one RCT in which this history was collected [74]. To date, the data on male circumcision and rates of HIV acquisition among men who have male-to-male sexual contact have been limited to observational studies. No prospective trial of male circumcision for reducing HIV risk among MSM has been conducted, although such studies have been proposed[77].

Some observational studies have shown higher rates of HIV acquisition among uncircumcised MSM compared with circumcised MSM. When controlling for the number of male sex partners and having had unprotected sex with an HIV-positive partner, circumcision was associated with 2-fold decreased odds of prevalent HIV infection (adjusted odds ratio [aOR] 0.5; 95% CI 0.25-1.0) in a vaccine preparedness cohort followed from 1995 to 1997 [78]. Self-reported circumcised status was associated with a two-fold decreased odds of prevalent HIV infection (aOR 0.5; 95% CI 0.25-1.0) in a cross-sectional survey of MSM in Seattle in the early 1990s[79], and the odds of being HIV infected were 5-fold lower among circumcised men in a cross-sectional survey of MSM in Soweto in 2008 (aOR 0.2; 95% CI 0.1-0.2)[80]. However, other observational studies have failed to show a benefit (or risk) of male circumcision. In a cross-sectional survey of black and Latino MSM in New York City, Los Angeles and Philadelphia, there was no evidence that being circumcised was protective against HIV infection, even among men who had reported engaging in unprotected insertive but not unprotected

receptive anal sex[81]. Also, in a retrospective analysis of male circumcision status and risk for HIV among MSM participants in a vaccine trial, no association was found, even among primarily insertive partners[82]. Similarly, no association was found in a study of MSM in Seattle[83, 84], or in an Australian study of MSM[85]. However, a subsequent prospective study of MSM in Australia did report a significantly reduced HIV infection risk in circumcised men who reported engaging primarily in insertive anal sex (HR 0.11; 95% CI 0.03–0.80)[86]. The authors noted that because more infections were associated with receptive intercourse, lack of male circumcision may have accounted for only 9% of the infections in the study overall. A study of Andean men reported similar results: circumcision was not protective overall, but was protective among men who reported mainly insertive intercourse[87].

The presumed mechanism of decreased HIV acquisition among circumcised men engaging in penile-vaginal sex is through decreased HIV entry and infection through target cells on the foreskin. Thus, if there is an HIV prevention benefit to circumcision for MSM, it is likely to accrue during insertive acts. Furthermore, the relative risk of HIV infection per sex act may be higher for insertive penile-anal sex than for penile-vaginal sex, due to higher HIV RNA concentrations in rectal secretions relative to vaginal or cervical secretions[88], lending plausibility to a benefit of circumcision for MSM when engaged in insertive anal sex. However, the risk of HIV acquisition among MSM engaging in penile-anal sex is greater for the anal receptive partner, than for the insertive partner[89, 90]. Additionally, relatively few MSM are exclusively insertive. Although not well studied, in some settings many or most MSM practice both insertive and receptive sex. In the limited studies conducted in the United States, approximately half of men self-identify as versatile partners (men who practice both insertive and receptive anal sex) and one quarter each identify as engaging either predominantly in insertive or predominantly receptive anal intercourse[91]. In another study, substantial proportions of partners who self-identified as predominantly insertive also report practicing receptive anal intercourse[92]. Engaging in unprotected receptive sex would dilute whatever risk-reduction benefit might be associated with being circumcised while engaging in insertive sex.

A recent Cochrane review of 21 observational studies including 71,693 participants related to male circumcision in MSM indicated that there is a potential benefit of male circumcision in prevention of HIV transmission among MSM, however the evidence does not support making a recommendation for male circumcision in this population[93]. More specifically, the overall pooled effect estimate for HIV acquisition involving 20 studies and 65,784 participants was not statistically significant (OR 0.86, 95% CI 0.70 to 1.06) and showed significant heterogeneity (I^2=53%). However, there were differing results in subpopulations based on having an insertive versus receptive role in MSM sexual relations. The results were statistically significant among 3,465 men in 7 studies reporting an insertive role (OR 0.27, 95% CI 0.17 to 0.44; I^2=0%), but were not significant among 1,792 men in 3 studies reporting a receptive role (OR 1.20, 95% CI 0.63 to 2.29; I^2 = 0%). Male circumcision was not significantly associated with the following STIs: syphilis (34,999 men, 8 studies; OR 0.96, 95% CI 0.82 to 1.13, I^2 = 0%), herpes simplex virus 1 (2 studies, 2740 participants; OR 0.90, 95% CI 0.53 to 1.52; I^2=0%), or herpes simplex virus 2 (5 studies; 10,285 participants; OR 0.86, 95% CI 0.62

to 1.21; I^2=0%). The overall quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was low[94].Thus, while there is biological plausibility and evidence from some studies to suggest a reduced risk for HIV infection in circumcised men as compared with uncircumcised men engaging in insertive anal sex with an HIV-infected male partner, other well-conducted observational studies do not indicate a protective effect, either in predominately insertive MSM, or overall among MSM. And, because of the greater risk of receptive anal sex, the role of male circumcision as a public health intervention to prevent HIV transmission among MSM appears limited based on current data.

HIV or other STI. A meta-analysis of unpublished as well as published data from 15 studies that quantitatively examined the association between male circumcision and HIV and other STI among MSM found little overall effect[95]. Among a total of 53,567 MSM participants, 52% of whom were circumcised, the overall weighted odds of being HIV-positive was slightly less than one among circumcised versus uncircumcised MSM (OR 0.95; 95% CI 0.81-1.11). There was also no significant association when stratified by study type (e.g., cross-sectional, prospective) or when limited to MSM who reported engaging exclusively in insertive anal sex. However, in three studies completed before the introduction of highly active antiretroviral therapy, male circumcision was protective against HIV (OR 0.47; 95% CI 0.32-0.69). No overall association was found between male circumcision and other STIs among MSM[96].

A subsequent U.S. Internet-based survey with 26,257 respondents also found that circumcision status did not significantly predict HIV serostatus or most STI diagnoses (syphilis, gonorrhea, chlamydia, HPV). Being uncircumcised was predictive of HSV-2 diagnosis in this study; however, condom use mediated this relationship, as circumcision was associated with higher rates of condom use[96].

STI. An observational study of MSM in Australia found that male circumcision was not associated with prevalent or incident HSV-1, HSV-2, self-reported genital warts, or incident urethral gonorrhea or chlamydial infection[97]. Being circumcised was associated with a significantly reduced risk of incident (HR 0.35 [95% CI, 0.15-0.84]) but not prevalent (OR 0.71 [95% CI, 0.35-1.44]) syphilis.

HIV transmission in other populations at high risk for HIV acquisition

Presumably, the mechanism through which male circumcision affects the rates of HIV acquisition is through insertive sex. Thus, there is no plausible reason why male circumcision would directly affect the HIV risk from other exposures, such as injection drug use, transfusions, health-care related occupational exposure, or vertical (mother-child) transmission.

Male circumcision and other health conditions

In addition to studies of male circumcision related to HIV acquisition, the following sections review other studies exploring the association between male circumcision and other health conditions including STIs (other than HIV), penile and prostate cancer, cervical cancer in female partners of circumcised men, urinary tract infections in infants, and other associated health risks, including effect on sexual function and penile sensation.

Sexually transmitted infections (STIs)

Male circumcision has been shown to reduce the risk for some other STIs in addition to HIV. The effect of male circumcision on susceptibility to other STIs has been assessed in a number of observational studies in men who have sex with women[98, 99]. Results from these studies have been mixed but suggest that male circumcision is associated with lower risk for some STIs. More recent data from the male circumcision RCTs show that circumcision is significantly associated with decreased incidence of herpes simplex virus type 2 (HSV-2)[7, 8, 100], and decreased prevalence of oncogenic types of HPV[8, 9] in circumcised men (Table 2). The trials provide evidence that male circumcision may reduce genital ulcer disease confirmed on physican exam[56], self-reported GUD in men[76], as well as female genital ulceration and some vaginal infections (bacterial vaginosis [BV] and trichomoniasas) in female partners[101]. The trials did not show any association between male circumcision status and gonorrhea[100, 102] and showed only weak evidence for protection against chlamydial infection[100]. In the one trial in which it was assessed, no association was found with syphilis[8], although syphilis had been strongly associated with lack of male circumcision in observational studies[99].

Although rarely fatal, STIs other than HIV are among the most common communicable diseases in the United States, and interventions that prevent STIs would result in substantial reductions in morbidity and cost of health services. Most STIs are asymptomatic and the most prevalent STIs are not reportable in the United States; thus, the incidence of these infections must be estimated. The most recent estimate is that 19.7 million new STIs were acquired in the United States in 2008, including infections with *Trichomonas vaginalis* (1.1 million), HPV (14.1 million), *Chlamydia trachomatis* (2.9 million), HSV-2 (776,000), *Neisseria gonorrhoeae* (820,000), and *Treponema pallidum* (55,400)[103]. Data on male circumcision and STIs in MSM are summarized above in the section "Male-to-male transmission."

Rates of STIs differ in the United States compared to sub-Saharan Africa. Thus, it is important to assess the magnitude of the incremental benefit of male circumcision on HIV infection due to its protective effect against other STIs. In a dynamic stochastic model, Boily and authors concluded that the protection of male circumcision against STIs contributes little to the overall effect of circumcision on HIV[104]. Analyses of the RCTs confirmed this result[7, 105], suggesting that differing rates of other STIs should not be a major concern in generalizing the HIV prevention results of the RCTs from one setting to another.

Genital Ulcer Disease (GUD). Male circumcision is associated with a reduction of HSV-2 and GUD in randomized controlled trials and a reduction of GUD due to syphilis or chancroid in observational studies.

GUD (various types). There is evidence of an association of reduction in GUD with male circumcision in two RCTs. In the Kenyan RCT, male circumcision was associated with a reduction in GUD (risk ratio = 0.52; 95% CI 0.37 – 0.73)[56]. This reduction occurred regardless of HSV-2 status. Male circumcision significantly reduced symptomatic GUD in HSV-2-seronegative men [Prevalence Rate Ratio (PRR) = 0.51,95%] CI 0.43–0.74), HSV-2-seropositive men (PRR = 0.66, 95% CI 0.51–0.69), and in HSV-2 seroconverters (PRR = 0.48, 95% CI 0.30–0.79)[56]. In the Ugandan RCT, male circumcision was also associated with a reduction in GUD (PRR 0.53, 95% CI 0.43-0.64)[6].

Herpes Simplex Virus (HSV-2). HSV-2 infection is often asymptomatic but can cause genital ulcers. Compelling evidence of the protective effect of HSV-2 acquisition from male circumcision is available from two of three RCTs. In the South African trial, the incidence rate ratio (IRR) for acquisition of HSV-2 was 0.66 (95% CI 0.39-1.12) for the intervention arm in the intent-to-treat analysis, and 0.55 (95% CI 0.32 – 0.94) for circumcised men in the as-treated analysis[100]. In the Uganda RCT among 1,684 intervention and 1,709 control participants who were HSV-negative at baseline, the adjusted HR in the intervention group for HSV-2 infection was 0.72 (95% CI 0.56-0.92) at 24 months in the intent-to-treat analysis[8]. In these two clinical trials, circumcised men were approximately 30% to 45% less likely to become infected with HSV-2 over 21 to 24 months of observation. In addition, investigators estimated the HSV-2 per-sex-act female-to-male transmission probability in South Africa, and found that there was a positive correlation between HIV and HSV-2 infections and that male circumcision had a protective effect on HSV-2 acquisition by males[106]. From the RCT in Kisumu, Kenya, including 1,391 men assigned to the circumcision arm and 1,393 men assigned to the delayed circumcision arm, male circumcision was not associated with incident HSV-2 (circumcised: uncircumcised risk ratio = 0.94; 95% CI 0.70-1.25)[56]. Investigators hypothesized that the reason that results from the Kisumu RCT were inconsistent with South African and Ugandan RCTs may have been due to location of lesions or test performance. For example, 37% of clinically detected genital ulcers were detected on the penile shaft rather than the foreskin mucosa in Kisumu, however, similar data were not reported for the other two RCTs. Also the sensitivity and specificity of the Kalon test for detecting HSV-2 were higher in sub-Saharan Africa (95% and 91%, respectively) compared to Kisumu, Kenya (92% and 79%, respectively)[107]. Evidence from observational studies has provided mixed results. In an early review of six observational studies, two found male circumcision was protective against and four found no association with HSV-2[98]. In a subsequent review of 10 observational studies related to HSV-2 serostatus, six studies found a reduced relative risk associated with male circumcision status, and the difference

was statistically significant for two of the studies[99]. Compared to uncircumcised men, circumcised men had a summary estimated relative risk for HSV-2 infection of 0.88 (95% CI 0.77-1.01). In a cross-sectional observational study of men in rural Tanzania, those circumcised before sexual debut compared to uncircumsed men were less likely to be HIV seropositive compared with non-circumcised men (adjusted OR = 0.50, 95%CI:0.25–0.97), and were also less likely to be HSV-2 infected (aOR = 0.67, 95%CI:0.57–0.80) or have genital ulcer syndrome in the past 12 months (aOR= 0.69, 95%CI:0.47–1.00)[108]. In a population-based observational survey in Kisumu, Kenya, conducted to estimate baseline male circumcision status and attitudes associated with male circumcision, circumcision status was not associated with HIV/HSV-2 infection[109]. Observational data from a cross-sectional study in the United States have not shown an association between male circumcision status and HSV-2 infection. In an evaluation conducted by the National Health and Nutrition Examination Survey of 3,850 U.S. boys and men 14-49 years of age who reported having had sex, Xu et al. found no association between self-reported circumcision status and HSV-2 infection, after controlling for potential confounders such as age, race/ethnicity and sexual behaviors[110].

Treponema pallidum. Syphilis, caused by *T. pallidum,* classically presents as a painless genital ulcer. A review of 11 studies in which genital ulcers were due either to chancroid or syphilis found statistically significant decreases in risk of genital ulcer disease among circumcised men[98]. In addition, of 14 studies that have assessed the association between male circumcision and a serologic diagnosis of syphilis, 13 found a reduction in risk associated with male circumcision, and the difference was statistically significant in four studies[99]. A summary estimate of relative risk for syphilis was 0.69 (95% CI 0.50-0.94) for circumcised versus uncircumcised men. However, there was no prevention benefit from male circumcision against syphilis acquisition in the randomized trials. In the Uganda RCT, syphilis was detected in 50 of 2,083 subjects (2.4%) in the intervention group, compared with 45 of 2,143 subjects (2.1%) in the control group[8]. Circumcised men were less likely to report genital ulcers; however, nearly all genital ulcers with an identified etiology were attributed to herpes virus infection and not syphilis.

Haemophilus ducreyi. *H. ducreyi,* the organism that causes chancroid, is now uncommon in the United States. Only one observational study was found that included serologic diagnosis, so a review included 6 other studies that were based on clinical diagnosis [99]. Six studies found a reduced relative risk for circumcised versus uncircumcised subjects, which was statistically significant in four. Relative risks varied widely, and no summary relative risk was estimated due to variability in study design.

Other STIs. Male circumcision is associated with a reduction of high risk HPV infections in randomized controlled trials while there are mixed results for other STIs described in this section.

Human Papilloma Virus (HPV). HPV is generally an asymptomatic infection, but oncogenic HPV (principally genotypes 16, 18, 31, and 33) are believed to be responsible for 100% of squamous cervical cancers, 90% of anal cancers, and 40% of cancers of the penis, vulva and vagina[111]. Penile squamous carcinoma (caused by carcinogenic HPV subtypes) has been strongly and consistently associated with lack of male circumcision [98] (*see section, Penile Cancers*). Cervical cancer has been associated with lack of circumcision in male partners of women in several case-control studies[112](*see section, Cervical Cancer*). Of three observational studies that looked at the prevalence of genital warts in men, one found male circumcision was protective, one found it increased risk, and one found no association[98]. In the Uganda RCT, a higher prevalence of high-risk HPV genotypes was observed among 287 men in the control group (27.9%) than among the 233 men in the intervention group (18.0%, adjusted risk ratio 0.65; 95% CI 0.46-0.90)[8]. Also in that trial, male circumcision reduced the incidence of multiple high-risk HPV infections, increased the clearance of high-risk HPV infections in HIV-uninfected men [113], reduced the prevalence and incidence of multiple high-risk HPV infections in HIV-infected men [114], and decreased penile high-risk HPV shedding[115]. In the trial in Orange Farm, South Africa, high-risk HPV genotypes were detected among 140 (22.3%) of 627 men in the control group, compared to 94 (14.8%) of 637 men in the intervention group (adjusted prevalence rate ratio 0.68; 95% CI 0.52-0.89)[9].

***T. vaginalis*.** Trichomoniasis, caused by the parasite *T. vaginalis,* is believed to be the most common curable STI in the United States. The infection is generally asymptomatic in men but can cause severe cervicitis, vaginal discharge and labial itching and irritation in women, and may increase susceptibility to HIV[116]. The association of *T. vaginalis* and male circumcision had not been previously studied in any major observational studies. In the South African RCT, the effect of male circumcision on *T. vaginalis* infections was measured by polymerase chain reaction (PCR) from urine specimens[100]. Circumcised men were less likely to have a prevalent trichomonas infection (1.7%) than were uncircumcised men (3.1%), with statistical significance in the as-treated analysis (aOR 0.47; 95% CI 0.25-0.92) and borderline statistical significance in the intention-to-treat group (aOR 0.53; 95% CI 0.32-1.02). However, in the Kenya trial, which measured *T. vaginalis* by culture in participants' urine and urethral discharge, no significant association between male circumcision status and trichomonas infection was found[102]. The Uganda RCT assessed trichomonas infections in female partners. The prevalence of *T. vaginalis* was found to be about half as high among the HIV-negative wives of married participants who were circumcised (5.9%) compared to HIV-negative wives of men who were uncircumcised (11.2%)(adjusted PRR 0.52; 95% CI, 0.05-0.98)[101].

Chlamydia trachomatis. *C. trachomatis* causes urethritis in men and cervicitis and pelvic inflammatory disease in women. Before accurate tests were available, chlamydial infection in men was often diagnosed syndromically as "non-gonococcal urethritis," after exclusion of gonorrhea by Gram stain. Of eight observational studies of non-gonococcal urethritis, two found that male circumcision was protective, three found that it increased risk, and three found no association[98]. In women, one cross-sectional study found chlamydial infection among female partners of circumcised men to be 5.6 fold lower than among partners of uncircumcised men (OR 0.18; 95% CI 0.05-0.58), as tested by the presence of antibodies to *C. trachomatis*[117]. In another cross-sectional study, *C. trachomatis* infection was not associated with circumcision status of the partner (HR 1.25; 95% CI 0.96-1.63)[118]. In the Uganda trial, there was no association between male circumcision and self-reported urethritis or discharge in men or women[76], and in the Kenya trial, no association was found between laboratory-confirmed *C. trachomatis* infection and male circumcision status among trial participants[102]. However, the South African trial showed a borderline significant association in the intention-to-treat analysis (aOR 0.56; 95% CI 0.32-1.00) between *C. trachomatis* infection among male participants in the circumcision intervention arm (2.1%) and control arm (3.6%); this association was non-significant in the as-treated analysis (aOR 0.75; 95% CI 0.42-1.32)[100].

Neisseria gonorrhoeae. Gonorrhea is caused by the bacterium *N. gonorrhoeae* and can lead to urethritis in men and cervicitis and pelvic inflammatory disease in women. Of seven observational studies, five found statistically significant decreases in risk in circumcised men and two found no association with circumcision status [98]. However, no association has been demonstrated in prospective trials. In the Uganda RCT, there was no association between male circumcision and self-reported urethritis or discharge in men or women[76]. In the South Africa trial, the prevalence of gonorrhea, tested by polymerase chain reaction in first void urine, was similar in the male circumcision (10.0%) and the control (10.3%) groups[100]. Similarly, in the Kenya trial, no association between male circumcision status and gonorrhea was found[102].

Penile and prostate cancers

Penile cancer is rare in developed countries, accounting for <1% of malignancies among men[119], but appears to be strongly associated with the lack of male circumcision. Aside from circumcision status, it is associated with a history of HPV infection and lifestyle choices such as smoking, poor hygiene and multiple sex partners. Invasive penile cancer is very rare in circumcised men. The lifetime risk for a U.S. male of ever being diagnosed with penile cancer is 1 in 1,437[120]. In a retrospective analysis of 89 cases of invasive penile cancer diagnosed from 1954 through 1997, 98% were in uncircumcised men; of 118 cases of carcinoma in situ, 84% were in uncircumcised men[121]. Schoen published a retrospective review of 5 studies with 592 cases of invasive penile cancer in the United States; none of the cases were in men who had been circumcised in infancy[122]. Daling et

al. have suggested that the protective effect of male circumcision may be by preventing phimosis [123]. In a population-based case-control study, the authors found that men not circumcised during childhood were at increased risk of invasive (OR 2.3; 95% CI 1.3-4.1) but not in situ (OR 1.1; 95% CI 0.6-1.8) penile carcinoma. Among uncircumcised men, phimosis was strongly associated with invasive penile cancer (OR 11.4, 95% CI 5.0-25.9). Racial/ethnic distribution of penile cancer in the United States reflects the varying prevalence of male circumcision. In an analysis of penile cancer among 6539 U.S. men identified through population-based registries during 1995-2003, Hispanic men had the highest age-adjusted incidence (6.58 per million), followed by blacks (4.02 per million) and whites (3.9 per million)[124].

The lifetime risk of prostate cancer among men in the U.S. during 2008-1010 was about 15%[125]. It was also one of the leading causes of cancer death among men, with 28,088 men dying from prostate cancer in 2009[126]. Infection with STIs has been associated with the development of prostate cancer in some studies[127-130] and not others[131-133]. In one meta-analysis, an increased risk of prostate cancer was associated with a history of any STI (OR, 1.5; 95% CI, 1.3-1.7)[134]. Risk factors for STIs have also been associated with prostate cancer, including earlier age of first sexual activity[135] and a greater number of sexual partners[131, 136]. Circumcision before first sexual intercourse was associated with a 15% reduction in risk of prostate cancer compared to that of uncircumcised men in a combined analysis using pooled data from 1754 cases and 1645 controls in two population-based case-control studies (95% confidence interval [CI], 0.73-0.99)[137].

Cervical cancer in female partners of circumcised men

In a meta-analysis of male circumcision status and cervical cancer in female partners, data from 7 case-control studies were pooled[112]. Circumcision was associated with significantly less HPV infection in men. In an analysis restricted to monogamous women, there was a nonsignificant reduction in the odds of having cervical cancer risk among women with circumcised partners (OR 0.75; 95% CI 0.49-1.14). When the couples with men with five or fewer lifetime partners (40% of the study population) were excluded, there was a significantly reduced odds of cervical cancer in female partners of circumcised men compared with the female partners of uncircumcised men (OR 0.42; 95% CI 0.23-0.79).

Urinary tract infections in male infants

Studies have consistently demonstrated decreased incidence of UTIs among circumcised compared to uncircumcised boys. A multicenter prospective study of 1025 febrile infants under 2 months of age found that 9.0% of the fevers were attributable to UTI. Of the uncircumcised male infants, 21.3% had UTIs compared with 2.3% of the circumcised male infants[138]. A large cohort study including all births (n=427,698) in U.S. Army hospitals worldwide between 1975 and 1984 demonstrated an increase in the total number of UTIs among male infants as the circumcision rate declined over time[139] .

A meta-analysis including 18 studies and 22,919 children, found a pooled UTI prevalence of 20.1% among febrile uncircumcised boys <3 months of age and a prevalence of 2.4% among febrile circumcised boys <3 months of age[140]. Another systematic review[141] included 12 studies and over 400,000 children and concluded that male circumcision was associated with a significantly reduced risk of UTI (OR 0.13; 95% CI 0.08-0.20; p<0.001).

Estimates of the net clinical benefit of the procedure have varied depending upon the assumptions made regarding complication rates of male circumcision itself. Using an estimate of 0.2% rate of complications (hemorrhage, surgical injury, infection) following male circumcision, one study found that 6 UTIs could be prevented for every complication[142] (*see section, Risks and adverse events associated with male circumcision).* In another study, an assumption of 2% complication rate resulted in the conclusion that 20 complications would occur for every 9 UTIs prevented[141]. Overall, UTIs are not common among male infants, with estimates of the annual rate of UTI in uncircumcised infants being 0.70% versus 0.18% for circumcised infants[143].

Other health conditions

The presence of a foreskin has been associated with various penile dermatoses, including psoriasis, infections (e.g., HPV, HSV, molluscum and candidiasis), lichen sclerosis and seborrheic dermatitis[144]. Balanitis, inflammation of the glans penis, or balanoposthitis, the inflammation of the glans and the prepuce, are painful conditions that occur more frequently in uncircumcised males[145-147]. In a retrospective cohort of boys, the total frequency of complications (balanitis, irritation, adhesions, phimosis, paraphimosis) was higher among uncircumcised than circumcised boys (14% vs 6%), but most conditions were minor[147]. A prospective longitudinal study of over 500 boys in New Zealand found rates of penile conditions after 1 year of age to be 5% in circumcised boys and 1% in uncircumcised boys. These conditions included phimosis, penile inflammation, inadequate circumcision, and post-circumcision infection. However, after 8 years of age, the collective rates in the boys in the study were 11% and 19%, respectively. The majority of these problems were for penile inflammation including balanitis, meatitis, and inflammation of the prepuce[145]. A separate study of penile hygiene in the United States found that subjects who retracted the foreskin when bathing were less likely to have smegma accumulation, inflammation, phimosis, or adhesions than those who did not. Significant correlations were also found between early instructions concerning hygiene and the type of hygiene practiced, suggesting that good hygiene can offer some of the advantages of circumcision[148].

Health conditions for which male circumcision is indicated

Specific medical indications for which male circumcision is indicated include phimosis, the narrowing of preputial orifice leading to an inability to retract the foreskin over the glans, and paraphimosis, the entrapment of a retracted foreskin behind the coronal sulcus. In the United States, phimosis is estimated to affect approximately 0.5 to 1% of uncircumcised males over 16 years of age. Phimosis may be confused with non-

retractable foreskins or preputial adherence to the glans, which occurs in babies and young boys[149]. This condition is a normal part of penile development, and foreskin separation from the glans occurs over time without intervention. Although male circumcision is the definitive treatment, phimosis may respond to topical steroids. Male circumcision may also be indicated for recurrent balanitis, also known as balanoposthitis, a swelling (inflammation) of the foreskin and head of the penis, if they do not respond to conservative medical treatment.

A study of 25,718 admissions for male circumcision in Western Australia that excluded neonatal circumcisions at birth, found the rate of circumcision (per 1000 person-years) decreased from 5.51 at ages 0-4 years to 0.39 at ≥15 years[150]. Most male circumcisions were for phimosis, and some of the circumcisions may have been unnecessarily done for non-retractable foreskins or preputial adhesions. The rate of male circumcision for balanoposthitis was 0.44 at ages 0-4 years and decreased to 0.04 at ≥15 years.

Safety and risks associated with male circumcision

Reported rates of complications in large studies of medically attended male circumcision in the neonatal period in the United States are approximately 0.2%[142, 151, 152], and vary by type of study, setting, operator and surgical technique. In a comprehensive risk-benefit analysis of infant male circumcision based on reviews of the literature and meta-analyses, it is estimated that over a lifetime, benefits exceed risks by a factor of 100:1[153].
The most common complications reported have been bleeding and infection, and are usually minor and easily managed[142, 151, 152, 154]. Other reported complications, including wound dehiscence, unsatisfactory cosmesis, skin bridges, urinary retention, meatal stenosis, chordee, retained or too-small Plastibell devices, "concealed" (or "buried") penis, major bleeding, injury to the urethra due to fistula, surgical mishap, and severe infection are rare[155] and may occur after discharge from the hospital. In Christakis' study of 130,475 circumcised neonates, 0.18% had hemorrhagic complications, 0.04% suffered injury to the penis, and 0.0008% had cellulitis; the overall complication rate was 0.22%[142]. A similar adverse event rate of 0.19% was observed in a retrospective cohort of 100,157 circumcised neonates, including local infection, bacteremia, hemorrhage, surgical trauma, and UTI[151]. In a smaller study, complications were associated with 4% of 361 neonatal male circumcisions (hemorrhage, infection, surgical revision) and 13% of 230 circumcisions performed after the neonatal period (adhesions, poor hygiene, meatitis, surgical revisions)[156]. A recent meta-analysis of 16 prospective studies from diverse settings worldwide that evaluated complications following neonatal and infant male circumcision found that median frequency of severe adverse events was 0% (range 0-2%). The median frequency of any complication was 1.5% (range 0-16%). Male circumcision by medical providers on children tended to be associated with more complications (median frequency 6%; range 2-14%) than for neonates and infants[157].

In a study using data from a large longitudinal healthcare reimbursement dataset, investigators estimated the incidence of adverse events (AEs) between 2001-2010 attributable to male circumcision, and assessed whether AE rates differed by the age range when male circumcision was performed (i.e., <1 year, 1-9 years, or ≥10 years of

age)[158]. Among 1,400,920 circumcised males, circumcision was performed in 95.3% male infants age < 1 year, in 2.0% of males between one and nine years, and in 2.7% of males age 10 years and older. Among those males age 10 years of older, 22.9% were age 10-18 years. The overall estimated crude and adjusted incidences of probable AEs were 0.31% (95% CI 0.30-0.32) and 0.23% (95% CI 0.21 – 0.24). When estimated by age group, the incidence of probable AEs was 0.4%, 9.06%, and 5.31% for males age <1 year, 1-9 years, and ≥ 10 years, respectively. This incidence of AEs was 10-20 fold higher for males in older age groups compared to infants. The hightest incidence rate differences (IRDs) AEs among circumcised newborn males compared to uncircumcised newborns included correctional procedures [1887 AE/million male circumcision (PMMC)][2], bleeding [998.24 AE/PMMC][3], and inflammation of the penis [168.36 AE/PMMC][4]. In comparing incidence rates of probable AEs between circumcised males age 1-9 years and circumcised neonates younger than age 1 year, the highest IRDs included correctional procedures [2947 AE/PMMC][5], bleeding [8,398 AE/PMMC][6], and inflammation of the penis [6421 AE/PMMC][7]. Finally, in comparing incidence rates of probable AEs between circumcised males older than 9 years compared and circumcised neonates younger than age 1 year, the highest IRDs included correctional procedures [29,460 AE/PMMC][8], inflammation [17,575 AE/PMMC][9], bleeding [7,346 AE/PMMC][10], and wounds [2,944.7 AE/PMMC][11].

Meatal stenosis may be a complication of surgery. In a prospective study, meatal stenosis was documented in 24 of 239 (7.3%) circumcised boys older than 3 years but no uncircumcised boys[159]. However, the study population was not clearly defined and the diagnosed cases were not independently confirmed. Other studies have found rates of

[2] Highest IRDs included repair incomplete circumcision [919 AE/PMMC], and lysis or excision of penile post-circumcision adhesions [757 AE/PMMC]

[3] Highest IRDs included intraoperative bleeding [896.23 AE/PMMC], and hemorrhage control [107.21 AE/PMMC]

[4] Highest IRDs included edema of the penis [1,116.59 AE/PMMC], and other inflammatory disorders of the penis/ cellulites of the penis [68.0 AE/PMMC]

[5] Highest IRDS included division of penile adhesions [42,034 AE/PMMC], repair of incomplete circumcision [30,389 AE/PMMC], lysis or excision of penile adhesion [12,573 AE/PMMC], and other repair of penis [15,968 AE/PMMC within 365- day window post-circumcision and 15,795 AE/PMMC within 1200-day window post-circumcision]

[6] Highest IRDs included intraoperative bleeding [7498.3 AE/PMMC], and hemorrhage control [807.76 AE/PMMC].

[7] Highest IRDs included edema of the penis [2605 AE/PMMC] and other inflammatory disorders of the penis/celluites of the penis [3816 AE/PMMC].

[8] Highest IRDs included division of penile adhesions [12,395 AE/PMMC], other repair of penis [9, 864 within the 356-day window post- circumcision and 9719 within the 1200-day window post-circumcision, repair of incomplete circumcision [3,388 AE/PMMC], and lysis or excision of penil post-circumcision adhesions [2,576.8 AE/PMMC].

[9] Highest IRDs included edema of penis [4,163 AE/PMMC] and other inflammatory disorders of the penis/celluities of the penis [4,163 AE/PMMC].

[10] Highest IRDs included intraoperative bleeing [6756.0 AE/PMMC] and hemorrhage control [569.38 AE/PMMC].

[11] Included open wound of penis without mention of complications [2944.7 AE/PMMC]

meatal stenosis as low as 0.9%[160]. Studies have implicated male circumcision in methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks. A case-control study of two outbreaks in 11 otherwise healthy male infants at one hospital identified circumcision as a potential risk factor. However, in no case did MRSA infections involve the circumcision site, anesthesia injection site, or the penis, and MRSA was not found on any of the circumcision equipment or anesthesia vials tested[161]. In a review of published MRSA outbreaks, Van Howe noted the male propensity for MRSA infection potentially related to circumcision[162].

Minimizing pain is an important consideration for the procedure. Appropriate use of analgesia is considered standard of care for male circumcision at all ages. As demonstrated by Banieghbal and colleagues, appropriate analgesia can substantially control pain[163]. In their study, 93.5% of neonates circumcised in the first week of life with appropriate analgesia gave no indication of pain on an objective, standardized neonatal pain rating system.

Because of their rarity, rates of severe complications are difficult to document. In a review article, Wiswell compiled data from a myriad of sources, including personal correspondence, to estimate the following rates of adverse events per circumcisions performed: excessive bleeding requiring ligature, 1 per 4,000; bleeding requiring transfusion, 1 per 20,000; severe infection requiring parenteral antibiotics, 1 per 4000; subsequent surgery (e.g., for skin bridges), 1 per 1000; repair of traumatic injury, 1 per 15,000; and loss of entire penis, less than 1 per 1,000,000[146]. He also noted three deaths due to male circumcision during the period 1954-1989.

A study from a large longitudinal healthcare reimbursement dataset in the U.S. estimated the IRD (subtracting out the background rate of AEs in uncircumcised newborns) for potential serious probable AEs to range from a low of 0.76 persons (95% CI 0.10-5.43) with stricture of male genital organ per million male circumcisions (PMMC) to a high of 703.23 persons (95% CI 153.92-245.66) with repair of incomplete circumcision PMMC[164]. Four amputations of the penis occurred in uncircumcised newborns and three partial amputations of the penis occurred in circumcised newborns [IRD = 1.58 95% CI -6.16- 3.02].

In a study of 1,239 infant male circumcisions using the Mogen clamp in Western Kenya, the overall adverse events rate was 2.7%[165]. Most AEs were mild or moderate and treated conservatively. One severe AE involving excision of a small piece of the lateral aspect of the glans penis was documented. AEs were more common in babies who were one month of age or older, resulting in the conclusion that infant male circumcision is optimally conducted within the first month of life.

Complication rates for medically attended adult male circumcisions were well documented in the three African clinical trials. They were of similar magnitude and severity, ranging from 2 to 4%, and most commonly were pain, bleeding, infection and unsatisfactory cosmesis[166]. Bailey et al. observed a 1.7% rate of complications in Kenya, the most common being bleeding and infection[74]. Auvert et al. reported complications in

3.8% of South African participants; of these, the most common complications were pain (31.7%), bleeding (15.0%), swelling or hematoma (16.7%), and problems with appearance (15.0%)[75]. Gray et al. reported moderate to severe complications (those requiring any treatment) in 3.6% of procedures in Uganda, all of which resolved with treatment[76]. There were no reported deaths or long-term sequelae.

In an observational follow-up study of males aged 12 years or older who underwent voluntary male medical circumcision (VMMC) between Nov 2008 and March 2010 in 16 clinics in Nyanza Province, Kenya, the adverse event rate among clinic system participants during the intra-operative period was 0.1% and post-operative periods was 2.15%. The rate increased to 7.5% among participants under active surveillance. Providers performing 100 or more procedures compared to those who performed fewer than 100 procedures were 63% and 39% less likely to perform a procedure resulting in an AE in the clinic and active surveillance systems, respectively, and had a shorter duration of male circumcision procedures (15.5 vs. 24.0 minutes, respectively). Those performing more than 100 procedures achieved an AE rate of 0.7% and 4.3% in the clinic and active surveillance systems, respectively[167].

In Uganda, it was determined that the mean time to complete male circumcision surgery was 40 minutes for the first 100 procedures and 25 minutes for the subsequent 100 circumcisions[168]. The rate of moderate and severe AEs ranged from 8.8% for the first 19 unsupervised procedures after training, 4.0% for the next 20-99 procedures, and 2.0% for the last 100. All AEs were found to resolve with medical management. Investigators concluded that more than 100 circumcisions needed to be completed in order to achieve optimum duration of surgery and that the first 20 procedures after completing training should be supervised.

Effect of male circumcision on sexual function and penile sensation

The foreskin is a highly innervated structure[169] and some authors have expressed concern that its removal may compromise sexual sensation or function[170]. However, in one survey of 123 men following medical circumcision in the United States, men reported no change in sexual activity and improved sexual satisfaction, despite decreased erectile function and penile sensation[171]. Furthermore, a small survey conducted among 15 men before and after circumcision found no statistically significant difference in sexual function or sexual satisfaction[172]. Other studies conducted among men after adult circumcision have found that relatively few men report that there is a decline in sexual functioning after circumcision; most report either improvement or no change[173-176].

Considerations related to male circumcision in the United States

Policy decisions regarding male circumcision need to be considered in light of the domestic HIV epidemic, rates of male circumcision in the United States, acceptability of both adult male and newborn male circumcision in the United States and abroad, risk compensation, policy issues, and cost-effectiveness, while addressing ethical concerns.

HIV infection in the United States

The epidemiology of HIV in the United States differs considerably from that of regions targeted by the WHO/UNAIDS recommendations and the sub-Saharan African areas in which the RCTs were conducted[10]. The overall prevalence of HIV infection (0.4%)[61] is considerably lower in the United States than in some other nations, e.g., Kenya (7.8%), Uganda (5.4%) and South Africa (18.1%), where the male circumcision clinical trials were conducted[177]. Further, most sexual transmission in the United States occurs among men who engage in male-to-male sexual contact, whereas in sub-Saharan Africa transmission is predominantly through heterosexual sex. It should be noted, however, that HIV prevalence is high in some U.S. communities (for example, 2.4% of all adults and adolescents in Washington, DC)[178] and social networks[179]. In an analysis of surveillance data from 12 urban areas, overall prevalence was between 1-2% in four cities, between 2 -3% in four cities, and nearly 4% in one[180]. Prevalence was 1-4% among blacks in all areas and was 1-2.2% for Hispanics in five areas. Heterosexual contact accounted for about 20% of HIV infections among men in three areas, and 33.8% in Philadelphia.

New HIV cases in the United States and 6 dependent areas are predominantly in males; adult and adolescent males who engage in male-to-male sex represent the largest risk group. Comparing 2008 to 2010, the number of new HIV infections in the general population of adults and adolescents remained stable, with 47,500 (95% CI: 42,000–53,000) new infections in 2008 and 47,500 (95% CI: 42,000–53,000) in 2010[11]. The rate of new HIV infections in 2010 was 18.8 per 100,000.

In 2011, it is estimated that approximately 50,199 new HIV diagnoses were made, of which 79% were in males; 10% new HIV diagnoses were in men or male adolescents who acquired HIV heterosexually, and 64% were in men or male adolescents who acquired HIV through male-to-male sex (61% MSM alone, 3% MSM and injecting drug use)[63]. In addition, it is estimated that among persons living with a diagnosis of HIV infection in the United States in 2010, 75% were men, 8% were among men who acquired HIV infection heterosexually, and 56% acquired HIV infection through male-to-male sexual relations (50% MSM alone, 6% MSM and IDU)[63]. As noted earlier, there are few data showing a benefit of male circumcision on the risk of HIV associated with penile-anal sex or oral sex between men, and thus the benefit of circumcision among MSM is uncertain.

HIV transmission to heterosexual men reporting sexual relations with an HIV-infected female accounted for 1 of every 10 new HIV diagnoses in 2011 and 8 of every 100 persons living with HIV in the United States in 2010[11]. Circumcision is likely to play a role in preventing HIV among men who engage in unprotected heterosexual vaginal sex, especially in communities where prevalence of HIV infection among women is high or among men with multiple sex partners. The potential benefit of male circumcision as an intervention to prevent HIV infection among men who have sex with women depends upon the likelihood of HIV exposure among such men, and thus, upon the prevalence of HIV among their female sex partners.

The applicability of newly proven HIV prevention technologies like male circumcision across racial/ethnic groups is a critical consideration. Of the new infections among

whites, blacks, and Hispanics in the United States in 2011, the highest rates of new infections per 100,000 population occurred in black men (112.8) and black women (40.0)[63]. The overall rate of new HIV diagnoses among men in the United States and 6 dependent areas is 30.9 per 100,000 population. The proportion of estimated new HIV diagnoses among men attributed to high-risk heterosexual contact was 10% overall; the proportions attributed to high-risk heterosexual contact was 14% among African American males, 9% among Hispanics, and 4% among whites[11]. This reflects a similar racial/ethnic distribution of HIV incidence among females in the United States. The HIV rate of new diagnoses of HIV infection for black women (40.0 per 100,000) is five times that for Hispanic women (8 per 100,000) and 20 times the rate for white women (2.0 per 100,000)[63].

Rates of male circumcision in the United States

The United States differs from some regions of sub-Saharan Africa in that most American men are already circumcised. The practice of circumcising male newborns for reasons unrelated to religious beliefs was introduced to the United States in the late 1800s[3], and by the 1940s, an increasing proportion of male children in the United States were born in hospitals and circumcised shortly after birth[181]. The percentage of newborns that were circumcised annually reached 80% after World War II, peaked in the mid-1960s, and has decreased somewhat in recent years. In 2002, approximately 1.2 million newborn boys were circumcised prior to discharge from the hospital[182]; in 1996, an estimated 142,000 male circumcision procedures were performed beyond the neonatal period; of these, 49,000 were in persons older than 15 years[183].

Four nationally representative surveys have examined the prevalence of circumcision among U.S. males: two among newborns prior to discharge from the hospital, one among adult men, and one among adolescent males and adult men. According to the National Hospital Discharge Survey (NHDS), 65% of newborn boys born in hospitals were circumcised in 1999, and the overall proportion of newborns circumcised was stable from 1979 to 1999[184]. The proportion of black newborns who were circumcised during this period rose from 58% to 64%, while the proportion of white newborns who were circumcised remained stable at 66%. Significant differences in rates of male circumcision exist by region. While the proportion of newborns born in the Midwest who were circumcised increased over this 20-year period from 74% to 81%, the proportion of newborns born in the West who were circumcised decreased over the same period, from 64% to 37%[184]. From 2000 to 2007, newborn male circumcision rates in the NHDS declined from 63% to 56% (CDC unpublished data). In another hospital discharge survey with different methodology (Healthcare Cost and Utilization Project National Inpatient Sample [NIS]), the rate of circumcision performed during newborn male delivery hospitalizations increased significantly from 48% in 1988–1991 to 61% in 1997–2000[185] and declined from 2000 to 2008 from 61% to 56%[186]. Male circumcision was more common among newborns born to families of higher socioeconomic status, in patients with private insurance or belonging to a health maintenance organization, and among those born in the Northeast and Midwest. On multivariate analysis, black newborns were

slightly more likely and newborns of other races much less likely to undergo male circumcision than whites[185]. These surveys document male circumcisions performed in hospitals and billed or coded in discharge diagnoses, but do not ascertain male circumcisions which were not billed or coded, were performed outside of hospitals (e.g., circumcision conducted in religious ceremonies), or were performed after the delivery hospitalization.

In a series of national probability samples of adults surveyed during 1999–2004 as part of the National Health and Nutrition Examination Surveys (NHANES), the overall prevalence of male circumcision among adult males in the United States was 79% and varied by race/ethnicity (88% in non-Hispanic white men, 73% in non-Hispanic black men, 42% in Mexican Americans, and 50% in men of other races/ethnicities)[110].

Similarly, in a followup study, data from the National Health and Nutrition Examination Surveys 2005-2010 were used to estimate the prevalence of male circumcision among men and adolescents aged 14-59 years in the United States. The overall estimated prevalence of male circumcision in this population was 80.5% and also varied by race/ethnicity (90.8% in non-Hispanic whites, 75.7% in non-Hispanic blacks, and 44% in Mexican Americans)[187, 188].

In a study of hospital discharge data (NHDS) which corrected for underreporting, the percentage of neonatal males in the U.S. who underwent circumcision decreased from 83% in the 1960s to 77% by 2010[153]. This decrease was accompanied by an increase in the proportion of Hispanics, who are typically noncircumcising, in Western states, and withdrawal of Medicaid coverage in 18 states[153].

Acceptability

Acceptability of adult male circumcision in the United States

It is not well understood whether American men and male adolescents at higher risk for heterosexual acquisition of HIV would be willing to undergo circumcision for partial HIV prevention, nor whether parents would be willing to have their newborns circumcised for the purpose of reducing risk of possible future HIV infection. A recent consumer survey was sent to a stratified, random sample selected from a panel of households across the country. Among 709 self-identified heterosexual uncircumcised men, when asked about the likelihood of getting circumcised if their healthcare provider told them that getting circumcised would reduce their risk of becoming infected with HIV, only 86 (12%) reported they would be likely or very likely to get circumcised, while 591 (83%) reported that they would be unlikely or very unlikely to get circumcised. Similarly, among the 52 homosexual or bisexual men who reported being uncircumcised who were asked the same question, 42 (81%) reported being unlikely or very unlikely to get circumcised. In contrast, in an analysis of data collected from MSM interviewed at gay pride events in 2006, over half of uncircumcised MSM and 70% of uncircumcised black MSM indicated that they would be willing to be circumcised if the procedure were proven to reduce risk of HIV among MSM[189]. Willingness was associated with black race

(OR 3.4; 95% CI 1.3–9.8), non-injection drug use (OR 6.1; 95% CI 1.8–23.7) and the perception that male circumcision reduces the risk of penile cancer (OR 4.7; 95% CI 2.0–11.9). Post-surgical pain and wound infection were the most commonly reported concerns about male circumcision in that study.

In a more recent consumer survey assessing the acceptability of male circumcision as an HIV prevention intervention among adult males and the potential for risk compensation in the continental United States, investigators mailed surveys to a random sample of 19,996 potential respondents of approximately 340,000 households. Among 10,108 male and female respondents (50.6% response rate), 4,892 were men (48.3%). In the analysis related to adult male circumcision[190], of 4,265 men with responses to the question regarding their circumcision status, 846 (19.8%) reported being uncircumcised. Completed survey responses to other questions critical to the analysis on acceptability of male circumcision were obtained for 789 of 846 uncircumcised men. Among the 789 uncircumcised men with completed survey responses, 13.1% reported they would be likely or very likely to get circumcised if their health care provider told them it would reduce their risk of becoming HIV infected by having sex with an HIV-infected woman. In addition, 4,310 of 4,892 male respondents responded to the survey questions needed to conduct the risk compensation analysis. Among these 4,310 male respondents, 17.7% strongly agreed, agreed, or were neutral about this, meaning that men who are circumcised do not have to worry about risks like not using a condom during sex or having more sex partners.

Adult and adolescent male circumcision could potentially have the largest impact on HIV acquisition in populations in which a low percentage of males are circumcised and there is a high risk for HIV transmission through penile-vaginal sex. As noted above, among racial/ethnic groups, Hispanic men have the lowest rates of circumcision and higher rates of heterosexually acquired HIV than white men, while black men have the highest risk of heterosexually acquired HIV infection. Further research regarding acceptability of male circumcision in these populations is needed.

Acceptability of adult male circumcision in sub-Saharan Africa

More research on the acceptability of adult male circumcision has been conducted in sub-Saharan Africa in countries where HIV prevalence is high and male circumcision is practiced less frequently. The studies discussed below addressed facilitators and barriers to male circumcision. Many of the perceptions about benefits and risks of male circumcision that were identified are likely to be widespread. While some of the facilitators and barriers may be culturally-specific issues to sub-Saharan Africa, others are universal in nature and help inform the U.S. discussion.

A review of 13 articles concerning male circumcision in nine sub-Saharan African countries found that a median of 65% of uncircumcised men reported willingness to be circumcised, but there was a wide range of acceptability by country (from 29% in Uganda to 81% in Botswana)[191, 192]. A range of acceptability of male circumcision among uncircumcised men in four districts in Uganda was reported to be 40-62%[192]. Factors

that increased acceptability of male circumcision in the studies from the review article and other studies include the perception of improved hygiene[192-200], protection from HIV and other STIs[109, 192, 193, 196-200], increased sexual pleasure[192, 193, 196-200], acceptance of procedure by female partner[201], and improved ease of condom use[193, 194].

Barriers to male circumcision include concerns about the pain associated with surgery[193, 194, 196, 197, 202], religious and cultural beliefs[194, 196-199, 203], the cost of surgery[193, 196, 203], complications from surgery[192, 193, 195, 197], lack of access to health care[193], concerns about contracting HIV during the procedure[192], need for financial assistance during the recovery period to help maintain family income[192], and beliefs about resulting changes in penile size, sensation, or performance[199].

The beliefs of women also have an impact on the acceptability of male circumcision, and their beliefs differ by country[191]. There are several reasons why women report that they prefer that their male partners be circumcised. Some women reported that they believed that it is easier for men to maintain good hygiene if they are circumcised[193, 196, 197, 199], some reported believing that male circumcision decreases their own risk of acquiring STIs[193, 197-199], some reported preferring circumcised sex partners and some believed that men enjoy sex more if they are circumcised[196, 198, 199]. In the RCT in Uganda, of 455 female partners of men circumcised as adults, 2.9% reported less sexual satisfaction after their partners were circumcised, 57.3% reported no change, and 39.8% reported an improvement[204].

Acceptability of newborn male circumcision in the United States

Newborn circumcision has generally been well accepted in the United States, as evidenced by the rates of parents choosing to circumcise their newborn sons. Parents have typically made the decision based more on social concerns or perceptions of improved hygiene rather than medical reasons[156, 205]. A 1999 survey among parents of young boys found that those whose sons were uncircumcised were generally less satisfied with the decision than those who had chosen to circumcise their sons, and felt that they had not received adequate information[206].

It is not clear whether more information on potential health benefits and risks of male circumcision would influence parents' decisions, particularly among racial/ethnic groups that do not typically elect to have their sons circumcised. In a survey of new parents, 76% responded that they probably or definitely would want circumcision for their male children[207] and few participants' attitudes changed after reading an AAP policy summary or after reading about the results of the RCTs on HIV and HPV risk reduction.

However, in a more recent telephone survey of nearly 10,000 respondents across the continental United States, sampled through random digit dialing, 88% of respondents said that they would definitely or probably circumcise a newborn son, including 65% who "definitely would" and 23% who "probably would"; 53% of all respondents (including those who said they would definitely have their sons circumcised) stated that they would be more willing to consider circumcision for a male newborn child based on information

provided about potential future HIV risk reduction[190]. Approximately one-third of those who probably would not circumcise a newborn son responded that they were more likely to circumcise as a result of the information of a partial HIV protective effect later in life. Greater odds of not being inclined to circumcise a newborn son were associated with individuals of Hispanic ethnicity and other race/ethnicity compared with non-Hispanic whites, uncircumcised men and men with unknown circumcision status compared with females, individuals with postgraduate versus high school education, individuals living in the South and West compared to the Midwest, and those who were not or only somewhat confident in the safety of routine childhood vaccines versus those who were confident or very confident.

In a study about attitudes and decision making about infant male circumcision in a predominantly Hispanic population in New York City, the parental decision in favor of circumcising a male infant was associated with parents who came from a culture and family that believed in circumcision and who believed that it was not too risky[208].

Investigators studying whether presence of state Medicaid coverage for infant male circumcision was associated with male circumcision rates in the United States, found that the average rate of male circumcision was 55.9% and states with Medicaid coverage for routine male circumcision had, on average, male circumcision rates that were 24% higher percentage points than states without such coverage. Hospitals with higher percentages of Hispanic patients also had lower circumcision rates[209]. As of 2012, coverage for male circumcision through the Medicaid program is denied in 18 states[210].

Acceptability of newborn male circumcision in sub-Saharan Africa

Although, some of the issues related to acceptability of newborn male circumcision in sub-Saharan Africa may be culturally-specific to this region, others are universal in nature and help inform the discussion of male circumcision in the U.S. In addition, some of the culturally-specific issues of sub-Saharan Africans may continue to influence their decision making around male circumcision even after migrating to the U.S. In Uganda, willingness of men to have their sons circumcised ranged from 60%-86% , depending on geographic region[192]. A higher proportion of circumcised (96%-100%) compared to uncircumcised men (59-79%) were likely to have their sons circumcised. Women's support of a son's circumcision ranged from 49%-95%, based on geographic region. To prevent HIV/AIDS or provide for a ''healthier future'' was the most common reason for willingness to support a son's circumcision. Concerns about male circumcision included cost, pain associated with surgery, perception that circumcision would signify a religious conversion, or that it would encourage their children to engage in risky sexual activity, and lack of information about male circumcision. Household survey participants and healthcare workers preferred male circumcision during infancy or childhood (0-9 years) compared to adolescence (10-17 years) or adulthood ($\geq$ 18 years)[192]. In Zimbabwe, acceptability of early infant male circumcision was high among most ethnic groups; concerns included issues related to safety, questionable motivations behind free service provision by health care providers, handling of the discarded foreskin, separation of traditional circumcision from the adolescent initiation process, and female nursing of an

infant's wound which would be considered taboo[211]. In Botswana, among mothers who were interested in circumcision, protecting the infant from future infections such as HIV and hygiene were the main reasons expressed for circumcising their infants, while the child's comfort or safety during the procedure and timing of the procedure at too young an age were concerns voiced by those not interested in the procedure[212]. Among 129 grandparents and parents participating in focus group discussions in Lusaka, Zambia most participants felt there were benefits for HIV prevention associated with circumcision, as well as advantages conducting circumcisions at a young age[213]. Among these same focus group participants, barriers to neonatal circumcision included concerns about pain and cultural identity. Factors associated with allowing infant males to be circumcised among parents participating in a case-control study at five government hospitals in Nyanza Province, Kenya differed by gender[214]. Among mothers, having a husband (infant's father) who was circumcised or agreeing with the husband (infant's father) about the infant male circumcision facilitated infant male circumcision. Among fathers, being circumcised and agreeing with the mother about infant male circumcision were factors associated with conducting infant male circumcision. The primary decision makers were found to be fathers in 66% of instances.

Provider attitudes and practices regarding male circumcision in the United States

Although many medical societies have addressed neonatal male circumcision[215-218], few systematic data are available regarding provider attitudes and practices. In a nationally representative self-administered cross-sectional electronic survey of 1500 physicians (510 family practitioners, 490 internists, 250 pediatricians, and 250 obstetricians/ gynecologists) conducted in 2008, 29% of respondents thought that the medical benefits outweighed the risks of newborn male circumcision, while 41% thought the benefits and risks were equal, and 20% believed that the benefits did not justify the risks[219]. Overall, 39% of physicians reported being somewhat or very familiar with data from the male circumcision RCTs including 34% of family physicians, 33% of internists, 51% of pediatricians, and 48% of obstetricians. Most family physicians, pediatricians, and obstetricians (53%, 59%, and 58% respectively) reported that data from the RCTs in Africa made no difference in their likelihood of recommending male circumcision for neonates. Among internists and family physicians, 57% and 58% respectively reported that these data made them more likely to recommend circumcision for uncircumcised male patients who engage in high-risk heterosexual sex, and 61% and 60% respectively also reported that these data made them more likely to recommend elective circumcision to MSM. In addition, 22% (n = 327/1,500) of physicians in this study reported not understanding the risks and benefits of newborn male circumcision well enough to counsel parents and 40% (n = 504/1,250) reported not understanding the risks and benefits well enough to counsel adult men, suggesting the need for more education of physicians regarding the latest male circumcision research in order to feel comfortable counseling adult men or parents of newborn male infants[220].

Study results from interviews of a nonrandom sample of key informants and health care practitioners serving the Hispanic community in Miami, including physicians, nurses, and other allied health professionals illustrated differing attitudes based on gender and

highlighted the importance of supporting healthcare workers in any efforts to counsel clients around male circumcision and its role as an HIV prevention strategy[221]. The acceptability of male circumcision among male healthcare providers was associated with acceptability of American Pediatric Association guidelines, and personal circumcision. Some male healthcare providers expressed skepticism regarding health benefits for sexually transmitted disease/HIV risk reduction. Female providers expressed the importance of parental financial burden, lack of information, and low acceptability among Hispanic men.

Cost-effectiveness

The medical costs of male circumcision must also be accounted for in considering the role of circumcision for HIV prevention in any setting. While male circumcision has been shown to be a cost-saving HIV prevention intervention in sub-Saharan Africa[222, 223], the calculus is different in the United States, where the costs of performing male circumcision as well as HIV treatment costs are higher, and the risk of HIV infection is lower. Another important factor driving the cost-effectiveness is the length of time between the intervention and when the benefits are experienced. The value of these benefits is discounted over decades for newborn male circumcision, but over a shorter time period for adult male circumcision.

One cost-effectiveness analysis of male circumcision in the United States showed a net negative impact of circumcision. However, like most other cost-effectiveness analyses of male circumcision in the United States, it was conducted prior to publication of the RCTs and focused on costs and benefits of related conditions other than HIV[224]; cost-effectiveness increases when these additional benefits are factored in. One evaluation of a large health maintenance organization database found the expected lifetime cost of male circumcision was small, compared with larger expected benefits[225]. Much of the benefit of neonatal male circumcision in that analysis derived from pre-empting the need for post-neonatal circumcision, which is substantially more costly. Two other studies published in 1991, which did not include an HIV prevention benefit, estimated that both costs and benefits were too small to play a substantial role in the decision whether to perform the procedure[226, 227].

A model estimating the impact of newborn circumcision on a U.S. male's lifetime risk of HIV from heterosexual contact showed that circumcision reduced the 1.9% absolute lifetime risk by 15.7% overall, by 20.9% for black males, 12.3% for Hispanic males and 7.9% for white males[228]. The number of circumcisions needed to prevent one HIV infection was 298 for all males, and ranged from 65 for black males to 1,231 for white males. Newborn male circumcision was a cost-saving HIV prevention intervention overall, as well as for black and Hispanic males. The net cost of newborn male circumcision per QALY saved was $87,792 for white males. Results were most sensitive to the discount rate, male circumcision efficacy, and cost. The main analysis did not take into account secondary prevention (i.e., HIV cases prevented among partners of circumcised males), the benefits of male circumcision in preventing other STIs, adverse events, and possible reduction in HIV risk from male-to-male sexual contact.

A population-based model of the effect of adult male circumcision in MSM indicated that over 20 years, circumcision could very slightly reduce (<1%) the number of new HIV cases among MSM (CDC, unpublished data). Although there are no conclusive data demonstrating a protective effect for MSM, the model assumed 50-60% protection from HIV for circumcised men engaging in insertive sex. The net costs of the procedure were less than $50,000 per QALY saved, which is considered a conservative threshold for cost-effectiveness. The model included the prevention of secondary cases of HIV. The reduction in new cases of HIV was small because the chief source of HIV infection among MSM is receptive anal sex and the model assumed no circumcision-related protection for receptive acts.

Investigators evaluated the reduction in infections associated with male circumcision and resulting health care costs associated with continued decreases in male circumcision rates. They estimated that if male circumcision rates continue to decrease in the United States, such decreases would likely be associated with increased infection prevalence and resulting increased medical expenditures for men and women. For example, a reduction in the male circumcision rate to 10%, a rate similar to that in Europe, would result in an increase in lifetime health care costs by $407 per male and $43 per female, and an in increase in net expenditure per annual birth cohort $505 million. The projected increase in HIV infections would be responsible for 78.9% of increased costs[229].

Investigators conducting a cost-effectiveness analysis for MSM in Australia similarly found that male circumcision could be cost effective or cost saving in some scenarios, although a relatively small percentage of HIV infections would be prevented by circumcision of MSM and the associated cost was high relative to other HIV prevention programs[230]. They estimated that 2-5% of HIV infections per year would be averted and that 118-338 male circumcisions would be required to prevent one HIV infection. Either circumcising 100% of all MSM or MSM aged 35-44 years were both cost-effective strategies.

A number of cost-effectiveness studies and modeling exercises have found that male circumcision would be a cost-effective HIV prevention tool in subSaharan Africa. Using mathematical modeling, The Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Health Organization (WHO), and the South African Centre for Epidemiological Modelling and Analysis (SACEMA) estimated that male circumcision among heterosexual men in areas with a low prevalence of male circumcision and a high HIV prevalence would be very beneficial; five to 15 male circumcisions would need to be performed in order to avert one HIV infection[231]. The estimated costs to avert one HIV infection would range from US$150 to US$900 using a 10-year time span. Investigators conducting a cost-effectiveness study in Botswana estimated that US$689 per HIV infection and 70,000 HIV infections through 2025 could be averted by scaling-up adult and neonatal circumcision to reach 80% coverage by 2012 , at a total net cost of US$47 million between 2012 and 2025[232].

In a cost-effectiveness study of male circumcision at different ages in Rwanda, an African country with an adult HIV prevalence of 3%, infant male circumcision was found to be less expensive than adolescent and adult male circumcision (US$15 instead of US$59 per procedure) and cost-saving despite a delay in realization of savings from infant circumcision. Adult male circumcision was neither cost-saving nor highly cost-effective when considering only the direct benefit for the circumcised man[233]. A compartmental epidemic model simulating the population-level impact of various male circumcision programs on heterosexual transmission in Soweto, South Africa, incorporated both gender-specific negotiation strategies related to condom use with the male circumcision program. Investigators determined that even modest programs offering circumcision would result in significant benefits and estimated that a five-year prevention program in which an additional ten percent of uncircumcised males undergo circumcision annually, would prevent 13% of expected new HIV infections over a 20-year period[234].

Other considerations

Risk compensation

The possibility that men may alter their risk behavior and engage in riskier sex practices following circumcision may undermine the preventive health benefits of male circumcision[235, 236]. In addition, it is possible that generalized dissemination of public health information regarding male circumcision may introduce complacency and greater risk behavior among men circumcised early in life, such as the period during infancy through young adulthood.

In general, however, risk compensation was not observed among circumcised participants in the majority of RCTs. A meta-analysis of secondary outcomes measuring sexual behavior for the Kenyan and the Ugandan trials found no significant differences between circumcised and uncircumcised men[43], and in a sub-sample of men in the Kenyan trial, a detailed longitudinal sexual risk assessment indicated no statistically significant differences in sexual risk propensity scores or in incident infections of gonorrhea, chlamydial infection, or trichomoniasis by male circumcision status[237]. A similar result for the RCT conducted in Kenya found no significant difference in risk behavior between circumcised and uncircumcised men over 12 months of follow-up[5]. More recently, during 4.79 years of trial surveillance of participants in the Rakai randomized trial of male circumcision, there was no evidence of significant self-selection or behavioral risk compensation based on male circumcision status[46]. However, in the South African RCT, during 2002-2005, the mean number of sexual contacts was statistically significantly greater for circumcised men compared to uncircumcised men at the visits during months 4 – 12 (5.9 vs. 5.0, $p<0.001$) and at the visits during months 13 - 21 (7.5 vs. 6.4, $p= 0.0015$), although the number of partners did not increase. [46]

In observational studies, the results appear to be mixed. In a population-based observational survey conducted to estimate baseline male circumcision status and attitudes associated with male circumcision in Kisumu, Kenya, some respondents

expressed a concern that circumcised men might engage in riskier sex or might become more promiscuous due to misperceptions about the degree of protection provided by male circumcision[109]. However, in this same study, circumcision status was not associated with increased high-risk sexual behavior or lifetime number of sexual partners[109]. Similarly, in Uganda, in a mixed-method study using survey and focus group methodology, some respondents also expressed a concern that circumcised men might engage in riskier sex or might become more promiscuous due to misperceptions about the degree of protection provided by male circumcision, however, the RCT failed to find evidence of this[192]. A cross-sectional survey of 1,257 sexually active men aged 15 years or older in Botswana found that circumcision was not significantly associated with condom use; 15% of circumcised men compared to 12% of uncircumcised men did not use condoms. Lack of condom use was significantly associated with religious beliefs, low level of education, marriage, drunkenness, and misconceptions regarding antiretroviral therapy[238]. Between 2007-2008, in a cross-sectional survey of 7,300 young men age 15-34 years in 20 rural communities in Tanzania, the prevalence of male circumcision was 40.6%. Circumcised compared to uncircumcised men were more likely to report having ever used a condom (adjusted OR = 2.62, 95% CI:2.32–2.95)[108]. Among 304 HIV-uninfected circumcised men surveyed in Cape Town, South Africa, men who were aware that circumcision offers protection against HIV compared to those who were not aware were more likely to agree that risk compensation might occur in association with male circumcision ([RR 1.19, 95% confidence interval [CI]1.06–1.32, P, 0.01), perceived lower risk of HIV infection when circumcised (RR 1.15, 95% CI 1.11–1.12, P, 0.01) and were more likely to report unprotected vaginal sex acts (RR 1.08, 95% CI 1.04–1.12, P, 0.01). Those who were more likely to agree that risk compensation might occur in relation to male circumcision were also more likely to be diagnosed with a chronic STI (odds ratio [OR] 1.64, 95% CI 1.06–2.53, P, 0.05)[239]. Another study in Cape Town, South Africa, found risk compensation among women, but not men, who were informed of the HIV-protective effects of male circumcision[240].

To date, there are few data to predict possible patterns of risk compensation in U.S. males. In one national survey of 4,892 U.S. men, 82% of circumcised and uncircumcised men agreed that even if being circumcised does reduce a man's risk of HIV infection from heterosexual sex, circumcised men still needed to concern themselves with safe sex practices[190]. Xu found few differences in sexual behaviors among U.S. men according to their circumcision status. In a more recent consumer survey assessing the acceptability of male circumcision for both adult men and newborn males as an HIV prevention intervention and the potential for risk compensation in the continental United States, investigators mailed surveys to a random sample of 19,996 potential respondents of approximately 340,000 households. Among 10,108 male and female respondents (50.6% response rate), 4,892 were men (48.3%) and 4,310 male respondents responded to the survey questions needed to conduct the risk compensation analysis. Among these 4,310 male respondents, 17.7% strongly agreed, agreed, or were neutral about the idea that men who are circumcised do not have to worry about the risks associated with not using a condom during sex or having more sex partners[190]. Among high-risk heterosexual men, defined as those who reported having had more than one sexual partner or a new sexually transmitted infection in the past 12 months, the odds of potential risk compensation were higher among 1) non-Hispanic blacks and men of other race/

ethnicity compared to non-Hispanic whites, 2) men reporting an annual household income < $60,000 compared to >$60,000, 3) men who were never married or widowed/divorced/separated compared to married men, 4) men who agreed versus disagreed that they have little control over the things that happen to them, and 5) men who were 45 years and older compared to 18–34 years of age.

Policy considerations regarding reimbursement

Until recently, most U.S. medical societies have adopted relatively neutral stances regarding the practice of routine neonatal male circumcision. In 1999, the American Medical Association stated: "Virtually all current policy statements from specialty societies and medical organizations do not recommend routine neonatal circumcision, and support the provision of accurate and unbiased information to parents to inform their choice,"[215]. The American Academy of Pediatrics (AAP) statement on neonatal male circumcision from that year, reaffirmed in 2005, concluded that "[data demonstrate] potential medical benefits…however, these data are not sufficient to recommend routine neonatal circumcision"[241]. Similar neutral statements were issued by the American Academy of Family Physicians[242] and the American Urological Association (AUA)[243]. The AUA states that "when circumcision is being discussed with parents and informed consent obtained, medical benefits and risks, and ethnic, cultural, religious, and individual preferences should be considered. The risks and disadvantages of circumcision are encountered early whereas the advantages and benefits are prospective."

However, in the wake of the male circumcision clinical trial results from Africa, the AUA has modified their recommendation to say that, "While the results of studies in African nations may not necessarily be extrapolated to men in the United States at risk for HIV infection, the American Urological Association recommends that circumcision should be presented as an option for health benefits (but)… should not be offered as the only strategy for risk reduction[244]. In addition, in 2012, after the AAP's Taskforce on Circumcision reviewed the latest evidence, the AAP updated its stance concluding that the new evidence indicates that the preventive health benefits of newborn male circumcision outweigh the risks and that the benefits of newborn male circumcision justify access to this procedure for families who choose it[245].

In two studies, reimbursement by Medicaid or private insurance for the costs of neonatal male circumcision, were associated with higher circumcision rates in hospitals compared to states which disallow Medicaid reimbursement or where patients did not have private insurance coverage[246, 185]. In one retrospective study of rates of neonatal and early childhood male circumcision conducted from 1977-2001 limited to two hospitals in the Midwest, insurance coverage was not correlated with rates of neonatal male circumcision[247].

Ethical considerations

Recommendations related to male circumcision must consider ethical issues in addition to medical benefits and risk. A subcommittee of the CDC Public Health Ethics

Committee (PHEC) composed of CDC staff and external non-governmental consultants from academia and a center for ethics was consulted in October 2009 to review the ethical considerations related to elective male circumcision in the United States. The ethical principles of beneficence (maximizing benefit and minimizing harm, both at the individual and societal level); autonomy (respect for individual values and choices); and justice (the obligation to fairly distribute risks, burdens and benefits, to minimize stigmatization, and to make decisions in a transparent fashion) were considered. Of particular importance were ethical questions related to parental decision-making on behalf of a newborn boy, targeting populations at high risk for HIV, and medical reimbursement for the procedure.

The subcommittee concluded that newborns cannot provide informed consent and so must rely on their parents or caretakers to determine and act in their best interests, raising the issue of autonomy in discussions of circumcision of male newborns. They took into account varying opinions about the decision-making process including that the decision about whether to be circumcised should be made by individuals when they are old enough to make their own informed decisions. It has been pointed out that a man with a foreskin can elect to be circumcised but if circumcised as a newborn, cannot easily reverse the decision[248, 249]. Others argue that it is a choice that parents should be able to make on behalf of their male children because of the strong evidence showing that the procedure is beneficial and the risks are minimal if performed competently[250-252]. Parents are generally given the authority to make decisions, such as vaccination, for their minor children based on their evaluative consideration of the child's best interests. Appropriately, this consideration takes into account social, cultural, and religious perspectives, as well as objective, scientific information about preventive health benefits and risks. Thus, in the opinion of the PHEC subcommittee, both a decision to circumcise and a decision to not circumcise are legitimate decisions, and either decision is an appropriate exercise of parental authority on behalf of a minor child.

There are advantages and disadvantages to performing male circumcision at various stages of life. The procedure is simpler, safer, and less expensive for neonates and infants than for adolescents and adults. However, the newborn has no ability to participate in the decision. Furthermore, although there is evidence of reduced urinary tract infections among male infants who have been circumcised, the benefit of the protective effect against STIs, including HIV, is delayed for many years, not accruing until the child becomes sexually active. It is possible that new, less invasive interventions (e.g., effective topical microbicides or vaccines) may be developed in the intervening years[251]. Delaying male circumcision until adolescence or adulthood obviates concerns about violation of autonomy. However, performing the procedure after sexual debut would result in missed opportunities for prevention of HIV infection[251, 253]. In the United States, previous sexual intercourse was reported among 32% of males age 15 to 17 years and 65% of males age 18 to 19 years[254]. Uptake of the procedure after the neonatal period is also likely to be lower due to the increased cost, greater likelihood of complications, and other barriers to male circumcision at a later age. The PHEC subcommittee concluded that the disadvantages associated with delaying male circumcision would be ethically

compensated to some extent by the respect for the integrity and autonomy of the individual.

The prevalence of HIV infection in the United States is not as high as in sub-Saharan Africa, and most men do not acquire HIV through penile-vaginal sex. Targeting recommendations for adult male circumcision to men at elevated risk for heterosexually acquired HIV infection would be more cost effective than offering routine adult male circumcision. Men may be targeted according to sexual practices or an elevated prevalence of HIV within a geographic region or race/ethnicity group. However, some groups at high risk for HIV infection may also be more likely to be members of certain racial or ethnic groups, thus leading to the perception that men are being targeted because of their ethnic/racial status rather than their risk for HIV infection. Furthermore, recommendations to increase rates of male circumcision in the U.S. to reduce male acquisition of heterosexually acquired HIV infection may result in stigmatization of uncircumcised men or groups of men who are not routinely circumcised should they choose to not undergo circumcision. Conversely, targeting populations at high risk may raise questions about distributive justice, if persons in groups that are not targeted do not have equal access to the procedure[251]. The PHEC subcommittee concluded that programs incorporating male circumcision should be undertaken with sensitivity to the beliefs and practices of communities affected, and potential participants must be provided with an accurate explanation of potential risks and benefits, as well as assurances of protection of their best interests and informed choice[250, 251, 255].

The PHEC subcommittee also noted that lack of health care insurance for some groups and lack of coverage for male circumcision by Medicaid in some states raises issues of distributive justice, and because data demonstrate that male circumcision has the potential to reduce the risk of HIV infection and other adverse health conditions, the procedure should be made available to all who want it.

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Appendix. Abbreviations Used in This Report

AIDS	acquired human immunodeficiency syndrome
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACOG	American College of Obstetrics and Gynecology
AE	adverse event
AMA	American Medical Association
aOR	adjusted odds ratio
AUA	American Urological Association
BV	bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUD	genital ulcerative disease
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HSV	herpes simplex virus
IDU	injection drug user
IRR	incidence rate ratio
MMWR	Morbidity and Mortality Weekly Report
MRSA	methicillin-resistant *Staphlococcus aureus*
MSM	men who have sex with men
NIS	National Inpatient Sample
NHANES	National Health and Nutrition Examination Surveys
PHEC	Public Health Ethics Committee
OR	odds ratio
PMMC	per million male circumcisions
PRR	prevalence rate ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	risk ratio
STD	sexually transmitted disease
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
UTI	urinary tract infection
VMMC	voluntary male medical circumcision
WHO	World Health Organization

Tables

Table 1. Reduction in risk of male HIV acquisition and male circumcision in randomized controlled trials

Reference	Setting	Number and age range of HIV-negative participants enrolled	Adverse events related to surgery (%), among HIV-negative participants	Cumulative HIV infection events / cumulative person-years of follow-up (incidence per 100 person-years)		Modified intention- to-treat analysis		Per protocol (as-treated) analysis	
				Intervention	Control	IRR (95% CI)	Efficacy*	IRR (95% CI)	Efficacy*
Auvert†	Orange Farm, South Africa	3,128 men aged 18-24 years	54 / 1495 (3.6%)	20 / 2354 (0.85)	49 / 2339 (2.11)	0.40 (0.24-0.68)	60%	0.24 (0.14-0.44)	76%
Gray§	Rakai, Uganda	4,996 men aged 15-49 years	178 / 2328 (8%) (3.6% moderate or severe)	22 / 3352 (0.66)	45 / 3392 (1.33)	0.49 (0.28-0.84)	51%	0.45 (0.25-0.78)	55%
Bailey¶	Kisumu, Kenya	2,784 men aged 18-24 years	24 (in 23 persons) / 1334 (1.7%)	22 / 1391(2.1)	47 / 1393 (4.2)	0.47 (0.28-0.78)	53%	0.40 (0.23-0.68)	60%

IRR = incidence rate ratio

***** Reduction in HIV incidence

† **Source:** Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Med* 2005;2(11):e298.

§ **Source:** Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet* 2007;369:657-66.

¶ **Source:** Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet* 2007;369:643-65.

Table 2. Summary of evidence on the risk of STI associated with male circumcision status in heterosexual populations

STI	**Summary of data**	
Etiology	**Population, type of study, location, result**	**Measure of association**
HSV-2	In men: In RCTs: - In Uganda, significant association - In South Africa, no significant association in intention to treat analysis; significant association in as-treated analysis - In Kenya, no significant association In observational studies: no significant association in meta-analysis	 adjusted HR 0.72, 95% CI 0.56-0.92* IRR 0.66, 95% CI 0.39-1.12 IRR 0.55, 95% CI 0.32-0.94† RR 0.94, 95% CI 0.70-1.25& summary RR 0.88, 95% CI 0.77-1.01§
High-risk HPV	In men, significant association in RCTs: - Uganda - South Africa	 adjusted RR 0.65, 95% CI 0.46-0.90* PRR 0.68, 95% CI 0.52-0.89¶
Trichomoniasis	In men: In RCTs: - In Kenya, no significant association - In South Africa, no significant association in intention-to-treat analysis; significant association in as-treated analysis I n female partners significant association in RCT: -In Uganda	 IRR 0.77, 95% CI 0.44-1.36** aOR 0.53, 95% CI 0.32-1.02 aOR 0. 47, 95% CI 0.25-0.92 †† adjusted PRR 0.55; 95% CI, 0.34-0.89 §§

Syphilis	In men: No significant association in RCT: - In Uganda In observational studies: significant association	 adjusted HR 1.10, 95% CI 0.75-1.65* summary RR 0.69, 95% CI 0.50-0.94) §
Chlamydial infection	In men: No significant association in RCTs: - In Kenya - In South Africa, intention-to-treat analysis; as-treated analysis In female partners: Not assessed in RCTs, mixed results in cross-sectional studies: - Significant association in one study - No significant association in another study	 IRR 0.87, 95% CI 0.65-1.16** aOR 0.56, 95% CI 0.32-1.00 aOR 0.75, 95% CI 0.42-1.32†† OR 0.18, 95% CI 0.05-0.58 ¶¶ HR 1.25; 95% CI 0.96-1.63
Gonorrhea	In men: No significant association in RCT - In Kenya (IRR 0.95, 95% CI 0.68-1.34) ** - In South Africa, intention-to-treat analysis	 IRR 0.95, 95% CI 0.68-1.34 ** aOR 0.94, 95% CI 0.69-1.29 aOR 1.02, 95% CI 0.74-1.32 ††
Chancroid	In men: - Not assessed in RCTs. - In observational studies, lower risk of chancroid in six out of seven studies (mostly assessed by clinical exam)	 no summary RR due to heterogeneity, individual study RRs: 0.12 to 1.11 §

aOR = adjusted odds ratio; BV = bacterial vaginosis; CI = confidence interval; GUD = genital ulcerative disease; HPV = human

BV	In female partners: - In Uganda, significant association with Any BV severe BV	 adjusted PRR 0.60, 95% CI 0.38-0.94 PRR 0.39, 95% CI 0.24-0.64 §§
Syndromes		
GUD	In men: - In Uganda RCT, significant association - In Kenya RCT, significant association In female partners: - In Uganda RCT, significant association	 PRR 0.53, 95% CI 0.43-0.64*** RR 0.52; 95% CI 0.37-0.73& adjusted PRR 0.78, 0.61-0.99 §§
Genital discharge	In men: - In Uganda RCT, no significant association In female partners: - In Uganda RCT, no significant association	 PRR 0.84, 95% CI 0.63-1.11 *** PRR 0.99, 95% CI 0.89-1.12 §§
Dysuria	In men: - In Uganda RCT, no significant association In female partners: - In Uganda RCT, no significant association	 PRR 0.97, 95% CI 0.77-1.21 *** PRR 0.97, 95% CI 0.75-1.21 §§

papillomavirus; HR = hazard ratio; HSV = herpes simplex virus; IRR = incidence rate ratio; OR = odds ratio; PRR = prevalence rate ratio; RCT = randomized controlled trial; RR = risk ratio; STI = sexually transmitted infection

*** Source:** Tobian AAR, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Eng J Med* 2009;360;1298-309.

† **Source:** Sobngwi-Tambekou J, Taljaard D, Lissouba P, Zarca K, Puren A, Lagarde E, et al. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. *J Infect Dis* 2009;199(7):958-64.

&**Source:** Mehta SD, Moses S, Parker CB, et al. Circumcision status and incident herpes simplex virus type 2 infection, genital ulcer diseae, and HIV infection. *AIDS* 2012; 26(9):1141-1149.

§ Source: Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: A systematic review and meta-analysis. *Sex Transm Infect* 2006;82(2):101-10.

¶ Source: Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. J Infect Dis 2009;199(1):14-9.

**** Source:** Mehta SD, Moses S, Agot K, et al. Adult Male Circumcision Does Not Reduce the Risk of Incident Neisseria gonorrhoeae, Chlamydia trachomatis, or Trichomonas vaginalis Infection: Results from a Randomized, Controlled Trial in Kenya. *J Infect Dis* 2009;200(3):370-8.

†† **Source:** Sobngwi-Tambekou J, Taljaard D, et al. Male circumcision and Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis: observations after a randomised controlled trial for HIV prevention. *Sex Transm Infect* 2009;85(2):116-20.

§§ Source: Gray RH, Kigozi G, Serwadda D, et al. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol* 2009;200(1):42 e1-7

¶¶ Source: Castellsague X, Peeling RW, Franceschi S, et al. Chlamydia trachomatis infection in female partners of circumcised and uncircumcised adult men. *Am J Epidemiol* 2005;162(9):907-16.

*** Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet* 2007;369:657-66.

††† **Source:** Turner AN, Morrison CS, Padian NS, et al. Male circumcision and women's risk of incident chlamydial, gonococcal, and trichomonal infections. 2008 *Sex Transm Dis*;35:689-95.