Summary of Peer Review Comments and CDC Responses to Second Round of Peer Review Comments for

*Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and other Health Outcomes**

Formerly titled:** ***Recommendations for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and other Health Outcomes

This document summarizes peer review comments and CDC responses to those comments during the second round of quality reviews required by the US Office of Management and budget before the publication of a highly influential scientific assessment (HISA). This second round HISA, entitled “Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and other Health Outcomes” is the final draft of the first round HISA entitled “Recommendations for Providers Counseling Male Patients and Parents Regarding Elective Male Circumcision and the Prevention of HIV Infection, STIs, and Other Health Outcomes”, which was revised based on both rounds of comments.

The second round HISA document with tracked changes highlighted in red were shared with peer reviewers. Comments for peer reviewers A and B have been divided into two sections. Peer reviewers were asked to focus their comments on the red highlighted tracked changes. This document provides responses to each peer review comment in the following order:

1) Copy of the original CDC passage from the updated HISA document reviewed by peer reviewers, including the red highlighted tracked changes made by CDC in response to the first round of comments.
2) Peer reviewer comment(s) to the red-highlighted revisions by CDC.
3) CDC response to the peer reviewer comment(s).

Other revisions in the final HISA document posted on the CDC website made as a result of the CDC clearance process rather than in response to public and peer review comments may not be reflected in this document.

The two peer reviewers were professors of pediatrics with expertise in HIV, sexually transmitted infections, and male circumcision.

Peer Reviewer A Comments

CDC passage 1:

o Other anticipated health benefits derive in part from future prevention of HIV and some STIs acquired through heterosexual sex. Eight percent of annual HIV diagnoses in the United States are among persons with infection attributed to heterosexual contact. STIs are very common, with human papilloma virus (HPV) infection of the anus or genitals occurring in mainly sexually active persons, although HPV vaccination is highly effective against many serotypes. Current risks for either HIV or other non-HIV STIs may not remain constant in the future and the future risk for any individual neonate, child, or adolescent cannot be definitively defined at the time that a circumcision decision is made.

Peer Reviewer B Comment 1:

I don't have changes to suggest for the document except to say that there is a typo in the second bullet on page 6. The word should be "sociodemographic".

CDC response 1:

This typographical error was corrected.

Peer Reviewer B Comments

CDC passage 1: (Methods section)

"The information provided in this policy note is based on an evaluation of available evidence on the health risks and benefits associated with ~~high quality~~ medically performed male circumcision and were developed to pertain to male adults, adolescents, children, and newborns, and caregivers of male minors charged in the United States.[4]"

Peer Reviewer B Comment 1:

See note below. Need to minimize pain and the risk of complications.

CDC response 1:

Information Item 4-B at the end of the male circumcision information summary document states:

"Medically performed neonatal, pediatric, or adolescent male circumcision should be done by trained clinicians using appropriate standards (or standard) infection control, analgesia, and anesthetic practices of clinical care, with appropriate use of anesthesia."

Inherent to the statement that male circumcision should be performed by "trained clinicians" using "appropriate standards of infection control, analgesia and anesthetic practices of care, with appropriate use of anesthesia" is to minimize pain and risk of complications.

No change made.

CDC passage 2: (Review of Evidence section; new sentence added by CDC, based on new evidence)

In a separate large randomized clinical trial of HIV preexposure prophylaxis in Kenyan and Ugandan serodiscordant heterosexual couples, male circumcision was associated with a 42% reduction in the incidence of syphilis in men and 59% in women." (initial version reviewed by SME)

In a prospective cohort study nested in a large randomized clinical trial of HIV preexposure prophylaxis in Kenyan and Ugandan HIV-serodiscordant heterosexual couples, male circumcision was associated with a percentage reduction in the incidence of syphilis (42% in men and 59% in women).(revised version after CDC clearance process)

Peer Reviewer B comment 2:

Inappropriate. This obvious cheery-picking. There are many studies that failed to demonstrate a significant association that should be mentioned. This would include all of the studies looking for an association between circumcision status and HIV infection that have been conducted in North America.[1,2,3,4,5,6,7,8] In fact, one study out of Puerto Rico found the prevalence of HIV infection to *significantly* greater in circumcised men.[7] If circumcision is protective against HIV in North America, one would have expected at least one of these studies to find significant

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[1] Mor Z, Kent CK, Kohn RP, Klausner JD. Declining rates in male circumcision amidst increasing evidence of its public health benefit. PLoS ONE 2007; 2(9): e861.

[2] Laumann EO, Masi CM, Zuckerman EW. Circumcision in the United States: prevalence, prophylactic effects, and sexual practice. JAMA 1997; 277: 1052-7.

[3] Thomas AG, Bakhireva LN, Brodline SK Shaffer RA. Prevalence of circumcision and its association with HIV and sexually transmitted infections in a male US Navy population. Naval Health Research Center. Report No. 04-10. 2004.

[4] Chiasson MA, Stoneburner RL, Hildebrandt DS, Ewing WE, Telzak EE, Jaffe HW. Heterosexual transmission of HIV-1 associated with the use of smokable freebase cocaine (crack). AIDS 1991; 5: 1121-6.

[5] Warner L, Ghanem KG, Newman DR, Macaluso M, Sullivan PS, Erbelding EJ. Male circumcision and risk of HIV infection among heterosexual African American men attending Baltimore sexually transmitted disease clinics. J Infect Dis 2009; 199: 59-65.

[6] Mishra V, Medley A, Hong R, Yuan Gu Y, Robey B. Levels and spread of HIV seroprevalence and associated factors: evidence from National Household Surveys. DHS Comparative Reports No. 22. Calverton, Maryland, USA: Macro International Inc; 2009.

[7] Rodriguez-Diaz CE, Clatts MC, Jovet-Toledo GG, Vargas-Molina RL, Goldsamt LA, García H. More than foreskin: circumcision status, history of HIV/STI, and sexual risk in a clinic-based sample of men in Puerto Rico. J Sex Med 2012; 9: 2933-7.

[8] Telzak EE, Chiasson MA, Bevier PJ, Stoneburner RL, Castro KG, Jaffe HW. HIV-1 seroconversion in patients with and without genital ulcer disease. Ann Intern Med 1993; 119: 1181-6.

evidence of it, but none of them have. For recommendations aimed at people living in North America, the studies performed in North America should not be ignored.

CDC Response 2:

This comment does not apply to the new sentence which deals with reduction in syphilis related to male circumcision, not to reduction in HIV. No change made.

CDC Passage 3 (Information item 3A-2, adult and adolescent males section)

"Male circumcision reduces, but does not eliminate, the risk of acquiring HIV and some STIs during penile-vaginal sex. In clinical trials, medically performed male circumcision reduced the incidence of genital ulcer disease (GUD) by 48% and the prevalence by 47%, reduced the prevalence of HR-HPV by 23-47%, and reduced the incidence of syphilis by 42% among circumcised men."

Peer Reviewer B comment 3:

Inappropriate. If this recommendation is going to rely on RCTs in determining what to recommend regarding HIV, it should do the same for syphilis. Only two of the RCTs evaluated circumcision's impact of the incidence of syphilis. Both showed a non-significant increase in the men randomized to early circumcision (OR=1.15, 95%CI=0.76-1.87)[9] 360: 1298-309.] and RR=1.22, 95%CI=0.41-4.42[10] Neither study properly adjusted for lead-time bias. After adjusting for lead-time bias the odds ratio is 1.21 (95%CI=0.81-1.81) and relative risk is 1.32 (95%CI=0.44-3.94).]

CDC Response 3:

CDC already describes the nonsignificant findings from the other two male circumcision RCTs in the "Background, Methods, and Synthesis of Scientific Information Used to Inform the '**Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and other Health Outcomes**'" both in the evidence table (Table 2) and in the text of the document describing the potential association of male circumcision and syphilis. These descriptions highlight that one of the above mentioned RCT studies of male circumcision[10] excluded syphilis-infected and HIV-infected men from being recruited into the study. Incidence of syphilis in the study by Mehta et al was very low and therefore was difficult to ascertain the relation between syphilis incidence and male circumcision. The brief evidence review in the information

[9] Tobian AAR, Serwadda D, Quinn TC, Kigozi G, Gravitt PE, Laeyendecker O, Charvat B, Ssempijja V, Riedesel M, Oliver AE, Nowak RG, Moulton LH, Chen MZ, Reynolds SJ, Wawer MJ, Gray RH. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med 360: 1298-309.

[10] Mehta SD, Moses S, Parker CB, Agot K, Maclean I, Bailey RC. Circumcision status and incident HSV-2 infection, genital ulcer disease, and HIV infection. AIDS 2012; 26: 26: 1141-9.

summary is not meant to be exhaustive. The reader is encouraged to review the background document to obtain more in depth details regarding the evidence.

The PrEP RCT study[11] allowed syphilis-infected and HIV-infected men into their study and had a higher syphilis incidence overall. This approach allowed investigators to better evaluate the potential association between syphilis incidence and male circumcision. However, in re-reviewing the methodology of the substudy of syphilis in relation to circumcision, it was noted to be a prospective study embedded in the PrEP RCT. Because the syphilis substudy is not an RCT, the sentence was amended as follows: "In clinical trials, medically performed male circumcision reduced the incidence of genital ulcer disease (GUD) by 48% and the prevalence by 47%, and reduced the prevalence of HR-HPV by 23-47%, ~~and reduced the incidence of syphilis by 42%~~ among circumcised men."

CDC passage 4:

- Male circumcision has not been shown to reduce the risk of HIV transmission to female partners. However, in clinical trials, medically performed male circumcision reduced the incidence of syphilis by 59%.

Peer Reviewer B Comment 4:

Inappropriate. There is no citation for this remark, so it is difficult to evaluate its accuracy. It does match the data published by Pintye et al. (reference 12)]. It is not appropriate to place this much emphasis on a single study, especially when (as for the statements the immediately follow) there are studies that failed to replicate these results.[12] It is readily apparent that these statements are taken from studies that have been cherry-picked to support a particular point of view as there are other studies that could be cited to support the opposite point of view.

CDC response 4:

The statistic of 59% reduction in incidence of syphilis in female partners had been cited earlier in the review of evidence paragraph of the information summary document[13] and in the "Background, Methods, and Synthesis of Scientific Information Used to Inform the "Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections and other Health Outcomes.""

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[11] Pintye J, et al. Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples. Lancet Glob Health. 2014;2(11):e664-671

[12] Turner AN, Morrison CS, Padian NS, Kaufman JS, Behets FM, Salata RA, Mmiro FA, Chipato T, Celentano DD, Rugpao S, Miller WC. Male circumcision and women's risk of incidence of chlamydial, gonococcal, and trichomonal infections. Sex Transm Dis 2008; 35: 689-95.

[13]Pintye J, Baeten JM, Manhart LE, et al. Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples. Lancet Glob Health. 2014;2(11):e664-671.

In re-reviewing the methodology of the substudy of syphilis in relation to circumcision, it was noted to be a prospective study embedded in the PrEP RCT. Because the syphilis substudy is not an RCT, the sentence was amended as follows:

"Male circumcision has not been shown to reduce the risk of HIV transmission to female partners. ~~However, in clinical trials, medically performed male circumcision reduced the incidence of syphilis by 59%."~~

The article by Turner et al, cited by the peer reviewer, did not study the potential association between syphilis and male circumcision as noted by the authors as a limitation of the study. Turner et al state in the discussion that "… an evaluation of MC and women's risk of syphilis or chancroid might have been informative, since MC has been associated with reduced risk of these two infections in men.[40] Unfortunately, we did not have incidence data on syphilis or chancroid in our cohort."

CDC passage 5:

Uncircumcised, HIV-uninfected men and male adolescents at increased risk for HIV acquisition through heterosexual sex should be counseled about the risk and benefits of male circumcision (See Box 1). When a decision is made to undergo male circumcision, a referral for surgical consultation and access to ~~high quality~~ medically performed male circumcision surgical services should be provided.

Peer Reviewer comment 5:

There are circumcisions that are performed "medically" that are not safe. Instead, it should be worded to reflect that the patient should have access to the procedure in a setting where the pain and surgical complications that accompany the procedure are minimized. Even under ideal conditions, circumcision can result in severe complications and death. As an aside the term "uncircumcised" is pejorative and proper term is "intact."[14] (all three forms exist and all are different).

CDC response 5:

Information Item 4-B states:

"Medically performed neonatal, pediatric, or adolescent male circumcision should be done by trained clinicians using appropriate standards (or standard) infection control, analgesia, and anesthetic practices of clinical care, with appropriate use of anesthesia."

[14] Wallace WG. An undeniable need for change: the case for redefining human penis types: intact, circumcised, and uncircumcised Clin Anat 2015; 28: 563-4.

The goal of using trained clinicians using “appropriate standards of infection control, analgesia and anesthetic practices of care, with appropriate use of anesthesia” is partly to minimize pain and risk of complications.

The CDC chooses to use the “uncircumcised” because it is a more commonly used and accepted term in the medical and scientific literature compared with the term “intact”.

No change made.

CDC passage 6:

When counseling parents about male circumcision for an adolescent minor, the adolescent should be included in the decision-making process about undergoing elective male circumcision. When counseling an adolescent inquiring about male circumcision, parents should be engaged in the discussion, unless the adolescent is legally emancipated. Minors may be deemed emancipated, giving them sole authority to make health care decisions on their own behalf under certain circumstances, which vary by state law; for example, if the minor 1) lives independently and is self-supporting, 2) is married, 3) is pregnant or a parent, 4) is in the military, or 5) is declared emancipated by a court as defined in the mature minor section.[19]

Peer Reviewer B Comment 6:

Inappropriate. Not sure why space was allocated to make this distinction when there are a number of issues that the Recommendations fail to address: such as the twelve-fold increased risk of circumcised male infants have for getting MRSA infections,[15] the normal anatomy and function of the foreskin, the ongoing ethical debate over whether circumcising an infant without his consent is morally permissible, whether recommending circumcision is culturally offensive, and why so many national medical organizations have now condemned the practice.

CDC Response 6:

The reviewer does not directly address the new sentence. The other comments brought up by the reviewer are duplicative of comments that have been made previously as a part of the formal review process and already addressed in the response to public comments and peer reviewers. No change made in reference to this comment.

CDC passage 7:

[15] Nguyen DM, Bancroft E, Mascola L, Guevara R, Yasuda L. Risk factors for neonatal methicillin-resistant Staphylococcus aureus infection in a well-infant nursery. Infect Control Hosp Epidemiol 2007; 28: 406-11.

o An estimated 32% of uncircumcised males compared with 9% of circumcised males will experience a UTI in their lifetime, suggesting that circumcision is associated with a 23% absolute decreased lifetime risk of UTI.[21]

Peer Reviewer B Comment 7:

Inappropriate. This needs to be deleted. It is based on severely flawed analysis written by a pair of unabashed circumcision lobbyists who have no training in performing such an analysis. Their review of the medical literature failed to include a number of studies that would have altered their results substantially. It also included a number of studies that did not address their research question. There are a number of glaring problems with this study. One should be tipped off that there may be a problem when previous estimates of the number needed to treat were 195 [To et al] and 111 [Singh] were suddenly reduced to 4.29. Much of the absolute difference in lifetime UTI risk can be attributed to the males 16 years of age and older and those 1 through 15 years of age. Only three studies looked at boys over 5 year of age. One looked only at boys with documented vesicoureteral reflux.[16] One looked only at boys with posterior urethral valves.[17] These boys are clearly not representative of the general population of boys. The third found eight UTIs, of which six were diagnosed on the basis of a bagged specimen (a method know to have a high false positive rate) and six of the boys were under 16 months of age at the time of diagnosis.[18] It is not appropriate to assume the risk of recurrent UTI for boys with vesicoureteral reflux (an unusual condition) or posterior urethral valves (a rare condition) apply to general population of boys who have never had a UTI and do not have a condition that predisposed to UTIs. As a consequence, there is no reliable evidence to assess the differential impact of circumcision on UTI risk between 5 and 15 years of age. One can make the assumption that the same risk that applies between years 1 and 5 applies through age 15 years. There is no evidence to support this assumption. The data for the risk between 1 and 5 years is also weak with a very wide confidence interval (OR=3.0937, 95%CI=0.5303-inf) based on a single study.[19] Consequently, the relative risk estimated for the 1 to 16 year olds by Morris and Wiswell does not apply to the general population.

For males over 16 years old, Morris and Wiswell depended on a single study and ignored three other published studies. The study they relied collected data from a sexually transmitted disease clinic and “determination of which patients had urine cultures obtained not rigorously standardized in these patients but was left to the individual’s clinician’s judgment.”[20] They failed to include one small study of incontinent elderly men in a nursing home in which

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[16] Alsaywid BS, Saleh H, Deshpande A, Howman-Giles R, Smith GH. High grade primary vesicoureteral reflux in boys: long-term results of a prospective cohort study. J Urol 2010; 184(4 Suppl): 1598-603.
[17] Mukherjee S, Joshi A, Carroll D, Chandran H, Parashar K, McCarthy L. What is the effect of circumcision on risk of urinary tract infection in boys with posterior urethral valves? J Pediatr Surg 2009; 44: 417-21.
[18] Kim KK. Preputial condition and urinary tract infections. J Korean Med Science 1996; 11: 332-4
[19]Craig JC, Knight JF, Sureshkumar P, Mantz E, Roy LP. Effect of circumcision on incidence of urinary tract infection in preschool boys. J Pediatr 1996; 128: 23-7.
[20] Spach DH, Stapleton AE, Stamm WE. Lack of circumcision increases the risk of urinary tract infection in young men. JAMA 1992; 267: 679-81.

circumcision made little difference (6/6/5/7[intact positive/intact negative/circumcised positive/circumcised negative]; OR=1.40, 95%CI=0.28-7.02);[21] a study looking at bacteriuria in men that found no significant difference between intact and circumcised men (14/11/8/13; OR=2.07, 95%CI=0.63-6.75);[22] and a study much larger than the one cited by Morris and Wiswell of men at a urology clinic at the VA that found the rate of bacteriuria trended toward being lower in intact men (23/309/23/261; OR=0.84, 95%CI=0.46-1.540).[23] When these three studies are added to the only study identified by Morris and Wiswell, the Dersimonian and Laird summary random effect odd ratio is 1.30 (95%CI=0.66-2.56, between-study heterogeneity chi-square (df=3)=3.93, p=.2691). This is markedly below the odd ratio Morris and Wiswell reported (3.41, 95%CI=0.916-12.7).

The lifetime prevalence of UTIs in the United States has been estimated to be 13.6% using NHANES III Data.[24] The cumulative risk for UTI by age 16 in the UK, according to Morris and Wiswell, is 3.6%. The risk of UTI in intact boys in first year of life is 1%. So the risk from age 1 to 15 years would be approximately 2.6% (3.6%-1%), and from 16 years on up about 10% (13.6%-3.6%). The prevalence of circumcision in the United States is about 75% and in the United Kingdom is about 20%.

If one accepts a 9.91-fold increase in risk of a UTI in the first year of life for intact boys, then 1% of intact boys and 0.1009% in circumcised boys would develop UTIs. Using the formula Morris and Wiswell used

$$p=(C*c)+((1-C)*R*c)$$

where C=circumcision prevalence, c = prevalence of UTI in circumcised males, p = prevalence of UTI in population, R = relative risk of UTI – intact versus circumcised. and solving for c one gets the following for the 1 through 15 year olds:

$$0.026=(0.20*c)+(0.80*3.0937*c)$$

Solving for c, c = 0.0097% and the prevalence in intact boys would be 3.01%

Remember these estimates are based on little solid evidence and are mostly speculation.

For those 16 and older:

$$0.10=(0.75*c)+(0.25*1.30*c)$$

[21] Nicolle LE, Harding GK, Kennedy J, McIntyre M, Aoki F, Murray D. Urine specimen collection with external devices for diagnosis of bacteriuria in elderly incontinent men. J Clin Microbiol 1988; 26: 1115-9.
[22] Lai FC, Kennedy WA 2nd, Lindert KA, Terris MK. Effect of circumcision on prostatic bacterial colonization and subsequent bacterial seeding following transrectal ultrasound-guided prostate biopsies. Tech Urol 2001; 7: 305-9.
[23] Lipsky BA, Inui TS, Plorde JJ, Berger RE. Is the clean-catch midstream void procedure necessary for obtaining urine culture specimens from men? Am J Med 1984; 76: 257-62.
[24] Griebling TL. Urologic Diseases in America Project: trends in resource use for urinary tract infections in men. J Urol 2005; 173: 1288-94

Solving for c, c = 9.30% and prevalence in intact male would be 12.09%

The absolute difference in overall lifetime prevalence would be 5.72%, which is much lower than the 23.3% reported by Morris and Wiswell. Instead of number need to treat of 4.29, the number needed to would be 17.48. Even these results should be taken with a grain of salt. These calculations are based on a small number of studies in males over 5 years of age all of which are of poor quality. The confidence intervals of the estimates indicate the findings are not statistically significant. While I did not have the time to perform a Monte Carlo simulation with these estimates, it is likely that the 95% confidence intervals would include outcomes in which UTIs were more common in circumcised males.

In conclusion the study by Morris and Wiswell is poorly executed, based on methodologically weak studies, inappropriate included a number of studies that shed no light on the risk of UTI for the general population, and failed to include several studies in adults that marked alter the final results. The study is several steps removed from reality. I would be very wary to make any pronouncement based on such weak evidence.

CDC Response 7: We have based our conclusions on the highest level of evidence among published studies. Published studies support the conclusion that uncircumcised males are more likely to experience a UTI in their lifetime. No change made.

CDC passage 8:

Although once diagnosed, most UTIs are treatable, serious complications may occur when UTIs are recurrent, difficult to treat, or left untreated. Such complications may include sepsis, pyelonephritis, and renal scarring and have been associated with the increased risk for long term consequences including hypertension, build-up of kidney waste products (uremia), and end stage renal disease

Peer Reviewer B Comment 8:

Inappropriate. This is hyperbolic and misleading. The long-term risks associated with urinary tract infections in infants are less than previously believed. Treatment with oral antibiotics has been shown to be as effective as treatment with intravenous antibiotics.[25] Males are most likely to have urinary tract infections in the first six months of life, yet UTIs occurring in the first twelve months of life are less likely to have renal parenchymal involvement.[26] A strong body of evidence now exists that UTIs rarely, if ever, lead to hypertension or persistent renal

[25] Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, Kearney DH, Reynolds EA, Ruley J, Janosky JE. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics 1999; 104: 79-86.
[26] Pecile P, Miorin E, Romanello C, Vidal E, Contardo M, Valent F, Tenore A. Age-related renal parenchymal lesions in children with first febrile urinary tract infections. Pediatrics 2009; 124; 23-29

dysfunction.[27,28,29,30,31,32,33,34,35,36,37] While prenatal ultrasounds find vesico-ureteral reflux more frequently in males, most cases in males resolve spontaneously. This may temporarily predispose males to urinary tract infection,[38,39] The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis but the risk is quite low after six months of age, by which time the reflux has often resolved spontaneously. Urinary tract infections should not be mischaracterized as an infection with life-long serious consequences, because the current medical literature does not support such a characterization. There have been no studies that end state renal disease is more common in intact males.

CDC response 8:

The statements made by the reviewer do not refute the above statement made about complications that may occur with UTIs. No change in response to this comment.

CDC Passage 9:

Other anticipated health benefits derive in part from future prevention of HIV and some STIs acquired through heterosexual sex. Eight percent of annual HIV diagnoses in the United States are among persons with infection attributed to heterosexual contact. STIs are very common, with human papilloma virus (HPV) infection of the anus or genitals occurring in nearly all sexually active persons regardless of sociodemographic differences.

Peer Reviewer B Comment 9:

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[27] Sreenarasimhaiah S, Hellerstein S. Urinary tract infections per se do not cause end-stage kidney disease. Pediatr Nephrol 1998; 12: 210-3

[28] Sreenarasimhaiah S, Hellerstein S. Urinary tract infections per se do not cause end-stage kidney disease. Pediatr Nephrol 1998; 12: 210-3

[29] Helin I, Winberg J. Chronic renal failure in Swedish children. Acta Paediatr Scand 1980; 69: 607-11

[30] Esbjörner E, Aronson S, Berg U, Jodal U, Linne T. Children with chronic renal failure in Sweden 1978-1985. Pediatr Nephrol 1990; 4: 249-52

[31] Esbjörner E, Berg U, Hansson S. Epidemiology of chronic renal failure in children: a report from Sweden 1986-1994. Swedish Pediatric Nephrology Association. Pediatr Nephrol 1997; 11: 438-42

[32] Wennerström M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after first urinary tract infection in childhood. Arch Pediatr Adolesc Med 2000; 154: 339-45

[33] Wennerström M, Hansson S, Hedner T, Himmelmann A, Jodal U. Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. J Hypertens 2000; 18: 485-91

[34] Wolfish NM, Delbrouck NF, Shanon A, Matzinger MA, Stenstrom R, McLaine PN. Prevalence of hypertension in children with primary vesicoureteral reflux. J Pediatr 1993; 123: 559-63

[35] Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics 2011; 128: 840-7

[36] Hannula A, Perhomaa M, Venhola M, Pokka T, Renko M, Uhari M. Long-term follow-up of patients after childhood urinary tract infection. Arch Pediatr Adolesc Med 2012; 166: 1117-22

[37] Craig JC, Williams GJ. Denominators do matter: it's a myth — urinary tract infection does not cause chronic kidney disease. Pediatrics 2011; 128: 984-5.

[38] Herndon CDA, McKenna PH, Kolon TF, Gonzales ET, Baker LA, Docimo SG. A multicenter outcomes analysis of patients with neonatal reflux presenting with prenatal hydronephrosis. J Urol 1999; 162: 1203-8

[39] Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol 1997; 80: 319-27.

Inappropriate. While HPV infections are common, most infections are transitory. A large, prospective multinational study of 4,033 men found that when it came to clearing HPV from the penis, the type of HPV most responsible for inducing cancer was cleared significantly more quickly in intact men. This study found no difference in the incidence of HPV infection between intact and circumcised men.[40] This is result is consistent with studies that sampled both the head and shaft of the penis. Studies that sampled only the head of penis consistently find HPV more commonly in intact men. This has been demonstrated using meta-regression.[41,42] In men who have HPV infections, HPV is more likely to be found only on the shaft of the penis in circumcised men and only one the glans of the penis in intact men. If one samples only the glans of the penis, one will overestimate the incidence/prevalence of HPV in intact men by at least 30%.[43,44] If one performs a meta-analysis of the studies that have measured the incidence of HPV by circumcision status, there is no significant difference.

CDC Response 9:

This comment does not adequately refute the statement made about the fact that STIs are very common. No change made in response to the peer review comment.

CDC Passage 10:

Most of the health benefits of male circumcision accrue after sexual debut (i.e., after becoming sexually active).

CDC Reviewer Comment 10:

Misleading. This needs to be rephrased that nearly all of the purported benefits are believed to become available at that time.

CDC response 10:

The reviewer does not limit his/her comments to the edit that was made (in red), nor does it refute the added clarifying sentence. No change made.

CDC Passage 11:

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[40] Albero G, Castellsagué X, Lin H-Y, Fulp W, Villa LL, Lazcano-Ponce E, Papenfuss M, Abrahamsen M, Salmerón J, Quiterio M, Nyitray AG, Lu B, Bosch FX, Giuliano AR. Male circumcision and the incidence and clearance of genital human papillomavirus (HPV) infection in men: the HPV Infection in men (HIM) cohort study. BMC Infect Dis 2014; 14: Article ID 75.]

[41] Van Howe RS. Human papillomavirus and circumcision: A meta-analysis. J Infect 2007; 54: 490-6

[42] Van Howe RS. Sexually transmitted infections and male circumcision: a systematic review and meta-analysis. ISRN Urol 2013: 109846]

[43] VanBuskirk K, Winer RL, Hughes JP, Feng Q, Arima Y, Lee S-K, Stern ME, O'Reilly BS, Koutsky LA. Circumcision and the acquisition of human papillomavirus infection in young men. Sex Transm Dis 2011; 38: 1074-81

[44] Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, Meyer C, Stern M, Koutsky LA. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 2004; 189: 677-85.

- Complications of medically performed male circumcision in the United States are typically uncommon and easily managed. Severe complications are rare in all age groups and occur in 0.23% of all circumcised males overall.23
    - Among newborns and children age 1 - 9 years, most frequently reported complications include bleeding and inflammation of the penis or incomplete wound healing or adhesions requiring the need for corrective procedures.[2]

CDC Reviewer Comment 11:

Inappropriate. This is not the most common complication. The most common complication is meatal stenosis that is seen in 5% to 20% of circumcised males.[45,46,47,48,49,50,51,52] Many, if not most of these boys require a meatotomy.

CDC Response 11:

CDC used a more up to date reference which included data on circumcision from 28,197 boys aged 1-9 years of age using The Charge Data Master (CDM) SDI Health's inpatient data set. This dataset gathers data "from a 20% convenience sample of all inpatient encounters of short-stay, acute care, and nonfederal hospitals from 48 states and Washington, DC, representing approximately 120 million unique hospitalized patients". The studies mentioned by Van Howe include small numbers of subjects and were not necessarily designed to describe the range of complications. Many of the studies he cites were conducted to describe a specific complication (i.e. metal stenosis). For example, the Van Howe study in 1997 included 213 circumcised boys 3 years and older from rural Wisconsin. The two Stenram et al. studies included only 117 young boys from Lund, Sweden. The study by Persad is a study of the "The clinical presentation and operative findings reported in 12 children who presented with meatal stenosis over a period of 3 years"; and was not designed to describe the range of complications. The goal of the study by Van How in 2006 was to describe the incidence of "meatal stenosis" in a consecutive sample of boys whose visit with the physician included a genital examination in a private primary care pediatric practice in rural northern Wisconsin. Including 329 circumcised boys. The study does not describe the frequency of other

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[45] Van Howe RS. Variability in penile appearance and penile findings: a prospective study. Br J Urol 1997; 80: 776-82
[46] Stenram A, Malmfors G, Okmian L. Circumcision for phimosis: a follow-up study. Scand J Urol Nephrol 1986; 20: 89-92
[47] Persad R, Sharma S, McTavish J, Imber C, Mouriquand PD. Clinical presentation and pathophysiology of meatal stenosis following circumcision. Br J Urol 1995; 75: 91-3
[48] Van Howe RS. Incidence of meatal stenosis following neonatal circumcision in a primary care setting. Clin Pediatr (Phila) 2006; 45: 49-54
[49] Joudi M, Fathi M, Hiradfar M. Incidence of asymptomatic meatal stenosis in children following neonatal circumcision. J Pediatr Urol 2011; 7: 526-8
[50] Griffiths DM, Atwell JD, Freeman NV. A prospective survey of the indications and morbidity of circumcision in children. Eur Urol 1985; 11: 184-7
[51] Stenram A, Malmfors G, Okmian L. Circumcision for phimosis--indications and results. Acta Paediatr Scand 1986; 75: 321-3
[52] Upadhyay V, Hammodat HM, Pease PW. Post circumcision meatal stenosis: 12 years' experience. N Z Med J 1998; 111(1060): 57-8.]

complications of circumcision so it is difficult to ascertain how common this is in comparison to other complications. Also we know little about why the patients presented to the primary care pediatric practice or whether the pediatrician is known for treating specific disorders that could bias the result. The Joudi article also is described as a study to determine the incidence of meatal stenosis in children following neonatal circumcision rather than a description of the frequency of various complications after male circumcision. The study by Griffiths included only 140 boys between the ages of 3 months and 14 years (mean 4.3 years) attending a urology clinic. The study by Upadhyay et al. was limited to boys with meatitis, and therefore does not describe the full range of complications. No change made in response to the peer reviewer's comment.

CDC Passage 12:

4-B. Medically performed neonatal, pediatric, or adolescent male circumcision should be done by trained clinicians using appropriate ~~according to accepted standards~~ (or standard) infection control, analgesia, and anesthetic practices ~~of clinical care, with appropriate use of anesthesia~~

Peer Reviewer B Comment 12:

Misleading. Ideally, the procedure should be performed with adequate anesthesia. Adequate anesthesia (i.e., general anesthetics) is too dangerous to use for an elective procedure in the first six months of life. Consequently, adequate anesthesia is not safely available for neonatal circumcision. Some national medical organizations have recommended delaying elective circumcision until six months of age until adequate anesthesia is safely available.[53]

CDC Response 12:

The sentence reads "appropriate (or standard) infection control, analgesia, and anesthetic practices". Therefore age would be taken into account when deciding which approach is best for limiting pain. No change made.

CDC Passage 13:

- Male circumcision reduces the risk of the female partners of circumcised men acquiring new infections with:
- Syphilis (by 59%)

Peer Reviewer B Comment:

[53] Leditschke JF. Australasian Association of Paediatric Surgeons. Guidelines for Circumcision. Hersion, Queensland, Australia; April 1996.

Inappropriate. Based on one study, whose other results are at odds with other published studies. If this recommendation is willing to make statements based on a single study, then it also needs to mention the two studies that have found a significant association between neonatal circumcision and being diagnosed with autism spectrum disorder,[54,55] and the one study that found a link between infant circumcision and hyperactivity (ADHD).[54]

CDC response 13:

The study[54] which found an association with autism and male circumcision focused only on ritual male circumcision which is outside the scope of these guidelines and has been critiqued as being methodologically unsound and biased.[56] Also, there is insufficient scientific evidence to support any statements about an association between neonatal circumcision and autism or hyperactivity. No change made.

CDC Passage 14:

On average, adult men who undergo circumcision generally report minimal or no change in sexual satisfaction or function. Those who enjoy the sensation of the foreskin during sexual relations will no longer experience that sensation.

Peer Reviewer B comment 14:

Inappropriate. It is more than just the sensation of the foreskin. Three studies have demonstrated that the sensitivity of the glans in the flaccid penis to fine touch is decreased in circumcised men.[57,58,59] Two studies have demonstrated that the foreskin is the structure of the penis most sensitive to fine touch.[58,60] Studies of adult men circumcised for medical indications report decreases in erectile function, penile sensitivity, and erectile confidence. Many men were not satisfied with the results of the procedure.[61,62,63] Circumcision also has a negative impact on the sexual experience of female sexual partners who, in a representative sample of

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[54] Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environ Health 2013; 12(1): 4

[55] Frisch M, Simonsen J. Ritual circumcision and risk of autism spectrum disorder on 0- to 9-year-old boys: national cohort study in Denmark. J R Soc Med; 2015; 108(7) 266-79.

[56] Morris BJ, Wiswell TE. 'Circumcision pain' unlikely to cause autism. J R Soc Med. 2015;108(8):297

[57] Bleustein CB, Fogarty JD, Eckholdt H, Arezzo JC, Melman A. Effect of neonatal circumcision on penile neurologic sensation. Urology 2005

[58] Payne K, Thaler L, Kukkonen T, Carrier S, Binik Y. Sensation and sexual arousal in circumcised and uncircumcised men. J Sex Med 2007; 4: 667-74

[59] Sorrells ML, Snyder JL, Reiss MD, Eden C, Milos MF, Wilcox N, Van Howe RS. Fine-touch pressure thresholds in the adult penis. BJU Int 2007; 99: 864-9.

[60] Bossio JA, Pukall CF, Steele SS. Examining penile sensitivity in neonatally circumcised and intact men using quantitative sensory testing. J Urol 2016; 195: 1848-53.

[61] Fink KS, Carson CC, DeVellis RF. Adult circumcision outcomes study: effect on erectile function, penile sensitivity, sexual activity and satisfaction. J Urol 2002; 167: 2113-6

[62]Collins S, Upshaw J, Rutchik S, Ohannessian C, Ortenberg J, Albertsen P. Effects of circumcision on male sexual function: debunking a myth? J Urol 2002; 167: 2111-2

[63]Coursey JW, Morey AF, McAninch JW, Summerton DJ, Secrest C, White P, Miller K, Pieczonka C, Hochberg D, Armenakas N. Erectile function after anterior urethroplasty. J Urol 2001; 166: 2273-6

the Danish population, reported significantly less likely to have their sexual needs fulfilled (adjusted OR 2.09; 95%CI 1.05-4.16), significantly more likely to have sexual function difficulties (adjusted OR 3.26; 95%CI=1.15-9.27), orgasm difficulties (adjusted OR 2.66; 95%CI 1.07-6.66), and dyspareunia (painful intercourse) (adjusted OR 8.45; 95%CI 3.01-23.74) with a circumcised partner.[64] This survey also found circumcised men had more orgasm difficulties (adjusted OR 3.26; 95%CI 1.42–7.47). A subsequent study from Belgium reported that circumcised men were significantly more likely to report decreased sexual pleasure, lower orgasm intensity, more effort required to achieve orgasm, unusual sensations on their glans (burning, prickling, itching, or tingling and numbness), and discomfort and pain on the penile shaft.[65] In a study out of Portugal, circumcised men reported significantly more problems with erectile dysfunction and pain during intercourse.[66] Several studies have indicated that circumcised men are more likely to have difficulties with premature ejaculation,[67,68,69] but other studies have demonstrated no difference.[70,71]; In order to be complete these studies need to included in the discussion.

CDC Response 14:

The CDC reviewed the literature, including but not limited to meta-analyses of the topic and discusses this topic at length in the background document. Based on this review, it states the following earlier in the policy statement: "on average, adult men who undergo circumcision generally report minimal or no change in sexual satisfaction or function." No change made.

CDC Passage 15:

The estimated annual rate of urinary tract infections (UTIs) in uncircumcised male infants is 0.70%. Male circumcision reduces the risk for infant UTIs by about 80%. Over a lifetime, circumcised males have a 23% lower risk of UTIs compared with uncircumcised males.

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[64] Frisch M, Lindholm M, Grønbæk M. Male circumcision and sexual function in men and women: a survey-based, cross-sectional study in Denmark. Int J Epidemiol 2011; 40: 1367-81

[65] Bronselaer GA, Schober JM, Meyer-Bahlburg HFL, T'Sjoen G, Vlietinck R, Hoebeke PB. Male circumcision decreases penile sensitivity as measured in a large cohort. BJU Int 2013; 111: 820-7.

[66] Dias J, Freitas R, Amorim R, Espiridião P, Xambre L, Ferraz L. Adult circumcision and male sexual health: a retrospective analysis. Andrologia 2014; 46: 459-64

[67] Tang WS, Khoo EM. Prevalence and correlates of premature ejaculation in a primary care setting: a preliminary cross-sectional study. J Sex Med 2011; 8: 2071-8

[68] Ferris JA, Richters J, Pitts MK, Shelley JM, Simpson JM, Ryall R, Smith AMA. Circumcision in Australia: further evidence on its effect on sexual health and wellbeing. Austr NZ J Public Health 2010; 34: 160-4

[69] Richters J, Smith AMA, de Visser RO, Grulich AE, Rissel CE. Circumcision in Australia: prevalence and effects on sexual health. Int J STD AIDS 2006; 17: 547-54

[70] Son H, Song SH, Kim SW, Paick JS. Self-reported premature ejaculation prevalence and characteristics in Korean young males: community-based data from an internet survey. J Androl 2010; 31: 540-6

[71] Shaeer O. The Global Online Sexuality Survey (GOSS): the United States of America in 2011 Chapter III — Premature ejaculation among English-speaking male internet users. J Sex Med 2013; 10: 1882-8. 1175,1176

Peer Reviewer B Comment 15:

Inappropriate. See earlier comments.

CDC Response 15:

See earlier CDC response. No change made in response to peer reviewer comment.

CDC Passage 16:

Most commonly reported complications among newborns and children age 1 to 9 years: bleeding and inflammation of the penis or incomplete wound healing or adhesions requiring corrective procedures.

Peer Reviewer B Comment 16:

Inappropriate. See note above: the most common complication is meatal stenosis

CDC Response 16:

See earlier response regarding meatal stenosis. No change made.

CDC Passage 17:

[§]Severe adverse events include outcomes such as permanent disabilities, disfigurements, and death.

Peer Reviewer B Comment 17:

Appropriate

CDC Response 17:

No change made.

CDC Passage 18:

Some men enjoy the sensation of the foreskin experienced during sexual relations, and such a sensation will not be present after circumcision; however, the bulk of scientific evidence states that men on average do not experience a loss of sexual pleasure or function because of circumcision.

Peer Reviewer B Comment 18:

Inappropriate. See note above.

CDC Response 18:

See earlier related CDC response. No change made.