A CDC-requested, Evidence-based Critique of the Centers for Disease Control and Prevention 2014 Draft on Male Circumcision: How Ideology and Selective Science Lead to Superficial, Culturally-biased Recommendations by the CDC

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[Author's Note: I was invited to the Centers for Disease Control and Prevention Consultation on Public Health Issues Regarding Male Circumcision in the United States for the Prevention of HIV Infection and Other Health Consequences *to give a presentation on "Evidence of Adverse Outcomes in Male Circumcision" on April 26, 2007. Several months after my presentation, I was informed by the CDC that I would be a peer-reviewer for their subsequent draft recommendations. Several times between 2007 and 2014, I was informed that the draft would soon be distributed for review. On December 2, 2014 the* New York Times *and other news outlets announced the release and contents of the draft recommendations. Later that day, I received the draft in an e-mail. I was given until January 16, 2015 to provide a review of the recommendations. I submitted my review on January 15, 2015. Subsequently, typographical, grammatical, and spelling errors were corrected, some sentences were revised to enhance their clarity, and the citations were properly sequenced to provide this version of my review. This is a review that provides a critique of, and a response to, the CDC draft, so the contents and organization of this analysis follow the outline of the CDC draft recommendations.]*

General Comments Regarding CDC Draft Recommendations and Background Documents

This peer-review of the Centers for Disease Control and Prevention's (CDC's) Draft Recommendations and Background Documents was generated after December 2, 2014 when the documents first became available. Because of the limited time in which to review and comment on these documents, there may be some topics that could have been addressed more completely, some topics that were addressed more than once, and some citations that may be missing. In the interest of time, the citations given in the review may not be sequenced properly, but each citation should be properly identified. There may be some grammatical and typographical errors because there was insufficient time to identify and correct them. The comments addressing the Recommendations draft are made in direct response to the statements in that draft and appear in italics. The evaluation of the Background draft does not use the statement-by-statement format. This is a peer-review of draft documents and the comments are directed at these documents. It

may be helpful for the reader to have copies of the drafts available.

Several things are remarkable about this draft.

First, is the obvious lack of scientific and scholarly rigor that went into preparing this draft. While it is stated that the writers of the draft performed a search of the medical literature, the evidence (in the form of the draft itself) indicates that their search was far from complete. Instead of collecting and analyzing data, they relied on review articles to do the work for them. One review article was published in 1983 — a bit dated to say the least. In some sections, the draft relied on opinion pieces as their sources of information. In areas where review articles were not available, the information provided was far from complete. For example, in reviewing the medical literature on the impact of male circumcision in North America, which is a major thrust of the draft, only two of the eight available studies are mentioned. Similarly, no serious attempt was made to review the harms, risks, complications, or pain associated with circumcision. The draft has only 255 references, some of which are redundant, which are only a small sampling of the material available in the literature. A PUBMED search using the search word "circumcision" on January 12, 2015 identified 6338 publications.

The draft also ignores basic epidemiological principles. It fails to apply the standards that are needed to identify when an intervention should be applied. Throughout the draft, it is assumed that circumcision will be successful as a primary prevention for HIV, when the data clearly demonstrate that it is ineffective as primary prevention. Even its role as a secondary preventive measure has only been evaluated in one study in the United States, which included a very small, limited population. For this very small population, modeling by the CDC has estimated that circumcision's impact on infection risk is nearly inconsequential. Policy should be based on more than one small subset of patients from a single study when several other studies fail to support this conclusion. It is clear that both the investigators of the randomized clinical trials and the CDC draft authors do not understand the epidemiological difference between efficacy (a positive finding in a research setting) and effectiveness (positive results in the real world).

The draft fails to adequately scrutinize the validity of the few studies it identified. It assumed the randomized clinical trials could not harbor any bias (the draft actually states this!) and did not question the methodology of these studies, although their methodology has been questioned extensively. Instead of accepting the study results at face value, the expectation of scholarly rigor would demand that these studies be carefully scrutinized, and a determination made as to whether the studies generated valid results and/or if the criticisms raised about these studies were convincing. The writers of the draft made no effort to question or analyze these studies.

If a student were to submit these drafts for consideration as a senior undergraduate or master's

thesis, they would fail based on their lack of scholarship. It appears the CDC was only going through the motions in preparing this draft. If the CDC had performed an adequate search of the medical literature and applied the expected level of scholarly rigor, their conclusions and recommendations would have been different. Perhaps that was the point. Perhaps the hope was, by releasing the draft with a selective bibliography, no one would recognize the lack of scholarly effort or call the CDC out on doing a subpar job. It worked for the American Academy of Pediatrics, and they seemed to get away with it. The difference is that CDC documents are open for public comment because it is a government agency. One would think that, after all of the embarrassment the CDC has endured in the recent past, they would want to put their best foot forward by publishing a rigorous, balanced, evidence-based assessment of male circumcision. That obviously did not happen.

Second, is the lack of attention to detail. Many of the citations given have the authors and journals incorrectly listed. Several of the citations require updating, while several of the citations were redundant. There are several misspellings in the manuscript. This indicates the CDC did not expend sufficient effort putting forth this piece of work, which is consistent with its lack of scholarly rigor.

Third, is the wanton disregard for the medical evidence. It is clear throughout that the writers of the CDC draft believe absolutely in the presumption that infant male circumcision can reduce HIV and sexually transmitted infections beyond a shadow of a doubt. As a consequence, the draft goes about finding evidence to support their presumption and primarily presents evidence supportive of this presumption, despite evidence to the contrary. The quality of the evidence supporting the presumption is never questioned. Any evidence that does not support their presumption is either ignored, criticized, or dismissed. As a consequence, the draft is laughably biased and reflects the expectation bias of its writers.

Fourth, is the lack of a thorough discussion of the foreskin and its anatomy, histology, physiology, and function. It is standard procedure for review articles of this type to review these topics to provide a basic science foundation. How can the CDC discuss the biological plausibility of sexually transmitted infections without a knowledge of the basic anatomy, histology, physiology, and function? This information must be included since health care providers must understand what is lost by removing the normal foreskin/prepuce. How else can they explain the impact of its removal to patients? This information is also an essential element of the disclosure given during the informed consent process.

Fifth, is how out of step the CDC is with the rest of the world. National medical organizations and human rights groups throughout the world, including the Council of Europe, are, in increasing numbers, denouncing infant circumcision as being medically unnecessary and a

blatant human rights violation. At this point in time, the CDC and the American Academy of Pediatrics are the last stronghold in the defense of infant circumcision. Remarkably, the draft fails to mention all the medical organizations outside of the United States who have weighed in with an opposing opinion on male circumcision. Is there some source of special knowledge the CDC has in its possession that allowed them to reach conclusions that are diametrically opposed to every other national medical organization (other than the American Academy of Pediatrics)? If it exists, why is it missing from the draft? Please provide enlightenment. If the CDC has a clue, they could at least share it.

Sixth, it took over seven years for the CDC to produce a substandard, scientifically unacceptable product, nearly identical in content to what was presented at the 2007 consultation.

Finally, the most remarkable thing is that the CDC is recommending clinicians and health care providers relay information that is counterfactual, incomplete, and biased to medical decision makers. In essence, they are deliberately encouraging health care providers to misinform their patients and thus commit medical malpractice.

The CDC needs to throw out this draft and start again from scratch, this time without a preconceived conclusion in mind. They need to review the entire medical literature, thoroughly scrutinize the studies in the literature, and properly apply basic epidemiological principles. When they have done so, they need to consult with experts from around the world to make sure their findings are not culturally biased. They also need to focus on the United States, not Africa.

The following comments are made in response to incorrect and/or misleading statements contained in the "Recommendations" section of the draft by the CDC. In most cases, these issues are discussed in further detail in the review of the "Background" document.

(Please note: The CDC comments are in regular print. The reviewer's comments are in italics.)

CDC draft: These recommendations are intended to assist health care providers in the United States who are counseling men and parents of male infants in decision making about male circumcision conducted by health care providers (i.e. medically performed) as it relates to the prevention of human immunodeficiency virus (HIV) infection, sexually transmitted infections (STIs), and other health outcomes.

Reviewer Comment: If the target audience is health care providers in the United States, why is so much of the Background Draft directed at what is happening in Africa?

CDC draft: Such decision making is made in the context of not only health considerations, but

also other social, cultural, ethical, and religious factors.

Reviewer Comment: Why should these factors be a consideration of the CDC or health care providers? Is the CDC suggesting that health care providers take on the role of shaman or cultural broker? Are these other considerations the real impetus for promoting male circumcision?

CDC draft: Although data have been accumulating about infant male circumcision for many years, clinical trials conducted in Africa between 2005-2010 have demonstrated safety and significant efficacy of voluntary adult male circumcision performed by clinicians for reducing the risk of acquisition of human immunodeficiency virus (HIV) by a male during penile-vaginal sex ("heterosexual sex").

Reviewer Comment: The clinical trials referred to did not assess the risk of acquisition of HIV by a male during penile-vaginal sex as these trials made no effort to determine the source of the infections they diagnosed during the course of the trials. These infections could have been from male-to-male sexual contact or from iatrogenic sources. Data from within these trials indicate that about 1/3 to 1/2 of the infections diagnosed during the trials were transmitted through non-sexual means. Furthermore, these trials have nothing to do with infants, and infant circumcision is never voluntary because the infant cannot give consent.

CDC draft: Three randomized clinical trials showed that adult male circumcision reduced HIV infection risk by 50-60% over time.

Reviewer Comment: Reporting the results in this manner is misleading. It needs to be stated that the reduction reported here is the relative risk reduction. What is of clinical importance is the absolute risk reduction, which in the case of these trials overall was 1.3%. This is the number that should be reported instead of the relative risk reduction. As the incidence of HIV infection in the United States is much smaller than in Africa, one would expect that if circumcision were effective in the United States, which has never been demonstrated, the absolute risk reduction would be quite a bit smaller. Again, the source of infection was not determined in the African studies making the results suspect and likely meaningless.

CDC draft: These trials also found that medically performed adult circumcision reduced the risk of men acquiring two common sexually transmitted infections (STIs), herpes simplex virus type-2 (HSV-2) and types of human papilloma virus (HPV) that can cause penile and other anogenital cancers, by 30%.

Reviewer Comment: These trials were methodologically flawed. For both HSV-2 and HPV, the trials failed to adjust for lead-time bias. By doing so, the findings for HSV-2 are no longer statistically significant. For HPV, the two trials only sampled the head of the penis, which would

result in intact men being over-diagnosed with HPV because circumcised men are more likely to have HPV on the shaft of the penis, which these researchers did not sample. As a consequence, their results can be completely explained on the basis of inadequate sampling. Subsequent large cohort studies have failed to find an association between circumcision status and genital HPV infections. The CDC is selectively citing studies that promote circumcision while ignoring studies, without a sampling bias, that do not support the practice of circumcision. In other words, the CDC is using a selective bibliography to cherry-pick the studies to support circumcision.

CDC draft: Since the release of these trial data, various organizations have updated their recommendations about adult male[8] and infant male circumcision.

Reviewer Comment: The CDC lists only organizations from the United States that have leaned in favor of circumcision. They fail to mention that national medical organizations from Norway, Sweden, Germany, Denmark, the Netherlands, Slovenia, Finland and others have condemned the practice of infant circumcision, both on medical and on human rights grounds. The Council of Europe also considers infant circumcision a human rights violation.

CDC draft: Much of the data related to HIV and STI prevention are from randomized clinical trials (RCTs) conducted among men in sub-Saharan Africa in regions with high rates of heterosexually acquired HIV infection.

Reviewer Comment: Three randomized clinical trials have been performed, which were basically one trial in three locations of Africa. There are over 100 other populations in which the association between HIV incidence or prevalence and male circumcision status has been assessed. Consequently, very little of the data available on HIV and STI prevention has come from the RCTs. As mentioned above, it is not known whether the infections in the RCTs were heterosexually acquired because the source of infection in these men was not determined. There is much more to this issue than is being presented here by the CDC. Some have argued that the randomized clinical trials were unnecessary since it was known prior to the trials that circumcision did not have an impact on HIV prevalence at the country level in several countries in Africa. Please read the response in the Background document.

CDC draft: While such factors limit the impact of medically performed male circumcision in reducing the overall HIV epidemic in the U.S., there is epidemiological data to suggest that some subpopulations in the U.S. are likely to benefit.

Reviewer Comment: The data indicate that the only subpopulation in the U.S. that has seen an association between circumcision and HIV prevalence were the males whose regular female sexual partners were HIV-positive. These data were from a very small subpopulation from a

single study, the results of which were not robust and have not been confirmed by other studies. Without such confirmation, the benefit for HIV-negative men who have HIV-positive female sexual partners remains to be seen. Modeling by the CDC indicates that such men are unlikely to benefit from circumcision, and the standard recommendation for these men is to always use condoms, consider pre-exposure prophylaxis, and to have the female partner lower her HIV viral load with anti-retroviral medications. Therefore, it appears that this CDC draft is not actually about decreasing HIV infection, but about some other underlying premise or other motivation.

CDC draft: In addition, African-American and Hispanic men have higher risk of HIV infection and lower male circumcision rates than men of other race/ethnicities.

Reviewer Comment: African-American men have a higher prevalence of HIV than Hispanic men and also a much higher circumcision rate. In several studies, the circumcision rate in African-American men is similar or higher than the circumcision rate in non-Hispanic Caucasian men.

CDC draft: 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.

Reviewer Comment: There is no evidence that any males in the United States would benefit from elective male circumcision. When one looks at the impact of circumcision on HIV prevalence in African countries, in at least eight countries the prevalence of HIV infection is higher in circumcised men than it is in intact men. This suggests that the results of the randomized trials from Africa do not even apply to Africa, let alone the United States. There is not a single study of infant circumcision that has found a significant protective effect against HIV. Most circumcisions in the United States are performed on infants. There have been eight studies looking at the impact of circumcision on HIV prevalence in North America. None of them have found a significant protective effect, and one found that circumcised men were at significantly greater risk of HIV infection. The preponderance of evidence indicates that the results of the trials in Africa do not apply to the United States.

Methods:

CDC draft: A CDC consultation was held in April 2007 to obtain input on the potential role of male circumcision in preventing transmission of HIV in the United States. A summary of the consultation, including a list of the participants has been previously published and helped define key issues for inclusion in this document.

Reviewer Comment: The list of participants reads like a Who's Who of Circumcision Advocates. *No group opposing circumcision was allowed any input. Only one physician was in attendance who had any record of publishing studies unsupportive of circumcision.*

CDC draft: These recommendations are based on an evaluation of available information on the health risks and benefits associated with high-quality, medically performed male circumcision and were developed to pertain to men and male newborns in the United States.

Reviewer Comment: If one reads the Background Draft, it becomes abundantly clear that only the available information on the health risks and benefits favorable to circumcision were considered. The evaluation basically used a selective bibliography to cherry-pick the studies that supported circumcision.

CDC draft: In these recommendations, the preventive benefits of male circumcision are generally expressed as relative-risk reductions (e.g., a 50% reduction from a 2% risk of an STI to a 1% risk), whereas any associated harm is expressed as an absolute risk (e.g., a 2-4% risk of adverse events).

Reviewer Comment: While it is refreshing that the CDC admits to using this deceptive practice, it would have been more appropriate to express those factors in terms of number needed to treat and number needed to harm. Readers of this draft will be unable to convert relative risk to absolute risk unless the absolute percentages or incidence rates are given. By giving only the relative risks, the CDC is guaranteeing that their readers will be deceived and unable to make an accurate comparison. This is unprofessional and unscientific. Health care providers realize that their patients are confused by relative risk, but patients can understand data when it is presented in terms of "number needed to treat-NNT" and "number needed to harm-NNH." By taking this step, the CDC is preventing health care providers from being able to present information to their patients in a manner which can be most easily and accurately assimilated.

CDC draft: Appropriate denominators are not available in many cases to establish an absolute risk for HIV and other STIs in higher-risk populations, e.g., heterosexual males at increased risk for infection.

Reviewer Comment: This is not true. The CDC has gone to great lengths to generate models and analyses to prove that circumcision is cost effective and will save lives. These models are based on estimates of the absolute risks that would be considered realistic in the population of interest. But, when it comes to having these estimates available so that health care providers can deliver useful information to their patients, all of sudden these estimates do not exist?! This selectivity in availability of estimates may indicate the presence of a very low absolute risk, which would make

the number needed to treat so high that no one would consider cutting off the most sensitive portion of their penis for such a minuscule possibility of a benefit.

Recommendations:

1. Consideration of factors associated with decision making

CDC draft: Health benefits and risks of elective neonatal, adolescent, or adult medically performed male circumcision should be considered in consultation with medical providers while taking into account factors associated with decision-making around male circumcision including religion, societal norms and social customs, hygiene, aesthetic preference, and ethical considerations.

Reviewer Comment: The Council of Europe and national medical organizations from a number of European countries consider neonatal circumcision to be a human rights violation, so this recommendation does not apply to neonatal circumcision, as the proxy consent provided for the procedure may not be valid. Regarding circumcisions for males who are able to provide their own consent, the disclosure process needs to be extensive and exhaustive since this is usually an elective, cosmetic procedure. Because it is usually an elective, cosmetic procedure, such a discussion should only take place after the male inquires regarding the procedure. Solicitation of circumcision without a clear immediate medical indication is considered unethical according to the American Medical Association. Performance of a procedure on a child, by a physician or health care provider, should be done based on medical need, not based on religion, societal norms or customs, vague notions of hygiene, or the aesthetic preference of an adult. To do otherwise, violates the child's basic human rights. Physicians are not cultural brokers. They have taken an oath to "Do no harm" and to do what is in the patient's best interest. In no respect is the removal of normal, healthy genital tissue in a child's best interest. Physicians do not routinely remove normal tissue from children for any other reason, so why would removal of the foreskin be the exception?

2. Counseling sexually active adolescent and adult males regardless of circumcision status

CDC draft: All sexually active adolescent and adult males should continue to use other proven HIV and STI risk-reduction strategies such as reducing the number of partners, and correct and consistent use of male latex condoms, and HIV preexposure or postexposure prophylaxis among others.

Reviewer Comment: If these steps are followed, there is no need to circumcise. Consistent condom use is over 99% effective in preventing HIV infection. Adding circumcision is

unnecessary, and encourages males to avoid using condoms in the belief that circumcision protects against HIV. This is known as risk compensation, which is already occurring in Africa with negative consequences.

3. Counseling uncircumcised sexually active adolescent and adult males

CDC draft: Prior to counseling uncircumcised sexually active adolescent and adult males about medically performed male circumcision, their HIV risk behaviors, HIV infection status, and the gender of their sexual partner should be assessed. The results of these assessments will inform the discussion with men about the risks and benefits of male circumcision.

Reviewer Comment: The term "uncircumcised," while widely used, is a pejorative term. One definition of the word "uncircumcised" is "spiritually impure: heathen: unregenerate." It is also a term that is technically inaccurate. For a man to be "uncircumcised," he would need to first be circumcised and then have the process reversed. By using the term "uncircumcised" or "non-circumcised," the CDC is making the underlying value-laden assumption that being circumcised is the preferred condition, when there is no evidence, other than cultural pressure, to support this. The most accurate, value-neutral term for a man with all of his original genital tissue is "intact" or "normal" or "natural." By continuing to use the term "uncircumcised," the CDC is identifying its pro-circumcision bias to anyone who is familiar with the semantics on this issue. Males who are indeed "intact" find use of the term "uncircumcised" to be hate speech because they are singled out as "different," supposedly "abnormal" and/or possibly "unclean." Nothing could be further from the truth. Profiling a group of people in this way is discriminatory, hateful rhetoric. Furthermore, counseling any sexually active intact adolescent about circumcision without provocation is malicious sadism. Teens, by their very state of emotional development, have self-image and self-esteem issues. This is especially true in regards to their primary and secondary sex organs. For a health care provider to engage in an unsolicited discussion of circumcision with an intact adolescent male, only sends the message to the patient that something is seriously wrong with their genitals and, by extension, there is something wrong with them and with their parents. Given that Hispanics are less likely to be circumcised than other ethnic groups in the United States, would such a discussion be interpreted as racist, anti-immigrant hate speech? What self-respecting health care provider would want to impose such emotional trauma on their patient when there is no benefit in doing so. It is important to obtain a good sexual history on patients, but extraordinarily few adolescents would fall into a category that might possibly impact their risk of HIV infection. Furthermore, the gender of an adolescent's sexual partner may, and likely will, change frequently over the years, so determining this information seems of little value. The limited time during an office visit with an adolescent male would be better spent discussing how to properly apply a condom.

3A. **Counseling uncircumcised heterosexually and bisexually active adolescent and adult males (i.e., men who have sex with women)**

3A-2. CDC draft: All uncircumcised adolescent and adult males who engage in heterosexual sex should be informed about the significant, but partial, efficacy of male circumcision in reducing the risk of acquiring HIV and some STIs through heterosexual sex, as well as the potential harms of male circumcision.

Reviewer Comment: There is no evidence in North America that male circumcision reduces the risk of acquiring HIV in the general population. If circumcision reduced the risk of HIV in the United States, why is the prevalence of heterosexually-transmitted HIV three times higher in the United States, where about 70% of sexually active men are circumcised, than it is in Europe, where less than 2% of sexually active men are circumcised? There is evidence that circumcision increases the overall risk of sexually transmitted infections through heterosexual sex. The premise of this section is incorrect, so what follows is of little or no value. If circumcision is of only "partial efficacy," but other measures are almost completely effective at preventing transmission of HIV, then why bother with circumcision at all?

- CDC draft: Men and male adolescents being counseled about male circumcision should be told that (see Box 1):
  - 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 was associated with reduced number of new herpes simplex virus type 2 (HSV-2) infections and reduced number of oncogenic types of human papilloma virus (HPV) among circumcised men.

Reviewer Comment: As mentioned above, the medical literature demonstrates that circumcision is not effective as a primary preventive measure for HIV infection. Also, circumcision does not reduce the risk of infections with HSV-2 or HPV. In fact, circumcision may actually increase the risk of such infections. The CDC is selectively citing methodologically flawed studies from Africa to make a claim that is not supported by the full body of research currently available.

- CDC draft: 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 male circumcision surgical services should be provided.

Reviewer Comment: Soliciting circumcision to males is not supported by the medical evidence and is unethical. Given the highly effective measures of secondary prevention, there is no need for a health care provider to mention circumcision.

3B. Counseling men who have sex with men (exclusively)

CDC draft: Although it is biologically plausible that male circumcision could benefit MSM during insertive sex, no definitive data exist.

Reviewer Comment: That it is "biologically plausible" circumcision may be a benefit is highly speculative and unsupported by any evidence in the medical research, either biologically or epidemiologically. Wishes and hopes are not data. There is no strong biological evidence to support the claim that male circumcision could benefit MSM during insertive sex.

CDC draft: Currently, there are no study results from RCTs including large enough numbers of MSM and results from observational studies are not conclusive among MSM overall or among MSM who practice exclusively insertive anal sex.

Reviewer Comment: This statement reveals that those within the CDC who generated this document do not understand basic statistics and research study design principles. Just because a study is larger does not mean that it will provide a statistically significant result to one's liking. Remember the Women's Health Initiative Study? It had the exact opposite result of what was predicted. The results of a study are not known until the study is performed. The current available data do not support the CDC's wish that circumcision would provide some benefit among MSM.

3B-1. CDC draft: Men who have sex with men should be informed that:

- The demonstrated benefits of male circumcision for HIV risk reduction apply to heterosexual (penile-vaginal) sex only.

Reviewer Comment: Several studies, two of which included more than 30,000 subjects, in the United States have failed to a find a risk reduction from circumcision in heterosexual men. Therefore, the CDC's statement is misleading and, in the US, false.

4. Counseling parents of male newborns, children, or adolescents

CDC draft: Health benefits and risks of elective neonatal, pediatric, or adolescent male circumcision should be considered in consultation with medical providers. In the case of discussion about neonatal circumcision, ideally such discussion should occur prior to the birth of

the child. Ultimately, whether to circumcise a male neonate or child is a decision made by parents or guardians on behalf of their newborn son or dependent child.

Reviewer Comment: Since neonatal circumcision is a non-therapeutic, purely cosmetic procedure, solicitation of the procedure is unethical according to the standards of the American Medical Association. Whether parents can legally and ethically make a decision on the child's behalf to undergo a non-therapeutic, purely cosmetic procedure has not been clearly decided. The current ethical standard is that procedures in children that can safely wait until the child can provide his own informed consent should be delayed until the child can provide that consent.

CDC draft: 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.

Reviewer Comment: Such counseling should only occur when the patient inquires about the procedure. To offer this information without an inquiry would be unethical, and potentially harm the adolescent's self-esteem and body image.

4-A. CDC draft: Parents and guardians should be informed about the medical benefits and risks of neonatal, pediatric, or adolescent medically performed male circumcision (see Box):

- During infancy, circumcised infants are less likely than uncircumcised infants to experience urinary tract infections (UTIs), although UTIs are uncommon during infancy.

Reviewer Comment: To be accurate, this statement should state that intact boys are more likely to be diagnosed with urinary tract infections, but they may not necessarily have more actual UTIs. Whether or not they actually have more urinary tract infections is unclear. It needs to be added that between 110 and 190 boys need to be circumcised to avoid one additional boy being diagnosed with a urinary tract infection. Parents and guardians should be reassured that urinary tract infections can be treated with oral antibiotics and rarely, if ever, lead to long-term kidney problems or hypertension. It should be added that multiple studies from Israel have found that urinary tract infections increase in boys following ritual circumcision. The bandaging used following a ritual circumcision may obstruct urine flow, leading to the urinary tract infection.

- CDC draft: Circumcised boys are less likely than uncircumcised males to experience balanitis and balanoposthitis.

Reviewer Comment: This statement needs to be deleted as it is factually incorrect. There is no

evidence to support this. Two studies found that circumcised boys under the age of three years were more likely to have penile inflammation than their intact counterparts. By providing health care providers with recommendations that are not factually accurate, the CDC is encouraging health care providers to provide parents and guardians with information that is not true. In other words, they are encouraging health care providers to violate the trust patients have in them and to engage in malpractice. If the provider is sued on the basis of providing the false information the CDC is encouraging, who is liable? The CDC should not put health care providers in the position of lying to their patients. (However, the entire CDC draft document is putting health care providers at risk for medical malpractice because of the fallacies it contains.)

- CDC draft: During adulthood, circumcised males are less likely than uncircumcised males to experience penile or possibly prostate cancer.

Reviewer Comment: The incidence of penile cancer is quite low, and it should be mentioned that the number needed to treat is between 4237 and 7184. Despite having a much higher circumcision rate in the United States, the penile cancer incidence rate in the United States is no different than what is seen in Europe among primarily intact males. The evidence on prostate cancer is so weak, inconsistent, and inconclusive, that it should not be mentioned, especially when the incidence in the US is quite high as is the circumcision rate. Pathological studies indicate that many males, up to 70-80% by the seventh and eighth decades, have microscopic prostate cancer at autopsy, which was not clinically detected. So, where is the benefit of being circumcised?

- CDC draft: Other anticipated health benefits derive in part from future prevention of HIV and some STIs acquired through heterosexual sex. The risk for any individual neonate, child, or adolescent cannot be definitively defined at the time that a circumcision decision is made; for example, current risks for HIV and STIs, such as those for a particular individual's racial/ethnic group or gender, may not remain constant in the future.

Reviewer Comment: Circumcised men have an overall STI risk that is greater than for intact men. Is this stating that infants are not at risk for sexually transmitted infections, including HIV? If this is the case, that would favor waiting until the child is old enough to provide his own consent. Since when do we remove healthy normal tissue from a baby to possibly prevent some unknown future risk of disease? There are other more pressing diseases to contend with, if this is the focus of the CDC.

- CDC draft: Considerations for the timing of male circumcision:
  - Neonatal male circumcision is, safer, and heals more rapidly than circumcision

performed on older boys, adolescent males, and men, and is less expensive.

Reviewer Comment: It is patently false that neonatal male circumcision is safer. This statement is based on myth, not on facts. The few studies that have made the appropriate comparison do not support this conclusion. There is no evidence that the wound heals more rapidly. There have been no studies in the medical literature that address wound healing and the Background draft does not address this claim. Since the foreskin has not separated from the glans in neonates, it is more likely that neonatal circumcision takes longer to heal and is more painful. Neonatal male circumcision is less expensive because it is not performed under general anesthesia, the only adequate anesthesia besides a caudal block. Neonates also are much easier to strap down without a major fight ensuing. The topical and local anesthetics that are used for neonatal circumcision do not provide adequate anesthesia, as has been demonstrated in multiple studies. The procedure is still quite painful when these are used. The pain associated with neonatal circumcision, even when topical and local anesthetics are used, has been linked to circumcised boys crying longer and louder when given vaccinations at four to six months of age and circumcised boys having a significantly greater risk of developing infantile autism, autism spectrum disorder, and hyperactivity. The availability of general anesthesia for circumcision performed in older males is another advantage of waiting until the male can provide his own consent.

- CDC draft: Male circumcision can also be conducted in adulthood when the individual can make the decision for himself. However, male circumcision after sexual debut could result in missed opportunities for:
    - HIV and STI prevention during the window period between sexual debut and circumcision

Reviewer Comment: This a cheap scare tactic designed to influence parents and teens into accepting circumcision before full adulthood. According to the CDC's own numbers, the risk of HIV infection under the age of 15 years is very low. How many 15 year olds are having unprotected sex with female partners who are HIV-infected? Similarly, the only STI that might be associated with circumcision status is syphilis, which is also very rare and easily treated with antibiotics. This risk is so low that there is no need to mention it. The only people who do mention it are the pro-circumcision lobbyists, who believe it may have some rhetorical value. STIs, HPV, HIV have been shown to be more common in circumcised males in North American studies.

    - CDC draft: Prevention of UTIs during infancy.

Reviewer Comment: The risk of UTI is small and none of the analyses that have been published

believe that circumcision is a cost-effective method to address this small risk. If an infant circumcision costs $285 (according to the CDC) and the number needed to treat is 195, then it would cost over $50,000 to prevent one urinary tract infection that can easily be treated with an antibiotic that costs less than $20. So, this is also a cheap scare tactic.

- CDC draft: The most commonly described complications of medically performed male circumcision in the United States are typically uncommon and easily managed.

Reviewer Comment: The most commonly described complications of medically performed male circumcision are the loss of the most sensitive portion of the penis (100%) and meatal stenosis (5% to 20%). Both are common and not easily managed. Once the majority of the fine-touch neuroreceptors are removed from the penis via circumcision, there is no way to grow them back. While there are thousands of circumcised men who spend years trying to stretch their remaining shaft skin so the glans of the penis can once again be covered, there is no way to restore the fine-touch neuroreceptors. Meatal stenosis (narrowing of the opening of the urethra) usually requires surgical enlargement of the urethral opening done under general anesthesia (the child might as well have waited to be circumcised to partake of such pain control). Consequently, neither of these complications is easily managed. Either the writers of this set of recommendations are intellectually obtuse, or they are purposely covering up the side effects of circumcision to portray the procedure in the most positive light possible. By ignoring the harms and complications of circumcision, of which there are hundreds, they are doing a disservice to the health care professionals, parents and patients who might rely on this information, and ultimately it is a disservice to society as a whole.

- CDC draft: Severe complications are rare in all age groups.

Reviewer Comment: It all depends on how "rare" and how"severe" and how "complication" is defined. But perhaps a more important discussion is whether any severe complications, regardless of their rarity, are acceptable following a non-therapeutic, purely cosmetic procedure performed on an individual who is unable to give his own consent?

- CDC draft: Among newborns and children age 1 to 9 years, most frequently reported complications include bleeding and inflammation of the penis or the need for corrective procedures.Complications occur in less than ½ % of infants, and in approximately 9% of children age 1 to 9 years.

Reviewer Comment: The complication rates in this statement come from a study based on data collected from a database. This study design typically misses between 90% and 95% of the complications when compared to the number of complications identified when performing a

chart review. This statement needs to be deleted and the complication rate from charts reviewed by the CDC, which revealed a complication rate of 3.1%, should be put in its place. Similarly, there are studies in which the complication rates of circumcisions performed in neonates were compared to the complication rates of circumcisions on older boys at the same time in the same place using the same criteria. The results have been mixed. In some, the complication rates were higher in newborns or there was no difference between the two groups. None showed a lower rate of complications in newborns.This effort to paint neonatal circumcision as having lower complication rates is purely a propaganda tool with insufficient quality evidence to support it.

- CDC draft: Among persons 10 years of age and older, the most frequently reported complications include those complications reported in younger children as well as wounds of the penis. Complications occur in approximately 5% of persons in this age group[15].

Reviewer Comment: The immediate complication rate for neonatal circumcision ranges from 2% to about 6%, with delayed complications being much higher. For example, meatitis (inflammation of the urethral opening) occurs in 20%, meatal stenosis in 5% to 20%, adhesions in 25%, skin bridges in 4.1% to 12.7%, subcutaneous granuloma in 4.97%, phimosis in up to 2.9%, hidden penis in 1%, and 1% of parents who insist on the circumcision being redone because they do not like the cosmetic outcome. The point is that neonatal circumcision may have a higher complication rate than when it is performed on boys 10 years and older.

- CDC draft: The American Academy of Pediatrics Taskforce on Circumcision states that the 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.

Reviewer Comment: This appeal to authority is inappropriate. The American Academy of Pediatrics Task Force on Circumcision in their report stated several times that they did not know the rate of complications following male circumcision. This may be related to the refusal of the Task Force to consider any case reports or case series in their limited analysis of the medical literature. Most reports in the medical literature of complications are in the form of case reports and case series. The Task Force also did not quantify the rate at which a male who was circumcised would reap any benefit from the procedure. Yet, with the rates of the benefits undefined and the rates of complications unknown, somehow the Task Force was able to say that the benefits outweighed the risks. Making such a statement defies the basic principles of mathematics. When pressed on how they reached their conclusion, the Task Force stated that they felt *the benefits outweighed the risks. So, their conclusion was not evidence-based but* feelings-based*. This conclusion was also criticized by thirty-eight well-regarded medical experts,*

primarily from Europe, who argued that this conclusion was culturally biased. Why does the CDC mention the Task Force report, which suffers from the same biases and lack of scholarly rigor as the Background Draft? Is it thought that reference to an equally pathetic effort will give the CDC's efforts some unearned credibility?

4-B. CDC draft: Medically performed neonatal, pediatric, or adolescent male circumcision should be done by trained clinicians according to accepted standards of clinical care, with appropriate use of anesthesia.

Reviewer Comment: What is appropriate use of anesthesia? Given that topical and local anesthetics, which are all that are available to newborns, do not provide adequate anesthesia, shouldn't the procedure be delayed until general anesthesia can be more safely employed? This has been the recommendation of the Australasian Association of Paediatric Surgeons since 1996. For any procedure, all people would elect to have adequate anesthesia, including all newborns. A physician or surgeon would be guilty of misconduct and malpractice for not providing appropriate anesthesia to a patient. But, for some reason, newborns fly under the radar because they are easily restrained and unable to communicate verbally. When parents make decisions on behalf of their children, they should do what the child would chose for himself. This is consistent with the American Academy of Pediatrics position on pain relief for neonates, which states that newborns should be given the same consideration in avoiding and relieving pain as older children and adults. The anesthetic used for neonatal circumcision ignores this consideration. What are "accepted standards" of clinical care? There are no guidelines on what constitutes a "good" circumcision. There is no consistency on how much tissue to remove, what method to use, what anesthetic to use, etc., which explains why there are so many complications related to this surgery. Furthermore, neonatal circumcisions are often performed by the least experienced member of the medical team: the medical student, intern or resident in training. This likely contributes to higher complication rates.

Box:

CDC draft: Health Benefits and Risks of Elective Medically Performed Male Circumcision

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- **CDC draft: Health benefits of elective male circumcision in adults and adolescents:**
    - Male circumcision reduces the risk of acquiring HIV infection through penile-vaginal sex by 50-60%, as demonstrated in three well-conducted clinical trials among adult men living in sub-Saharan Africa.

Reviewer Comment: There is no evidence that the findings of the clinical trials in Africa, which by several objective standards were not "well conducted," apply to male infants or to males living in North America, and there is ample evidence they do not apply. The existence of this

"health benefit" is highly speculative. There is no evidence to suggest that any benefit has been demonstrated for infant circumcision or for heterosexual men in North America. The reduction should be identified as a relative *risk reduction. The* absolute *risk reduction in these trials should be mentioned to provide a true comparison. For example, in the Ugandan study the absolute risk reduction was 0.67% with a number needed to treat of 149. These numbers need to be adjusted for the lower incidence seen in the United States. If one assumes the African results apply to the United States, and there is no evidence to support this assumption, then the absolute risk reduction would be 0.02% with a number needed to treat of 5000. At $285 per circumcision, this would cost $1.425 million to avoid one HIV infection. Not a good use of resources, especially when this is based on an assumption that is not consistent with the medical evidence. Even if the relative risk reduction is 10%, the number needed to treat would be 25,000 and cost would be $7.125 million. The CDC, by only mentioning the relative risk reduction, is hoping that readers will forget that 50% of a very small number is still a very small number.*

- CDC draft: In clinical trials involving heterosexual males living in sub-Saharan Africa, male circumcision reduces the risk of some sexually transmitted infections.
  - HSV-2: circumcised men were approximately 30%-45% less likely to acquire HSV-2 infection than were uncircumcised men.

Reviewer Comment: This statement is selective in the results provided and fails to note that these trials did not adjust their results for lead-time bias. Of the three randomized trials, one found virtually no difference (RR 1.06), and in only one was the difference statistically significant. When adjusted for lead-time bias, none of the trials had a result that was statistically significant. When the results of prospective studies on the incidence of HSV-2 infections by circumcision status are combined in a meta-analysis, and the studies are adjusted for lead-time bias, the results are not statistically significant. This finding is consistent with the meta-analysis results of observational studies that have looked at HSV-2 prevalence by circumcision status: no statistically significant difference. The CDC markedly overstates this difference. Their draft should also list the number needed to treat for these differences. For the study in Uganda, the NNT was 93, in South Africa 98.6, and in Kenya 261. If the incidence of HSV-2 is lower in the United States, the numbers needed to treat would be greater.

- CDC draft: HPV: circumcised men were approximately 30% less likely to be infected with high-risk strains of HPV associated with cancers than were uncircumcised men.

Reviewer Comment: The 30% reductions were only reported in two of the prospective studies, where only the glans was sampled. In multiple studies, it has been demonstrated that intact men who have HPV on their genitals are more likely to have the virus primarily on the glans, whereas

circumcised men who have genital HPV are more likely to have the virus primarily on the shaft of the penis. By not sampling the shaft of the penis, these studies guaranteed that HPV would be detected 30% more often in intact men, even if the infection rate on the genitals was the same in both circumcised and intact men. In other words, the 30% reduction can be completely attributed to their decision to only sample the glans of the penis, or to only report the results of the samples taken from the glans of the penis. The largest prospective study of HPV and male circumcision was published in 2014. This study sampled the male genitals properly, finding that circumcised men were at greater risk for genital HPV infections, but the difference was not statistically significant. It also found that HPV cleared significantly faster in intact men. The medical literature does not support the hypothesis that intact men are at greater risk for HPV infection. This myth evolved out of methodologically flawed studies that did not properly sample the penis.

- **CDC draft: Adverse events and risks associated with elective male circumcision of adults:**
    - For adult male circumcision performed by clinicians, the rate of adverse events is between 2% and 4%, with pain, bleeding, infection and unsatisfactory post-surgical appearance most commonly reported. While severe and/or long-term complications have been reported, they are so rare that they have not been precisely established.

Reviewer Comment: The low percentages reported in these studies indicate that, if a circumcision is to be performed, it should be performed during adulthood to reduce the risk of complications. At least in adulthood, the male can understand and accept the risks involved. Infant circumcision has much higher rates of adverse events. It is time studies were done to precisely establish all the complications from circumcision because it is doubtful they are rare.

    - CDC draft: Adult men who undergo circumcision generally report minimal or no change in sexual satisfaction or function.

Reviewer Comment: This statement is based primarily on wishful thinking supported by two studies with serious/fatal methodological flaws. The medical literature is replete with studies of circumcised adults who report decreased penile sensitivity, erectile problems, difficulty with insertion during coitus, and difficulty reaching orgasm. Two studies out of Africa used questionnaires whose questions would not have been able to detect a difference if one existed. The men in these studies, if the results are to be believed, are having the best sexual experiences on the planet as their rates of sexual dysfunction were 6 to 30 times lower than reported in other countries. The participants in these studies were, by African standards, extremely well paid for their participation, so it is unknown if this had an undue influence on their answers. There are several studies, including a representative national survey from Denmark, indicating that circumcision has a negative impact on sexual function. There are several studies that have found

circumcised men suffer from premature ejaculation significantly more frequently than intact men. Studies have also indicated that the female partners of circumcised men are significantly more likely to report a lack of sexual fulfillment and pain with intercourse. This statement needs to be changed to fit the currently available evidence.

- **CDC draft: Health benefits of neonatal male circumcision:**
    - 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%.

Reviewer Comment: The CDC needs to make a simple calculation to provide the number needed to treat using the numbers provided above: NNT=178.6. At $285 per circumcision, it will cost over $50,000 to avoid one urinary tract infection that can be treated with an antibiotic that costs less than $20. (Another example of : a large percentage of a small number is still a small number.) It should also be mentioned that urinary tract infections in children are not associated with later development of renal failure or hypertension. Recent recommendations from the American Academy of Pediatrics are that extensive work-ups following urinary tract infections are no longer needed.

    - CDC draft*:* In the U.S., the estimated lifetime risk of penile cancer for males is about 1 in 1,400 (0.07%) and that of prostate cancer is about 15%. Neonatal male circumcision reduces the risk of penile carcinoma by about 90% and may reduce the risk of prostate cancer by 15% compared to men who are uncircumcised.

Reviewer Comment: These statements are factually inaccurate and out of date. Using up-to-date numbers, the number needed to treat for penile cancer is between 4237 and 7184. There is new evidence that infant circumcision is not a significant factor in the prevention of penile cancer. Instead, the risk is from balanitis xerotica obliterans, which is the most common cause of pathologic phimosis, along with smoking, multiple sexual partners, and HPV infections. The 90% reduction rate cited above is obviously inaccurate. There have been only three case-control studies of penile cancer published in North America, none of which came close to showing a 90% reduction in penile cancer related to circumcision status. When two of these studies were controlled for adults with phimosis, lack of infant circumcision was not a risk factor. Breast cancer in males is more common than penile cancer at a rate of about 0.13%, but there is no discussion about removing male breast buds at birth. The evidence on prostate cancer is weak and inconsistent. Until good evidence is available, prostate cancer should not be part of the discussion. Prostate cancer is very common in this country despite the high rate of circumcision.

- **CDC draft: Adverse events and risks associated with neonatal male circumcision:**

- Adverse events: For male circumcision performed by clinicians,
  - the rate of reported adverse events is as follows
    - 0.4% in infants (age through 12 mo.)

Reviewer Comment: This estimate is from a study that collected its data from databases, which have been shown to only identify 5% to 10% of the complications, as compared to those that can be identified from a chart review. As a consequence, this number has no basis in reality, and it grossly underestimates the actual rates for adverse events and risks in neonates. Percentages for adverse events/complications are listed later in this review.

    - CDC draft: 9.1% in children (age 1-9 years)
    - CDC draft: 5.3% in persons (age 10 years and older)

Reviewer Comment: Older children and their parents are more likely to identify and complain about complications. Consequently, this number may be an overestimate. Yet, when compared to the well documented rates of complications following infant circumcision, older children may have lower complication rates.

  - CDC draft: Most commonly reported complications in all age groups include bleeding and inflammation of the penis, and correctional procedures.
  - CDC draft*:* The incidence of severe adverse events associated with male circumcision performed by clinicians, such as permanent disabilities, disfigurements, and death, is so low that rates have not been precisely established; these events have occurred, but are rare. Other major complications requiring intervention including major bleeding, and severe infection are uncommon.

Reviewer Comment: The disclosure of information to decision makers during the informed consent process for a non-therapeutic, cosmetic procedure needs to be exhaustive and complete. Circumcisions are performed primarily for cultural and religious reasons. Therefore, from a medical perspective, the consequences are much more likely to be negative than positive. Health care providers who perform circumcisions would be well advised to inform decision makers of all of the known complications/consequences because these may occur despite the skill of the provider. If an adverse or serious complication occurs, the health care provider will be able to document that such a complication was understood by the patient and signed off on. Some of the complications are so common following circumcision that they are not recognized as complications. Health care providers, when providing disclosure, also must discuss the normal anatomy, histology, and function of the foreskin so the decision maker is informed of what harm/ loss results from every circumcision. The CDC drafts do not mention the normal anatomy,

histology, or function of the foreskin, thus disadvantaging the health care provider who is reliant on these documents to properly inform decision makers. This major oversight on the part of the CDC requires attention.

Here is a list of consequences/complications:

Loss of foreskin, its function, and the majority of fine-touch neuroreceptors in the penis (100%)
— Associated increase in erectile dysfunction
— Possible increase in premature ejaculation
— Loss of penile sensation
— Loss of penilo-cavernosus reflex
— Increase in the sexual dysfunction of female sexual partners, including pain on intercourse

Adhesions (25%)

Meatitis (20%)

Meatal stenosis (5% to 20%) — most will require a meatotomy to widen the urethral opening to allow normal urine flow.

Skin bridges (4.1% to 12.7%)

Excessive bleeding (1% to 9%)

Bleeding (1% to 9%)

Subcutaneous granuloma (5%)

Preputial stenosis/phimosis (0.3% to 2.9%)

Hidden penis (1%)

Cosmetic concerns prompting parents to insist on a circumcision revision (1-2%)

Infection (1% to 2%)
— Methicillin-resistant Staphylococcus aureus (12-fold increase in circumcised males)
— Staphylococcal scalded skin syndrome
— Scrotal and penile abscess
— Erisipelas

— Septicemia
— Meningitis
— Osteomyelitis
— Group A Streptococcus
— Fornier's gangrene
— Tetanus
— Infections following oral-genital contact in ritual circumcisions:
— Herpes simplex
—Tuberculosis
— Syphilis

Necrosis of the penis (0.8%)

Surgical complications:
— Denudation of the penile skin leaving insufficient skin to allow for erection. Some men report pubic hair being pulled over the body of the penis when erect. Excessive skin removed at the time of circumcision is being reported more frequently.
— Urethral fistula
— Bivalving in which the scissor is inadvertently placed in the urethra and the glans is cut in half.
— Amputation of all or part of the glans
— Amputation of the entire penis
— Hematoma

Urinary retention (seen more commonly in ritual circumcisions)
— Bladder rupture
— Obstructive uropathy
— Renal failure
— Urinary tract infections

Penile edema

Hair strangulation (reported only in circumcised males)

Behavioral changes
— Newborn circumcision interferes with breastfeeding
— Newborn circumcision interferes with maternal-infant bonding
— Newborn circumcision interferes with normal sleep patterns
— Following circumcision, with or without anesthetic, boys cry longer and louder when given

their vaccinations at 4 to 6 months of age suggesting that circumcision may permanently alter pain perception.
— Circumcised boys have been found to have a significant association with an increased risk of autism in two studies. There are no contrary data.
— Circumcised boys are at a significantly greater risk of being diagnosed with hyperactivity disorder (attention deficit hyperactivity disorder).
— Circumcised men have a greater risk of having alexithymia (the inability to express emotions)
— Circumcised men have been found in two studies to identify themselves as gay/bisexual significantly more frequently than intact men

Complications of topical/local anesthesia:

Hematoma and bruising
Methemoglobinemia
Gangrene

Reviewer Conclusions:

The CDC recommendations are counterfactual and not evidence-based. The supporting evidence provided is extremely selective and biased. If the CDC had carefully scrutinized much of the supportive evidence they provided, they would have identified methodological weaknesses that would, if they were to act on the quality of the evidence, change their recommendations. Acknowledgement of the vast majority of the medical literature that the CDC ignored would have also altered their recommendations. There are significant oversights, omissions, and inconsistencies throughout that are critical knowledge for the intended audience of clinicians. By using a selective bibliography and by depending on speculation and hype, rather than science, to develop these recommendations, the CDC has placed clinicians and health care providers in an untenable position. In effect, the CDC, by making the recommendations it has, is asking clinicians and health care providers to misinform their patients, and by doing so, commit medical malpractice. As a consequence, the recommendations for the intended audience of health care providers are inconsistent with the medical evidence, reckless, and dangerous. The CDC should eliminate this draft and approach the topic using an evidence-based approach, hopefully with the involvement of experts from around the world on both sides of the discussion.

Reviewer Commentary on CDC Background Draft:

Introduction

The material presented in this section of the background document is riddled with inaccurate

statements and misrepresentations.

Male circumcision performed on an infant is not “voluntary.” The infant does not give consent. (Circumcision campaigns in Africa have become less and less “voluntary” and some adult males are being forcibly circumcised.) Consequently, this statement is false and needs to be revised.

It is not clear why reference CDC3 was chosen as it is a book written by a known circumcision advocate. There are basic research articles that should be cited instead.

Prevention of HIV continues to be an unlikely consideration in the decision to circumcise despite pressure by the CDC to make it so (see discussion below). Infants are not sexually active, so HIV prevention is not a concern for them, nor has infant circumcision been shown to have any impact on HIV acquisition or prevention. Prevention of HIV in adults can be obtained more effectively through non-surgical methods, primarily with the use of condoms.

When the draft states that male circumcision reduces the risk of male HIV acquisition through penile-vaginal sex, it relies on the results of the randomized clinical trials to make this claim.[1-3] The problem is that these trials did not make any effort to determine the source of the infections they diagnosed during their course, so it is unknown whether these infections were the results of penile-vaginal sex, male-to-male sexual contact, or iatrogenic infections. Without knowing where the infections came from, the claim that male circumcision reduces the risk of male HIV acquisition through penile-vaginal sex cannot be made.

The CDC draft portrays the perceived benefits in terms of relative risk reduction, but the risks are presented in terms of absolute risk. For example, the 50% to 60% relative risk reduction in HIV infections in the randomized clinical trials sounds like a big deal, but the absolute risk reduction was only 1.3%, which is a difference that many would not consider clinically of any value. It would be best if this draft presented the perceived benefits in terms of the number needed to treat (NNT), and presented the risks in terms of the number needed to harm (NNH) in order to compare them fairly.

In reporting on the 2007 recommendations of the WHO/UNAIDS, it should be explicitly stated that their recommendations did not apply to infant circumcision. Nor was there a consensus of opinion. In fact, those present describe the measure as being “railroaded through.”[4,5]

The statement, “Despite these overall differences, the results of the African trials are likely to have application to HIV prevention efforts in the United States,” is completely without foundation. While this may be what the CDC authors want everyone reading it to believe, it has no basis in fact. (The US situation is quite different from that in Africa, including having a first-

class medical system in place.) Making such an unsubstantiated statement is unscientific and should be left to the circumcision lobbyists.

The statement that African-American men "are known to be significantly less likely to be circumcised compared to white, non-Hispanic men," is, as discussed below, also untrue.[6-8] African-Americans in several studies have higher, or the same, overall circumcision rates in the US, as compared to whites. Hispanics have lower circumcision rates than either of these groups.

It is unclear why the CDC draft questions "whether parents would be willing to have their newborns circumcised to reduce possible future HIV and sexually transmitted infection (STI) risk," when there is no strong evidence that circumcising a newborn will reduce the risk of these infections. To date, not a single study has found neonatal circumcision to significantly reduce the risk of HIV. (Not to mention, the adult studies fail to show a significant reduction in any risk.)

This background document presents a very biased, one-sided summary of the data that support the practice of male circumcision while ignoring most of the medical literature that does not support the practice. When the medical literature is looked at in its entirety, male circumcision is not a medically sound intervention. While this background document is supposed to focus on the data in the context of the United States, it only considers two of the eight studies that have looked at the impact of circumcision on the risk of HIV infection.[8-15] None of these eight studies found a statistically significant positive effect for the intervention, and one found that circumcised men had a statistically significant higher prevalence of HIV than intact men.[14] Likewise, much of this background document is allocated to a discussion about circumcisions performed in Africa, which are of little interest and irrelevant to the target audience of US healthcare professionals and not within the scope of the charge the CDC was given in developing these drafts. The effort that went into providing the minute details regarding circumcision in Africa would have been better spent researching the anatomy, histology, physiology, and function of the foreskin (which this document completely ignores), researching the complications associated with circumcision, updating information on the risk of sexually transmitted infections, and analyzing the data in the literature rather than relying on the often misguided analysis of others in review articles and opinion pieces.

Methods to gather, synthesize, and interpret information

The material presented in this section of the background document is fairly straight-forward, but the question remains as to whether the CDC followed their listed methodology in generating this report. The evidence, in the form of the final product, indicates they did not.

The two-day consultation convened by the CDC on April 26-27, 2007 brought together a virtual

Who's Who of Circumcision Advocates and Lobbyists.[16] Given the likemindedness of nearly all the participants in attendance, it is not surprising they managed to produce a massive "group think" phenomenon. Their conclusions were more radical and less scientific than what the participants would have likely considered acceptable, if left to their own devices.[17] This experiment in "group think" resulted in what will be referred to as the "CDC group think presumption:" namely that findings of the randomized clinical trials of adult male volunteers in Africa would apply to infant males circumcised against their will in the United States. In reading the CDC draft, this presumption is presented as gospel truth, when the reality is quite the opposite, with the data currently available not in support of this presumption. It appears the CDC has adopted the attitude seen with other circumcision enthusiasts, in that the issue was not open for discussion or questioning.[18]

While the CDC draft states that "a systematic review was conducted" there is little or no evidence that such a review was conducted. Instead, the CDC draft relies on the information published in non-systematic review articles from 1983,[19] and 1998;[20] systematic reviews from 2000,[21] 2003,[22] 2005,[23] 2006,[24] 2008,[25,26] 2009,[27,28] 2010,[29] and 2011;[30] and opinion pieces from 1999,[31], 2000,[32] and 2014.[33] Beyond reporting what was found in these articles, there is little, or no, evidence of a literature search being performed. The small number of citations (255, of which there are several duplications) also suggests a very limited search of the medical literature. Such a short citation list leaves the writers of the CDC draft open to accusations that, rather than explore the entire scope of the medical literature, they limited their citations to those that supported the "CDC group think presumption." The literature search, that likely did not take place, ended in November 2012, which raises the question of what has been happening the last two years? Much of what the CDC draft contends to be true has been undermined by recent publications. [Note: "United Statates" is spelled "United States"]

The statement "Because they eliminate spurious causality and bias, RCTs are considered the most rigorous method for determining whether a cause-effect relationship exists between a treatment and an outcome," is clearly an overstatement. No research method can completely "eliminate" bias. The elevation of randomized controlled trials to the status of the gold standard is misplaced, as they often deliver results that are invalid.[34-37] Throughout this draft, the CDC reflexively genuflects in the face of any results from a randomized trial. But every study, regardless of its methodology, requires careful scrutiny. The CDC did not scrutinize these studies. In fact, as will be discussed below, the randomized clinical trials cited in the CDC draft have multiple sources of bias, which rendered their findings meaningless. Randomized clinical trials, such as these, with serious methodological flaws are less rigorous in determining cause and effect than well-designed observation studies. Just because a randomized clinical trial format was employed does not mean that its findings are valid.

When the draft states that "None of the primary authors of these recommendations reported a financial or other conflict of interest," does this include any conflicts from being an adherent of a religion that requires circumcision, being from a cultural background that has a high circumcision rate, being circumcised themselves, being married to someone who is circumcised, and/or having circumcised one's children? Circumcision status in participants is considered by many as a clear bias and a conflict that should be declared.[38] Such a declaration is important, as circumcision status or having a circumcised son clearly impacts what advice physicians give to parents regarding infant circumcision.[39] The conflict of interest on this issue goes well beyond financial considerations. Where is the list of the primary authors of these recommendations, or a list of those who served on the subcommittee of the CDC Public Health Ethics Committee? The makeup of these groups will be an important factor by many, when looked at in conjunction with the obvious lack of scholarship displayed in this draft, in determining how seriously to take the recommendations.

Summary of evidence

Conspicuously absent from the CDC draft is a discussion of the normal anatomy, histology, physiology and function of the male foreskin or prepuce. Nearly every review article on any medical topic begins with a discussion of the basic anatomy, histology, physiology, and function of the organs and tissues involved. The recent Task Force report of the American Academy of Pediatrics also failed to address this,[40] and members of the Task Force had to admit ignorance on this topic.[41] It is impossible to understand the impact of amputating a healthy structure from the body, if these characteristics are not understood. The vast majority of physicians in the United States do not have a working knowledge of the anatomy, histology, physiology, or function of the foreskin because they were never taught it in medical school, and medical textbooks contain little or no information on these topics.

The prepuce is a common anatomic structure of the male[42] and female[43] external genitalia of all human and non-human primates. The prepuce has been present in primates for at least 65 million years, and is likely over 100 million years old based on its commonality as an anatomical feature in mammals.[44] The prepuce is best understood not as a separate structure of the penis, but rather as an integral part of the penile skin system.

As a modified extension of the penile shaft skin, representing 22 to 33% of the overall length of the flaccid penis, the prepuce covers the glans, extends beyond it, folds back upon itself, and attaches just behind the corona glandis, providing adequate mucocutaneous tissue to cover the entire penis during erection. There is variability in the preputial coverage of the glans penis ranging from complete coverage to only partial coverage.[45] The portion of the prepuce extending beyond the glans can be quite long in children, while those of adults can be shorter. In many

boys, the “redundant foreskin” can be longer than the penile shaft. Based on measurements available in the medical literature, the average surface area can be calculated to be between 50 to 62 square centimeters.[46,47] In a randomized clinical trial in Rakai, Uganda, the surface area was calculated by “multiplying the length by the width of the foreskin,”[48] but their calculations would underestimate the surface area by half as it only accounts for one side of the prepuce. Correcting for the prepuce having two sides, the average surface area in this study was 74.2 square centimeters.[48]

The prepuce is perfectly designed to protect the glans, an internal organ. Tapered and double layered, it extends beyond the glans in a long, narrow, tube-like structure, terminating in the preputial orifice. The peripenic muscle sheet lines the skin, is continuous with the dartos muscle of the scrotum,[49] and lines the mucosal layer allowing the prepuce to maintain its close fit over the glans.[50] At the preputial orifice, the muscle fibers are arranged in a whorled manner and form a sphincter that keeps unwanted contaminants away from the sensitive mucosa.[51] This is most evident in the prepubescent male in whom the portion of the prepuce extending beyond the tip of the glans has a characteristic puckered appearance.

The preputial orifice is able to dilate 15 to 20 times its normal size to allow the glans to pass through without entrapment. This expandability increases with age and sexual maturity but may be negligible during infancy.[52] Premature and inappropriate attempts to retract and dilate the preputial opening of infants and children can damage and scar the prepuce, reducing elasticity and impairing sexual function.[53]

While the outer surface of the prepuce is similar to skin, the inner surface of the prepuce can be subdivided into two zones of mucosa. One consists of a prominent band of ridged mucosa, with several (8-12) transverse mucosal ridges or pleats, just inside the tip of the prepuce. This band merges with the frenulum on the ventral aspect of the penis. When the prepuce is fully retracted, the *ridged band* lies across the upper surface and sides of the shaft of the middle third of the penis.[54-56] Histologically, the ridged band has a rich vascular supply, explaining its deep red color, and a high concentration of fine-touch neuroreceptors (such as Meissner’s corpuscles, Pacinian corpuscles, genital corpuscles, and mucocutaneous corpuscles) that transmit fine touch, pressure, proprioception, and temperature.[55,57-68]

The other zone is the smooth, non-ridged, preputial mucosa, which does not have a high concentration of fine-touch neuroreceptors.

The frenulum, in conjunction with the smooth muscle fibers of the prepuce, helps return the everted prepuce to its forward position. The frenulum, like the ridged band, also contains a dense concentration of erotogenic nerve endings and is a primary orgasmic trigger. Along with the

prepuce, also the site of erogenous triggers, stimulation of the frenulum is particularly effective at producing erections. Retraction, rolling, and stretching of the prepuce triggers erotogenic stretch receptors, which comprise the bulk of the sexual sensations of the erect penis.[69]

Blood enters the penis via two principal arteries — the pudendal artery, which carries blood down from the pelvic region, and the femoral artery, which also supplies blood to the legs. Neither of these arteries is superficial, instead lying close to the corpus cavernosa/corpus spongiosa. They flow directly to and alongside the glans, supplying it with blood. Then, they continue down to the underside of the glans to the forward-most point of the frenulum where the arteries meet up with the venous system.

The primary route for venous return from the penis is through the foreskin. The superficial veins drain the skin of the prepuce and glans via a complex vascular plexus that traverses the inner prepuce. These superficial veins drain into larger veins that run up through the frenulum and up the sides through the ridged band. From the ridged band, the veins continue their route back through the skin and Buck's fascia along the corpus cavernosa/corpus spongiosa.

The male prepuce receives its somatosensory innervation via the dorsal nerve of the penis and branches of the perineal nerve (including the posterior scrotal nerves).[70,71] The dorsal penile nerve of the penis supplies sensory axons to the penile shaft and glans. One axon innervates the penile shaft and the urethra, while the other innervates the glans. Stimulation of the urethra results in contraction of the bulbocavernosus muscles enhancing penile rigidity. Impulses from the dorsal penile nerve also initiate reflex semen emission and power the contractions of the bulbospongiosum muscle that results in external ejaculation.[72-74]

There are portions of the penis, particularly the ventral side and the frenulum, that are partially or completely innervated by a branch of the perineal nerve,[75] which also can induce contractions of the bulbocavernosus muscle.[73] A portion of the fibers within the dorsal nerve carries autonomic branches and is responsible for the hemodynamic events of the distal corpus cavernosum and the glans penis."[72] Autonomic innervation of the prepuce arises from the pelvic plexus. The parasympathetic visceral efferent and afferent fibers arise from the sacral center (S2-S4), and sympathetic preganglionic afferent and visceral afferent fibers arise from the thoracolumbar center (T11-L2). The parasympathetic nerves run adjacent to, and through the wall of, the membranous urethra.[70]

Histologically, the foreskin is a specialized, junctional, pentalaminar structure. The prepuce is considered a *specialized* tissue because it contains elements that are present only in select portions of the body.

It is a *junctional* tissue because it the junction where the transition from skin to mucosa takes place. Analogous tissues include the eyelids, oral labia and the anus, which are also transitional between skin and mucosa. All of these transitional zones contain a high concentration of fine-touch neuroreceptors. In the oral labia, the absence of these neuroreceptors would result in constant drooling, and kissing would lose most of its erotic appeal. In the eyelid, constant tearing would be the rule. Likewise, the protective function of the eyelids would be severely handicapped if unable to sense the presence of contaminants. The function of these specialized, junctional tissues is remarkably similar: keep moisture on the internal mucosal surfaces and keep contaminants out.

It is *pentalaminar* in that it has five layers, with each layer having its own unique histological and functional features:

1. The external skin has already been described.

2. The dermis of the prepuce consists of vascular tissue, dense nerve trunks, Meissner corpuscles within the papillae, and scattered sebaceous glands. The dermis of the male prepuce appears to have more elastic fibers than the lamina propria of the prepuce. The elastic tissue of the prepuce dermis, along with the dartos muscle and frenulum, tether the prepuce and help return it to its anatomically correct position after erection.

3. The dartos layer is specific to the male prepuce and is not found in the female prepuce. It consists of smooth muscle fibers invested with elastic fibers. The delicate, attenuated penile dartos muscle surrounds the shaft of the penis and is continuous with the scrotal dartos muscle.[49] This layer's elasticity allows for the volume changes required for erection,[49] while the muscular component is responsible for the prepuce fitting closely over the glans.[50]In the distal prepuce (acroposthion), the muscle fibers are intertwined and arranged in a mosaic-like pattern in the infant,[50] causing the distal prepuce to pucker and close, acting like a one-way valve.[51] This is most notable when a young boy voids. As the urine is expelled from the bladder it must first build up enough pressure to overcome the preputial valve. Because of the elasticity of the prepuce, it is not unusual for the prepuce to balloon before enough pressure is generated and a urinary stream results. As a male ages and passes through puberty, the ratio of muscle fibers to elastic fibers decreases, explaining why, on gross inspection, the acroposthion is puckered in the infant and more relaxed appearing in the adult.[50] The increase in elastic fibers may be necessary for the uncomplicated eversion of the glans in the adult.

4. The lamina propria of the prepuce is highly vascular and has looser collagen than the dense collagenous lamina propria of the glans penis. The ridged band of the prepuce is near the tip (acroposthion) of the male prepuce and, in the unretracted prepuce, usually lies against the

glans. It is in the lamina propria of the ridged band that there is a high concentration of specialized neuroreceptors. All of these receptors have a capsule and an inner core composed of both neural and nonneural elements. The capsule is a continuation of the perineurium and the core includes preterminal and terminal portions of the nerve fibers surrounded by laminated layers of modified Schwann cells (laminar cells).[68] The Meissner corpuscles, genital corpuscles, and mucocutaneous receptors are similar in that there is a complex branching of the nerves within the corpuscular core, while the Pacinian corpuscle has a single nerve through the core that is surrounded by laminar cells to form an onion bulb configuration. The prepuce possesses a richer variety and a greater number of nerve endings than any other part of the penis.[76,77]

These corpuscular receptors represent one of the two primary somatosensory receptors in skin, the other being free nerve endings or nocioceptors.[67] While free nerve endings (pain, itch, and touch receptors) are found in most skin, the encapsulated receptors are concentrated in regions that require specialized sensitivity, such as at the fingertips, eyelids, lips, external genitalia, perianal skin, and transition areas between skin and mucous membranes.[68]

The glans penis is primarily innervated by free nerve endings and has primarily protopathic sensitivity.[78,79] Protopathic sensibility refers to cruder, poorly localized feelings (including pain, some temperature sensations, and certain perceptions of mechanical contact such as rubbing).[78,80] In the glans penis, encapsulated end organs are found in much lower concentrations and are found mainly along the glans corona and the frenulum.[78] The glans is best stimulated by the mechanical rolling pressure of the prepuce over its surface. By comparison to the prepuce, the glans is a neurologically “dumb” organ.[56][The only portion of the body with less fine touch than the glans penis is the heel of the foot.[81] The mucosal lamina propria is devoid of lanugo hair follicles, sweat, or sebaceous glands. The lamina propria is highly vascular.

5. The mucosal epithelium of the prepuce is the same as the squamous mucosal epithelium that covers the glans penis.[82] The mucosal epithelium contains Langerhan’s cells, but does not contain melanocytes. It provides the moist lining necessary for the preputial sac to function properly.

It is also important to recognize that separation of the foreskin from the glans of the penis is a gradual process. The glans penis and the inner prepuce share a common, fused mucosal epithelium at birth. The two opposing fused epithelial surfaces separate gradually over years as desquamated cells build up between the two layers when the proper hormonal and growth factors are present.[83] While the separation of the prepuce from the glans has been shown to be androgen dependent in rats,[84] the hormones and/or growth factors responsible for this separation are poorly understood in humans. The process of keratinization of the intervening epithelium begins anteriorly and posteriorly at approximately the same time and proceeds toward the center.

Anterior desquamation, because it is confined, can result in pearls of desquamated skin cells.

Øster demonstrated that preputial non-separation is very common in children and teenagers. The separation of the mucosa is usually complete by about age 17 years, with the median age being 10 years of age.[52,86,86] The newborn penis is in a state of evolution that may take many years until the common prepuce/glans mucosa separates, and the preputial orifice enlarges to allow complete exposure of the glans. Ignorant of the normal development of the penis, some physicians advocate childhood circumcision as a treatment of normal anatomy.[87] Even the 2012 Task Force report of the American Academy of Pediatrics incorrectly reported that "Most adhesions present at birth spontaneously resolve by age 2 to 4 months."[40] Lysis of preputial adhesions in childhood is ill-advised, since this process resolves spontaneously and forceable manipulation and retraction of the immature prepuce can lead to scarring, bleeding, phimosis, and psychological trauma.[88,89]

The foreskin plays a protective and erogenous role. Animal studies have found that surgically removing the prepuce disturbs normal copulatory behavior,[90-94] the ability to attract female sexual partners,[95-102] and it increases aggressive behavior.[103,104]

The foreskin keeps the surface of the glans penis clean, free of infection, smooth, moist, supple, and sensitive.[105]

The prepuce protects and preserves the sensitivity of the glans by maintaining optimal moisture, warmth, pH, and cleanliness. The foreskin may have a role in keeping the glans warm, much the way the dartos muscle in the scrotum helps regulate the temperature of the testes.[106] There are temperature sensors in the foreskin that regulate the blood flow to the penis and thus regulate the temperature of the glans penis. These sensors appear to also impact the positioning of the scrotum, which, in turn, affects how close the testicles are to the torso, how warm the testicles are, and how fertile the male is.

The foreskin also provides a protective covering over the glans. Without the foreskin, the glans becomes exposed to the elements and dries out. The surface of the glans goes from a shiny, smooth, wet mucosa to a desiccated, rough surface. There is debate whether the exposed glans seen in circumcised men becomes keratinized or not.[32,107] Men who have foreskins report that having the glans exposed for prolonged periods is often quite uncomfortable because the surface is more sensitive.

The decreased sensitivity of the glans in circumcised male adults has been documented in three studies that objectively measured fine-touch pressure thresholds of the glans in circumcised and intact men, which are discussed in further detail later in this review.[108-110]

Two studies have compared the vibratory perception thresholds of the glans in circumcised and normal men. Bleustein et al. in a study in which 76.8% of the men in the study had erectile dysfunction, found that vibratory perception thresholds were significantly higher in intact men using the raw data, but the difference was no longer statistically significant when adjusted for age, hypertension, and diabetes.[109] A study in China looking at vibratory perception thresholds before and at one, two, and three months after circumcision in 96 men found that the vibratory perception threshold increased significantly following the procedure.[111]

Intromission in the circumcised man is akin to thrusting the foot into a sock held open at the top. By contrast, the intact counterpart is like slipping the foot into a sock that had previously been rolled up.[112,113] Consequently, during coitus the complete phallus penetrates smoothly with the prepuce retracting as the glans advances;[114] however, when the circumcised penis is introduced, friction and chafing develop.[113-118] The double-surfaced prepuce provides the skin necessary to accommodate the expanded erect organ and to allow the penile skin to slide freely, smoothly, and pleasurably over the shaft and glans. This also facilitates smooth, gentle movement between the mucosal surfaces of the two partners during intercourse. The female is stimulated by moving pressure rather than by the friction from a penis with the prepuce missing.[50,118]

O'Hara and O'Hara, from their survey of women who reported having had both intact and circumcised male sexual partners, determined that intact men provide shorter penile thrusts during coitus that resulted in more clitoral stimulation for the woman. By contrast, circumcised men used longer, deeper thrusts to provide themselves with enough stimulation to maintain erection and reach orgasm.[115] Because the foreskin is designed to feel fine-touch, only small movements are needed for adequate stimulation. When the exposed glans is in the vagina, the foreskin is bunched behind the corona with the ridged band juxtaposed against the corona, which is the most sensitive portion of the glans. With this juxtaposition, small movements are all that are needed to keep an intact male aroused and tumescent.

The unique innervation of the prepuce establishes its function as erogenous tissue.[58] Fine-touch pressure threshold mapping has demonstrated that parts of the foreskin and frenulum are the most sensitive portions of the penis.[108-110] The foreskin sends signals to the bulbocavernosus muscle that results in arousal and tumescence of the penis. Therefore, the foreskin may have a key role in facilitating a normal penilo-cavernosus reflex.

McGrath's research has emphasized the important role of the frenular delta, the triangular area where the ridged band attaches to the frenulum,[119] the frenulum, and the ridged band in providing possibly 80% of the sensory input from the penis, and their contribution in orchestrating signals

to the bulbocavernosus muscle, which plays a key role in tumescence. The stimulation from these structures also provides an inhibitory function in dampening the signal of pressure and pain coming from the free nerve endings that make up nearly all of the sensory data from the glans. Without inhibiting the pain and pressure signals from the glans during coitus, the activity would be less enjoyable.

While the penilo-cavernosus reflex has not been fully studied, it is a neurological reflex at the sacral level that has a role in the ejaculatory process. Podnar found clinically this reflex could not be elicited in 22 (73.3%) of 30 circumcised men, but was absent in only 2 (6.9%) of 29 intact controls.[120] Podnar speculates that this missing reflex in circumcised men may explain the higher rate of premature ejaculation seen in circumcised men. The impact of circumcision on sexual function is discussed in detail later in this review.

As a mucosal surface, similar to the inside of the mouth, the lining of the alimentary canal, or the conjunctiva of the eye, the inner surface of the foreskin is an immunological organ.

The mucosal surface of the inner prepuce and the glans, like all mucosal tissues, requires constant lubrication. Because the glans does not contain any sebaceous glands, it relies on the prepuce for production, distribution and maintenance of proper lubrication. The male preputial sac is moistened by secretions from the prostate, seminal vesicle, and urethral glands of Liftre.[121] Urine is not a normal component of sub-preputial wetness. The rich vascular plexus of the prepuce mucosa facilitates production of a fluid transudate similar to that of the vaginal mucosa.[122]

Animal experiments reveal that, in the presence of hydrogen peroxide and halide or pseudohalides, soluble peroxidase in the prepuce has an antimicrobial activity.[123] Antibodies present in breastmilk supplement genital mucosal immunity in infants. Oligosaccharides in breastmilk are ingested, then excreted in the urine, where they prevent *E. coli* from adhering to the urinary tract and inner lining of the prepuce.[124]

The inner prepuce secretes cathepsin B, lysozyme, chymotrypsin, neutrophil elastase,[125] cytokine (a non-antibody protein that generates an immune response on contact with specific antigens),[126] langerin,[127] and pheromones such as androsterone.[128] Lysozyme, which is also found in tears, human milk, and other body fluids, destroys bacterial cell walls as well as inhibits and destroys Candidal species (yeast).[129] The prostatic and seminal vesicle secretions that provide the subpreputial moisture are known to be rich in lytic material.[121] Langerin, which is a C-type lectin, is specifically expressed by Langerhans cells and induces the formation of Birbeck granules. The langerin on the surface of the Langerhans cell captures the HIV viron and internalizes it to the Birbeck granules where it is destroyed. In this way, langerin keeps

Langerhans cells from internalizing HIV and activating T-cells by clearing the virus before getting the T-cells involved.[127]

Like other exposed mucosal surfaces, the inner lining of the prepuce and the surface of the glans are covered with bacteria. The composition of the normal flora can impact whether a disease takes place. For example, the presence of one microorganism can inhibit the growth of another organism.[130-137]

The subpreputial flora has been known to be affected by a number of factors such as a patient's age, general hygiene, medical history, sexual activity, and sexual predilections.[138,139] The role of the diversity in subpreputial flora has not been explored in terms of preventing infection, but there is a growing amount of information that allows us to understand the flora in the subpreputial space. Earlier studies had documented that the preputial sac is colonized by cornybacterium, gram negative anaerobes (especially bacteroides melaninogenicus), enterococci, enterobacteria, and coagulase-positive staphylococci.[140] The impetus to study the subpreputial flora in recent decades has been resurrected by circumcision enthusiasts in hopes of providing evidence of a biologic mechanism to support their theories that the foreskin increases the risk of urinary tract infections and HIV infections.[141-149]

The authors of these studies try to spin the changes following circumcision as beneficial, but without understanding the role of normal flora prior to circumcision there is no way to know if the change is beneficial. The latest speculation is that genital inflammation *might* be associated with bacterial antigens from bacteria that are not associated with sexually transmitted infections, and that this inflammation *might* activate T-cells, which *might* be necessary for the transmission of HIV through the mucosal surface. Therefore, they conjecture that changing the flora at the end of the penis is why circumcised men are at lower risk of HIV infections. There is no evidence that normal flora in the subpreputial space is associated with penile inflammation. One could more convincingly argue that the presence of a variety of anaerobes and a microbiota with more major players is more protective against infection and inflammation. It is when the spectrum of bacteria narrows, which is what occurs following circumcision, that infection is more likely to occur. Certainly, developed countries with low circumcision rates do not seem to suffer from higher rates of HIV or other pathologic infections of the genitals.

The problem with the conclusions reached by these circumcision enthusiasts, including the writers of the CDC draft, is that they are too simplistic, agenda-driven, and reek of confirmation bias.[18] Gram-negative organisms are not all bad. Colonic flora is primarily gram-negatives, yet considered normal. The assessment of microbiological findings and their correlation to clinical findings is difficult, in particular when quantitative determinations have not been done.[150] The presence of normal flora is not a disease state. The most common bacteria responsible for otitis

media, pneumonia, and acute sinusitis are normal flora in the nose, pharynx, and mouth. Rather than blame normal flora in a healthy individual and use this in an attempt to justify amputating healthy body parts, a better approach may be to ensure healthy flora in the subpreputial space by lowering the rate of Cesarean sections and perinatal antibiotic usage, but calls to do this have been largely ignored.[151-153]

The understanding of mucosal immunity is in its infancy. While the mucosa in our mouths, noses, and genitalia encounter pathogens constantly, we rarely are infected. The mechanisms of mucosal immunity are complex and poorly understood. The mucosal immune system protects against potentially invasive microorganisms using antigen-presenting Langerhans cells, dermal and epidermal T lymphocytes, cytokine-producing keratinocytes, and draining peripheral lymph nodes.[154] Most of the "heavy lifting" is performed by Langerhans cells that hang out on the surface of the epithelium.

Langerhans cells are a specific type of dendritic cell. On electron microscopic examination, they have a lobulated nucleus with a clear cytoplasm, rough endoplasmic reticulum, and a well-developed Golgi apparatus.[155] They possess a unique granule in the cytoplasm, which has a "tennis racket"-like appearance, that is responsible for the internalization and processing of antigens.[156]

Langerhans cells are the first line of defense to help the body recognize and process antigens, directing them towards lymphocytes or macrophages.[157,158] To understand how this happens, it may be helpful to follow a Langerhans cell through its life cycle. The Langerhans cell begins life in the bone marrow. It is released into the blood stream and is circulated to the dermal blood vessels where it finds its way to the surface.[159,160] Here the Langerhans cell takes up a suprabasal position with its processes extending between neighboring keratinocytes and joins a web of interconnected Langerhans cells that surveys the epithelial surface for antigens.[161-163] They make up 2 to 5% of all epidermal cells,[164,165] yet their long processes allow them to cover broad expanses of the epithelial surface. Once an antigen is identified, it is captured by the Langerhans cell.[166-168] Following antigen uptake, the major histocompatibility complex and co-stimulatory molecules are up-regulated on the surface of the Langerhans cells.[169] The Langerhans cell then migrates from the epithelial surface to the paracortex of the nearest draining lymph node where it activates T-cells by producing cytokines and by presenting the major histocompatibility complex-restricted antigen-specific molecules.[166,169-171] This in turn begins an antigen-specific immune response by the activated T-cell.[166] The Langerhans cell then will return to the epithelial surface and repeat the process.[172]

Perhaps the most studied example of Langerhans cell activity is in antigen-specific delayed-type hypersensitivity resulting from contact with substances containing nickel that leads to T-cell

responses.[165,167,173] Langerhans cells have also been documented fighting infections of human papillomavirus in the female genital tract and of herpes simplex virus on the lips.[167,168,174-176] They interfere with skin graft rejection from foreign donors,[167] and suppress tumor growth in mice.[177] Langerhans cells have been known to act like macrophages both in the allo-activating and in the antigen-presenting function.[168,178,179] It has been shown that smoking decreases the number of Langerhans cells.[180]

The location and densities of Langerhans cell populations have been mapped.[164,170,181-183] Langerhans cells are found in the normal dermis, the lymphatics and in draining lymph nodes, in mucous membranes of tongue and tonsils, esophagus and gastric mucosa, as well as in the mucocutaneous junctions of the vagina, rectum, uterine cervix, prepuce, and urethra.[168,184]

Much of the controversy about the purported role of circumcision in reducing the number of heterosexually transmitted HIV infections surrounds the theory that Langerhans cells act as the mode of HIV entry into the body. The bottom line is that Langerhans cells in the prepuce should be considered normal, rather than a pathologic entity requiring excision.[165]

A review of the scientific literature reveals that the actual effect of circumcision is the destruction of the clinically-demonstrated hygienic and immunological properties of the prepuce and intact penis. There are no histological studies to validate the claim that the sclerotic keratinization of the epithelium of the surgically externalized, desiccated glans penis, meatus, or scar of the circumcised penis creates a barrier against infection. The higher rate of sexually transmitted infections in circumcised males might well be the result of the loss of preputial immuno-protective structures.[185] The loss of the protective, self-lubricating, mobile, double-layered prepuce exposes the glans and meatus to direct friction, abrasion, and trauma. The surgically externalized and unprotected glans and meatus of the circumcised penis are constantly exposed to abrasion and dirt, making the circumcised penis less hygienic and prone to meatal stenosis.[186] The circumcised penis is more prone to infection in the first years of life than the intact penis.[187-190]

Effect of male circumcision on health outcomes

The material presented in this section of the background document does not adequately represent the medical evidence currently available. In most areas discussed in the CDC draft, the medical evidence taken as a whole does not support the conclusions reached by the writers of the CDC draft.

Biological plausibility

The material presented in this section of the background document is highly speculative and based on conjecture rather than actual data. The speculations presented suggest that the writers were given the outcome of interest, namely the "CDC group think presumption" that circumcision of infants will reduce the risk of HIV infection in adults, and then they were instructed to find any data that supported this conclusion: a classic example of confirmation bias. When the scientific process is followed properly, conclusions are data-driven instead of data being conclusion-driven.

This section begins with the statement, "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," which cites an opinion piece as its source.[32] As any part of the body can be a portal for infection, it does not follow that removal of that body part will decrease the risk of infections, nor should removal of normal tissue be given any serious consideration. This is a circular argument that begins with assuming the "CDC group think presumption" is true.

The statement, "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," uses citations from an opinion piece and a review article on an unrelated topic.[32,191] Interestingly, the opinion piece cited states that in a series of seven circumcised and six intact men, the glans was equally keratinized in both groups. Studies have found that the thickness of the epithelial layer of inner and outer foreskin are similar.[191,192] [Note: these references should replace CDC20, which listed the author's name incorrectly, as these studies have been published subsequent to the 2009 abstract cited.] Therefore, the underlying premise of this statement has been demonstrated to be untrue. For the same reason the statement, "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," which is also referenced to an opinion piece,[32] is unsubstantiated conjecture.

The importance of the statement, "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," is unclear. The circumcised penis is also exposed to the body fluids of the sex partner. The only way to avoid this is to avoid sex or wear a condom.

While it has been "postulated" that the foreskin may serve as a reservoir of sexually transmitted pathogens, there is no evidence that the preputial sac is conducive to viral survival. The facts speak against this. For example, there is no evidence that herpes simplex virus type 2 or human papillomavirus infections are more common in intact men (see discussion elsewhere). A large

prospective study recently demonstrated that human papillomavirus (any type, oncogenic, HPV-16) are shed significantly faster from the penis of intact men.[193] With evidence to the contrary, it is time to end this type of speculation. That normal flora anywhere in or on the body, let alone in the preputial sac, would have an inflammatory impact that would increase the risk of HIV infection is ludicrous.

Level of penile wetness has been shown to be a factor in one study, but, in the randomized clinical trial in Uganda, men who did not clean their genitals for the first ten minutes following intercourse had significantly lower rates of HIV infection than men who washed in the first three minutes.[194] This suggests that there may be something in the preputial wetness or in vaginal secretions that interferes with the infectiveness of HIV. Furthermore, women have constant vaginal wetness and the CDC is not speculating about their need to be circumcised.

The suggestion that higher numbers of immune cells on the inner foreskin that can more easily respond to infections, and other exposures, will result in an increase in viral susceptibility of the inner foreskin is counterintuitive. Mucosal immunity is based on immune cells doing their job. If they are responding to infections, this would suggest they are more effective at repelling infection. This is borne out by the fact that sexually transmitted infections overall (as discussed elsewhere) are more common in circumcised men.[185]

The increased risk of HIV infection in those with genital ulcers makes sense as the ulcers compromise the barrier that is effective in keeping infections out and activates the T-cells, which is considered part of the HIV infection process.

The mucosal immune system is quite effective in preventing HIV infections, as indicated by the low rate of transmission through penile-vaginal intercourse (1 per 1000 acts of unprotected coitus). It is only when high viral loads are present that infection is more likely to occur. The speculation surrounding the biological plausibility of the foreskin increasing the likelihood of HIV acquisition is strained and depends on the lining of the foreskin being thinner (which it is not), the preputial sac being more likely to harbor viruses (which it does not), and functional immune cells on the surface (which actually reduces the likelihood of infection). This theory is so farfetched and counterfactual, why would anyone believe it?

The statements made in this section are based purely on speculations that directly contradict the facts. Although these speculative claims have been repeated, *ad nauseam*, in the medical literature, there is no science to support them.

Male circumcision and the risk of HIV infection acquisition

Male acquisition of HIV infection from female partners

The material presented in this section of the background document is a confusing regurgitation of review articles that are incomplete and out of date.[21,22,24,27] More importantly, this section fails to address several key questions, namely whether the results of the randomized clinical trials from Africa[1-3] are valid, whether they apply in the United States, and, if applicable, to whom should they be applied.

Three randomized clinical trials were undertaken simultaneously in Africa with nearly identical methodology.[1-3] This lack of methodological variation is not a sign that the best methodology was used, but instead undermines the robustness of their findings. Because of this lack of variation, one might think of the trials collectively as one trial performed at three sites.[195] The results of the trials were remarkably consistent, to the point that some would consider the similarity of the results to be mathematically improbable. Because of the similarity in the results, one could argue that the studies were precise in their estimates, but with a lack of methodological variability the accuracy of their estimates cannot be assessed. More studies using a variety of methods reaching consistent results would provide a stronger testament to their accuracy. The accuracy of their estimates can be called into question because of the internal validity issues these trials share (discussed below) and the fact that their estimates of the treatment effect were greater than seen in observational studies. This is quite atypical as the treatment effect in randomized trials are typically about 25% to 30% smaller than seen in observational studies.

The methodology of these trials undermine the internal validity (how well the estimates generated by the trial reflect reality) in a number of ways. Perhaps the most important methodological flaw is that no effort was made to identify the source of the infections that were diagnosed during the course of the trial. By failing to do so, these trials cannot answer their research question of determining the impact of male circumcision on the heterosexual transmission of HIV from females to males because it not known how the infection was transmitted. Consequently, the CDC draft is incorrect throughout by suggesting these trials measured this form of transmission, when they clearly did not. This is important because some of the infections may have resulted from male-to-male transmission and some may have been transmitted through iatrogenic means. In the trial in Kenya, only 0.2% of the participants reporting having had male-to-male sexual contact.[2] For many in developed nations this would be considered an extremely low percentage, as male-to-male sexual contact is seen in the range of 5% to 10%. The low rate of men reporting male-to-male contact may reflect the extreme homophobia in sub-Saharan Africa. In Uganda, for example, their Anti-Homosexuality Act of 2014 will punish homosexual activity with life imprisonment (they were considering making it a capital offense). Given the extreme penalties and social stigmatization, admitting homosexual activity to researchers could result in dreadful consequences. Therefore, it is reasonable to

assume that, among the thousands of participants in these trials, many were having male-to-male contact. Consequently, the role of anal intercourse in transmitting HIV in this population is unknown.[196] Given that transmission rates between two men is more efficient and that this mode of transmission is not impacted by male circumcision,[25] the failure to identify the source of infection would likely impact their final estimates.

A surprising number of participants in these trials became HIV infected despite not being sexually active or always using condoms. Consequently, it is unlikely that their infections were sexually transmitted. Iatrogenic transmission of HIV is well documented in Africa typically from procedures in which the skin is punctured with instruments or needles that have not been properly sterilized.[197-208] This possibility should not have been a surprise to the trial investigators. In one African study, female and male virgins who were circumcised were more likely to be HIV-infected.[209] Some have argued that the iatrogenic spread of HIV in Africa is better able to explain the high prevalence of HIV rather than convoluted models that rely on multiple concomitant sexual partners and a high burden of sexually transmitted infections.[200,210]

In each of the trials, there were infections that could not be accounted for on the basis of sexual transmission alone. For example, in the South African trial 23 men, who accounted for 2076 person years, became HIV positive with either having no sexual contact or always using a condom (infection rate 1.11/100 person-years) compared to 46 infections in 2498 person-years among men who at least one episode of unprotected sex during the trial (1.84/100 person-years).[1] Assuming that all of the men in the trial had the same risk of infection through non-sexual transmission only, only 18 of the 69 infections can be attributed to sexual transmission (1.84 minus 1.11 per 100 person-years times 2498 person-years). In the Ugandan trial, 1252.1 person years and 6 infections can be attributed to men who reported no sexual partners for the duration of the trial (0.48/100 person-years).[3] When this baseline rate of infections in those who were not sexually active is subtracted from the total rate in the men who were sexually active, 35 of the 67 infections can be attributed to sexual transmission.

In the Kenyan trial, there were five men reporting no sexual activity in the first three months of the trial who subsequently seroconverted (0.73/100 person-years).[2] When this rate is subtracted from the rate seen in those who were sexually active, only 36 of the 69 total infections can be attributed to sexual transmission.

Without knowing the source of the infections they diagnosed, it is hard to determine what actually was measured in these trials and even harder to extrapolate their findings across the ocean to infants. How can the CDC base policy on trials that did not measure what they set out to measure?

The study methodology, which was nearly identical in each of the trials, had several built-in forms of bias, all of which would be likely to overestimate the treatment effect.

Expectation bias: At least one primary investigator was on record prior to execution of his trial expressing his impatience and stating that it was time "to begin investigations of the feasibility of acceptable male circumcision interventions in communities with high HIV and STD seroprevalence where circumcision has traditionally not been practiced."[31] So, it would appear that Bailey believed a randomized clinical trial was unnecessary, as the issue was already settled for him. Similarly, in the Ugandan trial, the researchers from Johns Hopkins dismissed the results of the six men who became infected despite no sexual partners noting, "these participants probably under-reported their sexual activity."[3] Infection in men who were not sexually active did not agree with their expectations, so the results were summarily dismissed. How many other unwanted results were similarly dismissed because they did not agree with the investigators' expectations. Furthermore, there is evidence of expectation bias on the part of the participants. These men agreed to participate because they believed that circumcision would lower their risk of HIV. Even after the informed consent process, more than half (57%) believed that circumcision would reduce their risk of infections.[211,212] Since the researchers and participants could not be blinded to which group a participant was assigned to, one would expect that participants would act differently based on their assignment and be treated differently by the researchers. Both researchers and those assigned to the intervention group would be expected to change their behavior to make the intervention pay off.

Selection bias: The men in these trials were those who were interested in undergoing circumcision. After the propaganda sessions in the roll-out before the trials, many men were convinced they wanted a circumcision in order to reduce their risk of HIV. When compared to the general population, one would expect that at least some of these men viewed themselves as, or were in reality, at greater risk for HIV infection. The percentage of men interested in a free circumcision, as evidenced by the current voluntary medical male circumcision programs, is less than 5% in most countries.[213-219] So, the participants in these trials are representative of only a small subset of the general population. As noted above, the motivation of the participants in these trials would be expected to alter their behavior.

Lead-time bias: The men who were randomized to be immediately circumcised were instructed to abstain from sexual relations or to always use condoms for the first six weeks following the procedure to allow for proper healing. The data reported in these trials was number of infections per time of potential exposure. Since those in the intervention group each had six weeks less of potential exposure, one would expect them to have a smaller number of infections. Avoiding lead-time bias is a fundamental principle of study design that is taught in the most rudimentary of courses on clinical study design. None of the randomized clinical trials adjusted for this bias in

their study design, and only one made an adjustment in their post hoc analysis.[1] This indicates either incompetence or a conscious omission that would increase the likelihood of producing data favorable to circumcision.

Intervention bias: The men who were randomized to the intervention group had more visits and exposure to the research team . This would give researchers additional opportunities to provide education on safe-sex practices and to emphasize how important it was for the trial participants to follow-up as requested.

Attrition bias: These trials had a substantial number of participants who were lost to follow-up. The number lost was 251 (8.0%) in South Africa,[1] 240 (8.6%) in Kenya,[2] and 493 (9.9%) in Uganda.[3] Those who were assigned to the intervention group were significantly less likely to be lost to follow-up (OR 0.83; 95%CI 0.73-0.95). One possible explanation is that men who were hoping for a free circumcision but assigned to the control group would see no purpose in staying in the study. Participants who are lost to follow-up are not the same as those who continue to participate. In the Kenyan study, they had a greater number of lifetime sexual partners and a higher prevalence of being seropositive for herpes simplex type 2 virus (Robert Bailey, personal communication). What is more concerning is that for every participant who become infected with HIV during these trials, there were 4.8 who were lost to follow-up. This is a serious missing-data problem.

Duration bias: The trials involved 24 or fewer months of follow-up. The shape of the trajectory following 24 months is unknown. It could very well be that over time the number of infections will be the same in both groups and circumcision may only slightly delay the time to infection. Several of the models have assumed that the trajectory seen in the first two years will continue for 20 years, based on faith more than science.[220-232] There is also growing evidence that HIV is losing its virulence.[233]

Early termination bias: All three of the trials were terminated early. Early termination, in and of itself, is more likely to result in an overestimate of the treatment effect.[234] It also amplifies any impact of the lead-time bias. Of interest, the Ugandan study had a Fragility Index[235] of 4, which suggests that findings of the study were not particularly robust. How can a study that is terminated early, have such a low Fragility Index?

Overpowered studies: These studies were powered to detect a 1% ARR difference in HIV incidence between the intervention group and the control group.[236,237] This explains the high number of participants in each trial. The important question is whether a 1% difference is clinically important, not whether the difference is statistically significant. If a 1% difference is not important, then demonstrating that this difference is statistically significant misses the point

of doing the studies. Studies with a large number of participants, such as these randomized clinical trials, are able to demonstrate a statistically significant difference for very small absolute differences, but when the absolute differences are so small, these studies can also have trouble distinguishing between real findings and background noise. With these trials, even though each source of bias may not be enough alone to explain the difference seen, their cumulative effects, since they all would work to overestimate the treatment effect, would be enough to explain the 1.3% absolute difference seen.

The randomized clinical trials, especially the Ugandan trial, have a number of unexplained anomalies. For example, in the Ugandan trial, those who reported consistent use of condoms had a trend toward a higher rate of HIV infection than in those who reported never using condoms (consistent condom use: 1.03/100 person-years; No condom use 0.91/100 person-years; RR 1.13; 95%CI=0.54-2.38, p=0.74).[3]

Given all of the problems with how the data in these studies were handled, it would be helpful if these data could be analyzed by independent experts, rather than researchers who have careers that depend on generating positive results. Even though the National Institutes of Health used our tax dollars to fund two of the randomized clinical trials, the data are not available to the public and are not subject to the Freedom of Information Act. Some have called on these data to become available,[238] but researchers of the studies from Kenya and Uganda have not complied.

There were several ethical concerns regarding the trials,[239,240] including that the financial incentives to participate (a free circumcision, money equivalent to two-weeks employment, cash for recruiting additional subjects, unlimited access to free condoms, and free health care for 21 to 24 months) were coercive. There is a lack of equipoise seen in both researchers and participants.[211,212] Based on the extremely pro-circumcision bias of the researchers, it is unlikely that participants were given full disclosure, particularly regarding the risks and long-term harms of the procedure, while obtaining informed consent. Furthermore, going into these trials, the researchers knew that circumcision would be less effective, more expensive, and more invasive compared to other interventions already available at that time (most notably condoms). Typically, trials that evaluate interventions that are known to be inferior to current therapies are not pursued because they violate the Helsinki Declaration.[239,241]

Finally, it is unclear whether these trials were necessary as demographic information was available prior to the initiation of these trials showing that, even if they generated a positive result, their results would not have external validity. Typically, when a new drug is developed it is subjected to a Phase III trial in a closely defined and monitored population. Phase IV studies take place once the medication is being used in the general population. In the case of male circumcision and its impact on HIV infection, the Phase IV type data were available before the

Phase III studies were designed. The Phase IV type data indicated that circumcision did not have any impact on a demographic level. For example, in South Africa HIV spread had similar dynamics of spread in the Shangaau and Xhosa tribes that are circumcised and the Zulu and Tswana tribes that do not circumcise. The fact that the researchers who performed the randomized clinical trials went ahead with the trials, despite the availability of this Phase IV type data, suggests that they were not properly educated in basic epidemiological methods, such as the difference between efficacious and effective, or that they chose to ignore basic principles of epidemiology when moving forward with these trials.

While randomized double-blinded placebo-controlled trials are considered the gold standard for testing a hypothesis, the quality of the information garnered from poorly designed randomized trials, such as the randomized clinical trials undertaken in Africa, can be below that of a well-designed observational study. The CDC draft places unearned importance on the results of these trials. While there are serious concerns about the internal validity of these trials, there is ample evidence that the trials lack external validity. While some circumcision advocates, including the writers of the CDC draft, have suggested that data collected from the participants in the trials after the completion of the trials[242-245] indicates that circumcision is effective (in addition to being efficacious), and thus has external validity, these participants would still be subject to the Hawthorne effect and the undue influence of the large financial advantages of having participated in the trials. These people should still be considered to be acting within a research setting as they likely received far more attention and education than men who would be getting circumcised outside a research setting, but the results should not be considered on the same quality level as a randomized trial.

The randomized clinical trials lack external validity. When there is a treatment effect in a clinical trial, it would be expected that such a treatment effect would be seen outside of research settings and in the population at large. This has not been seen. There are eight or more countries within Africa where the prevalence of HIV infection is greater in circumcised men than in intact men.[13,246-250] When the national survey data are included in a meta-analysis, no difference in HIV prevalence is noted by circumcision status (intact versus circumcised men random-effects summary OR 1.10; 95%CI 0.81-1.50).[251]

If the results from the three randomized clinical trials do not apply to the countries in Africa, do they apply to countries outside of Africa? While some ecological studies within Africa have suggested a correlation between circumcision prevalence and HIV prevalence,[252-255] [Note: citation CDC57 is an opinion piece and should not be cited in this context. The authors need to cite the original studies as included above.] other analyses have not found circumcision to be a factor.[256] When these methods are applied to developed countries, there is a significant positive correlation between circumcision prevalence and the prevalence of heterosexually-transmitted

HIV infections.[257] When only English-speaking countries are considered, there is a strong linear relationship between a country's circumcision rate and its rate of heterosexually-transmitted HIV (r^2=.9756).[258] If the writers of the CDC draft want to accept the results of those ecological studies in Africa showing that increasing circumcision rates correlate to decreasing rates of HIV infection, then they also need to accept the results of the recent study that found a statistically significant correlation between the prevalence of infant circumcision and the prevalence of autism.[259]

Before accepting the "CDC group think presumption" that the findings of the methodologically flawed randomized clinical trials of adult males in Africa would apply to infants circumcised in the United States, it is important to look at the evidence available. One approach would be to look at the entire body of literature on the association between HIV incidence and prevalence and circumcision status. This has been assessed in over 100 populations.[1-3,8-15,246,248-250,260-323] These include randomized clinical trials, prospective cohort studies, national surveys, and case-control studies and all of these study types can be informative. When study characteristics of the various populations are adjusted for, meta-regression[324] reveals that studies of general populations broadly, and outside of Africa in particular, do not support the hypothesis that circumcision lowers the risk of HIV infection. Meta-regression also indicates that as the prevalence of circumcision in a community increases the association between being intact and HIV infection increases.[325] This would indicate that circumcision has no role as primary prevention either in Africa or outside Africa.

A second approach would be to look at the studies that have been performed in North America on heterosexual men. None of them support the "CDC's group think presumption," and none of their findings in favor of circumcision are statistically significant. A 1991 study of men at high risk for HIV infection had an odds ratio (intact versus circumcised men) of 1.75 (95%CI 0.93-3.27).[11] A 1993 study by the same researchers found an odds ratio of 4.25 (95%CI 0.94-19.13).[15] A representative national survey found an odds ratio of 2.60 (95%CI 0.65-10.42).[9] A 2004 study from the US Navy found a slight decrease in risk for intact men with an odds ratio of 0.80 (95%CI 0.52-1.22).[10] A national survey in Haiti found a similar trend with an odds ratio of 0.67 (95%CI 0.33-1.35).[13] A very large study from an STD clinic in San Francisco found no difference with an odds ratio of 0.93 (95%CI 0.33-1.05).[8] Another large STD clinic study from Baltimore found the raw data had an adjusted odds ratio of 1.00 (95CI 0.86-1.15).[12] **None of these studies found a statistically significant difference.** Finally, a study from a STD clinic in Puerto Rico found that circumcised men had a significantly higher prevalence of HIV infection (OR 0.68; 95%CI 0.49-0.95).[14] When these studies are combined in a meta-analysis, the random-effects summary odds ratio was 1.21 (95%CI 0.78-1.88, between-study heterogeneity chi-square (df=7) = 91.64, p <.0001, I^2 = 91.3%) when raw numbers are used and 0.94 (95%CI 0.79-1.13, between-study heterogeneity chi-square (df=7) = 15.56 p=.0295, I2 = 48.7%) when the adjusted

odds ratio for the Baltimore study is used. Most of these studies were performed in high-risk men and no difference was documented. One would expect there to be even less of an association in general populations. Consequently, these data do not support the "CDC group think presumption."

Finally, the target population for circumcision needs to be delineated. The data clearly show that circumcision is unlikely to be effective if targeted at the general population. The US data, which is derived primarily from patients seeking care at STD clinics, indicates that circumcision would not be effective for high risk populations either, such as attendees of STD clinics. The sub-strata data from the Baltimore study, which made up only 1.4% of men seeking care at an STD clinic, suggest that there may be a slight role for circumcision in the subpopulation of men who are at *imminent* risk of infection, such as those who have a regular female sexual partner who is known to be HIV-infected. In this subpopulation, only 11 intact men were HIV infected and their findings had a Fragility Index[235] of 1, indicating results that are far from robust.[12] Policy decisions should be delayed until this association is replicated in multiple studies with sufficient robustness. Consequently, any discussion of circumcision related to the risk of HIV infection in the United States, if they should occur at all, should only be directed toward discordant couples with HIV-negative men who have regular sexual relations with known HIV-positive female sexual partners. There is no evidence to support suggesting circumcision for any other populations. For this small sub-population, there are a number of far more effective options such as condoms, pre-exposure prophylaxis, and anti-retroviral therapy for the infected sexual partner. Even a model developed by the CDC, that assumes the "CDC group think presumption" is true, has determined that circumcision would have minimal impact in preventing HIV infection in this population. So, why is the CDC contradicting its own findings by bringing forth the recommendations in this draft?

The bottom line is that data **does not support** the use of circumcision to reduce the risk of heterosexual transmission of HIV in the United States.

The material given in this section by the CDC is counterfactual, biased, and dangerous. The medical literature suggests that circumcision *might* have a *minimal* impact on the risk of HIV infection in a *very small* sub-population, but this needs further study before implementation. To extend the discussion of circumcision beyond this easily identifiable sub-population is reckless and would result in unnecessary physical and psychological harm. The fear-mongering implicit in this section makes the CDC look foolish and desperate. In the seven years since the CDC held its consultation, several things have happened that have taken circumcision out of consideration as an HIV preventive measure. AIDS researchers have adopted secondary prevention methods such as "treatment as prevention" that has changed infection with HIV from a death sentence into a chronic disease.[326] Similarly, the virulence of the HIV virus is weakening.[233] Finally, the roll-

out of circumcision in Uganda and Kenya has resulted in increases in the incidence of HIV in men in those countries.[327-329] Not to mention the number of men and boys who have died as a direct result of being circumcised in Africa, some **forcibly against their will**. The CDC would be better off expending its energies, and US taxpayers' money, promoting interventions that are not ineffective and harmful.

HIV infection transmission from circumcised men to female partners

The material presented in this section of the background document is incomplete with some of the material being misrepresented.

The early studies, which looked at whether the circumcision status of a woman's male sexual partner was a risk factor for women becoming infected with HIV, showed mixed results.[287,317,330-337] Since then, the evidence emerging fails to support the theory of male circumcision directly reducing the male-to-female transmission of HIV. The only randomized clinical trial addressing this issue found a marked increase in HIV infections in the female partners of men who had been circumcised.[338] The writers of the CDC draft give a very pro-circumcision spin to these results. The absolute risk increase for these women was 6%, which translates to a number needed to harm of almost 17. So, for every 17 circumcisions performed on an HIV-infected man with a female partner that was not infected, one would expect one additional female partner to become infected.. This study was terminated early, and rightly so, because early looks at the data indicated that the practice was too dangerous to continue. To state that the study was terminated because it was unlikely to show a favorable result may be technically accurate, but it belies the 50% relative increase in HIV infections. The pro-circumcision spin stating the study failed to show a difference is also true, but disingenuous since the trial was rightly terminated before the study had enough power to show a statistically significant difference if one existed. The study was also profoundly unethical because the women were not told their sexual partners had HIV — very reminiscent of Tuskegee. Shockingly, the authors of the study recommended that HIV-infected men undergo circumcision, with a total disregard for the increased risk of HIV infection the procedure foisted on female partners, because of the fear that these men would feel stigmatized if they were not circumcised.[338] Too bizarre to have been made up.

The two models that have assessed the impact of male circumcision on the incidence of HIV infections in women assumes the findings of the randomized clinical trials have both internal and external validity, both of which are risky assumptions.[223,339] The extremely speculative nature of these models should exclude them from being considered in formulating policy.

Male acquisition of HIV infection and other STIs from male partners

The material presented in this section of the background document is generally accurate, incomplete in a few areas, but needs to be more explicit in its conclusion, namely that circumcision is not a reasonable intervention in the prevention of HIV infection that might be acquired by men from their male sexual partners. A recent model published by the CDC assessing the effectiveness of various interventions in the prevention of HIV infection in discordant couples found that, for a man with a male partner who was HIV-infected, over a 10-year period, reliance on circumcision alone would nearly guarantee the man would become infected.[340] A major thrust that resulted from the CDC's 2007 consultation was an effort to find a link between circumcision and the risk of HIV infection in men having sex with men.[16] One opinion as to why the CDC took over seven years from the time of the consultation to the release of this draft was the hope of a breakthrough study that would demonstrate that circumcision reduced the risk of HIV infection in men having sex with men. Many at the consultation believed that such a finding would secure the practice of infant circumcision in the United States for decades to come, thus worth holding out for. The many studies on men having sex with men have overcome researcher expectation bias and failed to generate the results hoped for.

HIV transmission in other populations at high risk for HIV acquisition

The material presented in this section of the background document is appropriate.

Male circumcision and other health conditions

The material presented in this section of the background document is misleading. The medical literature does not support the claims that circumcision has a positive impact on the incidence or prevalence of penile, prostate, or cervical cancer. Likewise, it has no positive impact on the incidence of any of the sexually transmitted infections. It has no impact on the prevalence of any of the individual sexually transmitted infections, with the exception of syphilis, which fortunately is rare in the United States.[341] To mention these diseases and devote substantial discussion to them gives the false impression that circumcision in reality has an impact on these diseases.

Sexually transmitted infections (STIs)

The material presented in this section of the background document is biased, incomplete, and inaccurate.

This section is markedly incomplete. Instead of searching the medical literature, or even relying on recently published meta-analyses[185,342-345] as a starting point, this draft relies on non-systematic reviews/opinion pieces[20] and a meta-analysis that is over a decade old[24] as the source

of information. Consequently, the sections addressing the various sexually transmitted infections are woefully incomplete, inaccurate, and misleading. It has been over seven years since the CDC held a "consultation" on male circumcision[16] where it was decided to release recommendations concerning male circumcision. That should have provided enough time for their staff to search the medical literature, examine the data, and perform meta-analyses (although the only meta-analysis generated on the topic of male circumcision proved to have erroneous calculations requiring a three-page erratum in the *Journal of the American Medical Association*[25] [NOTE: The citation given in the CDC draft fails to include the reference to an extensive erratum published at: JAMA 2009; 301: 1126-9.] The summary effects odds ratio, when properly calculated, was 0.95. If the staff was going to rely on the work of others, they could have at least referenced the most up-to-date systematic reviews and meta-analyses. But several sexually transmitted infections, for which there are multiple studies in the medical literature, were nearly completely ignored, yet there are extensive discussions of chancroid, *Trichomoniasis vaginalis*, and the transfer of various infections to female partners, all based on a small number of studies. What explains such a low quality of scholarship? Laziness? Insufficient time? Preconceived bias? The CDC has had over 7 years to produce this draft, yet this response, written in less than 45 days, has more references and more detail covering ALL the evidence in the medical literature. Were there directives from leadership to present circumcision in the best light possible and to bury, ignore, or omit any studies to the contrary? Apparently, not out of the question. Given the poor quality of the effort to find (let alone evaluate) the evidence, how can this draft of the CDC be taken seriously by scientists, epidemiologists, or healthcare providers? This entire section needs to be scrapped, the evidence found and properly evaluated, and accurate information provided.

The statement, "Male circumcision has been shown to reduce the risk for some other STIs in addition to HIV," is factually inaccurate. The only STI that the medical literature may support as circumcision having a minimal reductive impact is in the prevalence of syphilis (see discussion below), but circumcision has not been shown to impact the incidence of syphilis. Consequently, the word "some" should be replaced with "possibly one."

It is clear that the writers of the CDC draft did not look carefully at, or critically evaluate, the sexually transmitted infection data from the African randomized clinical trials.[346-351] Even a cursory reading of the methodology of these trials would reveal that these trials made no attempt to minimize or provide any post hoc adjustment for lead-time bias. The men who were randomized to immediate circumcision were instructed to abstain from sexual relations or always use condoms for the first six weeks following the procedure to allow for proper healing. The data reported in these trials was: "number of infections per time of potential exposure." Since those in the intervention group each had six weeks less of potential exposure, one would expect them to have a smaller number of infections. Avoiding lead-time bias is a fundamental principle of study

design that is taught in the most rudimentary of courses on clinical study design. The fact that all three randomized clinical trials did not adjust for this bias, either in the study design or post hoc analysis, indicates either incompetence or a deliberate omission that would increase the likelihood of producing data favorable to circumcision. As will be shown in the sections below, adjusting for lead-time bias changes the outcomes of these studies. If one looks carefully at the prospective studies of genital human papillomavirus and male circumcision, the studies suffer from incomplete sampling to the point, as discussed below, that the treatment effect in these trials can be completely attributed to sampling bias.[352-354]

The statement, "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," while true, is misplaced hyperbole. As will be discussed in the sections below, the incidence and prevalence of none of the common sexually transmitted infections are impacted by circumcision. Only the prevalence of syphilis may be minimally impacted, but syphilis is very rare in the United States infecting only 9.8 per 100,000.[341] Consequently, the CDC draft is trying to jack up the importance of male circumcision through thinly veiled fear mongering, when the medical literature totally undercuts their message.

While the CDC draft discusses several of the sexually transmitted infections individually, it fails to address the impact of male circumcision on the overall risk of contracting a sexually transmitted infection of any type. In other words, the risk of any sexually transmitted infection versus no sexually transmitted infections. There have been 20 publications that have looked at the prevalence of any sexually transmitted infection by circumcision status, [9,10,14,248,260,271,275,355-368] and four prospective studies that have looked at the incidence of any sexually transmitted infection.[358,369-371] A meta-analysis of the studies of prevalence, in which the data in one study was stratified by race,[362] by number of life-time sexual partners in another,[9] and by the five populations in which data were collected in another,[260] yields a random-effects summary odds ratio (intact men versus circumcised men) of 0.86 (95%CI 0.74-1.01, between-study heterogeneity chi-square (df=26) = 303.00, p<.0001, I^2 = 91.1%). In the analysis, there was one clear outlier that reported an odds ratio of 1.51 (95%CI 1.41-1.62).[368] When this outlier is removed from the analysis, the between-study heterogeneity chi-square drops by 203.41, and the random-effects odds ratio is 0.82 (95%CI 0.74-0.92, I^2 = 73.9%).[185] This would indicate that when all sexually transmitted infections are considered together, circumcision significantly increases the risk of contracting a sexually transmitted infection. When the studies of incidence are stratified by study, the fixed-effect of the summary relative risk ratio is 0.91 (95%CI 0.78-1.07),[185] which, while not statistically significant, trends in the same direction of the studies of prevalence. **Therefore, an intact male is at lower overall risk of contracting a sexually transmitted infection.**

This finding should not be surprising as there have been several studies comparing the risk of genital discharge syndrome versus genital ulcerative disease by circumcision status,[12,185,265,372,373] which have been ignored in the CDC draft. Those studies on meta-analysis have found the risk of genital ulcerative disease versus genital discharge syndrome in intact men had a random-effects summary odds ratio of 2.24 (95%CI 1.63-2.24, between-study heterogeneity chi-square (df=4) = 17.94, p=.0013, I^2 = 72.1%)[185] Conversely, circumcised men would be twice as likely to have genital discharge syndrome versus genital ulcerative disease. Since genital discharge syndrome is far more common than genital ulcer disease, it makes sense that the ***overall*** risk of sexually transmitted infections may be **higher** in circumcised men. The data may not have been precisely collected in these studies, but they were not collected any less precisely than in the studies the CDC draft has elected to include.

This finding also makes sense on a biological level. Mucosal immunity is quite efficient in keeping invasive organisms at bay. By removing much of the penile mucosa and drying out the remaining mucosal surfaces, the natural immune system is disrupted. For example, the first line of defense on the mucosal surface are the dendritic (Langerhans) cells. With these cells removed by circumcision, the penis has fewer defenses against the garden-variety sexually transmitted infections, thus making them more prone, overall, to sexually transmitted infections. This may explain why, in a large prospective study, clearance of human papillomavirus occurred significantly more quickly in intact men than in circumcised men.[193]

Consequently, the recommendations for the intended audience of healthcare providers are biased, hyperbolic, and are missing essential information. Healthcare providers need to be told that **male circumcision may increase the overall risk of sexually transmitted infections.**

[Note: There are number of redundant citations in this section. For example, citations 74,75, and 76, are the same as citations 4, 5, and 6.]

<u>Genital Ulcer Disease (GUD)</u>

The only sentence under this heading is factually inaccurate and reflects a misinterpretation of the data. As will be discussed in the sections below, while GUD incidence was decreased in the only prospective studies to explore it,[347,350] the studies that looked at herpes simplex virus, after adjustment for lead-time bias, were not statistically significant.[347,350-352] It is not clear why this sentence fails to mention that the randomized clinical trials failed to find an association between circumcision and syphilis.[347,350] Is such an oversight because of a lack of attention to details or to give this section the proper pro-circumcision spin?

GUD (various types)

The material presented in this section of the background document is incomplete and confusing. One would expect the section to address GUD generally, but the discussion is quite specific about herpes simplex virus, which has its own subsection. The section fails to mention the 15 observational studies that have assessed the prevalence of genital ulcer disease by circumcision status.[12,15,261-263,269-272,374-378] When one of the studies with redundant data is excluded,[261] there is a positive association between having a foreskin and clinical presence of genital ulcers (random-effects summary odds ratio 1.60; 95%CI 1.34-1.92, between-study heterogeneity chi-square (df=13) = 31.09, p<.0001, I^2 = 66.8%).[185] Other meta-analyses have yielded similar results.[24,342]

The data from both of the prospective studies need to be adjusted for lead-time bias.[349,379] When the data are adjusted, the fixed-effect summary relative risk ratio is 1.62 (95%CI 1.27-2.07).[185]

Part of the reason ulcers are more commonly seen in intact men is that ulcers have a propensity for mucosal surfaces and mucocutaneous junctions. This is why cold sores are seen most commonly on the lips around the mouth, as this is a mucocutaneous junction. One could speculate that if the lips were surgically removed, the number of cold sore eruptions would also decrease. Similarly, the removal of much of the mucosal surface and the mucocutaneous junction from the penis may explain the decrease in prevalence.

Herpes Simplex Virus (HSV-2)

The material presented in this section of the background document is hyperbolic, incomplete, and misleading.

The authors of this section boast of "[c]ompelling evidence of the protective effect of HSV-2 acquisition from male circumcision is available from two of the three RCTs." The data from these studies tell a different story.[349,350,380] Two of the studies have results that were not statistically significant.[349,351] All three of these reports failed to adjust for lead-time bias. When the only study to show a statistically significant finding[350] is adjusted for lead-time bias, the difference is no longer statistically significant.[352] Even before making the adjustment for lead-time bias, the fragility index[235] for the study was 1, indicating that findings were not robust. The section fails to mention the cohort study by Dickson et al, which followed children from birth until 26 years of age and found no difference in herpes simplex type 2 virus serology (intact men versus circumcised men RR 0.99; 95%CI 0.49-2.00). When the data for the four prospective studies are combined (stratifying by study), the fixed-effect summary relative risk ratio (intact men versus circumcised men) is 1.23 (95%CI 1.04-1.46). When the data are adjusted for lead-time bias, the fixed-effect summary relative risk ratio is 1.15 (95%CI 0.97-1.36).[185] The large

impact on the summary relative risk ratio by a six-week adjustment to compensate for the lead-time bias suggests the data are neither robust nor "compelling."

Regarding observational studies, the CDC draft relies on a 1998 non-systematic review/opinion piece as a source of reliable information.[20] That "review" noted only six observational studies available at that time and was obviously missing several studies. The more recent 2006 review cited in the draft noted only 10 observational studies, but excluded two populations that had been reported previously[381] by the lead author of the review article.[24] Since this review was published, a study of 6187 men in India found that the seroprevalence for herpes simplex type 2 virus was significantly lower in intact men (OR 0.66; 95%CI 0.51-0.86).[382]

There have been 29 publications of observational studies addressing the association between genital herpes and circumcision status in men.[9,14,262,263,267,274,356,357,359-361,363,377,378,381-395] While one publication reported on four populations,[381] another stratified the data by age,[393] and another by country of origin.[363] When a meta-analysis is performed on these studies, the random-effects odds ratio is 1.18 (95%CI 0.998-1.39 , between-study heterogeneity chi-square (df=35) = 170.62 , $p < .0001$, $I^2 = 78.9\%$). The difference is not statistically significant.

Based on the data that currently appear in the medical literature, no position should be taken on the impact of male circumcision on the risk of infection with herpes simplex type 2 virus. The data are inconsistent, poorly collected, and meta-analyses do not show a significant difference.

Treponema pallidum (Syphilis)

The material presented in this section of the background document is also confusing as the authors refer to genital ulcer disease when this section should focus on syphilis. The 1998 non-systematic review/opinion piece[20] and the 2006 meta-analysis[24] cited in this section as the source for information on syphilis and male circumcision are out of date, and they do not come close to addressing the 29 observational studies in the medical literature that assess the association between the prevalence of syphilis and male circumcision status.
[8,9,260-263,267-269,271,273,356-358,360,362,374,376,377,382,384,396-402] One study looked at two populations[384] and one study was stratified by race.[362] A meta-analysis of these studies estimated the random-effects summary odds ratio (intact men versus circumcised men) to be 1.31 (95%CI 1.13-1.52, between-study heterogeneity chi-square (df=30) = 70.67, $p < .0001$, $I^2 = 56.1\%$). This is a drop in the summary odds ratio reported in the 2006 meta-analysis of 1.45.[24]

The incidence of syphilis in men not infected with HIV in Kenya and Uganda is 1.09 per 100 person-years, which is about the same incidence rate as HIV infections in the randomized clinical trials that were performed in those countries. The absolute risk reduction for a circumcised man

in this trial was 0.49 per 100 person-years at the ages when someone is most-likely to contract syphilis.[402] Given that the sexual transmission of syphilis is far more efficient than the rate of 1 infection in 1000 sexual encounters for HIV,[403] this would suggest that a substantial proportion of HIV infections are not spread through heterosexual contact alone.

The incidence of syphilis has been addressed in four studies.[349,350,358,402] In two of the studies, no adjustment was made for lead-time bias.[349,350] When the data are stratified by study, and adjusted for lead time bias, the fixed-effect relative risk ratio (intact men versus circumcised men is 1.09 (95%CI=0.82-1.45), and therefore, not statistically significant.

This section is little more than fear-mongering. The incidence of syphilis in men in the United States is low (9.8 per 100,000 in 2013).[341] Based on the prospective studies, there is no significant difference in the incidence of syphilis between intact and circumcised men.

Haemophilus ducreyi (Chancroid)

The material presented in this section of the background document is inaccurate and misinterpreted. The CDC draft cites a meta-analysis of six studies looking at chancroid, which found circumcised men had a reduced relative risk.[24] If the authors of this draft had looked at the meta-analysis, they would have found that three of the six studies included in their analysis did not assess chancroid directly[265,266,374] and nearly all of the between-study heterogeneity could be attributed to a single study.[404]

Weiss et al.[24] included several studies in their meta-analysis that were not strictly studies of chancroid and did not meet basic inclusion criteria because they lacked a direct comparison between intact and circumcised men for a specific diagnosis of chancroid.[265,266,374] In two studies, men with genital ulcers were not tested for chancroid but merely *presumed* to have chancroid.[265,266] In the third study, 31.4% had herpes simplex virus type 2 and only 22.9% had a positive culture for *Haemophilus ducreyi*.[374] Some of the remaining studies are now quite dated having been published in 1934,[397] 1949,[396] and 1975.[404] When the remaining studies of chancroid are included,[263,264,396,397,404] and the results of the study by Hand[396] are stratified by race, meta-analysis yields a random-effects summary odds ratio of intact men versus circumcised men of 1.33 (95%CI 0.52-1.33).[185] How much weight to give to these findings needs to be tempered by the high degree of between-study heterogeneity (chi-square (df=5) = 59.71, p<.0001, I^2 = 91.4%), the reliability of the clinical diagnosis in several of the studies, and the age of the studies. With the current data, it is not possible to say conclusively that circumcision has an impact on genital infections with *Haemophilus ducreyi*. It is not clear why this was included in the CDC draft when it does not really apply in the United States as chancroid is extremely rare, and the evidence gathered to date is of such poor quality.

Other STIs.

The material presented in this section of the background document is misleading. While randomized clinical trials in Africa reported a reduction in high risk HPV infections following circumcision, nearly all of this perceived reduction can be attributed to the researchers selective sampling practices.[352-354] This will be discussed further in the section below.

Human Papilloma Virus (HPV)

The material presented in this section of the background document is riddled with factual errors, is incomplete, and is a misinterpretation of the medical literature.

The statement, "Penile squamous carcinoma (caused by carcinogenic HPV subtypes) has been strongly and consistently associated with lack of male circumcision," is supported by a citation of a non-systematic review/opinion piece written by authors with a known pro-circumcision bias.[20] As will be discussed below, the medical literature does not support this statement, and the writers of the CDC draft should not rely on opinion pieces as though they are evidence-based citations.

The statement, "Cervical cancer has been associated with lack of circumcision in male partners of women in several case-control studies," can easily be demonstrated to be false. As discussed below, there are 16 studies that have looked for an association between cervical cancer and the circumcision status of a woman's male sexual partner and none have found a statistically significant association. The citation given for this statement also did not find a statistically significant association.[405] To be factually accurate and reflect the information that is currently available in the medical literature, this statement should read: "A significant association between cervical cancer and the lack of circumcision in male partners of women has never been demonstrated despite evaluation of this association in multiple case-control studies."

The CDC draft relies on a 1998 non-systematic review/opinion piece[20] as its source of information on genital warts, which noted only three studies had been published. To date, there have been 15 observational studies in 14 publications that have assessed the prevalence of genital warts in men based on their circumcision status.[14,263,356,357,360,361,394,398,406-409] When a meta-analysis is performed on these studies, the random-effects summary odds ratio (intact men versus circumcised men) is 0.82 (95%CI 0.65-1.04, between-study heterogeneity chi-square (df=14) = 37.07 , p=.0007 , I^2 = 59.5%).[185] This indicates that there may be a trend indicating that circumcised men are at greater risk for genital warts. When only studies assessing general populations are evaluated, the between-study heterogeneity is not statistically significant (chi-

square (df=6) = 8.61, p=.1969, I^2 = 18.7%), which is rarely seen in studies of sexually transmitted infections and male circumcision status, and the random-effects summary odds ratio is 0.78 (95%CI 0.63-0.96), a statistically significant difference.[185] These studies noted that genital warts in circumcised men were more likely to be found on the penile shaft.[356] Why would the writers of the CDC draft rely on a non-systematic review/opinion piece[20] that is 16 years old as a source of its information when several systematic reviews have addressed this topic more recently?[24,185,342] Was the goal of the CDC draft to be out of date and incomplete, or just to make headlines assuming no one would read the draft and see through the cover-up?

The CDC draft makes no mention of the 20 observational studies that have assessed the prevalence rates of genital HPV infection in men based on circumcision status,[355,405,406,410-426] or the three meta-analyses that have looked at these studies.[185,343-345] The draft may have avoided discussion of these studies because the results of several of the studies were biased by either sampling bias,[412] misclassification bias,[410,422,423] or both.[405] The type of HPV also varied from study to study with some reporting all HPV types, others only HPV types known to be carcinogenic/oncogenic, and other studies reporting their findings by all types, non-oncogenic and oncogenic.[414,416,418,419,426] It should also be noted that most genital HPV infections are transient and clear spontaneously.

Misclassification bias occurred in the studies where researchers relied on men to properly identify their circumcision status, but the men did so incorrectly. The most egregious example of this is the study by Lajous et al. out of Mexico in which 95 men reported being circumcised yet only 8.3% of them were noted to be circumcised on physical examination.[410] While the authors of this study had determined the circumcision status of the study participants based on physical examination, they reported their results based on the circumcision status as reported by the men. In effect, the study demonstrated that HPV risk was lower in men who thought they were circumcised rather than whether they were actually circumcised or not. The results using physical examination to determine circumcision status were not provided.[427] Evaluating all of the studies of prevalence using meta-regression[324] has demonstrated that studies that relied on patient report to determine circumcision status consistently and systematically significantly overestimated the association between having a foreskin and genital HPV.[185,343]

The impact of sampling bias is more easily quantified. Sampling bias occurs when only selected portions of the genitals are sampled for the presence of HPV. Selective sampling would not be a problem if doing so provided similar results to comprehensive sampling. For HPV on the male genitals, however, this is not the case. Several studies have shown that circumcised men who have HPV somewhere on their genitals are more likely to harbor the virus on the shaft of the penis.[355,411,415,420,426,428] Other studies have shown that genital warts are more likely to be found on the shaft of the penis in circumcised men as compared to the glans in intact men.[429] Two

studies out of the University of Washington found that, if only the glans is sampled, 45 to 47% of circumcised men with genital HPV will be detected.[365,429] In contrast, sampling only the glans of intact men will identify 65 to 66% of intact men who have HPV on their genitals. As a consequence, sampling only the glans of the penis will miss more HPV infections in circumcised men than it will in intact men. If the numbers from Van Buskirk et al.[428] are correct, the number of intact men expected to be infected with HPV infection would be the number of men identified by sampling only the glans increased by a factor of 1.514. Similarly, for the men who underwent circumcision, the number identified in the trial would be increased by a factor of 2.212. When an analysis of the entire medical literature is performed using meta-regression,[185,343] studies that sampled only the glans were demonstrated to have stronger associations between having a foreskin and having HPV infections. This finding was statistically significant, suggesting that sampling only the glans of the penis consistently overestimates the association between having a foreskin and genital HPV.

An added wrinkle to the finding that circumcised men are more prone to have HPV lesions on the shaft of their penis is that the penile shaft is the portion of the penis with the highest viral loads and the preferred location for HPV-16, which is the most oncogenic HPV type.[430] This would suggest that circumcised men might be more likely to pass HPV-16 to their sexual partners, thereby leading to an increase in cervical cancer.

The dilemma is: what to do with studies containing these obvious methodological flaws, which will have a significant impact on the odds ratios reported by these studies. One approach would be to adjust for these factors by adjusting the odds ratios in studies with sampling bias. Another, would be to adjust using meta-regression. And, the last would be to exclude studies with these methodological problems when performing a meta-analysis.

Twenty publications reported prevalence data on 25 separate populations. Five of these studies provided data on any type of HPV being isolated, as well as high risk HPV . Since high-risk HPV is of more clinical interest, these data were used in the meta-analysis with a random-effects summary odds ratio (intact men versus circumcised men) of 1.16 (95%CI 0.94-1.45, between-study heterogeneity chi-square (df=24) = 45.27, p = .0054, I^2 = 44.7%), which was not statistically significantly different.[185] This analysis included studies that were known to have either sampling bias or misclassification bias for which no adjustment was made. When adjusted for sampling bias using meta-regression, the random-effects summary odds ratio was 1.10 (95%CI=0.88-1.37). For studies that sampled only the glans, the random-effects summary odds ratio is much greater (OR=1.86, 0.99-3.46). When adjusted for misclassification bias using meta-regression, studies that relied on physical examination to determine circumcision status had a random-effects summary odds ratio of 1.08 (95%CI=0.88-1.32), which was not statistically significant. Studies that relied on patient report had a much greater random-effects summary

odds ratio (OR=2.16, 95%CI=1.18-3.99). When studies with known sampling bias or misclassification bias were excluded, the random-effects summary odds ratio was 1.01 (95%CI 0.80-1.28, between-study heterogeneity chi-square (df=15) = 28.82, p = .0164, I^2 = 44.5%).[185] This indicates that observational studies not tainted with methodological flaws have failed to establish an association between genital HPV infection prevalence and circumcision status in men. Is this lack of association why the CDC ignored these 20 publications?

There have been eight prospective studies that looked at the incidence of HPV infection in men by circumcision status,[193,348,350,410,428,431-433] but this CDC draft only mentions two of them. The two studies identified in the CDC draft are also the only two studies to find a statistically significant difference, the only two studies to find the greatest treatment effect (relative risk ratios of 1.51 and 1.54, with next highest being 1.19,[433] and the only two studies that reported only the results of samples taken from the glans without including samples taken from the penile shaft.[348,350] Clearly, the results of these two outlying studies were impacted by sampling bias. For example, in the Ugandan trial,[350] when an adjustment for sampling bias is made, the relative risk ratio (intact men versus circumcised men) was reduced from 1.54 (95%CI 1.11-2.17) to 1.09 (95CI 0.83-1.43), with the difference no longer being statistically significant. As a consequence, the difference in incidence between intact and circumcised men reported by the Johns Hopkins team can be completely explained by their failure to sample beyond the glans of the penis.[352] Likewise, in the South African trial,[413(CDC9)] adjusting for sampling bias reduces the relative risk ratio from 1.51 (95%CI=1.17–1.97) to 1.06 (95%CI=0.88-1.29), with the difference no longer being statistically significant.[353] These studies also failed to adjust for lead-time bias. When adjusting for both sampling bias and lead time bias, the relative risk reduction in the Ugandan trial would be 0.96 (95%CI 0.73-1.26) and in the South African trial 0.99 (95%CI 0.82-1.21).

The story on sampling bias, however, goes deeper. In 2007, researchers from Johns Hopkins reported at the beginning of their randomized clinical trial that, “Two subpreputial and shaft swabs were also obtained for future testing of human papillomavirus infection.”[3] However, in the 2009 report of their findings, only the results from swabbing the glans were reported. The results from swabbing the shaft of the penis were not included in their report.[350] In 2011, the same team reported the results of HPV cultures from the glans *and* the penile shaft collected at the 12 month follow-up visit of the randomized clinical controlled trial participants.[434] It remains unclear why the researchers from Johns Hopkins would selectively report the results in this fashion, especially given the fact that Weaver at al. had published their findings of a differential in HPV acquisition based on the site of sampling on male genitals in 2004.[429]

When the prospective data are stratified by study, the fixed-effect summary relative risk ratio is 1.05 (95%CI 0.88-1.25), which indicates that circumcision has no effect on the incidence of

genital HPV infections in men. When the Ugandan and South African data, which account for nearly all of the between-study heterogeneity, are corrected for sampling bias and lead-time bias, the summary relative risk reduction is 0.97 (95%CI 0.91-1.04).

The CDC draft must include the results of the "*HPV Infection in Men*" (HIM) study: a prospective study of HPV in men that looked at the risk of new HPV infections by circumcision status.[193] This study was to be the ultimate prospective cohort study on the topic. Preliminary reports from the study appeared in such high-profile journals as the *International Journal of Cancer* and *The Lancet*.[414,435] The study included 4033 participants aged 18 to 70 years. In the study, they sampled the glans, the penile shaft, and the scrotum. Men were evaluated every six months for a median of 17.5 months. Participants came from Florida, Mexico, and Brazil, and the results were stratified by country of origin. The hazard ratio for oncogenic HPV was 0.90 (95%CI%=0.76–1.06) indicating a non-significant trend for circumcised men to have a higher incidence overall of HPV infections. No difference was seen for HPV-16. HPV of any type, oncogenic HPV, and HPV-16, cleared significantly more quickly from the intact penis then the circumcised penis (any HPV: hazard ratio (HR) 0.85; 95%CI 0.80-0.91, oncogenic HPV: HR 0.83; 95%CI 0.75-0.92, HPV-16: HR 0.56; 95%CI 0.42-0.75).[193] This significantly faster clearance of HPV from the intact penis is the opposite finding seen in other smaller studies.[370,432,436-438]

Two additional comments:

First, the study by Castellsequé et al. combined the data from seven studies in five countries on three continents.[405] Analysis of the data from this study presented several statistical challenges that the authors of the study did not correctly deal with, and the editors of the *New England Journal of Medicine* let slide by. The challenge was the small number of circumcised men in four of the five countries and a small number of intact men in the fifth country. In order for asymptotic statistical methods, which rely on the assumption that values follow a normal distribution, to provide accurate results there needs to be more than 5 (some say more than 10) subjects who conform to each classification. Of the twenty classifications (five countries by 4 outcomes), seven have 5 or fewer subjects in them. The authors used asymptotic statistical methods, even though this would not yield valid results. They should have used exact statistical methods instead. In other words, the small number of circumcised men in Brazil, Columbia, Spain, and Thailand, and the small number of intact men in the Philippines made for an unstable statistical model. Furthermore, it renders stratified analysis nearly impossible, if the analysis wants to control for the country from which the data was collected. For example, if the prevalence is much greater in one country that has a very low circumcision rate, results may be attributed to circumcision that should instead be attributed to the country of origin.

Second, the data from the randomized trial in Kisumu, Kenya has never been clearly presented. In 2012, Bailey and Moses's group published the results of their data on high-risk HPV, but they did not report the number of circumcised men or intact men who became infected with high-risk HPV. Instead, they reported that intact men developed more flat lesions that were more likely to harbor high-risk HPV.[439] On the face of it, and from the title of their publication, it may sound as though intact men were at greater risk for an infection with high-risk HPV, but this is not the case. While intact men were at greater risk for flat lesions, circumcised men were at greater risk for papular and pearly lesions. While the papular and pearly lesions are less likely to harbor high-risk HPV, they are much more common than the flat lesions and more common in circumcised men. For example, 33 men in the study had flat lesions, while 133 and 187 men had papular and pearly lesions, respectively. Of the men with flat lesions, one was circumcised and 32 were intact. Of the flat lesions 22 were found to harbor high-risk HPV. Papular lesions were found in 91 circumcised men and 42 intact men. Of the 133 papular lesions, 28 harbored high-risk HPV. Pearly lesions were found in 112 circumcised men and 75 intact men. Of the 187 pearly lesions, 49 harbored high-risk HPV. Based on these numbers, one can back-calculate and estimate the number of men expected to have been infected with high-risk HPV based on circumcision status. Considering there were 124 intact men and 151 circumcised men, the odds ratio was 1.45 (95%CI=0.89-2.38), a difference that is not statistically significant. This should not be a surprise as this study sampled both the glans and penile shaft of the study participants and reported the results on all of the samples they collected. It is not clear why the straight-forward number of intact and circumcised men who became infected with high-risk HPV has never been revealed publicly.

The CDC has placed its entire wager behind two outlier studies with serious methodological flaws whose results are not consistent with the rest of the medical literature. The analysis is incomplete, biased, and misinterpreted the small fraction of the data in the medical literature that the CDC considered.

Trichomonas vaginalis

The material presented in this section of the background document does not contribute adequately to the discussion to even merit inclusion. The entire section could be tersely reduced to one sentence: The impact of circumcision on trichomoniasis in men and their female sexual partners has received limited study with conflicting results.[346,347,440] There are no studies outside of Africa by which to gauge the importance of these infections.

In reporting the results by Mehta et al.,[347] the writers of the draft give results of the "as-treated" analysis as being statistically significant and the "intention-to-treat" results as having "borderline statistical significance." The standard is to report only intention-to-treat results. Doing otherwise

undermines the whole purpose of a randomized trial. Crossover, which in these trials would entail men randomized to be circumcised not undergoing the procedure and men randomized to not be circumcised undergoing the procedure, does not in most cases happen randomly. By reporting the as-treated results, the writers of the CDC draft knowingly reported potentially biased results. While they may believe they are justified in doing so because it furthers their cause of promoting circumcision, they should know better on an epidemiological level. Intention-to-treat analysis may be more conservative in estimating treatment effects, but it does not introduce the bias of differential crossover and it is more reflective of the reality of patient non-compliance. The writers should also know better than to use the phrase "borderline statistical significance." This phrase is similar to being "kind of pregnant." While the statistical significance has been somewhat arbitrarily set at a p-value of .05 by Ronald A. Fisher, it is the standard everyone abides by. In this case statement, the as-treated results should not have been presented, and the intention-to-treat results should have been described as showing a trend that is not statistically significant. Once again, the writers of this draft are either improperly trained in statistics and epidemiology, or they are trying to promote circumcision unjustifiably. These epidemiologically inappropriate phrases were used by the authors of the studies in an effort to spin their results in the most favorable fashion. The fact that writers of the CDC draft accepted this language without question also indicates that they did not read these studies carefully enough to properly evaluate the methodology and data generated in order to develop their own conclusions. The CDC had over seven years to carefully read the small percentage of studies in the medical literature they decided to include in this draft. This should have taken a matter of weeks. What did the CDC with the rest of the time?

Chlamydia trachomatis

The material presented in this section of the background document is very confusing. It is not clear if the authors of this section were purposely being obtuse. The statement that "chlamydial infection in men was often diagnosed syndromically as 'non-gonococcal urethritis,' after exclusion of gonorrhea by Gram stain" is an oversimplification. Several studies collected data on both chlamydia and non-specific urethritis,[9,263,355-357,359-361] which, in the era of testing for both chlamydia and gonorrhea, is its own entity. This section would be best if divided up into sections of 1) genital discharge syndrome, 2) non-specific urethritis, and 3) *Chlamydia trachomatis*.

Several studies examined the association between circumcision status and the prevalence of genital discharge syndrome, which includes any genital infection that results in an urethral discharge, such as gonorrhea, chlamydia, and non-specific urethritis. The CDC draft makes no mention of the studies that assessed men for genital discharge syndrome except to mention the single study that looked at its incidence in Table 2. The draft fails to mention the eleven studies that have compared the prevalence of genital discharge syndrome in men by circumcision status.

[12,248,261-263,269-271,375-377,442] When the results of these studies are combined in a meta-analysis, the random-effects summary odds ratio (intact men versus circumcised men) shows a trend toward genital discharge syndrome being more common in circumcised men (summary OR 0.92; 95%CI 0.78-1.09, between-study heterogeneity chi-square (df=10) = 52.13, $p < .0001$, $I^2 = 78.9\%$). It is not clear why the CDC draft failed to consider this information.

The one study that measured incidence failed to adjust for lead-time bias.[350] When this adjustment is made, the relative risk ratio (intact men versus circumcised men) is reduced from 1.11 (95%CI 0.77-1.61) to 0.98 (95%CI 0.68-1.42).

The CDC draft relies on a 1998 non-systematic review/opinion piece for its information on non-specific urethritis and tallies the results of the studies rather than performs a meta-analysis.[20] A systematic review of the medical literature will uncover 12 studies on the prevalence of non-specific urethritis.[9,263,266,355,357,359-361,363,383,398,442] When the data from these studies are combined in a meta-analysis, the random-effects summary odds ratio (intact men versus circumcised men) is 0.76 (95%CI 0.63-0.92, between-study heterogeneity chi-square (df=11) = 39.78, $p<.0001$, $I^2 = 69.8\%$.)[185][353] This result indicates that circumcised men are at a statistically *significantly increased* risk for non-specific urethritis.

This section on *Chlamydia trachomatis* makes no mention of the 16 observational studies that looked for an association between prevalence of Chlamydia and circumcision status in men.[9,14,263,355-361,364,369,377,443-445] If one of the studies that presented redundant data is excluded,[261] the random-effects summary odds ratio for these studies (intact men versus circumcised men) is 0.94 (95%CI 0.76-1.17, between-study heterogeneity chi-square (df=14) = 36.16, $p=.0010$, $I^2 = 58.5\%$). It is unclear what harm there would be in the CDC reporting these results, except that the meta-analysis indicates a non-significant trend that circumcised men are at greater risk for Chlamydia.

There have been three studies published, which looked at the incidence of Chlamydia by circumcision status in men.[346,347,358] The two studies identified by the CDC failed to correct for lead-time bias. The fixed-effect summary relative risk ratio for the three studies (intact men versus circumcised men) is 1.26 (95%CI 1.02-1.57); however, when the two studies are adjusted for lead-time bias the result is no longer statistically significant (RR 1.19; 95%CI 0.96-1.49).[185]

The CDC did not make the effort to gather or properly interpret the evidence that is currently available in the medical literature. Instead, it wasted its time and space giving the details of the two conflicting studies regarding the risk of Chlamydia in women based on the circumcision status of their regular male partner.[446,447] The conclusion that would be most accurate and helpful for the intended audience of healthcare providers is that circumcision may increase the likelihood

of urethritis, including Chlamydia and non-specific urethritis.

Neisseria gonorrhea

The material presented in this section of the background document is woefully out of date and incomplete. The CDC draft cites a 1998 non-systematic review article as the source of its material,[20] which notes that five of seven observational studies list a statistically significant decrease in gonorrhea prevalence in circumcised men. This review was incomplete at the time it was published. There have been 24 studies that have assessed the association between circumcision status and gonococcal infections.[9,14,261-263,267,268,355-363,377,383,396-398,441-445] Two of the studies presented redundant data[261,262] and only four had associations that were statistically significant.[267,356,360,446] But a tally of positive studies, a much used rhetorical device,[20,31] is not the proper method of determining the overall findings in the medical literature. When one of the redundant studies is excluded,[261] the data reported by Hand[396] and Schrek[362] are stratified by race and the data reported by Laumann et al.[9] are stratified by the number of lifetime sexual partners, the random-effects summary odds ratio of intact men versus circumcised men was 1.03 (95%CI 0.88-1.21, between-study heterogeneity chi-square (df=27) = 95.97, p<.0001, I^2 = 70.8%). Since an odds ratio is 1.00 when two groups have identical risks, there is no difference in the risk of gonorrhea based on circumcision status.

This holds up in studies on the incidence of gonorrhea. Three studies have looked at this issue.[346,347,358] Two of them suffered from lead-time bias.[346,347] None of them found a statistically significant difference. The fixed-effect summary relative risk ratio (intact men versus circumcised men) for the three studies was 1.10 (95%CI 0.91-1.34). When the two studies with lead-time bias are adjusted for, the summary relative risk ratio is 1.04 (95%CI 0.86-1.27).[185]

The data from the medical literature clearly demonstrates that circumcision does not impact the risk of gonorrhea.

Based on what is presented in the CDC draft, the authors of this draft are either incompetent reviewers of the medical literature or are purposely trying to deceive the public and their intended audience of healthcare professionals. Reliance on a non-systematic review that is little more than an opinion piece, in which only seven observational studies were identified, when a simple PUBMED search would have quickly identified many of the 23 observational studies and two systematic reviews with meta-analyses,[185,342] is inexcusable. Is this just willful incompetence, or is there an institutional directive to misrepresent the evidence in the medical literature?

Penile and prostate cancers

The material presented in this section of the background document is incomplete, misleading, and contains inappropriate citations.

Penile cancer is extremely rare (0.6 to 0.8 per 100,000 person years), less common than breast cancer in men. In the United States, the incidence of penile cancer occurs at rates that are similar to or lower than rates in other developed countries where circumcision is rarely practiced, such as in Japan, Germany, Iceland, Spain, Sweden, Switzerland, United Kingdom, Yugoslavia,[448] Denmark,[448,449] Finland,[448,450] and Norway.[448,451] Also, as the percentage of circumcised septuagenarian and octogenarian men has increased, there has been no corresponding decrease in the incidence of penile cancer in the United States. Both of these findings suggest that, on a population level, circumcision has little or no impact on penile cancer. This information needs to be included in the CDC draft discussion.

The discussions of any case series or reviews of case series should be excluded[452,453] because, without control groups and with a changing prevalence of circumcision in men at the age at which penile cancer is likely to occur, the numbers from these publications have little or no epidemiological value. [Please note that reference CDC121 lists the wrong study. Instead of Schoen EJ, Colby CJ, Ray GT. Newborn circumcision decreases incidence and cost of urinary tract infections during the first year of life. Pediatrics 2000; 105: 789-93, the citation should be to: Schoen EJ, Oehrli M, Colby CJ, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics 2000; 105(3): e36.] While the CDC draft focuses on one case-control study.[454] it should also include the results of the other two case control studies.[408,455]

The study by Maden et al. found that men who had never been circumcised were at about three times greater risk for penile cancer (OR 3.04; 95%CI 1.79-5.15), while intact men with pathologic phimosis were at six times greater risk (OR 6.23; 95%CI 3.18-12.19).[455] But, when the control group is age adjusted, the findings are less spectacular and not statistically significant (OR 1.19; 95%CI 0.77-1.85). This study did not adjust for phimosis in its analysis. A case-control study by Tseng et al.[408][440] yielded similar results to that of Daling et al.[454] For Tseng et al., the presence of phimosis increased the risk of penile cancer 16-fold. When adjusted for phimosis, lack of neonatal circumcision was not a significant risk factor.[408] All three studies emphasize that phimosis, rather than neonatal circumcision, is the more important risk factor. Half of the cases of invasive penile cancer can be attributed to oncogenic HPV viruses.[456] As is discussed elsewhere in this response, there is no significant association between circumcision and carriage of oncogenic HPV. The link between phimosis and penile cancer may be balanitis xerotica obliterans, the most common cause of pathologic phimosis with a cumulative incidence of 0.6% by 15 years of age,[457] which is increasingly being recognized as a precancerous

condition.[458-471] Consequently, the focus should be shifted to efforts that minimize infections with oncogenic HPV (such as use of condoms and use of the HPV vaccines) and early recognition and treatment of balanitis xerotica obliterans.

The section should also include a realistic discussion of the risk of penile cancer. For example, the 2012 American Academy of Pediatric Task Force on Circumcision noted that the incidence of penile cancer was 0.58 per 100,000 *person-years*.[40] Using this incidence for penile cancer in the United States, the lifetime risk (average life span 72 years) would be 0.000417512, or a lifetime risk of 1 in 2395. The Task Force report noted that the relative risk reduction for penile cancer by circumcision was between 1.5 and 2.3. If you take the lifetime risk of penile cancer and reduce this incidence rate by a factor of 2.3, the result, 0.0001815, would be the expected lifetime risk for penile cancer in circumcised men. The absolute risk reduction would be the difference between the two rates: 0.0004176 minus 0.0001815 or 0.0002360, so the number needed to treat would be 4237. If, however, the relative risk reduction is 1.5, the number needed to treat is 7184. If it takes 7184 circumcisions to prevent one case of penile cancer and each circumcision costs an average of $285 paid at the time of the procedure,[472] the cost to avoid one case of cancer is $2,047,440. However, the money for the circumcision was spent at the time the male was circumcised not at the time the male developed penile cancer, which is usually around 80 years of age. Therefore, for 80 years, the opportunity of having that cash available, which was spent at the time of the procedure, has been lost. If that money was put out at 3% interest for 80 years, the opportunity costs would be $21,786,584. If the money were to earn 5% interest for 80 years, the cost of preventing one case of penile cancer would be$101,474,076. This is the true cost of preventing one case of penile cancer. Obviously, neonatal circumcision to prevent penile cancer is NOT cost-effective nor justifiable from a public health standpoint.

The discussion of circumcision and prostate cancer should be deleted. The argument put forth by the writers of the CDC draft borrows from that proposed by Morris and colleagues,[473] which is based on several tenuous assumptions. The first is that the risk of prostate cancer is increased by sexually transmitted infections. As the writers of the CDC draft note, the medical literature on this point is mixed, showing populations at low risk for sexually transmitted infections being sometimes at greater risk for development of prostate cancer.[474] Even if one accepts this contentious assumption, one would need to demonstrate that circumcised men are at lower risk of sexually transmitted infections. Instead, the medical literature indicates circumcised males are at an overall greater risk of sexually transmitted infections. Since a single infectious agent has not been identified as being associated with a greater risk of prostate cancer, it is more likely that infectious agents associated with urethritis would impact the health of the prostate. Urethritis is not reduced, and may be increased, with circumcision.

The CDC draft mentions only one observational case-control study, of the many that have been

published, on the topic of prostate cancer as associated with circumcision.[475] The writers of the CDC draft fail to mention several important aspects of this study. Circumcision status was determined by self report, which is known to be notoriously inaccurate. The study did not find a significant association between prostate cancer and a history of sexually transmitted infections (OR 1.05; 95%CI 0.87-1.27), which undermines their working hypothesis. The adjusted odds ratio for the risk of prostate cancer (circumcised versus intact men) reported in the body of the study was 0.87 (95%CI 0.74-1.02), which was not statistically significant. Therefore, as a whole, this study does not support their contention. Other concerns about the validity of this study have been raised.[476]

Isolating the impact of circumcision on the risk of prostate cancer has been difficult. For example, race and ethnicity are important factors. When compared to controls with benign prostatic hypertrophy, circumcised non-Jews had a significantly greater risk of prostate cancer than Jews (OR 3.23; 95% CI 1.56–6.69). This would indicate that race/ethnicity are more important than circumcision.[477] A British study failed to consider race or ethnicity, so circumcision status may have been a marker of race and/or socioeconomic status.[478] In an American study, there was an interaction between race and circumcision status.[479] When Jews are excluded, several studies have failed to find a significant association between circumcision status and prostate cancer.[480,481] Also, no association has been demonstrated between circumcision status and PSA levels.[482] On a population level, if circumcision decreased the risk of prostate cancer, one would expect as the circumcision prevalence increased in the United States, the incidence of prostate cancer would decrease, but the opposite has occurred.[483] One would also expect the age-adjusted incidence of prostate cancer in European countries to be higher than that in the United States, but it is lower in Denmark, Finland, Iceland, Norway, and Sweden,[484] as compared to the United States.[483]

Several of the studies relied on patient report to determine circumcision status[475,478,479] and failed to adjust for risk factors known to influence prostate cancer risk. The combination of poorly executed studies, along with an unproven theory linking prostate cancer to sexually transmitted infections, the lack of evidence linking sexually transmitted infections to circumcision status, and the lack of evidence linking circumcision to prostate cancer on a population level should have indicated to the writers of the CDC draft that this topic was not worthy of inclusion in the draft.

In summary, penile cancer is very rare, more rare than male breast cancer, and its link to neonatal circumcision, based on recent studies, is tenuous. An evidence-based discussion of circumcision should not include any discussion of prostate cancer.

Cervical cancer in female partners of circumcised men

The material presented in this section of the background document is limited to one select substrata of a single study.[405] The study from which this substrata was extracted did not properly analyze the data. The data were collected in studies from five different countries, yet were not stratified by country. In four of the countries, only a small number of men were circumcised. In the fifth country, only a small number of men were not circumcised. Since cervical cancer rates can vary by geography, it is important to stratify the data by geography. The analysis in this study failed to do this. If they had performed the analysis properly, this selected substrata when further stratified by geography would have necessitated the use of exact statistics, which the authors of the study did not use. Exact statistics revealed much wider confidence intervals. Even with the stratification they performed (monogamous women with male partner with 6 or more lifetime sexual partners), it is interesting to note that the raw numbers found little or no difference (OR 1.02; 0.71-1.47). Furthermore, with reporting the results of the selected substrata the finding should have been subjected to a Bonferroni adjustment, but was not. By doing so, the threshold p-value would be divided by 3. Consequently, this statement is based on evidence that was misinterpreted.

This section also exhibits significant omissions that are critical for the intended audience of clinicians. The single study cited in the background document on this topic did not find a statistically significant association between cervical cancer in women and the circumcision status of their male sexual partners.[405] There have been 15 other studies that have reported on the association between cervical cancer and the circumcision status of a woman's male sexual partner. None of them found an association that was statistically significant.[405,485-499] (One study reported a p-value of .045,[495] but this was not properly calculated. Using Fisher's two-sided exact test, the p-value is .0733.

The CDC has focused on a substrata of one of 16 studies while ignoring the other 15 studies in order to find a statement that supported their conclusion. This is a clear case of confirmation bias.

Urinary tract infections in male infants

The material presented in this section of the background document is overly optimistic and misinterpreted. The data on which the report relies have been extracted from observational studies that contain a number of methodological flaws that make it difficult to ascertain whether urinary tract infections were properly diagnosed in these studies. For example, many studies use only bacteriuria as a diagnostic criteria, which would include the 1% of children who, at any given time, will have asymptomatic bacteriuria. To properly make the diagnosis of urinary tract infection, there must be evidence of inflammation.[500] Similarly, urine specimens collected in bags placed over the genitals are often used to screen for urinary tract infection. This method has

a high false positive rate, especially in girls and normal boys, with a contamination rate of 65% to 70%.[501-503] This may lead to an oversampling of intact boys. There may also be a differential in health care seeking behaviors.[504] For example, Hispanic boys, who are more likely to have normal genitals, seek health care more frequently,[505] and therefore are more likely to be diagnosed, often incorrectly, with a urinary tract infection.

The reference to the 1987 study of US Army hospitals worldwide[506] that noted an increase in the total number of urinary tract infections as the circumcision rate declined overlooks the fact that the data collected by the authors were not consistent over time.[507] For example, the rate of diagnosing urinary tract infection decreased significantly from 0.16% in the first three years of the study to 0.07% in the last three years of the study. (RR 0.462; 95%CI 0.338-0.633).[504] The yearly rates of urinary tract infections in circumcised boys ranged from 0.07% to 0.23%, which the authors characterized as being "relatively consistent."[506] The rate of urinary tract infections in boys with normal genitals increased from 0.87% to 1.09% between the two time spans (OR 1.25; 95%CI 0.96-1.61). The association between circumcision and urinary tract infection was not consistent over time. The odds ratio for intact boys being diagnosed with a urinary tract infection in the first three years of the study was 5.51 (95%CI 4.08-7.44) and in the last three years of the study was 14.91 (95%CI 10.48-21.21). Both of these estimates are outside the 95% confidence interval for the odds ratio estimated for the entire time span of the study (8.69-12.15). This undermines the internal validity of the study.[507]

Several studies suffered from misclassification bias in that the circumcision status could not be correctly identified.[508,509] The studies generated from the database of US Army hospitals worldwide also made no attempt to determine if there was the possibility of misclassification bias. In a chart review performed by the Centers for Disease Control, 15.7% of the boys circumcised neonatally did not have it documented on the hospital chart's face sheet, which is the source of database information.[6] In the US Army studies, if 15% of the boys circumcised did not have it documented on the face sheet, as many as 78.1% of the boys thought to be intact may have actually been circumcised. If one adjusts for this possible non-differential misclassification, the US Army data from 1974 to 1983 would yield an odds ratio (intact males versus circumcised males) of 4.13 (95%CI 3.34-5.11), while the data from 1984-88 would yield an odds ratio of 4.07 (95%CI 3.28-5.05). These odds ratios are more in line with those estimated in other studies.

One model has been published that estimated the impact of confounding on the association between circumcision and urinary tract infections. If one begins with the assumption that the rate of true urinary traction infections is the same in intact and circumcised boys, modeling of confounding factors — such as frequency of medical visits, likelihood of collecting a urine sample, urine collection method, et cetera — will result in making a diagnosis of urinary tract infection (a combination of true positives and false positives) 4.27 times more frequently in

intact boys.[510] Consequently, the associations that have been measured between circumcision and urinary tract infection may have been largely the result of confounding factors rather than a true association.

This is consistent with the HMO data collected by Altschul who found a high rate of misdiagnosis of urinary tract infection when he compared information garnered from the medical chart as opposed to the HMO's database. When proper diagnostic criteria are applied, the urinary tract infection was much lower than reported from the US Army data.[511] In a study of 603 intact Japanese boys aged 0 to 15 years, none had ever reported having had a urinary tract infection.[85]

An important omission in the background report is that at least seven studies out of Israel indicated that urinary tract infections occur at a higher rate following infant circumcision.[512-518] This increased risk of urinary tract infection may be related to techniques used in ritual circumcision to control the bleeding that may restrict urine flow, thus leading to the urinary tract infection. Parents who desire a ritual circumcision for their son need to be aware of this risk.

The increase in diagnosis of urinary tract infections may be because parents are instructed to retract the foreskin on a regular basis in order to clean the head of the penis. This is inappropriate advice resulting in manipulation of the urethra and the equivalent of "honeymoon cystitis." Consequently, these infections may be iatrogenic.

An important omission in this section is that the long-term risks associated with urinary tract infections in infants are less than previously believed. For example, it has been demonstrated that treatment with oral antibiotics is as effective as treatment with intravenous antibiotics.[519] Urinary tract infections that occur in the first twelve months of life are less likely to result in renal parenchymal involvement.[520] There is now a strong body of evidence that urinary tract infections rarely, if ever, lead to hypertension or persistent renal dysfunction.[521-528][38-45] While males are more likely to have vesico-ureteral reflux noted on prenatal ultrasound, most cases resolve spontaneously. This temporarily predisposes males to urinary tract infection,[529,530] but the risk is quite low after six months of age, by which time the reflux has resolved. The recommended evaluation for infants with urinary tract infection is less rigorous than previously recommended.[531] Urinary tract infections should not be mischaracterized as an infection with life-long serious consequences, because the medical literature does not support such a characterization.

Comparing the rate of urinary tract infections to the rate of immediate complications associated with infant circumcision drawn from database sources is inappropriate and can be easily misinterpreted. Doing so also deviates from standard epidemiological practices and is misleading. As discussed elsewhere, the rates of complications following infant circumcision have not been well or consistently measured. Consequently any comparisons would have little

meaning. Citing a study with one of the lowest reported complication rates (0.2%[532]) to be used for comparison reflects a potential bias of those generating this report. A more apt comparison would involve comparing the rate of urinary tract infection with the rate of meatal stenosis following circumcision. Meatal stenosis rates range from 5% to 20% and often require surgical correction (meatotomy),[186,533-537] while the rate of urinary tract infection is 0.7%.[538] In this comparison, there would be approximately 3 to 15 meatotomies performed for every urinary tract infection. Yet, this is not a standard epidemiological approach. The most appropriate approach is to calculate the number needed to treat. This number has been estimated to be between 111[23] and 195.[538] The average cost of an infant circumcision, according to investigators at the CDC, is $285.[472] Consequently, one would need to spend between $31,635 and $55,575 to prevent one urinary tract infection that can be treated with a course of oral antibiotics that cost less than $20.

Other health conditions

The material presented in this section of the background document is highly selective, omits several important studies, and gives credence to studies with serious methodological flaws.

The authors of the draft rely heavily on the 2000 study of Mallon et al.[394] This study has two fatal methodological flaws. The first is that it was undertaken in a dermatology practice, thus is subject to referral bias. If primary care physicians are capable of taking care of penile dermatoses in circumcised males, they may be less likely to refer them for specialty care. Therefore, penile dermatoses in circumcised men would be underrepresented in a dermatology practice. Consequently, it is impossible to say whether this referred population is representative of the general population. The second fatal flaw is that the study had a control group of men seen in the dermatology clinic who did not have penile problems. The control group had a circumcision rate of 47.8%. Britain has a national circumcision rate of 21%.[539] If one had a control group with a circumcision rate of 21%, the positive findings of the study are negated.

There are a number of important oversights in this section of the draft. For example, in the 1986 study by Herzog and Alvarez, the differences in prevalence of balanitis, penile irritation, and phimosis based on circumcision status were not statistically significant.[505] In the 1988 study by Fergusson et al., penile inflammation was more common in circumcised boys in the first three years of life and overall there was no statistically significant difference.[190] For reasons that are unclear, the authors of this draft cite an opinion piece written by a known circumcision advocate to support their assertions.[540] Citing review articles and opinion pieces is inappropriate and not considered scientifically valid or evidence-based.

Regarding the risk of balanitis (which includes balanitis, posthitis, and balanoposthitis), this section of the CDC draft has several important omissions. First, in a 1982 study of over 1000

intact Chinese boys only 0.08% (95%CI 0%-0.24%) had signs of active balanitis, while only 0.65% (95%CI 0.20%-1.10%) had ever had balanitis.[541] Second, in a 1997 study of Japanese boys, they found one case of balanitis in 1283 (0.08%) three year old boys.[542] Third, is a 1989 study in Britain that found the cumulative risk of balanitis by age 7 to 14 years of age to be 4%, with most patients having a single episode easily treated with topical agents.[543] Finally, a 2007 report,[187] which updated a 1997 study[186] of 468 boys, found that among 473 boys under three years of age, intact boys were significantly less likely to have penile inflammation than circumcised boys (OR 8.01; 95%CI 1.31-329.15). After three years of age, there was no difference.

Regarding the risk of pathologic phimosis, this section fails to mention that the cumulative risk of phimosis in intact English boys is 0.6% in the first 15 years of life[457] and 0.42% in Chinese boys,[541] while the risk of phimosis following circumcision ranges from 0.3% to 2.9%.[544-546] There have been three studies directly comparing the rates of phimosis in normal and circumcised boys and none have found a statistically significant difference.[186,190,505]

The section fails to mention that meatitis/meatal ulceration is common in circumcised males and rare in intact males. It is most commonly seen in the first few months of life. The inflammation is thought to be the result of constant irritation from urine, stool, and friction from rubbing against a diaper.[547] One report noted that meatal ulcers were seen in 20% of newborns in the first 35 days following circumcision.[548] In 219 circumcised boys under 3 years of age, 19.1% had meatitis, a rate significantly higher than in intact boys in whom it was not seen (p=.030).[186]

A review of the entire medical literature does not support the contention that circumcision has a positive impact on phimosis, balanitis, and meatitis. Consequently, the recommendation for the intended audience of health providers is misleading, not justified, and not appropriate.

Health conditions for which male circumcision is indicated

The material presented in this section of the background document is, for the most part, somewhat accurate. However, the statement that circumcision is the “definitive treatment” for phimosis is confusing. Phimosis can be physiologic, which requires no treatment, or it can be pathologic, which requires treatment. Circumcision should not be considered first line therapy for pathologic phimosis. Balanitis xerotica obliterans (BXO) is the most common cause of pathologic phimosis. Fortunately, it is rare. Some, but not all, cases of BXO will respond to topical steroid application. A high response rate of phimosis to topical steroid application has been repeatedly demonstrated.[549-571] Likewise, there have been many reports of surgical techniques that correct phimosis without removing any tissue.[572-587] Several systematic reviews and cost-benefit analyses have indicated that circumcision is the least favorable method of

treating phimosis and the standard of care is shifting to topical steroids as the first line of therapy followed by surgery, if topical therapy fails.[588-590] The language of the draft needs to reflect this shift.

Safety and risks associated with male circumcision

The material presented in this section of the background document is highly selective and ignores studies that do not agree with the CDC's apparent goal of presenting infant circumcision as being safer than it actually is. Most of this section is spent reviewing studies that derived their data from databases,[532,591,592] which will underestimate the rate of complications by at least 10-fold, if not more. [Note: Reference CDC164 is listed incorrectly and should be: El Bcheraoui C, Zhang X, Cooper CS, Rose CE, Kilmarx PH, Chen RT. Rates of adverse events associated with male circumcision in US medical settings, 2001 to 2010. JAMA Pediatr 2014; 168: 625-34.]

When assessing the rate of complications reported in the medical literature, several factors are important. Some immediate complications are common and their frequency can be easily estimated. Others have been reported in case series, where the authors report their experiences with several patient episodes. Many of the more uncommon complications have been reported as case reports. From case series and case reports, it is hard to estimate the frequency of a particular complication. Certainly, not every complication is reported in the medical literature, and a number of barriers keep unusual complications from being reported. The complication needs to be recognized as related to, associated with, or caused by the procedure, and authors need to be willing to take responsibility for the complication. Next, the person identifying the complication has to decide whether to pursue reporting the complication, and they must have the time and resources to perform the task. Once the case report or case series is written and submitted, it is unlikely to get published unless the new report adds something to what has already been published. Medical journals are publishing fewer case reports, so a case report often needs to be shopped around to several journals before it finds a home. Most authors will give up submitting after a couple of rejections. Consequently, some have estimated that for every case report published in the medical literature, there may be 100 to 1000 unreported cases.

Imprecise and inconsistent definitions for what constitutes a complication, such as how much post-operative bleeding is permissible, also muddies the waters. Definitions may be more or less inclusive, often depending on what message the author wants to convey. This expectation bias is blatant in some studies. For example, in the African randomized clinical trials of adult male circumcision, very low complication rates(1.3% to 3.6%), lower than those commonly reported for infant circumcision, were reported for the procedure and delayed complications were not assessed.[1-3] It would appear that the aim was to present adult male circumcision as a low-risk procedure in advance of the planned circumcision roll-out. Because the definitions and criteria

for inclusion of complications vary so widely, any attempt to perform a systematic review and meta-analysis of the medical literature on this topic would be a fool's errand, and assigning any worth to conclusions reached in the process would be pointless.[29][Note: citation CDC157 does not properly list the authors of this study.] Any such analyses are not worthy of mention. If mentioned at all, the extreme limitations in studying this topic need to be stressed.

What constitutes a complication by a researcher's definition also affects the reported incidence of that complication. If bleeding complications included those patients who had any oozing of blood following circumcision, then the complication rate would be much higher than if bleeding complications included only those who required sutures. For example, in the study by Gee and Ansell the definition of "really significant" is arbitrary. One could easily include all of the hemorrhages requiring sutures (15), all of the denudation patients (2), half of the dehiscence patients (4), and all of the Plastibell being too tight(7). Instead of 14 patients who had "really significant" complications, the number tripled to 42.[593]

Many studies are limited by how long they follow their subjects. As a consequence, many of the delayed complications will be missed. For example, the database study by Christakis et al. only considered complications noted during the perinatal admission. As expected, they saw virtually no infectious complications.[532] Infections resulting from circumcision would be expected to occur days after the procedure, a time when nearly all these patients would have been discharged from the hospital. Likewise, the database study by Wiswell and Geschke looked only at the complications occurring during the first month of age.[591] This study, by design, would miss nearly all the cases of skin bridging and adhesion formation, buried penis, meatal stenosis, and inadequate or cosmetically inferior results.

Pediatric urologists are faced on a daily basis with the complications resulting from infant circumcision. Nearly all of these complications are not seen in the immediate post-operative period. One pediatric urologist noted that of 235 boys referred to him in a 24-month period with circumcision complications, about half of them required additional surgery. His experience is typical for his surgical sub-specialty. In the United States, a third of pediatric urologists report having served as an expert witness in circumcision injury cases. Substantial malpractice claims have been paid for circumcision-related injuries.[594]

The study design and method of data collection can also have an impact on estimating the rates of complications. Higher complication rates will be documented in a group followed prospectively over a short period of time with scheduled follow-up examinations, as compared to a group followed retrospectively over a decade. When looking for complications prospectively, the complications are proactively observed and recorded. For example, a prospective study found an excessive bleeding rate of 8.9% to 9.9% following infant circumcision.[595] Retrospective

studies typically see excessive bleeding following 1% to 2% of circumcisions.

In a retrospective study, only those complications recorded in the chart, usually in the nurses' notes, are available. Complications not documented in the chart would be missed. Therefore, the complication rates in chart reviews would be lower than in a prospective study. Chart reviews, including one published by the CDC, have documented complication rates of 2% to 6%.[6,593,596] Still, a chart review will uncover more complications than searching a database for diagnostic and procedure codes. For a complication to be tallied in a database, it not only must be recorded in the medical record, but it also must be listed as a discharge diagnosis. Only the most severe, life-threatening complications will be picked up in a database study. This does not mean that severe complications will not also be missed in a database. For example, an infant who had a third of his glans amputated using a Mogen clamp, resulting in a $2.3 million malpractice judgment awarded in 2009, did not have this complication listed on the medical record's face-sheet, so it would not have been entered into the database.[597] As a consequence, the complication rates for the database studies, which are in the range of 0.1% to 0.2%,[532,591] are ten times lower than the complication rates in chart review studies.

If studies whose data are mined from databases miss approximately 90% to 95% of the complications, do they serve any purpose? They would if their results can be extrapolated to accurately reflect reality. To demonstrate this, one would need to perform either a blinded prospective data collection or a chart review data collection in which information for the database is simultaneously generated to assess how well these sources of information correlate. To date, such a study has not been published. Consequently, the studies of complication rates that are based on databases do not provide useful information and should not be taken seriously when developing policy. While the CDC draft elaborates on the numbers generated by one such study, [592] the time spent by these researchers would have been better spent collecting useful information.

This study, with its markedly flawed data, makes the claim that complication rates are greater if circumcision is delayed beyond the newborn period. The problem is that data collection and reporting methods differ in the two age groups, which alone could explain the difference. The only reliable studies to assess this question are those that compared two age groups using the same evaluation tools, the same skill in practitioners, in the same environment, at the same time. Only a handful of studies have done so, and they do not support the authors' claim. In one study, complications were only seen in those who were circumcised at under 72 hours of life.[544] In the second, the Gomco clamp was found to have more bleeding complications in older boys than in neonates.[598] In a third study from Iran, no difference in the complication rate was found between age groups.[599] In a fourth study from Saudi Arabia, a greater rate of complications was seen in circumcisions performed in the neonatal period.[600] Several studies have indicated that the

Plastibell should not be used after the neonatal period.[601,602]

The CDC draft, citing a 1983 review article,[19] provides an incomplete list of complications following infant circumcision. The CDC draft should have included a complete list of complications and, where available, estimates of their likelihood. While this information is not available in the CDC draft, this information is essential for the intended audience of healthcare providers, so they can provide adequate disclosure to patients or their proxies for the fully informed consent process to be valid. Considering that infant circumcision is a purely cosmetic procedure performed primarily for cultural reasons, the required level of disclosure is higher than for procedures for which there is a clear medical indication. For this reason, providing complete disclosure should be the standard of care prior to infant circumcision. This would include a listing of all the known complications resulting from infant circumcision. Doing so not only fully informs the person providing consent/permission, but it also protects the healthcare provider performing the procedure should a complication develop as a result of the procedure.

Bleeding: Bleeding can be minor or require the application of clotting enhancers, suturing, and/or blood transfusions.[591,603,604] It can result in cardiac arrest,[605] or exsanguination.[606] Some patients will lose enough blood that a blood transfusion is needed.[591,593,596,607-610] In circumcisions performed on older children, post-operative bleeding is often the reason for hospital admission following the outpatient procedure.[611,612] The penis and the foreskin, which is fed by the frenular artery and is a frequent source of bleeding, are highly vascularized structures. Bleeding complications can occur with any of the techniques used without regard for the experience or expertise of the operator.[613,614]

The complication rate from bleeding varies widely with study design, the definition of excessive bleeding, and the attitude of the researcher toward circumcision. For example, in a prospective study designed to determine the incidence of hemorrhagic diseases and the impact of vitamin K, 9.87% of circumcisions resulted in abnormal bleeding.[595] A chart review by Gee and Ansell found a bleeding rate of 1.0%,[593] while data from a database noted excessive bleeding in 0.083% with 0.028% needing ligatures applied and 0.003% requiring transfusion.[591] Healthcare providers also need to recognize that excessive bleeding following circumcision may be the first sign of an undiagnosed bleeding disorder.[615-624]

Infection: Following circumcision, the newborn is at greater risk for infections because of the open wound involving the entire surface of the glans, which then sits in a diaper exposed to urine and feces. For several days following circumcision, a greenish-white, fibrinous discharge forms over the circumcision wound, which will exhibit a mixture of flora, including Klebsiella, Enterobacter, and Acinetobacter.[625] Infections can also be caused by *Staphylococcus aureus*,[626] *Escherichia coli*,[627] Group A ß-hemolytic Streptococcus.[628,629] A positive bacterial culture cannot

differentiate between colonization and tissue invasion.[625] Because of the high frequency of purulent-appearing exudate from the wound, it is difficult to differentiate this exudate and erythema, which results from an open wound, from that of an infection. Estimates of the frequency of infections following circumcision vary considerably as there is a tendency not to ascribe a poor outcome to an elective procedure.[629] The Plastibell, because it involves necrotic tissue adhering to the wound, may be associated with more infections and is linked to tissue necrosis and gangrene.

Staphylococcal infections (including MRSA): Several studies have found a higher rate of Staphylococcal skin infections in the first weeks of life in males, especially among those circumcised, as compared to females.[188,189,630-638] More recently, several outbreaks of neonatal cutaneous MRSA infections have been reported, primarily in circumcised boys.[639-649] In only one outbreak reported had none of the infected boys been circumcised.[650] One case-control study was able to document that a circumcised newborn boy was at 12 times the risk of developing a MRSA infection compared to a newborn boy that was not circumcised.[651] In describing this study, the CDC mischaracterizes and downplays the results as the "hospital identified circumcision as a potential risk factor," when the study found a statistically significant association. It is revealing that in instances where studies are favorable to circumcision the CDC draft does not downplay these associations. In one case report, MRSA was recovered from the circumcision wound of a newborn infant whose mother had staphylococcal toxic shock syndrome.[652] The frequency of staphylococcal infections varies from study to study, but in one series of circumcisions performed with a Plastibell, 10.7% developed impetigo.[653] The increase in staphylococcal infections following circumcision is not unexpected. Studies have shown that circumcision alters the normal flora from primarily gram-negative organisms to gram-positive organisms, including staphylococci.[141-144]

Staphylococcal scalded skin syndrome: Case reports and cases series of staphylococcal scalded skin syndrome following neonatal circumcision have been reported.[653-656] In one series of 75 circumcisions performed with a Plastibell, 2.7% developed staphylococcal scalded skin syndrome.[653]

Abscesses of the penis and scrotum following circumcision have been reported in a number of case reports.[628,657-660]

Erysipelas, a skin infection usually caused by Streptococcus that can lead to Fornier's gangrene, has been reported following circumcision.[661,662]

Group A ß-hemolytic Streptococcus infections have been reported following infant circumcision during outbreaks in neonatal nurseries.[663,664]

Acute post-streptococcal glomerulonephritis has been reported following an infected circumcision.[665]

Diphtheria infections, before widespread vaccination programs, were reported following both ritual and medical circumcisions.[666,667]

Syphilis: In the late 1800s, there were many reports of syphilis following neonatal circumcisions from oral-genital contact during the procedure performed by infected *mohelim*.[668]

Tuberculous: Reports of penile tuberculosis following ritual circumcision were commonplace in the first half of the twentieth century.[669-673] Most often, the history involved the wound being sucked by the mohel, who would invariably be found to have tuberculosis.[674,675] Cases continued to be reported well into the twentieth century.[676-678]

Herpes simplex virus is also spread via the oral-genital contact that can occur during ritual circumcision with some cases resulting in death or brain damage.[679-682] When these infections were discovered in New York City, Tom Frieden, current director of the CDC and the Commissioner of the New York City Department of Health and Mental Hygiene at the time of the herpes outbreaks, and Susan Blank, the chair of the American Academy of Pediatrics Task Force on Circumcision, did nothing to stop these easily preventable infections.

Tetanus following ritual circumcision has been reported in multiple case series.[682-689]

Septicemia, which is an overwhelming, systemic, life-threatening infection can follow circumcision.[660,690-697] Once the bacteria have entered the bloodstream, the infection can spread throughout the body. Reports have noted pneumonia,[698,699] empyema,[660] soft tissue abscesses,[660] osteomyelitis,[694,698,700,701] septic arthritis,[660,694,701,702] pyelonephritis,[698] peritonitis,[703] bilateral femoral head necrosis,[694] umbilical arteritis,[628] gangrene,[702,704,705] suppurative inguinal lymphadenitis,[694] and meningitis.[627,629,694,705,706] Sepsis following circumcision can also lead to disseminated intravascular coagulopathy, jaundice, congestive heart failure,[697] peripheral circulatory collapse,[698] hypothermia,[697] and death.[654,693,696,699,707,708]

Fornier's gangrene, which is necrotizing fasciitis of the perirectal, perineal or genital area, resulting in gangrene of the overlying skin,[709] has been repeatedly reported in the medical literature,[710-721] following both tribal circumcisions[722] and circumcisions performed in a medical setting.[704] These serious, life-threatening cases emphasize the necessity of informing parents of the uncommon, but potentially serious, risks of neonatal circumcision.[723]

Surgical complications include total denudation of the penis[718,724-732] and the removal of too much shaft skin.660,[733-736] Even with proper technique, especially with the clamp techniques, it may be difficult to estimate how much skin is removed. The removal of too much skin is so common that many practitioners may view the results as normal.

Urethral fistula following circumcision has been reported in a number of case reports and case series.[83,720,732,737-756] This complication requires careful repair by experienced specialists.[757]

Other surgical complications, such as multiple pyogenic granulomas,[758,759] subglandular stricture, [760] and scrotal trauma[761-763] have been reported following circumcision.

Plastibell retention/pseudoparaphimosis: If the Plastibell ring does not fall off within eight days, a complication is likely to result. The Plastibell ring can dislocate proximal to the glans, where it can mimic paraphimosis, also known as pseudoparaphimosis. The dislocated ring can result in compression damage, ulceration of the corona and proximal glans, and edema and vascular congestion distal to the ring. Removal of the ring with a wire cutter is often needed. Reports in the medical literature have included significant long-term penile deformities,[732,764-769] signs of urinary obstruction,[770] pseudoparaphimosis,[765-768,771-773] and strangulation of the penis.[774] The incidence of pseudoparaphimosis following use of a plastic bell circumcision device has been reported to range between 0.27%[593] to 1%[765] to 1.6%.[596] The risk of a Plastibell tracking back onto the shaft and needing to be removed using a ring cutter is 3.6% and incomplete separation is seen in 5.9% of patients.[775] Another study found ring retention in 2.1%, with 0.8% developing necrosis and 0.9% developing pseudoparaphimosis.[776] In one series, primarily in neonates, there was an 11% retention rate.[614]

Bivalving: Inadvertent placement of scissors into the urethra while attempting a dorsal slit resulted in surgical bivalving of the glans.[731,777]

Penile necrosis/ischemia is a serious complication that has been noted in a number of case reports and case series.[6,660,704,718,746,763,776,778-795] In one series the rate of necrosis was 0.8%.[776]

Amputation of the penis and glans: Since several of the devices used to perform circumcision involve a “blind” amputation of the foreskin, there are multiple case reports and case series reported in the medical literature related to partial or complete amputations of the glans. [628,696,705,731,741,750,755,762,796-822] Since many of these reports are in the form of describing techniques to reattach the inadvertently amputated tissues, the number of actual cases might be much greater. These amputations are often the source of malpractice cases. In some instances, it was decided to raise these boys as girls.[801]

Acute urinary retention, typically from bandages that are too tightly wrapped around the wound in ritual circumcisions, or a Plastibell ring obstructing the meatus, has also been reported.[593,705,762,823-826] In a series of older boys circumcised with a Plastibell, 0.35% complained of urinary retention.[826] In follow-up of 99 boys circumcised at a mean age of 4.3 years, 19 did not pass urine for more than 12 hours. Five boys held out for several days (maximum 3 days) with one requiring readmission.[533] In a study of older boys circumcised with a Plastibell, 56.3% had difficulty with micturition.[827] In a study of healthy male neonates, the mean time to voiding was 5.3 (SD=2.5) hours after the procedure with the longest duration to post-circumcision voiding being 11.5 hours.[828] In another study of circumcised newborns, the mean time to post-circumcision voiding was 4.97 hours (SD=3.35). A few (0.38%) took more than eighteen hours after circumcision to void.[829]

Other complications from urinary retention, such as bladder rupture,[830] obstructive uropathy,[831] acute renal failure,[831-833] and urine advancing in subcutaneous fascial planes[834] have also been reported.

The tight bandaging technique used in ritual circumcision also places the boy at greater risk for urinary tract infections.[512-518]

Leg cyanosis, both unilateral[835] and bilateral,[836] gastric rupture from air swallowed while crying during the procedure,[837] pulmonary embolism,[838] pneumothorax,[839] erythema multiforme,[840,841] myocardial injury, tachycardia, heart failure,[842,843] and impotence (in adult men)[844,845] have all been reported following circumcision.

Apnea/Apparent life-threatening events have been reported,[846,847] with a rate of 3.85% of prolonged apnea following the procedure.[847]

Chilling was noted to be a problem when circumcision was performed just after delivery.[848]

Hyperbilirubinemia (jaundice). Since it has been shown that breastfeeding and bottle feeding are adversely affected by neonatal circumcision, one would expect that circumcised boys might be at greater risk for hyperbilirubinemia. While not studied directly, two studies in American infants have found boys to be at greater risk for hyperbilirubinemia.[849,850] In the Canadian database used to determine the rate of urinary tract infection based on circumcision status, it was discovered that circumcised boys were significantly more likely to require hospitalization (excluding hospitalizations for urinary tract infection) during the first year of life.[538] This differential could be due to hospitalizations for hyperbilirubinemia. This is an area open for future research.

The presence of a hypospadias is an absolute contraindication to circumcision, yet circumcisions

have been reported being performed on boys with a hypospadias.[593,851] There have been reports of techniques to correct hypospadias in circumcised patients,[852-855] and techniques to repair hypospadias without a circumcision leaving the penis with a fully intact appearance.[856]

Hematoma following circumcision is fairly common.[753,857] The rates have been reported as 0.46%,[776] 0.98%,[858] 6.1%,[827] and 7.7%.[695] It is one of those complications so common that it is not usually considered out of the ordinary, and therefore, is not likely to be identified as a "complication."

Delayed complications: Most studies attempting to compile the complication rates for circumcision do not collect data long enough to capture the long-term complications.

Meatitis is a common finding as most circumcised boys shortly after the procedure will have erythematous meatal openings. Most physicians unaccustomed to examining the meatus in intact males would consider the inflamed meatus to be a normal feature of the circumcised penis.[547,548] The inflammation is thought to be the result of constant irritation from urine, stool, and friction from rubbing against a diaper.[859] The rates of meatitis are approximately 20%.[186,548]

Meatal stenosis, which has been recognized as a complication of circumcision for some time, may be the most common complication following circumcision.[186,533,535,536,545,604,614,741,860-884] In 1881, Mastin stated that narrowing of the meatus was the rule for Jews, not the exception, and meatotomy (the surgical correction of meatal stenosis) was designated by many Jews as their "Second Circumcision."[885] Symptoms associated with meatal stenosis include penile pain at the initiation of micturition, narrow high velocity stream, the need to sit or stand back from the toilet bowl to urinate, abdominal pain, enuresis, dysuria, urinary urgency, urinary frequency, straining to urinate, urinary dribbling, and urinary retention.[535,870,879,886,887,888] The meatal slit at the urethral opening should be 25% to 30% of the diameter of the glans.[860] The meatal opening is significantly smaller in circumcised males and meatal stenosis occurs almost exclusively in the circumcised penis.[46,538,873,889] (Most physicians do not know what constitutes a normal meatal opening, if they have never examined an intact male or been educated about the normal penis. The CDC should focus its efforts on educating health care providers about normal penile anatomy, care of the normal intact penis, and on diagnosing and appropriately treating the complications of circumcision.)

The incidence of meatal stenosis following infant circumcision is found in 2.8% (requiring meatotomy),[533] 7.3%,[186,536] 32.1%,[871] 3.55%,[614] and 20.4%.[537] For boys circumcised later in life, the incidence is 11.1% (necessitating meatotomy)[545] and 7.95%.[538] A report of 58 meatotomies performed on circumcised boys on an outpatient basis in one year's time in a single practice[874] suggests that urethral meatotomy is a very common procedure in the United States. The writers

of the CDC draft need to be congratulated on finding the study with the lowest reported rate (0.9%) of meatal stenosis following circumcision in the literature[599] while turning a blind eye to the remainder of the medical literature. They accept this outlying study without question, yet take a cheap shot at the methodology of a study whose results have repeatedly been verified.[536] Such behavior is both unscientific and unprofessional. One cannot help but notice that the CDC draft is only critical of studies that show circumcision in a neutral or negative light. It gives the impression, either rightly or wrongly, that the CDC is pursuing a specific pro-circumcision agenda with this draft.

Meatal stenosis obstructs the flow of urine and can lead to urinary tract infections, vesicoureteral reflux, hydronephrosis, obstructive uropathy, and renal failure.[880,881,887,890-892]

Hidden Penis, Buried Penis, Concealed Penis, Trapped Penis, Webbed Penis, Inconspicuous Penis: These conditions have generated much discussion on how to define them and how to treat them.

A concealed penis is a penis that is inconspicuous because of an overlying fold of abdominal fat. A buried penis refers to a penile shaft that is buried below the surface of the prepubic skin and has also been used to describe a partially or totally obscured penis caused by obesity or by a radical circumcision. A true buried penis is a congenital anomaly that includes an abnormally large suprapubic fat pad and dense dysgenetic dartos fascial bands that tether the penis inward. This requires surgical intervention.

A webbed penis consists of midline skin webs which bind the ventrum of the penis to the scrotum with an abnormal insertion of the scrotum onto the ventral aspect of the penis.[893-902]

Because the skin and dartos fascia are inadequately attached to the underlying Buck's fascia, the corporeal bodies telescope proximally without the skin and dartos fascia covering. Because the penis is suspended from the pubis by the suspensory ligament, it remains fixed, but the fat does not. Fat descends over the penis and covers it.[900-903]

Many intact boys have baby fat surrounding the undeveloped penile shaft. Most of these patients will develop normally, with the excessive baby fat in the pubic area regressing and the penis lengthening under the influence of endogenous testosterone.[897,901,904]

Failing to recognize a "hidden or buried penis" at birth makes the condition worse and more difficult to correct down the road if the boy is circumcised. There are multiple case reports of buried penis following circumcision,[752,762,905-910] and most case series of patients undergoing repairs for this problem are populated with boys who were circumcised as infants.

[546,894,899,901-904,911] This has also been reported as a problem in circumcised adults.[912]

Circumcision is a problem for these patients, with buried penis, because the base of the shaft skin is not properly attached to the base of the tunica albuginea, so the shaft skin will be bunched up around, and distal to, the sulcus of the glans. Because nearly all of the shaft skin is in a location where it is typically removed by a clamp device, nearly all of the shaft skin is at risk for removal.[893] Since the synechiae that fuses the glans to the inner surface of the foreskin is removed, there is nothing to hold the penis away from the body, so the penis becomes buried in the scrotum and fat pad.[893,910] With the penis completely buried, the circular scar from the circumcision can constrict resulting in phimosis.[893] This often gives the appearance of "redundant foreskin."[83,893,903,908]

This leads the parents to blame the physician for an "inadequate" circumcision. Despite reassurance from the physician,[899] some parents will demand that the child be re-circumcised, and indeed many of these children will be referred to the urologist for re-circumcision.[913] Attempts to re-circumcise, which entails removal of more penile skin, often makes the condition worse, by further burying of the penis, and it makes reconstruction more difficult.[893,913-915] The repair is a complex procedure, which is only made more difficult if the patient is circumcised.

The consensus among pediatric urologists is that infants with buried penis should not be circumcised as it can result in serious consequences.[893,913,916] The take home lesson from all of this is: if the penis appears too small, it should not be circumcised unless it can be demonstrated that it is not a buried penis.[893]

It is difficult to estimate the incidence of buried penis. In a series of 313 neonatal circumcisions performed with a Mogen clamp, one developed hidden penis.[544] It is not known if this rate is low because the incidence is low or because researchers did not successfully identify those for whom circumcision was contraindicated. In one series of healthy boys, 20.1% of boys in the first year of life had a glans that was completely covered,but only 0.9% would be considered to have a buried penis/preputial stenosis.[186]

Iatrogenic phimosis/preputial stenosis: Iatrogenic phimosis occurs when the head of the penis is trapped behind the circumcision scar. The skin remaining after circumcision can develop a circular cicatrix that contracts and draws the proximal skin over the glans forming a resistant phimosis. Since 1895, multiple case reports have appeared in the literature.[544,917] The incidence has been reported as 1.7% in older boys,[534] 0.3% in infants using the Mogen clamp,[544][67] 2.9% using the Gomco clamp,[546] and 0.9% using a variety of other circumcision techniques.[186] Given that the cumulative incidence of pathological phimosis in intact boys by 15 years of age is 0.6%,[457] phimosis following circumcision occurs with equal frequency as in boys who are not

circumcised.

Cosmetic concerns: Parents, to a large degree, have their infant sons circumcised for cosmetic reasons: primarily so the boy's genitals will look like the father's genitals. Since there is a wide variety to be had in the appearance of the circumcised penis, both in children[186] and adults,[46] the intended outcome is unlikely to occur.[918] The desired outcome of a fully exposed glans on an infant in the first year of age is the exception,[186] and parents and older boys are often not pleased with the cosmetic outcome.[776,919] In a series of boys circumcised with a Plastibell, 33.1% of patients experienced cosmetic complications, and 20.8% claimed to have experienced psycho-social problems because of the appearance of the penis after the operation.[920] In a comparison of the Plastibell versus standard free-hand technique in older boys, favorable cosmesis was seen in 60.9% with the Plastibell and 44.9% with standard technique.[827] Consequently, the primary care physician is bombarded with parental concerns that not enough skin was removed. While reassurance is warranted in nearly all cases, there are a substantial number of patients who will doctor-shop until they find someone willing to re-circumcise their infant.[921] Re-circumcision to address cosmetic concerns is a commonly performed procedure,[607,922] but, in the case of a buried penis, it will make the situation worse.[893,913-915] In one study, the rate of inadequate circumcision prompting a surgical revision was 2.8%.[190] In other studies the rate of re-circumcision ran about 1%.[923-925]

Adhesions: There is some debate whether the adhesions are the result of inadequate stripping of the inner prepuce away from the glans at the time of circumcision[926] or the reattachment of the epithelium of the inner prepuce to the epithelium of the glans.[927,928] Adhesions have been noted in 15.3% of newborns at their first office visit,[929] 10% at the one-month well-child visit,[927] and in 25.6% to 27.6% of circumcised boys overall. Fortunately, with age the prevalence decreases.[186,930]

The adhesions which form following circumcision are more dense than the connections normally found between the inner prepuce and the glans.[927]

Parents must be taught how to care for the circumcised penis by pulling back on the penile skin and exposing the glans on a regular basis, so adhesion formation can be avoided.[929] It has been suggested that daily application of petroleum jelly for three weeks following the procedure may decrease the rate of adhesion formation.

Many physicians wrongly believe the proper treatment is to tear the adhesions apart, but this can lead to skin bridges and further scar tissue formation. Most adhesions will resolve spontaneously.

Skin bridges: Some adhesions will form a permanent bridge from the circumcision wound to the

surface of the glans. Skin bridges can cause tethering of the penis, entrapment of debris, curvature of the penis, and pain on erection.[927,929] Several case reports have appeared in the medical literature describing this complication.[931-933] Skin bridges are commonly seen by urologic practices.[933] The prevalence of skin bridges was 4.1% in circumcised boys under 3 year of age,[186] Among adult circumcised males, skin bridges were noted in 12.7%.[46]

Keloid formation: Keloids are hypertrophic scars that do not decrease in size over time. Although penile keloid formation is rare, it has been reported following circumcision.[934-940] The treatment consists of intralesional steroid injections, surgical excision, or a combination of the two.[934,939,940]

Subcutaneous granuloma: A subcutaneous granuloma following circumcision has been described as an "indurated, confluent, red-violet plaque, freely movable over the underlying tissue, 0.3-1.0 cm wide of firm consistence, surrounding the penis in the neighborhood of the coronal sulcus. Its surface is smooth and the borders are distinctly defined."[941][These lesions are found on the penis in 4.97% of circumcised boys.[942]

Epidermal cysts have been reported following circumcision.[771,943-946]

Penile edema: Acquired penile edema in adult males has been reported since 1928 under a wide variety of names.[947-962] The entity has been described as "a painful, hard, nodular, translucent cord that suddenly appears in the penis and is usually confined to the coronal sulcus,"[822][835] or as a "hard worm-shaped lesion" on the dorsum of the coronal sulcus.[956] The edema comes on suddenly and is self-limited.[960-962] It is typically seen in circumcised, sexually active men often after vigorous, frequent, or prolonged sexual intercourse.[948,950,952,954,956,957,960-962] In a series of genital dermatoses presenting to a dermatological referral practice, "idiopathic penile edema" was seen only in circumcised men ($p<.01$).[394]

In most series, the circumcised penis appears predisposed to this condition.[948,955,959-967] It has been postulated that the circumcision scar interferes with normal lymphatic drainage.[948,955] Alternatively, penile edema has also been attributed to decreased vaginal lubrication,[961] which is a common condition in vaginal intercourse involving a circumcised penis.[115] Inadequate lubrication leads to abrasions of the penile skin, which, in turn, can result in antigen transfer and subsequent hypersensitivity.[963] The uniform success of a variety of interventions[950,951,954] suggests that this condition is benign and self-limited. Acquired penile edema affecting pediatric or adolescent males has been reported less frequently.[963,965-968] Based on one prospective series, the incidence in pediatric patients was estimated to be 0.62%.[186]

Following adult circumcisions, penile cutaneous horns can develop. Many of these may harbor

malignancies.[969-971]

Hair strangulation occurs when a human hair becomes inadvertently wrapped around an appendage, usually a finger or a toe. Once the hair gets wet it contracts and cuts into the appendage. There have been multiple case reports of penile strangulation by a hair.[865,972-981] Some cases have resulted in urethral fistulas and partial or complete amputation of the penis.[975,976,981-983] The hair typically becomes entrapped in the coronal groove.[979] Of the more than 70 cases reported in the medical literature, all but one case occurred in circumcised males.

Two studies determined that the size of the adult penis is significantly smaller in circumcised men.[46,47] This is important information that needs to be disclosed as part of the informed consent process.

Psychological sequelae: The aftermath of infant circumcision shares many of the attributes of post-traumatic stress disorder;[984] however, there has been little study to confirm or deny this hypothesis. There is solid evidence to indicate that imprinting happens in the perinatal period, which can have long-term consequences when these infants become adults.[985-992] Given that circumcision is more traumatic (in terms of provoking a cortisol surge) than gastric suctioning, one would expect that it might have long-term consequences. This has been seen in two studies in which it was found that male infants who had been circumcised shortly after birth cried longer and louder than girls and intact boys when given vaccinations at 4 to 6 months of age.[993,994] The studies concluded, “Because memory of pain is believed to be important in subsequent pain perception, and the main structures for memory are functional in the neonatal period, it is conceivable that pain from circumcision may have long-lasting effects on pain response and/or perception.”[993] Subsequently, it has been demonstrated that inadequate analgesia for initial procedures in young children may reduce the effectiveness of analgesia in subsequent procedures.[995] One study found a positive statistically significant association between circumcision rates and the rates of autism in boys.[259] A recent national, register-based cohort study from Denmark found that circumcised boys were at significant risk for developing autism spectrum disorder by ten years of age (hazard risk (HR) 1.46; 95%CI 1.11-1.93) and at greater relative risk for infantile autism before five years age (HR 2.06; 95%CI 1.36-3.13). This same study found that circumcised boys were at greater risk for developing hyperactivity disorder (attention deficit disorder) (HR 1.81; 95%CI1.11-2.96).[996] The link between attention deficit disorder and circumcision has been suspected for some time given that it has a higher rate in boys and it is diagnosed more frequently in the United States than in Europe. Another preliminary study indicated that circumcised adults are more likely to have alexithymia (difficulty in identifying and expressing feelings).[997] Further study is needed in each of these areas.

Cansever performed psychological testing on Turkish boys before and after ritual circumcision. Following circumcision, there was a decrease in IQ, a decrease in body image, disturbance in sexual identification, an increase in regressive traits, and an increase in aggressive behavior, especially toward their mothers.[998] While there has been little study of the psychological sequelae of infant circumcision, there is no evidence to suggest there is no harm.[999]

A potential impact on sexual identification following infant circumcision needs further study. In a study of men seeking care at a sexually transmitted disease clinic in San Francisco, circumcised men were statistically significantly more likely to identify themselves as men having sex with men (OR 1.13; 95%CI 1.10-1.16).[8] The same lead author collected similar information in a sexually transmitted disease clinic in Tel Aviv with similar results (OR 1.57; 95%CI 1.11-2.22).[1000] This finding needs further research. Based on these studies, part of the disclosure in the informed consent process needs to include the statement that there are currently preliminary findings indicating that circumcision is associated with a higher rate of autism, attention deficit disorder, and identifying oneself as gay/bisexual.

Behavioral changes: Richards et al. present both circumstantial and direct evidence that circumcision of male infants leads to behavioral changes.[1001] Several early behavioral gender differences, noted in studies performed in the United States,[1002-1006] have not been noted in similar studies performed in Britain or The Netherlands.[1007-1010]

Changes in Sleep Pattern: When circumcised males were compared to genitally intact boys and girls, they showed less active sleep time, more time awake and agitated (active awake and crying awake), longer latencies to sleep[1011-1013] and more extreme long non-REM sleep periods.[1012] Sleep patterns were correlated with rapidity of drops in cortisol levels.[1014] Sleep changes have not been documented in newborns with prolonged crying.[1012]

These findings need to be placed in context. Changes in the amount and type of sleep and the latency to sleep are indicative of stress. The immature human infant has a limited capacity to actively avoid stressful stimulation and responds to such stimulation with the “conservation-withdrawal” pattern. This leads to increases in non-rapid-eye-movement (non-REM) sleep, which is the low point on an arousal continuum, where thresholds to sensory stimulation are high and motor activity is low.[1015] REM states probably represent the operation of maturational processes in the central nervous system of the neonate, which are primarily related to physiological processes not yet influenced by experience. These maturational processes are part of an unfolding genetic progression, phylogenetically preformed for an average expectable environment. The processes involve the establishment of the necessary connections within the central nervous system as well as in behavioral integration. By comparison with adult sleep, prototype REM sleep is poorly organized. But, in the neonate, it only takes three months of

development to organize it.[1016] An increase in non-REM sleep has been observed following heel lancing.[1016] Circumcision without anesthesia in a newborn is followed by prolonged non-REM sleep, which is consistent with the "conservation-withdrawal" theory. Newborns usually begin their sleep cycle with REM sleep, but following heel lancing, they began sleep with a lengthy period of non-REM sleep. Following either selective interruption of REM or non-REM sleep or deprivation of total sleep, neonates exhibit a propensity to recover quiet non-REM sleep rather than active REM sleep. The quiet sleep priority may be related to "stress" or wakefulness and fatigue.[1017] Consequently, an inborn adaptive response to stress is to produce a quiescent state with high sensory thresholds.[1016] A "common sense" guess about the effects of a continual disruptive stimulation for a newborn would be that an infant would sleep less and cry more; however, in the period following circumcision infants have an increase in light sleep and a decrease in deep sleep,[1012-1016,1018,1019] but they cried the same amount of time as before circumcision. Consequently, these changes in sleep pattern following circumcision are a much more accurate measure of the stress of circumcision than is crying.

Interruption of maternal-infant bonding and changes in breastfeeding: A study of the effects of circumcision on maternal-infant interactions noted a trend toward fewer intervals of uninterrupted feeding, with infants who were circumcised sucking on their bottles harder, faster, and more concertedly than those not circumcised. This, in turn, made them less available to their surroundings and less able to interact with their mother. This finding lasted for approximately twenty-four hours following the procedure.[1020] Dixon et al. also established that circumcision disrupts feeding and impairs infant/maternal attachment.[1021] In babies who breastfeed, feeding deteriorates following circumcision.[1022] Lactation consultants noted that boys circumcised before breastfeeding has been established subsequently have more problems establishing breastfeeding. However, boys recovering from traumatic birth, but not circumcised, have fewer breastfeeding difficulties.[1023]

Death: Deaths following circumcisions have been acknowledged for a long time, as noted in the Talmud, and unfortunately they continue today.[1024-1027] Reports of death following circumcision have been related to exsanguination,[1028,1029] bronchopneumonia,[1030] secondary pulmonary tuberculosis,[672,1031-1033] secondary sepsis,[660] secondary meningitis,[629] and undisclosed reasons.[691] The incidence of death following circumcision is unknown. Each year there are reports of multiple deaths in Africa of boys following their ritual circumcision that initiates them into manhood.[1034-1047] In developed nations, the most common estimate, approximately 1 in 500,000,[1048] is at best a guess. Gairdner reported between 9 and 12 deaths out of 90,000 circumcisions performed each year in the United Kingdom for an incidence of 1 in 7,500 to 1 in 10,000.[181]

The primary obstacle to obtaining an accurate estimate of the incidence of death from

circumcision is the underreporting of circumcision as a cause or contributor to death. Instead of listing circumcision as a cause of death, the infection or hemorrhage/exsanguination that led to the baby's demise is listed. Incomplete and inaccurate death certificates for pediatric deaths are not uncommon. In a study of children with heritable disorders who died while in a pediatric intensive care unit, the underlying disorder was not listed on the death certificate 41% of the time.[1049]

An example of this was a clinical-pathological conference published in *The Journal of Pediatrics* involving a newborn who died of an overwhelming echovirus infection. For reasons that are unclear, the patient was circumcised at 4 days of age, which "was complicated by persistent oozing of blood." While this was mentioned in the case report, the authors did not discuss the role the circumcision may have played in the patient's fatal outcome.[1050] This struck some readers as odd that "an infant with respiratory distress and suspected of sepsis would be subjected to a stressful procedure such as a circumcision."[1051] The authors of the case report responded that "it was the attending pediatrician's judgment that the infant had improved to the point where he did not interfere with the obstetrician's and parent's decision to go ahead with this procedure, but following the circumcision, the clinical course rapidly deteriorated."[1052] Did the sudden deterioration in this patient coincide with the circumcision or did the circumcision contribute to the patient's demise? Without mention during the clinical-pathological conference of circumcision contributing to his death, it can be assumed that circumcision was not mentioned on the death certificate.

Of note, in England and Wales, the Registrar-General's tabulations for deaths in children under 5 years from "circumcision or phimosis" showed a dramatic drop with the decrease in the number of circumcisions performed. During 1942-49, between 11 to 19 deaths occurred each year, while in 1950 and 1951 the number of deaths were six and one, respectively.[1053]

One of the hardest comparisons for commentators on this topic to resist is that between the risk of death from circumcision and the risk of death from penile cancer. Gellis, a highly respected pediatrician, noted that, "It is an uncontestable fact at this point that there are more deaths from complications of circumcision than from cancer of the penis."[1054] Others have estimated that at least 41 children will die from circumcision for each case of penile cancer prevented.[1055] If the incidence of death following circumcision and the incidence of death following penile cancer are roughly equal, then they should be given equal weight during the disclosure portion of the informed consent procedure. Since the risk of death from circumcision is on par with the risk of penile cancer, this deserves a prominent place in the discussion of risks, benefits, and harms.

Bollinger estimated there may be approximately 117 deaths per year in the United States that can be attributed to infant male circumcision (9.01 per 100,000).[1056] These death rates are on par with

those reported in Brazil.[1057]

The studies relying on data collected from databases[532,591,592] are only picking the low-hanging fruit, so to speak,. Thus, they do not provide a valid picture of the true rates of complications. Their results are only useful as a rhetorical device for those who want to promote circumcision, such as the American Academy of Pediatrics[40,1058,1059] and the writers of the CDC draft. Any discussion of their results should focus on the unreliability of this data collection method for this purpose and their role in distorting the discussion.

Throughout the CDC draft, pain is cited as a major concern by those considering the procedure. Yet, the draft glosses over the issue of pain in a brief paragraph citing a methodologically incomplete study with perhaps the highest efficacy for infant circumcision anesthesia in the entire medical literature.[1060] As will become clear from the discussion below, the writers of the CDC draft had to dismiss a broad swath of studies in order to isolate this outlying study.

It is important to make clear that noxious stimuli are perceived as more painful in newborns compared to older children and adults.[1061] There are several reasons for this. First, the human brain learns following a noxious stimulus and compensates for the stimulus. With novel noxious stimuli, such as tearing the prepuce from the surface of the glans and crushing the prepuce, the brain does not know how to filter or tolerate it, so consequently the stimulus is more raw and intense in an infant. For example, an infant's spinal sensory nerve cells are more excitable than an adult's, making their spinal reflex response to a harmful stimulus more intense and prolonged.[1062] Second, infants do not have fully developed, fully functioning descending inhibitory nerve fibers that attenuate noxious stimuli from the periphery. Consequently, noxious stimuli that reach the brain are more intense.[1062-1064] Third, endogenous opioids, which are responsible for postsynaptic modulation of pain signal transmission, have levels in neonates several logarithms in magnitude lower than reported in adults. Consequently, endorphin release is unlikely to provide the neonate relief from many sort of pain.[1062]

Researchers typically do not study a complete evaluation of pain in newborns. For example, the study cited in the CDC draft[1060] used only the Neonatal/Infant Pain Scale[1065] to assess pain. The Neonatal/Infant Pain Scale gives a score of 0 to 2 for six factors: facial expression, crying, breathing, arm positioning, leg positioning, and alertness. Given that part of the study's protocol was to give formula, breastmilk or a 20% sucrose solution ad libitum, to restrain the arms and legs during the procedure, and to use of a pacifier, these interfered with interpretation of facial expressions and the ability to accurately assess three of the six factors of the scale. In general, scales that rely only on behavioral signs can be misleading. A pacifier can reduce crying, but will have no impact on cortisol levels.[1066] A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain.[1067] For example, Johnston and Stevens

found strong correlations between three facial scores, but they were not related to the physiological variables, and the physiological variables did not correlate with each other.[1068] Slater and colleagues, after directly measuring spinal nociceptive reflex withdrawal activity and nociceptive brain activity, concluded that the reduction in clinical observational scores following noxious events in newborns should not be interpreted as pain relief.[1069]

Raw noxious stimuli are relayed to the brain via small myelinated (A delta) fibers and unmyelinated C fibers.[1062] Simultaneously, the hypothalamus triggers a chain of events that results in the adrenal glands secreting cortisol, epinephrine, and norepinephrine. Epinephrine in turn accelerates the respiratory rate, dilates the bronchi and bronchioles, potentiates muscle contraction, and increases blood pressure and heart rate.[1070] The pain message and its response are wired through a complicated, redundant, widespread neurologic information processing system with both conscious and emotive components. This network is part of the phylogenetically most primitive nervous system, and as such, is functional early in development.[1071-1074] The average newborn can differentiate the intensity or invasiveness of stimuli with the magnitude of their physiologic and behavioral responses reflecting the intensity of the stimulation.[1075] Pain is also largely a subjective experience, which makes assessment of pain in newborns more difficult and comparisons of pain levels in neonates with older children nearly impossible. Performing circumcisions without anesthesia has allowed researchers to study the parameters of extreme pain in experiments that would not have been allowed on laboratory animals.[1076-1079] Some have argued that the placebo-controlled trials of various topical and local anesthetics for infant circumcision violated the Helsinki Declaration.[1080]

Because pain in the newborn is expressed in a number of ways and focusing on one modality of expression provides a limited view, studies of pain in newborns should make a broad assessment of all pain parameters in order to get a complete picture. Studies should assess all of the following.[1081]

1. Crying: The duration and pitch of crying can give an indication of the degree of pain and stress.[1082] There is a direct relationship between cry acoustics and vagal tone.[1083] Cry duration, as opposed to cry acoustics, is not as reliable a measure of stress and pain as compared to vagal tone and cortisol levels. There is a positive correlation between cry duration and both cortisol levels and behavior state following circumcision, except when a pacifier is used.[1018,1066]

2. Facial expressions: A variety of facial expression and behavior state scores have been used to quantify neonatal pain, with inter-observer scores showing reasonable reproducibility. Average behavioral state scores during circumcision are positively correlated with increases in serum cortisol levels.[1019]

3. Vital signs: Pain is associated with drops in blood oxygen levels and increases in heart rate, respiratory rate, and blood pressure.

4. Vagal tone: Reactivity and regulation of the autonomic nervous system, as measured by vagal tone, is a very sensitive measure of stress. A decrease in vagal tone is a quantitative indicator of the central nervous system's response to pain that parallels other measures of neonatal pain.[1062,1081,1083] Decreases in vagal tone are proportional to the invasiveness of a procedure.[1062,1083]

5. Cortisol levels: Activity in the hypothalamic-pituitary-adrenocortical axis has long been linked with the concept of stress and arousal. Cortisol levels, which can now be measured in the saliva thus avoiding the stress and pain of drawing blood, will surge as a result of pain. The rise in cortisol levels, often seen hours after the stressful event, may be the most sensitive measure of pain in a newborn.[1084] There is increasing evidence that cortisol surges may impact long-term aspects of infant development.[1016,1085-1087]

6. One group of investigators was able to measure pain-specific brain activity recorded by electroencephalography and identified by principle component analysis. They also measured the magnitude and latency of the spinal nociceptive reflex withdrawal. This direct measure of nociceptive spinal cord and brain activity was found to be more accurate than observational pain scores and changes in facial expressions.[1069]

Infant circumcision is very painful and needs to be placed within the same context as all other painful procedures performed on neonates. Gunnar et al. found circumcision elicited more behavioral distress and evoked a larger cortisol response than blood sampling, weighing, or physical examination.[1089] In a study of post-operative pain following "minor" surgery, the pain of circumcision was behind only tonsillectomy and orchidopexy, making it more painful than sinus surgery, otoplasty, strabismus repair, dental extraction, urethral repair, hernia repair, reset of limb fracture, and revision of the thumb.[1090] In a study of the magnitude of an infant's response to procedures, such procedures as the insertion of a gavage tube, physical examinations, nose cultures, and insertion of an umbilical arterial catheter were considered mildly invasive procedures. Arterial punctures, venous punctures, and heelsticks were considered moderately invasive procedures. Circumcision, lumbar punctures, and eye examinations for retinopathy of prematurity were considered highly invasive procedures.[1075] In a survey of 467 clinicians (nurses and physicians) working in level II and level III nurseries asked to rate the painfulness of 12 common bedside nursery procedures, circumcision was considered the most painful procedure (tied with chest tube insertion). Circumcision was considered more painful than endotracheal intubation, insertion of gavage tube, tracheal suctioning, arterial or venous cutdown, lumbar puncture, intramuscular injections, insertion of an umbilical artery catheter, insertion of peripheral intravenous line, heel stick, and insertion of radial or tibial arterial catheter.[1091]

The signs of pain seen during infant circumcision include surprisingly high-pitched crying,[1082,1083] changes in facial expressions,[1019] a drop in blood oxygenation with hypoxemia,[1092-1099] significant increases in heart rate, respiratory rate, and blood pressure,[1014,1018,1019,1081,1200] and a significant decrease in vagal tone.[1083] Direct measures of nociceptive spinal cord and brain activity during infant circumcisions have not been reported in the medical literature. To properly assess the pain of infant circumcision, all of these need to be measured.

Because of the highly invasive nature of infant circumcision, providing adequate anesthesia is indicated. While United States law requires that effective anesthesia and analgesia be provided for veterinary and laboratory animals,[1077-1079] it appears this does not apply to human newborns. In an effort to alleviate the pain of circumcision, a number of interventions have been implemented and assessed. These include comforting measures, sucrose nipple, acetaminophen, dorsal penile nerve block, topical anesthesia, injection of local anesthesia, alternative restraints, and different circumcision methods.

Despite improvements, compared to placebo and dorsal penile nerve block, studies looking at these interventions still showed significant departures from baseline status in regards to vital signs, vagal tone, and cortisol levels, indicating that the procedure was not pain-free. Therefore, **none** of these methods have been shown to provide *adequate* anesthesia.[847,1018,1019,1022,1066,1089,1093-1099,1101-1115] A cynic might note that topical and local anesthetics are used in infant circumcisions more to benefit the parents than the child.

The complications of topical and local anesthesia include bruising and hematoma formation,[847,1114,1116-1118] gangrene of the penis,[1119] and methemoglobinemia.[1119-1133]

More effective methods of anesthesia, such as general anesthesia and caudal blocks,[1134-1150] are not used because of the difficulty, and the associated risks, of using them in infants. According to the standards established by the American Academy of Pediatrics, neonates should receive the same pain relief measures as those afforded to older children and adults.[1151] To accomplish this, circumcision would need to be delayed until general anesthesia can be more safely delivered. In keeping with this recommendation, the Australasian Association of Paediatric Surgeons recommends deferring the procedure until at least six months of age.[1152]

Claims that circumcision is less painful when performed on an infant have not been substantiated with any evidence. The fact that noxious stimuli are more painful for the neonate, along with the known inadequacy of topical and local anesthesia, provides evidence to the contrary. There are also differences in the procedure between infancy and later in life that make it more uncomfortable for the neonate. For the majority of males older than fifteen years of age, the inner

surface of the foreskin is no longer attached to the surface of the glans.[52,85,86,1153] In newborns, nearly all of the glans is attached to the foreskin. Unlike circumcision of an older male, infant circumcision requires tearing the two structures apart, which is akin to pulling a fingernail from the nail bed. This open wound is exposed until it heals within a few weeks. For an older individual, there is no open wound on the surface of the glans.

Healthcare providers need to include, as part of the disclosure element of the informed consent process, that currently used methods of anesthetics do not provide adequate anesthesia for the procedure, and that the procedure is still unacceptably painful when these agents are used.

Missing from this section is a recognition of the harm that accompanies removal of the foreskin, which contains nearly all of the fine touch neuroreceptors of the penis, and thus deprives the male of the functions the foreskin provides. The normal anatomy, histology, physiology, and function of the foreskin are discussed earlier in this response, but they were completely left out of the CDC's draft. Removal of this specialized tissue would be expected to result in changes in function. Harm also comes in the form of pain, and in the form of no longer being whole or feeling whole. By ignoring the harms of the intervention, the writers of the CDC draft are ignoring medical evidence and aligning themselves with the "harm denialists" on this issue.

While the sections outlining the complication rates of circumcisions performed on adults and infants in Africa are interesting, this information is peripheral and unlikely to be of interest to healthcare providers in the United States. As noted above, the low complication rates seen in the randomized clinical trials might indicate that complication rates are lower for circumcisions performed on adults than on circumcisions performed on infants.[1-3,1154]

Finally, one specific comment. The CDC draft includes the following statement: "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." It gives as its citation an opinion piece,[33] which based its calculations on a selective bibliography and a number of other like-minded opinion pieces written by the same author.[473,1155-1159] To accept this ratio, one must live in a fantasy world where the incidence of phimosis is 10% (instead of 0.6%[457]), where the incidence of balanitis is 10%(instead of 0.65% to 4%[541,543]), where circumcision is a risk factor for urinary tract infection in elderly men in their dotage (it is not one), where hypertension and end-stage renal disease are associated with urinary tract infections (they are not), where prostate cancer risk is lower in circumcised men (it is not), where penile cancer is 20 times more common in intact males (instead of at most 3 times[455]), where HPV and herpes risk is reduced by circumcision (it is not), where cervical cancer risk is associated with the circumcision status of the male sexual partner (no studies have found such an association), where risk of infection is 0.2% (instead of 1% to 2%), where the risk of bleeding is

0.1% (instead of 1% to 2%), where the risk of repeated surgery/skin bridges is 0.1% (instead of 4% to 12%[46,186]), where meatal stenosis never happens (instead of 5% to 20%,[186,533-537] and where there is never a loss of sensitivity or any sexual dysfunction following circumcision. If one takes the complication rate compiled reviewing the charts of newborn males by the CDC (3.1%)[6] as a baseline and applies the 100:1 ratio, then every circumcised men should reap, on average, 3.1 benefits being circumcised. This is patently absurd. So, why would the writers of the CDC draft accept and propagate a ratio, from an opinion piece written by an individual whose scientific rigor in these matters has been called into question repeatedly,[1160] that is clearly implausible? Why did they not perform a comprehensive literature review of their own? What has the CDC been doing on this topic for the past seven years? Clearly, reference to this preposterous "ratio," and the opinion piece that generated it, needs to be deleted from the final draft. Any healthcare provider that informs a parent or patient that the ratio of benefits to risk exceeds 100:1 is putting themselves at risk of a lawsuit for making such a wildly unsubstantiated claim. It has been argued that, by taking the scientifically unsupported position it has, the American Academy of Pediatrics is susceptible to successful litigation for misleading healthcare providers.[1161]

Effect of male circumcision on sexual function and penile sensation

The material presented in this section of the background document is highly selective and ignores studies indicating circumcision has a negative impact on sexual function and penile sensation. It also misrepresents the findings of some of the studies cited.

There are a number of important omissions. For example, the 2007 study by Sorrells et al. "expressed concern that its [the foreskin's] removal may compromise sexual sensation or function," based on their mapping of the fine-touch thresholds of the penile surface in 68 circumcised men and 91 men with normal, intact genitals. Mapping revealed that the most sensitive portion of the penis is that which is removed by circumcision, the circumcision scar is the most sensitive location on the circumcised penis, and the sensitivity of the glans (head) of the penis is significantly less in circumcised men.[108] Decreased sensitivity in the glans when flaccid in circumcised men has been documented in two other studies that the CDC draft has omitted.[109,110] In one study, the difference was statistically significant using the raw data, but was no longer statistically significant when adjusted for age, hypertension, and diabetes.[109] In the other study with only 20 men in each group, the difference is shown in Figure 2, but the data are not provided and the significance of the difference is not assessed.[110]

The section fails to mention that the penilo-cavernosus reflex, which is related to the ejaculation process, is significantly more difficult to elicit in circumcised men than in men with normal genitals.[120] This may contribute to the higher rates of sexual dysfunction seen in circumcised

men.

In addressing studies that looked at penile problems in men before and after circumcision, the CDC draft demonstrates several important oversights. For example, in the 2002 study by Fink et al., they fail to mention that men in this study reported a significant reduction in erectile function (p=.01) and decreased penile sensitivity (p=.08). A perceived problem or difficulty as a result of the procedure was reported by 38% of the men studied.[1162] The 2002 study by Collins et al. would, because of its small size, not be expected to provide any results that were statistically significant. This is unfortunate because, of the 15 men who were circumcised as adults, all but one had a penile problem. The fact that there was no measured improvement in sex drive, erection, ejaculation, problem assessment, or overall satisfaction suggests that the procedure was a failure.[1163] There are a number of similar studies the draft has omitted. For example, Coursey and colleagues included a control group of men who were circumcised for "phimosis or other benign indication" in a study designed to measure the impact of anterior urethroplasty on erectile function. Of the men who underwent circumcision, 27% reported worsening of their erectile function after the procedure.[1164] In a study of 95 men undergoing circumcision in China, erectile dysfunction increased following the procedure (p=.001). These men also reported increased problems with weakened erectile confidence (p=.04), and difficult insertion during coitus (p=. 03). Improved satisfaction following the circumcision was reported in only 34 patients (p=.04). [116] Similarly, a study from Portugal of 62 men circumcised for medical reasons reported a significant increase in erectile dysfunction and difficulty reaching orgasm following circumcision.[1165]

The CDC draft mentions two other studies in passing,[1166,1167] without providing details. The first study was performed in Turkey where most men undergo circumcision to satisfy a religious requirement, making it difficult to properly interpret the results.[1166] In the second study, while there was no difference in the overall mean of the International Index of Erectile Function, satisfaction was only 61% following the procedure.[1167]

The draft mentions the results of two studies that assessed sexual function before and after circumcision in men who were enrolled in the randomized clinical trials in Kenya and Uganda. [1168,1169] Because these studies were large and part of a randomized clinical trial, the results have been given more weight than they deserve. There are several reasons to distrust their conclusions. The studies from Africa show rates of sexual dysfunction that were orders of magnitude lower than studies performed outside of Africa. For example, in the study by Krieger et al.[1168] the prevalence of premature ejaculation was 4.27% (95%CI 3.12%-5.41%) and the prevalence of trouble achieving orgasm was 1.26% (95%CI 0.62%-1.89%) while the prevalence in the other studies performed outside Africa were 30.59% (95%CI=29.74%-31.43%) and 11.19% (95%CI=10.61%-11.77%), respectively. In the study by Kigozi et al.,[1169] the prevalence

of lack of sexual desire was 0.80% (95%CI 0.35%-1.25%) while the prevalence in the other studies was 28.83% (95%CI 27.99%-29.66%). Similarly, the two African studies together had a prevalence of erectile dysfunction of 0.93% (95%CI 0.57%-1.29%) and prevalence of dyspareunia of 1.13% (95%CI 0.72%-1.54%), while the prevalence in other studies was 18.16% (95%CI 17.47%-18.88%) and 3.47% (95%CI 3.13%-3.81%), respectively. These vast differences suggest either cultural differences in what these conditions entail, unwillingness to disclose the presence of sexual dysfunction, or the coercive impact of the large subsidies men received for their participation in the studies. These subsidies could explain their eagerness to tell the researchers what the researchers wanted to hear. Of course, it could be that these sexual problems occur 3 to 36 times less frequently in Africa. If that is the case, as someone jokingly suggested, Uganda and Kenya should consider developing tourism campaigns that would tout coming to these countries for the "best sexual experiences on the planet."

The extremely low rates of sexual problems that were documented in Africa are examples of both the element of ceiling effect[1170] and of asking non-differentiating questions. With sexual satisfaction measured at rates exceeding 98% when surveyed both before and after circumcision, there is no room to move up (thus pinned against the ceiling). It is also not known how high the level of satisfaction actually is because the ceiling (the limitation of the assessment tool) acts as a barrier. For example, if the ceiling score is set at 100 and the average score before circumcision was 125, the best one could score would be 100 because of the ceiling in place. The few scores below 100 would bring the average to slightly below this. If the average score after circumcision was 112 (a 10% decrease), the best one could score would be 100, so the score after circumcision would be similar and this 10% decrease would not be detected. Similarly, a 10% increase in the score following circumcision would also be missed using the tools these researchers employed. Consequently, the negative findings of these studies are meaningless.

The questions asked in the survey were also so vague that they would not have been able to demonstrate a difference in sexual function, if one existed. As Morten Frisch, MD, has noted, "I am not surprised that these studies provided little evidence of a link between circumcision and various sexual difficulties. Several questions were too vague to capture possible differences between circumcised and not-yet circumcised participants (e.g. lack of a clear distinction between intercourse and masturbation-related sexual problems and no distinction between premature ejaculation and trouble or inability to reach orgasm). Thus, non-differential misclassification of sexual outcomes in these African trials probably favoured the null hypothesis of no difference, whether an association was truly present or not."[1171]

The draft omits mention of several studies that have addressed the impact of circumcision on sexual function and how it impacts the female sexual partner. A 1999 study of women who had sexual experiences with both intact and circumcised men found that they strongly preferred sex

with an intact penis.[115] While this study may have suffered from selection bias, as the participants were volunteers who responded to an announcement in an anti-circumcision newsletter and classified advertisements in magazines, its results were replicated in a cross-sectional national survey in Denmark. The Danish survey demonstrated that the female sexual partners of circumcised men were 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).[1172]

This Danish study also documented that circumcised men were more likely to report frequent orgasm difficulties (adjusted OR 3.26; 95%CI 1.42–7.47).[1172] In a survey of 1059 normal and 310 circumcised men, Bronselaer and colleagues 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.[1173]

The draft does not address the issue of premature ejaculation. One Turkish study found that following circumcision, the intra-vaginal ejaculation latency time increased by 20 seconds (a statistically significant difference), which certainly should be enough extra time to help their female partners achieve orgasm.[1174] While several studies have shown no difference in the rates of premature ejaculation between normal and circumcised men,[1175,1176] this does not mean that studies in which a statistically significant difference is found can be ignored. For example, a study by Tang et al. found a four-fold increase in premature ejaculation in circumcised men (adjusted OR 4.881; 95%CI 2.346-10.153).[1177] In a representative household sample of Australian men, circumcised men were significantly more likely to report premature ejaculation (OR 1.41; 95%CI 1.14-1.75) and erectile dysfunction (OR 1.39; 95%CI 1.08-1.79).[1178] This was consistent with an earlier Australian survey that found circumcised males were more likely to report premature ejaculation (OR 1.28; 95%CI1.15-1.42).[1179] The studies of the effect of circumcision on sexual function indicate a negative impact.[1180] It also warrants mention in the informed consent discussion that circumcision may have a deleterious impact on sexual function, but further study is needed to fully evaluate the impact.

The CDC draft only performed a cursory exploration of whether circumcision impacts sexual function or penile sensitivity and only cited negative studies while ignoring the many positive studies. Their discussion is inadequate and not evidence-based.

Considerations related to male circumcision in the United States

HIV infection in the United States

The material presented in this section of the background document is incomplete and somewhat misleading.

It should be noted that while the HIV prevalence is high in several cities, the circumcision prevalence, especially among African-Americans, is high as well.

The statement, "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," is another restatement of the CDC "group think" presumption, and has no factual foundation.

The discussion about which ethnic and racial groups should be targeted for circumcision is moot. As discussed elsewhere, the medical evidence indicates that the only population that should be targeted for possible discussion of circumcision are HIV-negative men who have regular sexual contact with an HIV-positive female sexual partner. And, as modeling by the CDC has demonstrated, circumcision has very little impact over the long term in how frequently these men will become infected.[340]

While HIV infections continue to occur in the United States, most infections are in men having sex with men and intravenous drug users, groups that will not benefit from circumcision. If circumcision was to have a protective effect against female-to-male transmission of HIV, one would have expected the United States to have a lower prevalence of heterosexually-transmitted HIV than similarly situated developed countries with low circumcision rates. The prevalence of heterosexually-transmitted HIV is several times higher in the United States than in Europe. The United States has already completed the circumcision experiment, and the results show it has failed to protect its population from HIV infections. Our experience in the United States indicates that circumcision is a factor that is not worthy of the attention that CDC has expended on promoting it. This is a complete waste of taxpayers' money both here and in Africa. Taxpayers would be astounded at the amount of their money being used to fund programs in Africa involving mass circumcisions promoted by propaganda campaigns, unethical solicitation, coercion, and misinformation.

Rates of male circumcision in the United States

The material presented in this section of the background document is fairly straight forward, but there are some additions and corrections that need to be made.

While it is true that circumcision unrelated to religious beliefs was introduced into the United

States in the late 1800s, it needs to be added that circumcision was introduced as a "cure" for masturbation. A more appropriate citation for this is also needed. The current citation,[1181] does not give the complete title of the book (*Circumcision: Timely Information for Parents and Professionals from America's #1 Expert on Circumcision*) and is not written by a medical historian, but rather an unabashed circumcision advocate. Several other citations, written by medical historians would be more appropriate.[1182-1185]

There needs to be an acknowledgement that we do not have a mechanism in place in this country to accurately determine the number of infant males being circumcised here. For example, one 1968 study found that 30% of circumcisions were not documented in hospital discharge summaries,[1186] and another extensive chart review performed by the CDC found that 15.7% of circumcisions that are documented in medical charts were not documented on the facesheet, from which data are collected into databases.[6] Likewise, self-report of circumcision status is often unreliable.[260,1187-1192] It should also be noted that several studies have indicated that the circumcision rate in blacks is similar or higher than in non-Hispanic whites. For example, data from Atlanta from 1985 to 1986 by the CDC found that 95.9% of blacks were circumcised as opposed to 86.7% of whites (OR 3.75; 95%CI 1.58-10.25).[6] Mor et al., in a study of 58,598 male patients in San Francisco, found that, in males born in 1960 or after, blacks were more likely to be circumcised than non-Hispanic whites.[8] Similarly, Mansfield et al. found 86.8% of blacks were circumcised as opposed to 89.6% of whites (OR 1.30; 95%CI 0.95-1.79).[7]

The assertion that male circumcision is more common among newborns born to families of higher socioeconomic status may no longer be true. It may have been true when data were collected in 1988 to 2000,[1193] [Note that CDC185 reference lists the authors of the study incorrectly] but there is increasing evidence that as maternal education levels increase circumcision rates decrease. With the advent of the internet and medical literature searches available to the public, parents with higher levels of education are increasingly choosing not to circumcise their sons. This is consistent with the fact that physicians are less likely to circumcise their sons as compared to the populations they serve.[112]

The purpose of this section is unclear. The reader should take away two clear conclusions: first, that the rate of infant circumcision in United States is declining; second, that the method of collecting circumcision prevalence data is highly flawed and unreliable. It is unclear whether the purpose of the section was to raise alarm over the falling circumcision rates or to reassure circumcision advocates that all is not lost. In either case, the inclusion of this section in the draft needs further justification.

Acceptability of adult male circumcision in the United States

The material presented in this section of the background document is tainted by an underlying false assumption: that American men and adolescent males who have normal genitals are at increased risk for heterosexual acquisition of HIV. As discussed elsewhere, the data do not support this assumption. With that in mind, one has to assess whether the data collection documented in this section was based on their faulty premise. The authors of the 2008 CDC study by Begley et al. asked gay men, "If Scientific studies in the United States among men who have sex with men showed that circumcision reduced the risk of HIV infection, would you be willing to be circumcised as an adult?"[1194] Given that, as discussed elsewhere, there is no evidence of circumcision being a risk factor for HIV infection in men having sex with men, the question carries as much validity as asking, "If the moon is made of cheese, would you prefer that it be cheddar or gouda?" The authors in the CDC 2011 study by Gust et al. also clearly begin with an unproven assumption.[1195][The citation as given in the draft does not list the authors correctly.] The question asked in the survey was, "If your health care provider told you that getting circumcised would reduce your risk of becoming infected with HIV, how likely would you be to get circumcised?" The study did not include a control question which would be, "If your healthcare provider told you that there is no evidence in the United States to suggest that circumcision reduces the risk of HIV in United States how likely would you be to get circumcised?" By not including this alternative question, it is impossible to know how much of the response is based on scare tactics alone. It would appear that the scare tactics have continued and are now extended to this draft. The low response rate of normal men willing to undergo circumcision, even in the face of the CDC's scare tactics, reflects that men with normal genitals recognize the value of having normal genitals and would be willing to pursue other, more effective, avenues of decreasing their risk of HIV infection.

The statement, "Adult and adolescent male circumcision potentially has 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," is not applicable in the United States for several reasons. There is no evidence that circumcision has an impact on risk of HIV transmission through penile-vaginal sex, as the randomized controlled trials in Africa did not assess the origins or mode of transmission of the infections they documented.[1-3] As discussed elsewhere, none of the studies in North America of heterosexually- transmitted HIV infections have found circumcision to be a significant risk factor.[8-15] Finally, the United States has, by developed-nation standards, a very high prevalence of circumcision and a very high prevalence of heterosexually-transmitted HIV. As noted in this section of the draft, African-Americans have the highest prevalence of heterosexually-transmitted HIV, but the CDC neglects to mention that African-Americans also have the highest prevalence of circumcision, on par with non-Hispanic whites. If anything, this would indicate that circumcision is either a marker for other socio-behavioral or ethnic factors, or, if it has an impact on HIV risk, it is clinically inconsequential and, therefore, not worthy of pursuit. It appears as though the CDC is trying to create additional

demand for circumcision in an unreceptive market. Consequently, the recommendations for the intended audience of health care providers are unjustified and inappropriate.

Acceptability of adult male circumcision in sub-Saharan Africa

The material presented in this section of the background document has little or nothing to do with how circumcision relates to HIV infection in North America. Since when is the CDC the arbitrator of health care in Africa? And, why is U.S. tax money being used to promote a surgery of unproven benefit in Africa? How is this part of the charge that was given to the CDC by the "consultation" in 2007?

A little history lesson: generating acceptability of adult male circumcision in sub-Saharan Africa began as an important precursor to the randomized clinical trials. While circumcision advocates believed that they made a legitimate case based on a handful of observational studies for using circumcision as a preventive measure for HIV infection,[31,1196-1198] mainstream HIV researchers demanded randomized clinical trials.[1199] For a randomized clinical trial in Africa to demonstrate a statistically significant difference, it needed to be powered to document a 1% absolute risk reduction. Consequently, several thousand participants would need to be recruited.[236,237] In order to garner enough participants, the investigators for the randomized clinic trials implemented sessions within the communities in which the trials were to take place that disseminated pro-circumcision propaganda under the guise of assessing acceptability of male circumcision as a strategy to reduce sexually transmitted diseases and HIV infection.[1200-1207]These propaganda sessions had three effects: they convinced enough men to enroll in the overpowered clinical trials, they introduced an expectation bias on the part of the participants, and they undermined the validity of the informed consent process in the trials. Given the pro-circumcision bias of the researchers, it is unlikely that participants were given full disclosure, particularly regarding the harms of the procedure. This is evident in the consent form used in the trial undertaken in South Africa, in which none of the adverse effects of circumcision are listed.[1] There is direct evidence that participants did not show understanding of what was told to them as most (57%) believed, even after disclosure, that circumcision would reduce their risk of infections.[211,212] This would certainly affect the behavior of the participants and contribute to participant expectation bias. So much for equipoise.[1208]

The effectiveness of the propaganda campaign was based on illusory or fabricated factors designed to increase the acceptability of male circumcision. For example, there is no evidence that male circumcision improves hygiene. There is no evidence that male circumcision improves the use of condoms, but there is evidence that condoms slip off more frequently in circumcised men.[1209] There is no evidence that male circumcision increases sexual pleasure, but, as discussed above, ample evidence to suggest that circumcision interferes with the sexual pleasure of both

the male and his female partner.[115,1165,1172,1173] The evidence that circumcision protects against sexually transmitted infections is, as discussed elsewhere, also lacking.

The propaganda campaign had an interesting unexpected impact on women. For example, while women in Tanzania had heard the expression "partial protection," they had no idea what it meant.[1210] In a South African study, it was found that women who perceived circumcision as reducing the risk of HIV infection were less likely to use condoms in their last sexual encounter, generally, and with circumcised partners of positive or unknown HIV status. Men were more likely to use condoms.[1211] Similar findings have been reported from Kenya.[1212]

There is also the belief among women in some parts of Africa that circumcision reduces the male-to-female transmission of HIV,[1213] where the opposite may be the case.[338] This indicates that the impact of circumcision on risk compensation in Africa may be driven more by the attitudes and misperceptions of women than those of men. Women may be the ones more susceptible to, or aware of, the advertising and marketing endeavors of those promoting circumcision.

A major barrier to the rollout of adult male circumcision in Africa was that acceptability of the intervention for HIV prevention was much lower than the circumcision advocates had anticipated. They believed that, if it could be demonstrated in randomized clinical trials that circumcision reduced the risk of HIV infection, normal African men would swarm to have their foreskins removed. This did not happen. There was some initial interest in male circumcision programs from men who, likely for religious or cultural reasons, would have requested circumcision anyway and saw this as an opportunity to obtain a free circumcision performed under more sterile conditions. By 2012, with the exception of Kenya, the roll out of adult male circumcision programs has been an abysmal failure. For example, of the men targeted to be circumcised only 4.8% have been in Uganda, 0.7% in Rwanda, 11.1% in Zambia, 1.5% in Namibia, 6.5% in Botswana, 7.0% in South Africa, 12.7% in Tanzania, 0.4% in Malawi, 2.9% in Zimbabwe, 4.7% in Mozambique, and 0.2% in Lesotho. Only Kenya, Swaziland, and Ethiopia had a response rate over 20%.[1214] In response to the poor uptake, circumcision advocates held sessions at the 2012 XIX International AIDS Conference in Washington, DC, to announce that male medical circumcision was being rebranded as a way of building intimacy and improving one's sex life with the phrase "Reshape your Relationship." Since women tend to take responsibility for "relationships," the advertising is shifting towards women, who ironically are more likely than men to encourage risk compensation, and women are more at risk of becoming infected with HIV from their male partners.[1212,1213]

Over 100 articles have been published assessing the rollout of adult male circumcision in Africa. Nearly all of them have focused on the wrong outcome: increasing the number of men

circumcised. Instead, the focus should be on looking for the most effective and efficient way of reducing the number of people who become infected with HIV.

To give you an example of how pathetically desperate circumcision advocates are to increase the acceptability of adult male circumcision in Africa, the *Journal of the American Medical Association* in 2014 published a study to determine what impact **bribing** African men would have on the acceptability of male circumcision in Kenya. When offered a free circumcision without any bribe, only 1.6% of intact men were interested. When a bribe worth $15 was offered, the number of men accepting the bribe increased the percentage to 9.0%.[1214] Keep in mind that Gross National Income per capita in Kenya in 2013 was $1160,[1215] this would be equivalent to a $691 bribe in the United States ($53,470 GNI per capita in 2013).[1216] Models of the impact of circumcision on overall HIV incidence in Africa reported their results based on reaching compliance levels of 55%,[229] 60%,[220] 70%,[230] 80%,[222,225,228] 95%,[224] and 100%.[221,223,226,227,231,232] If one assumes that the increase in compliance has a linear relationship to an increase in the amount of the bribe offered, then the bribe amount needed for the percentage to increase from 59% to 60% would be $147.81 and to increase from 79% to 80% would be $199.89. The average bribe needed to get to 60% compliance would be $71.60 and to get to 80% would be $97.49. The cost of these inducements would more than double the marginal costs of the circumcision programs. If the relationship between compliance and the amount of bribe is non-linear, the cost to bribe men to get circumcised might be even greater. Other adult male circumcision programs in Africa have resorted to bribery to get men to participate.[1217] Bribery and coercion tactics violate basic research ethics and would not be allowed in the US, so how is this allowable in Africa?

The call for African men to become circumcised has also led to a number of men and boys being forcibly circumcised.[1218-1227] Given tribal tensions, between tribes that traditionally circumcise and those that do not, this was a predictable consequence of the widespread propaganda encouraging circumcision. There have also been reports of boys being told they would not be allowed to play football (soccer) unless they were circumcised.

Efforts to increase the acceptability of adult male circumcision in sub-Saharan Africa are based on misinformation and deception, consequently, the material in this section is inappropriate, and fraudulent. African circumcision has little or nothing to do with the United States and other developed countries.

Acceptability of newborn male circumcision in the United States

The material presented in this section of the background document misses several key points. The CDC draft fails to mention that the acceptability of newborn male circumcision in the

United States may be, in part, driven by the fact that the procedure is solicited by physicians, nurses, and hospitals. At the first prenatal visit, mothers are routinely asked whether they would want a son circumcised. The question is repeated upon admission for the perinatal hospitalization. For parents who have done little or no research on the topic of infant circumcision, this can be interpreted as a recommendation to have the procedure performed on their son. Parents who do not want their sons circumcised have often reported that they are asked multiple times during the hospitalization whether they want their son circumcised, with many of them reporting that they are harassed and outright bullied by the hospital staff. The degree to which parents are intimidated into circumcising their sons has received little study.[1228] Such solicitation is considered unethical under the guidelines of the American Medical Association because the procedure removes healthy tissue, and circumcision will benefit the physician's and hospital's pocketbook more than it will benefit the patient.[1229]

This CDC section fails to address the impact of the physician's circumcision status on the advice delivered to parents. In a survey of Canadian physicians, circumcised male physicians were almost five times as likely to recommend circumcision (OR 4.76; 95%CI 3.00-7.55) and those physicians with circumcised sons were six times more likely to recommend circumcision to the parents of their male patients (OR 6.22; 95%CI 3.83-10.10). Those who said they based their recommendation on the medical evidence were twice as likely to recommend against circumcision (OR 1.95; 95%CI 1.29-2.95).[39] One can only speculate whether this CDC draft has been influenced similarly. It is reasonable to question whether the circumcision status of a physician or the physician's children, and the associated bias thereof, should be disclosed to parents. The same could be said regarding the authors of this draft and whether their inherent biases should be disclosed to the public.

Whether parents have the moral or legal authority to choose circumcision on behalf of their sons will be discussed in a later section.[1230] Parents do not have to provide a justification in order to direct the healthcare provider to circumcise their son, unlike the removal of any other healthy body part. Likewise, physicians would not agree to blithely removing any other healthy normal body part from an infant or child without a disease being present.As noted in the citations given in the draft report, studies of the reasons parents choose circumcision for their sons have not been updated since the 1980s.[923,1231] If these studies were to be repeated today, cultural conformity would likely be the most common justification.

The authors of this section accept the interpretation provided by Adler et al. of their survey data, which reflects the bias of the study's authors more than the data they collected.[1232] The study indicates that physicians were not supportive of parents deciding not to circumcise their sons and perhaps berated them for not doing so. The conclusions reached by the authors is not surprising. The parents of intact boys, by virtue of being asked so many questions about circumcision,

would have to wonder if there was something about circumcision they were not told. If, however, complete disclosure, consistent with the current standard applied to other procedures, were provided, parents who had already chosen to circumcise their sons would not want to be confronted with the litany of complications and harms associated with the procedure. Their minds are already made up and providing information has little impact.[1233] [This is another citation that has not been updated. The article was published in 2010.] For these parents, any information is too much. It would have been more appropriate for the survey to have asked if too much information was provided. This is a clear example of expectation bias on the part of researchers impacting the methodology of a study to ensure the preconceived outcome was obtained.

The study by Gust et al. is perhaps more contrived.[1195] The study collected data based on an unproven premise: that infant circumcision would have an impact on HIV risk in the United States. As noted elsewhere, there are no studies of infant circumcision that have demonstrated a significant association with HIV prevalence or incidence, and no studies in North America that have found circumcision to be protective against HIV infection.[8-15] This is another example of asking, "If the moon is made of cheese etc…… ?" The study by Wang et al. is also based on a similar faulty premise.[1233]

The inclusion in this section of whether or not there is state Medicaid coverage of infant circumcision is inappropriate and irrelevant. The only reason to include this topic would be because the CDC has an underlying motivation to promote circumcision in order to increase demand for circumcisions, thereby increasing physician reimbursement. It has been argued that under the current federal statute, it is illegal for states to reimburse physicians for performing circumcisions on infants as it is an "unnecessary, elective, cosmetic surgery on healthy boys, usually performed for cultural, personal or religious reasons."[1234] While there is an association between Medicaid coverage and infant circumcision rates, it does not follow, as Leibowitz et al. suggest,[1235] [Again the citation in the draft fails to include all of the authors.] that providing Medicaid coverage would increase the circumcision rates in these states where the rates have been historically low.

Acceptability of newborn male circumcision in sub-Saharan Africa

The material presented in this section is totally ludicrous. Why should the U.S. care about uninformed opinions regarding infant circumcision from propagandized Africans?

The material in this section is not evidence-based, but based on uninformed opinions of populations that are vulnerable to false propaganda.

Provider attitudes and practices regarding male circumcision in the United States

The material presented in this section is incomplete with multiple omissions. For example, it is stated that "many medical societies have addressed neonatal male circumcision," yet only the American Medical Association, the American Academy of Pediatrics, the American Academy of Family Physicians, and American Urological Association are cited. Many medical societies outside of the United States *have* addressed neonatal male circumcision. It is odd that the draft report is taking a global perspective when assessing the acceptability of adult and infant male circumcision in Africa, yet is provincial when it comes to the opinions of medical societies. Is there something in the opinions of medical societies outside of the United States that authors of this draft find troublesome? The draft needs to include the opinions of medical societies outside of the United States. More importantly, the CDC needs to provide insight on how they have access to "special knowledge" that the rest of world is missing, which led them to reach such a discordant conclusion.

The Royal Dutch Medical Association in 2010 noted that there is no convincing evidence that infant circumcision, which constitutes a human rights violation, is useful or necessary, and there are good reasons for legal prohibition of the practice, consequently "it is reasonable to put off circumcision until the age at which such a risk is relevant and the boy himself can decide about the intervention, or can opt for any available alternatives."[1236]

The Swedish Medical Association recommends a minimum age of 12 years for performing a circumcision as it requires fully informed consent from the boy.[1237]

The Finnish Union of Medical Doctors (Suomen Lääkäriliitto) is opposed to infant circumcision because of its risk, pain, and the injury inflicted.[1238]

The Swedish Pediatric Society came out against infant circumcision characterizing it as an "assault on boys."[1239]

The Danish College of General Practitioners has stated that infant circumcision is tantamount to abuse and mutilation.[1240]

In 2012, the Berufsverbands der Kinder- und Jugendärzte (the German national organization of Pediatrics) condemned the practice of infant male circumcision.[1241]

Medical organizations in British Columbia and Saskatchewan have come out against infant circumcision.[1242,1243]

As noted below, several national medical associations consider infant male circumcision a human rights violation.[1236-1238,1244,1245]

Other medical organizations from Canada, Britain, and Australia have adopted a position where the practice is tolerated, but not endorsed, encouraged, or recommended.[1246-1248]

Having taken an exceptional position, the CDC needs to provide an exceptional justification: one that should take our breath away. They need to defend their position on an international stage, something the American Academy of Pediatrics had trouble doing in 2012 when they did not recommend circumcision, but stated they *"felt"* that the benefits outweighed the risks.[1249-1252] So, instead of providing an evidence-based evaluation, the American Academy of Pediatrics provided a feelings-based evaluation. The CDC has taken a more extreme position and runs the risk of embarrassing itself and the United States once again.

The studies cited by the CDC in this section give a mixed message. On one side, it is well-documented that physicians are very poorly educated regarding normal male anatomy and infant male circumcision,[1253] and on the other, physicians are encouraged to act on their clearly uninformed opinions.[1254] The surveys conducted of physicians are reminiscent of push-polls used by politicians, where conducting a survey is a premise for propagandizing. These "studies" contain those elements. At a conference held in the Fall of 2013 in South Carolina at the Pitts Lectureship in Medical Ethics, members of the 2012 American Academy of Pediatrics Task Force on Circumcision confessed ignorance regarding the function of the foreskin.[41] If policy-makers on this issue are ignorant, what can be expected of the average medical professional? Education is sadly needed, but it should not take the form of clearly subjective, biased pro-circumcision propaganda peddled by the misguided American Academy of Pediatrics task force on circumcision, or what is currently proposed by the CDC. It has to be evidence-based, not culture-based. This may be difficult, as the circumcision status of the physicians and their children has a substantial impact on whether a physician recommends circumcision.[39,1254] It is not surprising that European physicians, where there is no cultural pressure to be circumcised, have different attitudes towards protecting newborn males from harm.

The material presented in this section is the result of a very narrow ideological focus.

[Note: The American Pediatric Association (Does this organization even exist? There is an American Pediatric Society that is populated with pediatric researchers and the Academic Pediatric Association that is populated by academic pediatricians who teach general pediatrics) does not have guidelines on circumcision, but the American Academy of Pediatrics has published several Task Force reports on circumcision.]

Cost-effectiveness

The material presented in this section is selective in favor of circumcision. It presents findings in a biased manner where the positive aspects of circumcision are emphasized, while studies that expose the weaknesses of circumcision are dismissed, omitted, or ignored. Some statements are factually untrue. For example, the statement, "While male circumcision has been shown to be a cost-saving HIV prevention intervention in sub-Saharan Africa" is not supported by the citations provided.[227,232] These references are mathematical models based on assumptions. The models are only as good as the assumptions and do not measure costs in the real world. They only provide conjecture as to what might happen in the real world if the assumptions turn out to be true. As far as these models are concerned, the calculations are based on reaching universal male circumcision within the targeted populations. As noted earlier, the efforts to roll out adult male circumcision are far below this goal.[213-219] Until actual, real-life data are collected, this statement is inaccurate. Furthermore, the randomized clinical trials have multiple biases and flaws, which discount any perceived benefits.

Several of the cost-effectiveness and cost-utility analyses published prior to the release of the results from the randomized clinical trials focused on circumcision's impact on urinary tract infections and they found the procedure wanting.[1255-1257] The 2004 analysis by Van Howe,[1258] which used a Markov analysis and estimated the variability of its findings using Monte Carlo simulations, provided a comprehensive analysis of the costs and health states that may be impacted by infant circumcision. It included the baseline assumption that an intact male had, based on published meta-analyses available at the time, an odds ratio of 1.78 (95%CI 1.33-2.37) of being more likely to become infected with HIV through heterosexual transmission. This assumption is consistent with the results of the randomized clinical trials, yet the cost-utility analysis found that infant circumcision resulted in a lifetime increase in costs ($828. 42 per patient) and a decrease in health (15.30 quality adjusted life-years per 1000 males), results that were ignored by the CDC in this draft.

By contrast, the CDC draft propagates the misrepresentation of the findings of a cost-analysis published by Schoen et al.[1259] A cost-analysis calculates the difference between the costs incurred by an intervention and costs that are saved as a result of the intervention. The benefits and risks are reflected in their respective monetary costs. In the cost analysis by Schoen et al., infant circumcision resulted in more costs than it was able to recoup in benefits ($27 per circumcision). In other words, circumcision cost more money than it saved. To conclude that "the expected lifetime cost of male circumcision was small, compared with larger expected benefits" reveals that the authors of the cost-analysis and the authors of this section do not understand that any benefits are already included in the analysis (in monetary form) and their conclusion is, in effect, an inappropriate attempt to count the benefits twice, which is beyond the scope of a cost-

analysis. This indicates a bias, or incompetence, on the part of the CDC.

The statement, “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,” is made without reference or citation. Where is the evidence? Post-neonatal circumcision, which a recent study published by the CDC estimates as costing on average $1885, is more expensive than neonatal circumcision (average cost $285).[472] Most of this expense is related to the use of general anesthesia. Considering, as discussed earlier, that local and topical anesthesia do not provide adequate anesthesia for the procedure, this may be money well spent. Post-neonatal circumcision is rarely indicated, and it is never indicated in the healthy neonate. For example, the cumulative risk by age 15 of pathological phimosis is 0.6%[457] and the cumulative incidence of balanitis is 0.65%.[541] Consequently we would expect that only 1.3% of boys would have a medical indication for a post-neonatal circumcision. This is consistent with the experience in Denmark were 1.6% of boys are circumcised by age 15 years.[449] This translates into a number needed to treat of between 63 and 77. It is not clear what benefit there is in spending between $18,000 and $22,000 to prevent one post-neonatal circumcision that costs $1885. The study from Hart-Cooper et al., does point out that American physicians diagnose phimosis more commonly than physicians in Britain. Based on their data, in the first year of life boys in the United States are circumcised for phimosis far more frequently than boys in Britain (2247.7 per 100,000 person-years; 95%CI 2355.5-2142.9 versus 1.97 per 100,000 person-years; 95%CI0.278-14.012; RR 1138.31; 95%CI 160.26-8086.09).[472,457] This indicates that either physicians in the United States do not know how to properly diagnose phimosis requiring circumcision, or they use the diagnosis of phimosis to secure reimbursement for elective circumcisions, or both. Since true pathologic phimosis is rare under five years of age, it might be more cost effective for insurance companies to not pay for the procedure unless the child is over five years of age, failed a course of steroids, and had the diagnosis of balanitis xerotica obliterans confirmed.

This section of the draft report pays extensive attention to a cost-effectiveness analysis generated from within the CDC.[1260] As can be the case with secondary analysis, this analysis has a “garbage-in:garbage-out” problem. It almost appears as if the conclusion was determined first, and then the assumptions were sought out to justify the conclusion. To construct a cost-utility model that is most favorable to infant circumcision, the model would assume the highest efficacy rate, the highest prevalence of HIV, no complications from circumcision, and the lowest discount rate; this cost-utility did all these things. The basic assumptions, upon which the analysis is based, are each suspect.

First, it was assumed in the model that the lifetime risk of HIV infection for a male in the United States is several orders of magnitude higher than reported by other studies. Based on the numbers used in the model, 1 in 16 African-American males in the United States will become HIV

infected in his lifetime. So, for every two women that get breast cancer there will be one African-American male who will become HIV-infected. This is inconsistent with data collected in a national probability sample by the University of Chicago in which 0.35% (9 of 2577) of men 18 to 59 years of age were HIV-infected.[9] Why the five-fold difference?

Second, the model assumed a 60% efficacy in preventing heterosexually transmitted HIV for circumcision over a lifetime. There are several reasons to doubt the validity of applying 60% to populations in the United States. The first, as discussed earlier, are questions regarding the internal validity of the three randomized clinical trials. It is also unlikely that a 60% reduction in risk would be seen over a lifetime. The trials followed their subjects for, at most, 24 months. There is nothing to suggest the same linear trajectory would continue over 40 years. It is impossible to know whether the pattern would continue as linear, exponential, or whether it reaches a ceiling and stops. It could easily be that circumcision merely delays infection and the overall prevalence is the same over a lifetime. In the African randomized clinical trials, 1% of circumcised men became infected each year. So, if one assumes a linear model, between ages 20 and 80, one would expect approximately 40% of the men circumcised in these trials to become infected with HIV. Given that the prevalence of HIV in South Africa is slightly higher in circumcised men, this may be the case.[246] The second reason to doubt the 60% efficacy is that the results in Africa, which involved high-risk, well-compensated men who were willing to be circumcised, may not apply to a program of circumcising all males, regardless of their risk of HIV-infection, in the United States. Sansom et al., argue that data collected from people at highest risk for HIV infection (such as regular sexual partners of HIV-infected individuals) should be the basis for a program of circumcising regardless of risk profile. There is no evidence that 60% efficacy applies to males at low risk, and plenty of evidence to the contrary.[325] Finally, results from a study of adults may not apply to infants. To date, there have been no observational studies to indicate that infant circumcision has any significant impact in reducing HIV-infection rates.

Third, the model assumed that African-Americans have a lower circumcision rate than whites, yet there is ample evidence to contradict this, as is mentioned earlier.[6-8] If African-Americans have a risk of heterosexually transmitted HIV infection five times higher than non-Hispanic whites, this would indicate that circumcision is not an important factor in HIV-prevention and African-Americans do not benefit from the supposed 60% protective effects of circumcision. Before contemplating a model of infant circumcision, the lack of correlation between circumcision rates and heterosexually transmitted HIV-infection rates between ethnic groups needs explanation.

Fourth, it was assumed that infant circumcision had no impact on the length of stay of the perinatal hospitalization. It has been demonstrated that one in six males circumcised as newborns

will spend an extra day in the hospital.[7]

Sixth, as for other "harm-denialists," the CDC assumed that infant circumcision had no complications. Previous cost-utility analyses have found that the more common adverse events have the most impact on the cost-utility of infant circumcision.[1257,1258] For example, at least 5% of circumcised boys develop meatal stenosis that requires a meatotomy.[186,533-537] At $1500 per procedure, this adds $64.41 (3% discount for 5 years) to the cost of each circumcision. Another 1-2% end up having a circumcision revision, at substantial increased costs. MRSA infections are 12 times more common in infants that are circumcised.[651,1251] While heterosexually transmitted HIV infection is a relatively rare event, it may be of similar frequency as the severely botched circumcisions in which part of the glans is amputated, or there is a serious, life-threatening infection or hemorrhage. The analysis needs to consider the cost of treating these complications, the multi-million dollar malpractice settlements, and the devastating impact on health. Death is another well-documented complication of circumcision.[1262] While the exact number is unknown, some have estimated that between 100 and 200 deaths are related to infant circumcisions each year in the United States.[1056] If rare catastrophic events are to be considered on one side of the ledger, they need to be considered on the other.

The CDC also failed to compare infant circumcision to other interventions such as limiting the number of sexual partners, using condoms, early treatment of sexually transmitted infections, and secondary prevention measures such as treating HIV-positive individuals with anti-retroviral therapy. All of these options are known to be more effective, less invasive, and less expensive than circumcising all infants.

High-risk behavior will not manifest itself in infancy, so interventions should be directed at those who are sexually active. With all of these serious flaws in this model, it makes it looks like the CDC is trying too hard and is willing to say anything to make the hard sell for infant circumcision. Consequently, the results of this model cannot be taken seriously.

The model developed by Kacker et al. is equally unjustifiable as it is based on assumptions gleaned from outlier studies that are methodologically unsound when compared to the entire body of the medical literature.[1263] To the researchers from Johns Hopkins these numbers may ring true; to others, their analysis is unabashedly one-sided and biased. The analysis presents the most extreme case. That the CDC presented the results of this analysis indicates their lack of respect for the scientific method and their underlying pro-circumcision bias.

The models for MSM are also based on wildly unrealistic protection rates for the insertive circumcised partner. It is unclear why this section gives so much space to wildly speculative, non-reality based models and little or no space to models that are evidence-based.

As mentioned earlier, the models predicting the impact of adult circumcision on the HIV epidemic in Africa is thwarted by the lack of internal and external validity of the randomized clinical trials performed in Africa, the assumption that the effect remains linear over decades, and the incredibly limited response to the various circumcision roll-out programs. The poor response is not a surprise. First of all, when men learn they still need to wear condoms, they will see no point in getting circumcised (circumcision is either worthless or redundant). Second, HIV research has moved far beyond circumcision to the point where circumcision as prevention is rapidly becoming a footnote in the history of the HIV pandemic: an interesting historical oddity that popped up along the way. Third, treatment as prevention makes so much more sense. It works better, it is cheaper, it protects those who might be exposed through unclean medical equipment, it protects women, and it is not ultimately dependent on wearing condoms. Fourth, there is evidence that HIV is losing its virulence.[233] In the seven years since circumcision exploded onto the scene, its flame is flickering and about to be extinguished.

Other considerations

Risk compensation

The material in this section is incomplete and fails to place the results of studies in proper perspective. The CDC draft does not properly emphasize how important risk compensation is in the whole scheme of HIV prevention. In 1994, Blower and McLean formulated a model showing how the implementation of an HIV vaccination program with a vaccine of only 60% efficacy could easily increase the incidence of HIV infections, if risky behaviors are only slightly increased.[1264] Similar failures have been seen with vaccine programs using vaccines with efficacy in this range, such as the cholera vaccine.[1265] Another analogy is relying on birth control that is only 60% effective.[1266] Even with the most rudimentary modeling, it can be demonstrated that small changes in condom use can undermine any possible advantages of large-scale circumcision programs, resulting in more infections following implementation of a circumcision roll-out and billions of dollars spent.[251]

The measurements of risk compensation in the men who participated in the randomized clinical trials[2,211,242,1267,1268] need to be interpreted with caution.

First, the results may reflect the Hawthorne effect: participants knew they were being watched, so this fact alone likely altered their behavior.

Second, The participants in these studies were highly compensated for their participation. For example, in the Kenya study, in addition to the US equivalent of about $12,000 in goods and

services for participating in the randomized clinical trial, participants were paid the US equivalent of about $800 more to be in the study assessing risk compensation. This may have motivated the participants to tell the researchers what they wanted to hear.

Third, defining risk compensation as only applying to those who believe there is a change in the risk of becoming infected with HIV after circumcision is atypical. Risk compensation has to do with changes in behavior, whether people are conscious of the changes or not. In the example of wearing seat belts, risk compensation applies equally to those who consciously think they can drive faster because they have a seat belt on and also to those who drive faster on an unconscious level because they have a seat belt on.

Their working hypothesis, that the belief in the power of circumcision makes a man less fatalistic, thus more cautious, is counter-intuitive. If men think circumcision will make them live longer since they are less likely to be infected with HIV, they will likely live a bit more recklessly from a sexual standpoint. If the fatalism theory were true, we would expect to see intact men, who believe in the power of circumcision, be more cautious than the circumcised believers because they would perceive themselves at higher risk.

A much more likely hypothesis is that people who are risk-averse are more likely to pursue whatever they think will decrease their risk. They are more likely to believe that circumcision will help them and undergo circumcision for this reason. They are also more likely to have fewer partners and not engage in other risky behaviors.

This has implications for men in Africa who become circumcised as part of "voluntary" male medical circumcision campaigns. Early adopters were more likely to be those who believed in the power of circumcision. These men may account for the 2% to 5% who participated before March 2012.[213] The rest of the men are less likely to believe in the power of circumcision and need further persuasion, including bribes,[1215,1217] to consider participation. These are the men who will be less risk-averse. Consequently, one would expect a slight delay in detecting the impact of risk compensation. This is not to say that risk compensation is not already having an effect on national levels. For example, Uganda, which saw dramatic drops in the incidence of HIV infections using a program of "Abstinence, Be Faithful, Condoms,"[1269] has seen an increase in the incidence of HIV infections.[327] Kenya, which has seen the largest uptake in its circumcision roll-out has also seen an increase in HIV incidence since the roll-out.[328,329] This has occurred despite evidence that the incidence of HIV infections peaked globally in the late 1990's and has been gradually decreasing since then.[625]

This section omitted a few relevant studies. For example, Limburgh et al. found that participants in South Africa did not have a complete understanding of how circumcision is protective and,

while they expected to continue using condoms following circumcision, they did not expect others in the community who underwent circumcision to do so.[1270] In a study by Grund and Hennick in Swaziland, most men had more responsible attitudes in the first 12 months following circumcision, but a minority exhibited increased sexual risk-taking, especially during a brief period of sexual experimentation shortly after circumcision.[1270] The problem is that small overall changes in risk taking is all that is needed to increase HIV infection rates. Reiss et al. also reported a minority of men (16%) who abandoned condom use and increased the number of sexual partners following circumcision.[1271] In a study from South Africa by Nkosi, they found that males who had traditional circumcisions were associated with the greatest level of risky behavior; intact men had less risky behavior than men who were medically circumcised (adjusted OR 0.71; 95%CI 0.40-1.25).[1272]

Westercamp, and the team responsible for the Kenyan randomized clinic trial, somehow have found no evidence of risk compensation.[1273] One cannot help but note the conflict of interest here on the part of the investigators. For a research group, any finding of risk compensation would undermine the importance and relevance of their randomized clinical trial, the pinnacle of their career. These results also conflict with a survey published of men and women in Kisumu, Kenya. Intact men were divided into those who preferred to get circumcised and those who did not. The intact men who preferred to get circumcised were significantly more likely to never use, or inconsistently use, a condom (OR 2.7; 95%CI 1.6-4.7) and to have one or more casual sexual partners (OR 1.9; 1.03-3.6).[378] This would indicate that men who were interested in circumcision were those who were exhibiting more high risk behaviors than those not interested in circumcision. There are multiple reports outside of the medical literature to indicate that risk compensation is a concerning issue.[1274-1279]

Two studies have indicated that women may have more influence on how much risk compensation takes place.[1211,1212] These were unexpected findings, which could further derail the circumcision roll-out in Africa. The women told their male sexual partners they did not have to use condoms if the men were circumcised. Nothing less would be expected considering the propaganda campaign going on in Africa.

Because the incidence of heterosexually transmitted HIV is much lower in the United States than in Africa, infant circumcision has never been shown to be associated with a lower risk of HIV, and none of the studies from North America have found that circumcision significantly lowers the risk of HIV, a discussion about risk compensation in the United States is about as important as debating whether pigs can fly.

An excellent discussion on the issue of risk compensation as it relates to circumcision and HIV infection in Africa appears in a *Nature* article by de Lange,[1280] in which it is noted that a change

in risky behaviors, such as a decrease in condom use following circumcision, could mean that circumcision "could have the opposite effect in the long run. People might be more likely to get HIV than if they were not circumcised at all." (Quoting Michel Garenne). The other problem is that Africans, both men and women, are getting a mixed message. On the one hand, circumcision is supposedly the "breakthrough that will end the AIDS pandemic in Africa," but on the other hand, "everyone still needs to wear condoms." Another factor that could develop with time is that, as the sensitivity of the glans is lost following circumcision,[108] the willingness to further decrease the sensitivity of the glans by wearing a condom may drop even more. It is also unclear whether the counseling, which supposedly accompanied the procedure, will impact risky behaviors in the long run.

The materials in this section are irrelevant for health care providers in the United States. For health care providers in Africa, it is important to emphasize that small changes in behavior, or a big change in behavior by a few, can have a huge impact, negating any gains.

[Note: The discussion about the findings of Xu et al. has the wrong citation it should be reference 110 instead of 190.]

Policy considerations regarding reimbursement

The material presented in this section of the background document is off point. Why should the CDC be concerned about physician reimbursement? Professional organizations, such as the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Urological Association, may have an interest in lobbying for physician reimbursement, but it is not clear why the CDC would be interested in this topic.

This section of the draft fails to note the trend that is taking place among obstetricians. In a 1998 report, 70% of obstetricians reported performing at least one circumcision per month (as opposed to 35% of pediatricians),[445] although their scope of practice includes only female reproductive organs. A 1994 article indicated that pediatricians are happy to have obstetricians perform infant circumcisions and obstetricians are happy to have pediatricians perform infant circumcisions.[1281] The shift away from obstetricians/gynecologists performing circumcisions has become more formalized in recent years when Intact America was refused a booth at the national meeting of ACOG (American College of Obstetricians/Gynecologists) because male circumcision is not considered within the scope of obstetrics. Opinion pieces have been published supporting this position.[1282] Other obstetricians have published their success in shifting the burden of performing circumcisions away from them and onto the pediatricians or family medicine physicians in the community.[443]

While national medical organizations within the United States may have taken a position on infant circumcision, it does not mean that their positions are evidence-based. In fact, the American Academy of Pediatrics' position has been criticized as being based on culture.[1249] This section also misrepresents the position taken by the American Academy of Pediatrics. Instead of "concluding that new evidence indicates" that the benefits outweigh the risks, the Academy's Task Force has taken the position that "These benefits were ***felt*** to outweigh the risks of the procedure."(emphasis added)[1237] So, the conclusions of the American Academy of Pediatrics are based on *feelings* rather than evidence. This may explain why none of the other national pediatric organizations in the world have reached a similar conclusion. One of the Task Force members has recently noted he hopes the CDC report is not viewed as being as biased as their report.[1283] The fallacy in this discussion is an appeal to authority: in this case, the authorities are themselves culturally biased.

It is not surprising that circumcision rates are higher when parents do not need to pay out of pocket. However, the Midwest has a high circumcision rate because of high demand. This may explain why the study in the Midwest, where demand is the highest, found that insurance coverage did not affect the circumcision rates.[1284] Given that infant circumcision is a purely cosmetic procedure, one would expect that it would not be paid for by third party payers. Furthermore, it is not the CDC's role to be in the business of justifying financial reimbursement for physicians.

[Note: Reference CDC246 is the same as CDC209. In CDC246, the first authors last name is misspelled.]

The material in this section is relevant for health care providers who depend on the income they generate from infant circumcision and would like to see higher reimbursement rates from programs such as Medicaid. The problem is that the CDC should not be involved in efforts to improve physician reimbursement especially when it is not clear whether Medicaid can legally pay health care providers for performing circumcision, a cosmetic surgery, on non-consenting infants.[1234]

Ethical considerations

The material presented in this section of the background document is markedly incomplete, and reflects a socio-cultural bias in favor of circumcision because of its normalized status as a birth ritual in the US, in contrast to most other nations with advanced healthcare systems.

For example, the Royal Dutch Medical Association,[1236] the South African Medical Association, [1244] the Finnish Medical Association,[1238] the Tasmanian Law Reform Institute,[1285] and

representatives of four leading Swedish physician organizations[1237] have all concluded that infant male circumcision is a human rights violation and should be legally restricted. In addition, on October 1, 2013, the Council of Europe passed a recommendation endorsing a child's right to physical integrity and a resolution discussing the right to physical integrity in more detail. The Council specifically supported genital autonomy for children by opposing several practices including male circumcision, female genital mutilation, and early childhood medical interventions in the case of inter-sex children.[1286]

If the CDC wishes to advance a moral viewpoint that stands in contrast to those adopted by peer organizations in other Western countries, it would do well to engage directly with the arguments and analyses that have been presented by those peer organizations, and attempt to show, systematically, why those arguments are not convincing. To ignore the published viewpoints of distinguished medical organizations in peer nations, all of which have gone to great lengths to assess the moral permissibility of circumcision in light of widely-accepted ethical standards, gives the impression that the CDC is not concerned with the pressing moral issues raised by this controversial surgery.

Consistent with this impression is further concern about the composition of consultants at the CDC 2007 consultation. It reads, to put the point bluntly, like a *Who's Who of Circumcision Lobbyists*.[16] In the reporting on the consultation, it is stated, "Invited participants included epidemiologists; researchers; health economists; ethicists; physicians; and representatives of practitioner associations, community-based organizations, and groups objecting to elective circumcision." However, no one from any of the major groups objecting to elective infant/child circumcision was in fact invited to the consultation (correspondence with Georganne Chapin, JD, Founding Executive Director of Intact America; Marilyn Milos, RN, Co-founder and Director of the National Organization of Circumcision Information Resource Centers (NOCIRC); John Geisheker, JD, Director and General Counsel of Doctors Opposing Circumcision (DOC); J. Steven Svoboda, MS, JD, Founder of Attorneys for the Rights of the Child). Also, no one from a group objecting to elective circumcision was invited to participate in, or provide materials for, the subcommittee of the CDC Public Health Ethics Committee. The draft does not provide a citation for the findings of the subcommittee. Nor does it disclose any cultural or religious affiliations of committee members that might have bearing upon the question of non-financial conflicts of interest. Finally, given the same reasoning for deeming male circumcision of non-consenting minors justifiable, would the subcommittee agree with the 2010 American Academy of Pediatric policy statement on female genital cutting,[1287]—later retracted—which stated some forms of female genital cutting are permissible? Is there a compelling reason why females should be protected and not males?

This section provides only cursory treatment of the many important ethical issues that are raised

by the circumcision of non-consenting minors.

Regarding the five major principles of bioethics,[1288] it has been argued that circumcision fails to pass any of them. For infant circumcision to be morally permissible, it must pass *all* five. This section of the draft only included three of the five principles.

1. Beneficence (maximizing benefit and minimizing harm, both at the individual and society level): This has been addressed in the cost-utility analyses that have been published. In the analysis that included complications, impact on urinary tract infections, impact on sexually transmitted infections (including HIV), and was properly discounted for time, it concluded that circumcision wasted money and resulted in an average decrease in quality-adjusted life years.[1258] To conjure up a rare benefit, another analysis needed to overestimate the incidence of HIV five-fold, fail to consider any complications, and make a number of unjustifiable assumptions.[1260] The differences in these analyses can be explained on the basis of what Sarah Waldeck, a law professor at Seton Hall University School of Law, calls the "*multiplier effect*."[1289] Simply put, those who have accepted the social norm of infant circumcision will overemphasize the importance of studies documenting a benefit regardless of their methodological weaknesses, and will ignore or minimize the importance of studies showing evidence of a neutral or negative impact from infant circumcision. Considering that this draft does not address the function of the foreskin and does not adequately address the multiple harms associated with its amputation, how can the CDC acknowledge any negative consequences related to male circumcision? This draft also selectively cites studies, regardless of their methodological weaknesses, that support male circumcision. This indicates that the draft is strongly influenced by social normality and its recommendations are strongly influenced by cultural, or other, factors.

2. Autonomy (respect for individual values and choices): Infant circumcision fails to satisfy this principle. There is no compelling medical reason to circumcise an infant. In such a situation, the Committee on Bioethics of the American Academy of Pediatrics recommends waiting until the child can provide his own fully informed consent.[1290] Circumcision, by virtue of the fact that it breaks the skin, violates the infant's bodily integrity. One of the most universally accepted basic human rights is the right to bodily integrity and security of person.[1283,1291,1292] As a result, it is not very difficult to make a cogent argument that infant male circumcision is a human rights violation.[1293] It is widely held that no one has the right to violate the human rights of another human except in extreme circumstances.[1294] Consequently, the child's right to self-determination should be respected. There are two ways to approach an infant's autonomy when it comes to infant circumcision. The first is to decide for the child on the basis of what he would choose, if he was able to provide his own fully informed consent, without parents projecting their value system on the child.[1294] Given that adult males rarely [1295] chose to undergo circumcision without a medical indication, the substitute judgment test requires that it not be performed on an infant

(who cannot effectively resist). The second approach is based on Joel Feinberg's concept of the right to an open future. Briefly, a child should have rights that should be saved for the child until he is an adult, or what he calls "rights in trust." These are the sort of rights an autonomous adult would have, but a child would be too young to exercise them. They are "rights that are to be saved for the child until he is an adult, but which can be violated 'in advance' before the child is even in a position to exercise them." Following such violations, a child upon reaching adulthood would find that certain options would already be closed.[1296] The concept of a right to an open future has been adopted by subsequent ethicists.[1297] Certainly, infants, whether male or female, have a right to their complete genitals coming into adulthood. The right to bodily integrity should be a "right in trust" that Feinberg envisioned. Consequently, it has been argued that infant circumcision violates an infant's right to an open future.[1298] Subsequent analysis has determined that physical violations do carry more moral weight than non-physical violations.[1299] In either case, violating the infant's developing/future autonomy by cutting off the most sensitive portion of his penis without his permission is a matter for great moral concern. Since autonomy is considered by some to be the primary principle of modern bioethics,[1300] there needs to be a compelling reason to violate anyone's autonomy, especially someone who is vulnerable. No such reason has been provided in this draft.

3. Justice (the obligation to fairly distribute risks, burdens, and benefits, to minimize stigmatization, and to make decisions in a transparent fashion): When circumcision is performed on an infant at the parents' behest, the parents do not assume any of the risks, the infant does. The infant has no say in the matter, yet takes on all of the harms and risks associated with the procedure. Such a shift of risk onto someone who cannot consent is inconsistent with the concept of justice. Obviously the risks are not fairly distributed. Infants who are circumcised for religious or cultural reasons or for misguided beliefs that it improves hygiene, which covers the vast majority of circumcisions, undergo the procedure for what parents believe is their religious or cultural obligation. Consequently, the infants are being used instrumentally as a means to satisfy ends determined by their parents.[1299] In Kantian ethics, anyone of moral worth should not be treated as a means to an end, but always as an end in themselves.[1301] Treating a human being instrumentally in this fashion is in direct opposition with our modern concept of justice.[1302]

Likewise, the randomized clinical trial which purported to find that circumcision of HIV-infected men increased the relative risk of infection in female sexual partners by 50% placed an increased risk of HIV infection on women who were unaware of their partner's HIV status.[338] This abuse of the principle of justice was one of several reasons why this study was perhaps the most unethical study since Tuskegee.[1303-1305]

If the CDC was interested in minimizing stigmatization, it would abandon the use of the term "uncircumcised," which is now considered by many to be pejorative. One definition of the word

"uncircumcised" is "spiritually impure: heathen: unregenerate." It is also a term that is technically inaccurate. For a man to be "uncircumcised," he would need to first be circumcised and then have the process reversed. By using the term "uncircumcised" or "non-circumcised," the authors of this draft are making the underlying value-laden assumption that being circumcised is the preferred condition, when there is no evidence, other than cultural pressure, to support this. The most accurate, value-neutral term for a man with all of his original genital tissue is "intact." By continuing to use the term "uncircumcised," the CDC is identifying its pro-circumcision bias to anyone who is familiar with the semantics on this issue. Males who are indeed "intact" find use of the word "uncircumcised" to be akin to hate speech because they are singled out as "different," supposedly "abnormal," and/or possibly unclean."[1181] Nothing could be further from the truth. Profiling a group of people in this way is unjustified, discriminatory rhetoric.

The use of this terminology has racist and anti-immigrant overtones. With the exception of a few immigrants who come from circumcising cultures, most immigrant males have intact genitals. The overall tone of this draft unnecessarily and counterfactually characterizes normal, intact males as inferior and disease-laden. The draft also places more credence with investigators who focus on certain racial and ethnic groups for increasing circumcision rates.[345] Less than a third of the world's men are circumcised, and nearly all of them are circumcised for religious or cultural reasons. Why would the CDC want to stigmatize the majority of males on the planet? Many intact males who read the American Academy of Pediatrics 2012 Task Force report[1306] interpreted the Academy's position as thinly veiled hate speech (personal communications). The CDC's recommendation may be interpreted as even more insulting.

If justice requires that decisions be made in a transparent fashion, then major reform is needed in the informed consent process that accompanies infant male circumcision. This is needed to ensure full disclosure is provided, that those providing proxy consent understand what they are providing consent to, and that those providing consent do so voluntarily without being coerced or solicited.[1307-1309] Currently, the level of disclosure provided is far below the standard expected for similar elective procedures.[1228,1231,1310] One study in which full disclosure was provided resulted in parents becoming very upset with the physicians providing the disclosure.[1311] This may reflect that many parents are unaware circumcision leads to any harm or complications, and parents have usually made up their minds about circumcision based on social or cultural factors. They may not want to hear about any untoward effects because this creates cognitive dissonance. But, this does not excuse physicians from their duty to provide full disclosure. Sometimes, this information will dissuade parents from agreeing to a circumcision for their son. Full informed consent also protects the health care provider in the event of an adverse outcome. Even in the adult circumcision roll out in Africa, the men are not given full disclosure regarding the harms and complications of circumcision. The fact that bribes are becoming necessary to recruit adult

males to undergo a free circumcision[1214] is an evident sign that the decision process is less than transparent.

Is it justifiable for parents to impose circumcision on their sons when there are more effective, less expensive, less invasive methods of preventing urinary tract infections, sexually transmitted infections, HIV infections, and penile cancer? Imposing such inefficiencies in a nonconsensual fashion onto an infant in the name of parental convenience is both unfair and unjust. If an infant cannot choose his preferred method of prevention, the parent at least should choose a more efficient, less expensive, less invasive measure.

The two principles omitted in this section of the draft are:

4. Non-maleficence (does the procedure avoid permanently diminishing the patient in any way that can be prevented?): Circumcision permanently removes the most sensitive portion of the penis.[54,55,108] Some would argue this is the intent and purpose of the procedure,[1312,1313] and certainly it was the intent when circumcision was first introduced in the United States and Britain as a "cure" for masturbation.[1183-1185]

5. Proportionality (will the final result provide a net benefit to the patient in proportion to the risk undertaken and the losses sustained?): Decisions are made in everyday life based on proportionality. If a shop is asking too much money for an item, they may have trouble selling it because the price is out of proportion to the value the customer has assigned to the item. For infant circumcision proportionality works on two levels: the physical and the moral. It fails on both levels.

The measure of proportionality on the physical level has already been assessed with the roll-out of adult circumcision in Africa. Men who live in countries with some of the highest prevalence levels of HIV infection in the world have been subjected to well-financed advertising and have been offered a free circumcision, but they are only agreeing to undergo the procedure 1.6% of the time unless they are given an additional bribe.[1214] The advertising programs have informed these men regarding the ease and simplicity of the procedure, the lack of complications, and the overwhelming benefits in protecting them from sexually transmitted infections and HIV, yet only 1.6% are interested in a circumcision paid for by the Bill and Melinda Gates Foundation, the Clinton Foundation, and PEPFAR. How could this be explained? These men have a foreskin. They know how it works, what it does, and how it feels. It seems that they recognize on a physical, biological level that the resultant harm of removing the foreskin is out of proportion to the unlikely benefits, especially when the same benefits can be more easily and effectively obtained using methods that do not involve the removal of sensitive, functional tissue. Instead of recognizing the value that men have assigned to their foreskins, advocates of mass circumcision

spend their time trying to discover the inducement that will entice these men to get on the circumcision bandwagon.

On the moral level, the value of one's wholeness and the ability to exercise one's autonomy are important elements in the equation. David Lang [1314] and Wim Dekkers[1315,1316] have identified totality and wholeness as important issues in the ethical debate over circumcision. Lang applies the principle of totality to argue that "the good of the whole overrides the good of a part if [the loss of] that part is truly (not merely hypothetically or speculatively) a threat to the well-being of the whole."[1317] In other words, all parts of the body form a cohesive, integrated unit.[1314] This principle complements the principle of bodily integrity. Lang argues that, since circumcision disrupts normal sexual function, the principle of bodily totality is violated.

For Dekkers, "wholeness" has four aspects: biological, experiential, intact, and inviolable.[1315,1316] Biological wholeness refers to anatomical and functional integrity, which is conceptually similar to Lang's notion of totality. Excising erogenous genital tissue violates this sense of wholeness. Experiential wholeness is not dependent on biological wholeness, but is a phenomenological view of the human body in which the body is a "lived body." By altering responses to subsequent painful stimuli[993,994] and altering normal penile reflexes,[120] removal of the foreskin may negatively impact experiential wholeness. One aim of medicine is, or should be, to restore this sense of intactness and completeness — to make the body whole again, not to introduce deficiency. For medical practitioners to remove functional tissue runs against this aspect of wholeness. Inviolable wholeness is an outgrowth of a Kantian principle that violating the body also violates the person's dignity.[1299] According to this principle, the integrity of the body is a necessary condition for the fulfillment of human moral purposes, and respect for the integrity of the body is necessary for proper moral sensibility.

Circumcision also violates an infant's sense of wholeness without consideration. On a contractual level, such a one-sided transaction would not be binding. Proportionality is not achieved as the infant is not compensated for this loss. The loss of the protection of bodily integrity, security of person, and self-determination (autonomy) are also not adequately compensated for. According to John Rawls, depriving one of a basic human liberty is only morally permissible if doing so enriches or enhances one of the other basic human liberties.[1302] During infant circumcision, the basic human right to bodily integrity and security of person is violated without compensation. It is thus not proportional.

The possibility of death, although rare, following infant circumcision, which has not been reported following circumcision in older boys and adults, also violates the principle of proportionality. This potential outcome may be grounds enough for delaying the procedure until the patient is old enough to grant his own fully informed consent.

This section states that “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.” This statement has several problems. First, at least one of the citations given for this statement does not make this assertion. The 2003 article by Benatar and Benatar does not contend that there is strong evidence favoring circumcision or a minimal risk, but rather that the benefits and risks are balanced and given the non-medical benefits, which they fail to identify, circumcision is morally permissible.[1318] Second, there is clear debate over the value of the evidence. As noted by Waldeck, circumcision status and the prevalence of circumcision within a culture will impact how evidence is prioritized and interpreted.[1289] So, it is telling that the CDC cites the opinion piece in favor of circumcision published in the *British Medical Journal*,[1319] but failed to cite the opinion piece arguing the opposing view that accompanied it.[1320] Others have put forth such utilitarian arguments,[1321-1323] but such arguments have been challenged because of their dependence on false analogies, speculation, selective bibliographies, being oblivious to the harms and risks of the procedure, and fallacious reasoning.[1299,1317,1324-1327] The importance of unproven benefits and ignored harms needs to be part of the debate and not just accepted because it makes one feel better about being circumcised. Furthermore, many circumcisions are performed by those least competent to be doing the procedure: medical students, interns, residents, physician assistants, etc. And, few, if any, health care providers are adequately educated about the anatomy of the foreskin, which explains the high number of complications surrounding its removal.

Second, it is merely assumed that parents have the authority or “right” to have parts of the genitals of their children amputated. The concept of parental rights is a legal fiction that has outlasted its usefulness. When women and children were considered property/chattel, such property rights made sense. As the moral worth and status of children is increasingly being recognized, treating children as property/chattel is becoming more difficult to rationalize. One legal scholar has noted that parental rights are only invoked when the parents are doing something that is not in the child’s best interests.[1328] It has been argued that parents do not have the “right” or the authority to violate their child’s basic human rights and that this prohibition extends to infant circumcision.[1329] One could argue that the onus is on those who want to encourage or defend infant circumcision to make a positive argument to justify violating an infant’s right to bodily integrity and security of person based primarily on parental judgment.

While parents are given the authority to vaccinate their children, infant circumcision has little in common with vaccination other than that they are both implemented on infants or children. Circumcision removes tissue that is irreplaceable and that serves specific functions; vaccines stimulate the production of antibodies by the immune system to fight off infections.

The claim that infant male circumcision acts like a vaccine has been made by a number of circumcision enthusiasts.[1,1330-1339] They use this analogy because the average person understands the concept of vaccination and has seen the ability of vaccines to greatly reduce the incidence and prevalence of a number of serious and non-serious illnesses. A highly effective vaccine against a life-threatening infection can have an almost miraculous impact, but most are not aware that a vaccination program using a vaccine with only 40% to 60% effectiveness will ultimately increase the number of infections.[1265] Circumcision enthusiasts use the vaccine analogy because they want people to associate the miracles brought about by vaccines to also be associated with infant male circumcision, in the hope that those opposing infant male circumcision would then be thought of as irrational and unwilling to do what is in their child's best interest.

The analogy between vaccination and circumcision is spurious:

1. Vaccines target specific illnesses that are either common, infectious, or carry significant personal or public health consequences. Circumcision does not.

2. Only vaccines that have been demonstrated to be effective in decreasing the risk of severity of the targeted illness are released for use on the public. Nearly all of the vaccines that are commonly used are effective in more than 85% of those vaccinated (an exception is the influenza vaccine). Typically, vaccines that only reduce the risk by 40% to 50% are often not used.[247,1265,1340,1341] Circumcision has not been clearly demonstrated to be effective, let alone provide more than 85% protection. By making the analogy, circumcision enthusiasts are trying to get people to believe that circumcision has these high levels of protection.

3. Vaccines do not permanently remove any body parts. Circumcision does. As Wayne Hampton notes, "Circumcision is a subtraction whereas vaccination is the addition of immunizing agents to the bloodstream. Circumcision is a loss while a vaccine is a gain."[1342] Removing the foreskin, with its functioning mucosal immunity, subtracts from the value of the body as a working system. A vaccination adds to the value of the body as a working system by boosting the immune system. This is morally interesting, especially from a utilitarian standpoint, because the net effect of a vaccination is improved function both on an individual and a societal level, while this is not true for circumcision. It is also interesting from a Rawlsian perspective because a vaccine program serves the purpose of justice as it improves life, especially for those who are the most vulnerable.

In a similar vein, circumcision is more invasive than vaccination. To make the analogy of circumcision being similar to vaccination plausible, circumcision enthusiasts would need to demonstrate that circumcision is not excessively invasive, but this cannot be demonstrated.

4. Vaccines typically have been shown to have a positive cost-effectiveness or a reasonable cost-utility. Circumcision has not.[1258]

5. The long-term effects of vaccinations have been well studied and documented. This has not happened with circumcision. Even the 2012 Task Force report from the American Academy of Pediatrics acknowledges that the long-term risks of circumcision are unknown. A registry and compensation system exists to address unfortunate outcomes of vaccination, yet no such system exists for circumcision.[1342]

6. Vaccination programs have decreased the incidence/prevalence of the targeted diseases. The illnesses associated with circumcision have not decreased and in several instances have increased. The diseases that have been targeted by vaccination programs, for the most part, have been either illnesses with a high incidence and/or with associated significant morbidity/mortality.[1340] While vaccination programs have clear public health benefits, both for the individual and society overall, any such benefits for circumcision, if they exist at all, are miniscule by comparison.[1344]

7. The level of acceptable risk for the public for vaccinations is very low and well below the risks associated with infant male circumcision.

8. The diseases targeted by vaccines typically have a high incidence, often the majority of the population is at risk, otherwise a vaccination program would not be worth pursuing. By contrast, the illnesses circumcision is presumed to prevent are uncommon, rare, or nonexistent.[1348]

9. When circumcision apologists and enthusiasts link circumcision and vaccination, they need to be aware that by doing so they may undermine the efforts of vaccination programs. Clearly, parents who do their due diligence will discover circumcision is questionably effective at best. By linking circumcision and vaccination, parents may be given the false impression that vaccinations are as ineffective as circumcision. Claims of a public health benefit should be limited to interventions that actually have a positive impact on the health of the public.

The argument provided by Benatar and Benatar posits that the legitimacy of parental authorization of infant male circumcision is based on the vaccine analogy.[1318] The points of their argument can be summarized as follows:

1) There are parts of the world where diseases against which children are frequently vaccinated are now uncommon.

2) The necessity of such vaccination for the individual child is neither clear nor immediate.

3) There are small but real risks from vaccination (including death).

4) The child is unable to give consent for vaccination.

5) The power to consent can be deferred to proxy decision makers or delayed until the child is old enough to give consent himself.

6) Delaying vaccination can undermine its benefit.

7) It is reasonable for parents or other guardians to make decisions on behalf of a child that are in the child's best interests.

8) "The role of a parent is not simply to save children from immediate catastrophe, but is to protect and foster a child's long-term best interests."

9) Therefore, "parents may consent on behalf of their children not only to vaccination but also to such procedures as orthodontics and various non-medical interventions, including schooling."

A point by point rebuttal follows:

1) Not only is this true, but vaccination programs are effective. (Although, it translates into fewer sick visits at our office and less revenue for physicians. If the CDC translated their interest in increasing physician income generated from circumcision, they would also come out against vaccinations.)

2) The presumption that vaccinations have no clear necessity for the individual is unsubstantiated. If a vaccine did have not a clear indication, it would no longer be given. This is the case for small pox. Vaccination programs against smallpox were discontinued after it was determined that smallpox had been eradicated. Vaccines can also be justified on the basis of public health considerations.[1343] To say that vaccines have no clear indication for the individual is foolhardy. Herd immunity may reduce some risk, but does not eliminate risk. If it did, the pertussis and measles outbreaks in unvaccinated children that emerge on a fairly regular basis would not take place. Consequently, there is always a potential advantage to the individual to be vaccinated. This presumption is not only wrong but extremely dangerous. If this erroneous position was adopted by a sufficient number of people, even the positive impact of herd immunity could be lost, leading to a public and personal health disaster.

The Benatars's entire argument is dependent on this false assumption. If vaccines had no

benefits, then parents would not be allowed to authorize their use. It is only because they have benefits that parents can direct medical personnel to administer the vaccines. People are allowed choices and parents can forgo vaccinating their children. When they do so, it is common practice to have parents sign a waiver indicating they are aware of the benefits of the vaccine, yet they wish to forgo its administration to their children.

3) Agreed.

4) Agreed, but given the benefits of the vaccine, it is both in the child's best interest and also something the child would choose for himself if able to.

5) Agreed.

6) Agreed.

7) Partially agreed. The language should be altered to state it is reasonable for parents to consider making *some* decisions on behalf of the child that are believed to be in the child's best interests. For example, a girl with a gene that puts her at high risk for breast cancer, one could argue that a prophylactic double mastectomy would be in her best interests, but not a decision that the parents should make on her behalf. The American Academy of Pediatrics Committee on Bioethics notes that: parental decisions are limited to those where there is an immediate danger, and that decisions which can safely wait should be delayed until the child can have input into the decision.[1238]

8) Agreed. But parents also have the responsibility to be the child's guardian, which includes the duty to protect the child's basic human rights,[1318] protect the child's right to an open future, [1296-1298] and not treat the child instrumentally.[1242,1299]

9) Their argument can only apply to vaccination because this is what the authors used as their set of conditions. This conclusion cannot be extended to orthodontics, other non-medical interventions and schooling without demonstrating that these interventions are similar to vaccination in all respects. Vaccination has no clear association with "various non-medical interventions." This is merely a bait and switch to other false analogies, which are not nonconsensual violations of bodily integrity and security of person.

Comparing choices for education has no discernible connection to making medical choices for a child who cannot choose for himself. At the age where education outside the home is offered, the child can have a varied amount of input. There is also disagreement about the authority of parents to force children to undergo education that is not in their best interests[1346]

This is also a false analogy that does not apply to infant male circumcision because, as a society, we consider education necessary to become a good citizen[1347] and we believe delaying education will undermine its effectiveness. Education is clearly in the child's best interests, and it is something the child would have chosen for himself once he becomes competent.

While, in the *opinion* of the undefined, unpublished findings of the subcommittee of the CDC Public Health Ethics Committee, the decision either to or not to circumcise is an appropriate exercise of parental authority, the CDC draft fails to recognize that many disagree with this opinion. For example, all of the national medical organizations who have come out against infant circumcision and have characterized it as a human rights violation are not mentioned by the CDC.[1236,1238,1240,1241,1244,1245,1250] Legal scholars have questioned the legitimacy of parents violating their child's human rights and best interests under the rubric of "parental rights" because such actions only result in harming children.[1293,1327,1346,1347] It has been argued, given the moral status of infants being increasingly recognized,[1292,1347] that infant circumcision may be the last holdout in which parental rights are recognized.[1329] The rest of the Western world recognizes that parents do not have the authority to violate their child's basic human right to bodily integrity and security of person.

Did this CDC subcommittee consider whether this same parental authority would allow parents to direct health care professionals to cut the genitals of their daughters? The same ethical principles would apply. There is some evidence that female genital cutting has medical benefits in decreasing the risk of HIV infection[1348] and a significantly shortened second stage of labor.[1349] Proponents of female genital cutting maintain the procedure also decreases a woman's risk of sexually transmitted diseases. At least one study has documented that female genital cutting has no impact on sexual fulfillment or the ability to have an orgasm.[1350] In 2010, the American Academy of Pediatrics Committee on Bioethics released a statement, in an effort to acknowledge cultural diversity while ignoring the moral status and human rights of children, stating some forms of female genital cutting are morally permissible.[1287] The report generated such a negative response that the Academy was forced to "retire" the statement 31 days later.[1351,1352] It would certainly be unfair and unjust if the subcommittee were to treat males and females differently.

The justification for the moral permissibility of infant male circumcision in the CDC draft, and as argued by other circumcision apologists,[1340] is based on the presumption that the procedure is safer and simpler when performed on newborns and infants. Unfortunately, presumptions are not data.[1353] As addressed earlier, the evidence does not support the contention that there is an advantage to circumcision being performed in infancy, other than the ease with which the boy can be restrained.

The CDC draft should also refrain from fear-mongering. Apparently, those who wrote the draft must be concerned over the remote possibility of missing an opportunity to prevent an HIV infection in a male who becomes sexually active before he has the chance to get circumcised. How many 14-year-old males are going to get HIV from their 14-year-old girlfriends? While the age of sexual debut may be getting younger, the rate of heterosexually transmitted HIV infection is extremely rare through sexual contact with other young people. There is no evidence in North America that any HIV infections are prevented by circumcision,[8-14] so there is no reason to lose sleep over the number of HIV infections potentially caused by a delay in circumcision. Likewise, neonates are not sexually active.

The statement, "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," contains several inaccuracies. First, as discussed in detail earlier, there is no properly controlled experimental evidence that later circumcision has a greater likelihood of complications. There are numerous case reports of infant deaths resulting from male circumcision in the US medical literature, but none known of adolescent or adult deaths as a consequence of circumcision. Adolescents and adults are capable, unlike neonates, of expressing pain and requesting adequate pain relief, of noting excessive bleeding and infection. They would also have undergone a thorough pre-operative history and physical exam noting any possible reasons to not have surgery. Neonates undergo circumcision surgery without knowing whether they have any underlying medical problems such as hemophilia, and many premature neonates are circumcised while still undergoing care in the NICU. If surgery under general anesthesia is unacceptable for neonates, then any surgery should be postponed until adequate pain relief can be provided. Circumcision is done to infants because it can be done, not because it is safer with fewer complications. (see complications section.)

It is also unclear what the other barriers to male circumcision might be in adolescents or adults. Somehow, teenagers are able to undergo orthodontia, which is much more time consuming than circumcision. Some teenagers manage to undergo cosmetic surgery during school vacations. It is unclear how there would be significant barriers, if circumcision would be considered so terribly important. If the CDC and American Academy of Pediatrics have their way, there should be no financial barriers to this cosmetic surgery. What this statement is missing are the real reasons that uptake is lower after the neonatal period. After several weeks of bonding with their baby, parents are less likely to put their baby through a painful procedure. The older boy, who has experience with his foreskin, would consider the suggestion of cutting off his foreskin, which at that point may have acquired a distinct value to him as sensitive tissue, as imprudent. "Why would anybody want to do that?" is a typical response. The foreskin is a valued possession that even a young boy knows enough not to relinquish.

The subcommittee recommended that circumcision be an "informed choice" but fails to consider that informed consent is impossible for infant circumcision.[1231] This is an important issue that warrants debate, but it was apparently not addressed by the subcommittee. The Europeans do not think parents can provide informed consent, and certainly the infant cannot either. Many would contend that adolescents are also unable to give consent.

Finally, the lack of health insurance coverage for male circumcision is not an issue of justice because circumcision is a cultural practice. It is typically not the role of government, and definitely not the role of Medicaid,[1234] to support cultural practices. By supporting one cultural practice, those who do not participate in that practice are discriminated against. If, as appears to be the case with this draft, the CDC is applying pressure on ethnic groups that have traditionally kept their infants genitally intact, then they are enforcing an unwanted hegemony. The reduction in risk of HIV infection and other adverse health conditions is illusory. This leads to the question of why the CDC is so interested in implementing this hegemony.

Tables

Both tables are highly selective in the data presented and need to be completely revised. Results for which there was clear sampling bias and/or lead-time bias need to be adjusted accordingly. The results of meta-analysis of observational studies need to be included. All of the prospective studies of incidence need to be included and updated.

Closing Comments

What is going on at the CDC? After taking over seven years, the CDC finally generates recommendations that mimic the talking points propagated by circumcision enthusiasts. But, this is only the latest in a string of bizarre actions taken by people within the CDC who have been addressing the issue of male circumcision. The first action was taking up the issue at all. Heterosexually-transmitted HIV infection is only 10% of the HIV infections seen in the United States and 70% or more of the sexually active males in the United States are already circumcised. Many of those males with HIV are/were circumcised, so how did circumcision help them? Why is "circumcision to prevent HIV" even an issue in the United States? It does not make sense to expend the energy on such a highly circumcised population unless the action was intended to maintain a high percentage of circumcision for some other reason.

The next action was to convene the consultation in 2007, inviting nearly every prominent circumcision enthusiast on the planet. Of the 50 or so people from outside the CDC invited to attend, only one had ever published studies that were not favorable to the practice of circumcision. Not much diversity represented there. This would make it sound as though there is

only one scientist in the world who has published such studies. Clearly, there are plenty of scientists who could have voiced an alternative viewpoint and who would have been willing to attend the consultation, but they were not invited. Only one was invited, as the token dissenting voice. A similar tactic was used when the WHO/UNAIDS rammed through its approval of circumcision in Montreux in 2007, where Gary Dowsett was the token voice of opposition.[5] It is not surprising that this experiment in "group think" provided the CDC with all the ammunition it needed to move forward. In 2009, the CDC held a conference in Atlanta on circumcision and HIV. They invited Inon Schenker of Operation Abraham and the Jerusalem AIDS Project to give a presentation. The last slide in his presentation was a photograph of a completely naked, genitally intact male on whom the figure of an elephant had been drawn around the penis so that the intact penis looked like an elephant's trunk. The words "Yes! A circumcision please!" had been added to the photo. Such a crass insult to every intact male was uncalled for. Apologies have obviously been in order, and requested, but never granted. It is not apparent why the CDC would tolerate what was clearly intended to be hate speech.

It is not clear why the CDC would purposely publish recommendations and a supporting background document that they must know is not evidence-based. By doing so, the CDC has placed health care providers in the untenable situation of committing malpractice, by disseminating false information, thereby placing their patients at unnecessary risk. Why would they want to embarrass themselves in this fashion? Is the CDC so infiltrated and controlled with circumcision advocates that producing something this biased and unscientific was mandated from the top? There is evidence that Peter Kilmarx, who initially headed up this project, was part of an email mailing list of circumcision advocates in 2006. How much contact between officials at the CDC and pro-circumcision lobbyists would a freedom of information request reveal? Is the CDC somehow beholden to the pro-circumcision lobby? Is this draft a concession to the lobby to demonstrate that the CDC was willing to do their bidding? One has to wonder how much of the effort to "prove" that circumcision prevented HIV and other sexually transmitted diseases in Africa was actually not about helping those in Africa, but more about maintaining the current rates of circumcision in the United States, keeping them from going into free fall. The narrow, single-minded focus of the CDC in this draft supports this contention.

What will the CDC do now that their biased, culturally-based position has been exposed as being scientifically fraudulent? How can anything the CDC says or does be taken seriously after one has followed their subjective handling of this issue over the years? It is time to save face. Trash this draft and start over.

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