Newborn Male Circumcision for Prevention of Sexually Transmitted Infections in the United States: A Systematic Review

By

Eric Crossen

A Master's Paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Public Health Leadership Program.

Chapel Hill

2009

Advisor: Russell Crossen, MD 7/12/09
Second Reader: Dan Jonas, MD 7/18/09
ABSTRACT

PURPOSE: To clarify whether circumcision of newborn males in the U.S. reduces the risk of sexually transmitted infections (STIs) later in life.

DATA SOURCES: I searched the MEDLINE database (1948 through July 2009), Cochrane Library, and EMBASE. Other relevant articles were located through hand searches of bibliographies.

STUDY SELECTION: I reviewed the literature for systematic reviews, randomized-controlled trials, cohort studies, case-control studies, and cross-sectional studies conducted in the United States that compared the effect of newborn male circumcision versus no circumcision on the development of various STIs among adolescents and adults, including: gonorrhea, chlamydia, syphilis, chancroid, HIV, HSV-2, HPV, hepatitis B and C.

DATA EXTRACTION: I abstracted the relevant data from the included articles.

DATA SYNTHESIS: I identified 13 relevant studies described in 12 articles. Studies examining the association between circumcision status and STIs differed in the risk profile of their study populations. Study populations could be described as general male population, high-risk heterosexual males, or men who have sex with men (MSM). Two studies of the general male population found no association between circumcision status and an array of STIs. Seven studies of high-risk heterosexual males had mixed results with no consistent findings suggesting protection against a particular STI. Some evidence from the four studies of MSM suggested a protective effect against HIV, although these results were inconsistent across all the studies.

CONCLUSION: There is insufficient evidence to conclude whether newborn circumcision does or does not protect against STIs among U.S. males. Overall, the quality of evidence was fair. High-quality prospective studies are needed to further assess the effects of circumcision especially in high-risk U.S. men.
INTRODUCTION AND BACKGROUND

I. THE ISSUE OF CIRCUMCISION

Circumcision of newborn males is a frequent practice in the United States. According to the National Center for Health Statistics, 57.4% of male newborn infants in the U.S. were circumcised during hospitalization in 2004. Although male circumcision persists as one of the most common surgeries in the U.S. and the world, it remains the subject of scientific and social debate. Multiple factors fuel the controversy about whether newborn males should be circumcised, including research demonstrating potential medical benefits as well as concerns about surgical complications. Additionally, cultural influences including religion and other familial, societal, and community norms play important roles in determining whether male infants are circumcised.

Frequently cited reasons for newborn circumcision include religious and social importance, and health-promoting and preventive effects. In Judaism and Islam, circumcision is a significant life event for male infants and adolescent males, respectively. Social norms are an important factor even in the absence of religious influence, as a father's circumcision status strongly influences the decision to circumcise his newborn. Male circumcision has also been reported to decrease the risk of infantile urinary tract infection (UTI), penile cancer, and some sexually transmitted infections (STIs), and HIV infection in endemic regions of Africa.

Common arguments against routine male circumcision cite the potential for surgical complications, desire to avoid inflicting pain upon the infant, unethical imposition of elective surgery on the infant, and cost of the procedure. Complication rates for neonatal circumcision range from 0.2 to 3%, and most commonly involve bleeding or infection. Although physiologic indicators of pain, such as "increased heart rate, prolonged crying, and
decreases in oxygen tension", have been documented in infants during circumcision, studies show that local anesthesia substantially reduces this response suggesting that pain can be managed effectively. Because newborns lack the capacity to make an informed choice about circumcision, some may argue that it is unethical to subject a child to a procedure that is unessential to the child’s current health. However, in our society we have deemed it the parents’ responsibility to determine if circumcision is in the child’s best interest. Finally, the cost of circumcision varies widely among medical providers and settings, and is not covered by all Medicaid programs and many private insurance plans, indicating the potential financial cost posed by circumcision.

Both vehement supporters and speculative critics of circumcision can be highly vocal about their viewpoints, making circumcision a hotly contested issue. This debate will likely continue to evolve as scientific research sheds new light on the connection between circumcision and health.

II. HISTORICAL, CULTURAL, AND GEOGRAPHICAL CONTEXT

Origins of circumcision

The origin of male circumcision is uncertain. Anthropologist Sir Grafton Elliot Smith hypothesized that the custom of circumcision began as early as 15,000 B.C in Egypt. Physical evidence of circumcision is found in Egyptian mummies and is corroborated by ancient wall carvings at Egyptian tombs that depict the act of circumcision, dating the custom’s genesis to at least 6,000 years ago. The Egyptians may have practiced circumcision to promote hygiene and prevent schistosomiasis (infection with the blood fluke, Schistosoma hematobium). Although this evidence points toward Egypt and Eastern Africa as the point of origin, other historical accounts describe circumcision existing among Native Australians and Native
Americans at the time of their first contact with Europeans.\textsuperscript{16} This suggests that the practice of circumcision may have developed independently at multiple sites across the globe.

Historically, circumcision has not always been promoted as a health-related practice. In fact, circumcision may have initially been a symbol of conquest over others. In ancient Egypt, captives were circumcised to indicate their status as slaves.\textsuperscript{16} Biblical passages refer to David circumcising his defeated foes and presenting their foreskins to the King Saul as a dowry (1 Samuel 18:25-27). Circumcision may also have significance at the time of harvest in some cultures or may simply serve as a marker of cultural identity like a tattoo or piercing.\textsuperscript{16}

Ritual circumcision

Regardless of circumcision's original purpose, the practice spread to multiple cultures worldwide and, in many instances, took on special religious importance. In some African cultures, males are circumcised at birth.\textsuperscript{16} Ritual circumcision also plays a significant role in both Judaism and Islam. Abraham is a principal figure in both Judaism and Islam and the central role of circumcision in these religions may stem from the biblical account of Abraham. In Genesis 17, God entreats Abraham to circumcise himself and his sons as an outward symbol of their covenant with God (Genesis 17:13).

In Judaism, circumcision (Brit/Bris milah) is performed on the eighth day of a newborn male's life, signifying the newborn's entry into Jewish tradition. Although mothers may have performed the ritual originally,\textsuperscript{16} the responsibility of circumcising newborn males eventually transferred to mohels. These trained ritual circumcisers possess both surgical skills as well as knowledge of Jewish tradition and law. They introduced specialized tools for circumcision and continue to practice ritual circumcision today.\textsuperscript{19}

Circumcision is also highly prevalent in the Muslim world. Of all males who are circumcised worldwide, 68% are Muslim.\textsuperscript{14} Although ritual circumcision is not specifically mentioned in the Koran, its importance is documented in the Sunnah (the recorded teachings
and actions of the Prophet Mohammed, who according to tradition was born without a foreskin\(^{20}\) and the practice is strongly encouraged. For Muslims, circumcision (tahara, or purification) represents a young male's introduction to the Islamic faith and is a sign of belonging.\(^{20}\) Muslims may undergo circumcision as early as the first week of life or as late as puberty, with seven being the preferred age.\(^{20}\) There is no Islamic corollary to the Jewish mohel and males are typically circumcised in hospitals or clinics.

From uncertain origins, the practice of circumcision became globally pervasive and the importance of ritual circumcision in various cultures and religions facilitated this spread. Yet not all circumcisions today are ritualistic. Some modern societies practice routine circumcision for non-religious reasons. Routine circumcision is influenced by and evolved alongside ritual circumcision; however, these practices have important differences (e.g. involvement of medical professionals, use of anesthesia) that underscore the need to examine routine circumcision as a distinct issue.

Routine circumcision

Up until the 19\(^{th}\) century, no evidence exists to indicate that physicians extensively performed circumcision.\(^{16}\) Early reports of circumcision in the medical literature demonstrate the procedure's role in treating phimosis,\(^{18}\) but do not describe any preventive benefits. By the late 19\(^{th}\) century, however, some physicians began endorsing circumcision as a life-extending procedure and as a cure for a variety of ailments ranging from paralysis to rectal prolapse to asthma.\(^2\) Another notable indication for circumcision during this period was excessive masturbation.\(^{21}\) The procedure gained widespread popularity by the early 20\(^{th}\) century and countless physicians began recommending routine circumcision of newborn males. In the late 20\(^{th}\) century, many physicians began questioning whether circumcision was medically necessary and medical organizations in countries such as Australia and Canada actually recommended against routine circumcision.\(^{22,23}\) Circumcision rates in these countries
subsequently declined, yet statements by the American Academy of Pediatrics in the 1970s that “there is no absolute medical indication for routine circumcision of the newborn,” resulted in a more modest decline.\(^2\)\(^,\)\(^24\)

Circumcision in the U.S.

The World Health Organization estimates that 30% of males worldwide and 75% of U.S. males have been circumcised.\(^14\) Circumcision is much more common in the U.S. than in South America, Central America, and much of Asia.\(^4\) Among developed countries, circumcision is much more common in the U.S. than in Canada\(^25\) (about half of males are circumcised), Australia, and most of Europe.

In the U.S., circumcision frequency has changed over time and also varies with geographic location, socioeconomic status, and racial/ethnic group. The annual incidence of male circumcision in the U.S. reached its peak at about 85% in 1965.\(^26\) The previous recorded low was 31% in 1932.\(^26\) In the past decade, annual circumcision incidence hovered around 60%, with a recent low of 55% in 2003 and slight increase to 57% in 2004.\(^27\)

In the last fifteen years, there have been prominent regional differences in circumcision incidence. Hospital discharge data indicates that the highest incidence of circumcision has been in the North Central/Midwest region, where about 80% of newborn males were circumcised annually over the last decade and a half.\(^27\) The Northeast and South regions maintained annual circumcision incidence between 60-70% during the early 1990s, but recently the incidence of circumcision in the South has dropped as low as 55% in 2006.\(^27\) Meanwhile, the Northeast continued to exceed the national average at about 64% in 2006.\(^27\) The region with the lowest incidence of annual male circumcision is the West, with rates ranging from 31% in 2003 to 34% in 2006.\(^27\) The annual incidence in the West has been consistently below the national average.\(^27\) Of note, these figures underestimate the true incidence of newborn circumcision because they only account for those circumcised prior to hospital discharge.
Circumcision rates also vary according to families’ access to care. Circumcision is more common among families with higher socioeconomic status. This trend will likely continue as insurers, including Medicaid, drop coverage for newborn circumcision. Additionally, data from the National Health and Social Life Survey suggest that whites are more likely to be circumcised in the U.S. (81%) than several minority groups including blacks (65%) and Hispanics (54%).

III. WHY FOCUS ATTENTION ON CIRCUMCISION?

A large proportion of the U.S. population has at some point considered whether or not to circumcise a male infant. For many parents, this choice is dictated by religious traditions or cultural values, while for others personal preferences and family norms play a central role in the decision-making process. However, the circumcision decision also has potential health consequences for their infants. With this confluence of factors affecting a parent’s decision to pursue this elective procedure, physicians are ethically obligated to consider the medical ramifications of the procedure and preferences of families as they counsel parents or make policy recommendations.

One of the most frequently cited medical benefits of circumcision is a reduced frequency of UTIs in childhood. Most UTIs in males occur during the first year of life and many studies have found that uncircumcised males are at increased risk for UTI, especially during the first year of life. A recent systematic review of 12 studies on this topic concluded that circumcision appears to reduce a male’s risk of UTI within the first 10 years of life from 1% to 0.13%. Although this corresponds to a dramatic relative reduction, the baseline risk for UTI is low, even among the group at greatest risk (younger than one year of age). Given the 1% risk among normal boys for contracting a UTI, 111 boys would need to be circumcised to prevent one UTI.

The literature on the connection between circumcision status and penile cancer is difficult to evaluate, but recent reviews indicate that uncircumcised men have a slightly higher
risk of developing penile cancer, probably due to increased rates of phimosis in this population, rather than human papillomavirus (HPV) infection.\textsuperscript{7-9} Given the extremely low prevalence of penile cancer in the United States — estimated at 0.3-1.0 per 100,000\textsuperscript{9} — the implications of this risk increase are difficult to determine. However, considering the severity of this disease, any potential increase in risk may factor into some parents' decision-making processes.

Circumcision has also been suggested to decrease the risks of contracting STIs. A 2006 meta-analysis confirmed that circumcised men are at significantly lower risks for syphilis and chancroid than uncircumcised men.\textsuperscript{11} However, the substantial heterogeneity of included studies (e.g. study location, high-risk populations vs. low risk populations, methods for assessing circumcision status) limits the certainty of these findings, as well as their applicability for neonatal circumcision in the general U.S. population. Evidence for associations between circumcision and other STIs is even less convincing. This same meta-analysis found no significant difference in the risk of genital herpes between circumcised and uncircumcised males,\textsuperscript{11} and a more recent systematic review and meta-analysis established that uncircumcised men are no more likely to have gonorrhea or Chlamydia than their circumcised counterparts.\textsuperscript{10}

Considerable research has also investigated the relationship between circumcision status and HIV infection. According to the American Academy of Pediatrics (AAP):

There does appear to be a plausible biologic explanation for this association in that the mucous surface of the uncircumcised penis allows for viral attachment to lymphoid cells at or near the surface of the mucous membrane, as well as an increased likelihood of minor abrasions resulting in increased HIV access to target tissues.\textsuperscript{4}

A 2005 systematic review including 37 observational studies on HIV and male circumcision suggests that circumcision is associated with decreased rates of HIV acquisition within high-risk groups, but not among the general population.\textsuperscript{28} A 2009 systematic review by the same author
reports that there is strong evidence that circumcision dramatically reduces HIV acquisition in heterosexual men (38-66% reduction over two years). This 2009 review differs from the 2005 review in that it only analyzes the results of three recent randomized-controlled trials from Africa that investigated the protective effects of circumcision against HIV.

These recent randomized-controlled trials of male circumcision for HIV prevention in Kenya, Uganda, and South Africa are seminal studies and have ignited considerable interest in whether circumcision in the U.S. could achieve similar reductions in risk of acquiring HIV and other sexually transmitted infections. The WHO now fully supports male circumcision as an "important strategy for the prevention of heterosexually acquired HIV infection in men," However, there is still uncertainty about how these results extrapolate to the U.S. population, especially given the differences in HIV epidemics and circumcision prevalence between African countries and the U.S.

For example, in 2007, the prevalence of HIV (among adults 15-49 years-old) in South Africa, Kenya, and Uganda ranged from 5.4-18.1%, whereas HIV prevalence in the U.S. was 0.6%. Most sexual transmission of HIV in South Africa, Kenya, and Uganda occurs through male-female intercourse. In the United States, the majority of sexual transmission of HIV occurs among men who have sex with men (MSM) who represented 71% of HIV infections among adult and adolescent males in 2005. In addition, the HIV serotypes differ by geographic location with certain viral types afflicting African populations and other types infecting people in the U.S. All of these differences could alter the effectiveness of circumcision for HIV prevention when translated to the U.S. Additionally, these studies do not resolve the uncertainty about the role of circumcision in preventing other STIs.

IV. SCIENTIFIC UNCERTAINTY ABOUT CIRCUMCISION AND STIs
Associations between male circumcision and prevention of sexually transmitted infections (STIs) are inconsistent in the medical literature. There are some negative studies, some positive studies, and some studies with methodological flaws that make their results uncertain. The lack of data establishing definitive and significant protective effects from circumcision, in combination with the low rates of complications for this neonatal procedure, has created a state of clinical equipoise surrounding this health-related decision. This is reflected in the American Academy of Pediatrics’ current policy statement, written in 1999 and reaffirmed in 2005, which states that there is insufficient scientific evidence to either recommend or discourage neonatal circumcision from a medical standpoint.4

In their 2005 policy reaffirmation, the AAP dedicates significantly more space to discussion of the relationship between circumcision and UTI risk than STI risk. This is likely due to the disparate states of evidence for UTIs and STIs at the time the AAP issued the policy statement when there was greater scientific consensus supporting the role of circumcision for decreasing UTI risk. They specifically state that, “Evidence regarding the relationship of circumcision to STD in general is complex and conflicting.”4 Given the considerable uncertainty of evidence when the previous AAP statement was issued, and in light of new evidence demonstrating the substantial preventive effects of circumcision after the newborn period, an up-to-date systematic evidence review on circumcision for STI prevention could help inform future recommendations about routine circumcision for preventive purposes.

Thus, to direct medical guidelines and research we need a systematic review to address whether circumcision of newborn males in the U.S. reduces the risk of STIs later in life.
METHODS

FOCUSED QUESTION

The focused question for this review is: Does the circumcision of newborn males in the U.S. prevent STIs among adolescent and adult males?

The uncertain role of circumcision in preventing STIs deserves special attention because of the substantial burden of suffering imposed by a range of STIs in the U.S. STIs are far more common than the two other health outcomes commonly associated with circumcision status, male UTIs and penile cancer. I decided to include a range of STIs in this review. Different STIs may serve as important outcomes because they are widespread (e.g. chlamydia, human papillomavirus), associated with substantial morbidity/mortality (e.g. syphilis, HIV), or both. In all instances, I plan to look at these outcomes as they occur among adolescents and adults because exposure to STIs does not occur until after the onset of sexual activity.

The STIs addressed in this review include HIV, human papillomavirus (HPV), syphilis, chancroid, herpes simplex, chlamydia, gonorrhea, and hepatitis B and C. This list is based on the volume of studies published on specific infections found in a general background search of the literature on circumcision, specific outcomes examined in previous reviews, and burden of suffering (e.g. disease prevalence, morbidity, mortality) associated with specific diseases. To simplify analysis, these STIs can be broken into subgroups including: 1) Genital ulcerative diseases (syphilis, chancroid, herpes simplex); 2) Mucopurulent diseases (chlamydia, gonorrhea); and 3) Other viral STIs (HIV, HPV). STIs within these subgroups share certain characteristics including disease processes and symptoms. Disease outcomes within subgroups could be similarly affected by circumcision, which may influence interpretation of the results. Furthermore, these logical subgroups facilitate presentation of results.
ELIGIBILITY CRITERIA

The eligibility criteria for studies in this systematic review are displayed in Table I and summarized here. Studies that met each of the following criteria were included in the review:

1. Targeted U.S. males as study population;
2. Included circumcision in the newborn period as the study intervention or exposure (if case-control studies);
3. Included detection of STI among adolescent and young adult males confirmed by laboratory and/or clinical diagnosis as the study outcome;
4. Study design was systematic review, randomized-controlled trial, non-randomized-controlled trial, cohort study (retrospective and prospective), case-control study, or cross-sectional study; and
5. Published after 1948.

I excluded studies with international target populations and studies including circumcision outside of the newborn period from formal review. However, I kept these studies for reference (e.g. background, discussion).

Table I. Eligibility Criteria*

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>- Males in the United States</td>
<td>- International populations, women</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>- Circumcision in newborn period</td>
<td>- Circumcision outside of newborn period</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>- Compared to no circumcision</td>
<td>- Lack of comparison</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>- Diagnosis of STI among adolescent and adult males confirmed by laboratory diagnostics and/or clinical diagnosis</td>
<td>- No STI confirmed, UTI pathogen, Penile cancer, Persistent infection</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>- Systematic reviews, RCTs, NRCTs, cohort studies (retrospective and prospective), case-control studies, cross-sectional studies</td>
<td>- Case reports, case series</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>1948-present</td>
<td></td>
</tr>
</tbody>
</table>

*STI = sexually transmitted infection; UTI = urinary tract infection; RCT = randomized-controlled trial; NRCT = non-randomized-controlled trial
To be included, studies needed to designate detection of STI among adolescent and adult males confirmed by laboratory and/or clinical diagnosis. Centers for Disease Control (CDC) surveillance data indicate that adolescents and young adults have the highest rate of STIs compared with other age groups in the U.S. I focused on this age range not only because of disease burden but also because I predicted that investigators would be unlikely to measure STI outcomes much later in adulthood for reasons of impracticality.

SEARCH STRATEGY

I searched MEDLINE, Cochrane Database, and EMBASE for relevant publications from 1948 through April 2009. I consulted a health sciences librarian to assist the development of my search strategy. Using a combination of key words and Medical Subject Headings (MeSH terms) pertaining to male circumcision and STIs, I identified relevant citations and stored them in an EndNote X2 database. The search terms used for each database search are displayed in Table 2.

Table 2. Search strategy by database

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
<th>Result</th>
</tr>
</thead>
</table>
After identifying and resolving areas of overlap between the searches above, I reviewed both abstracts and then full-text articles for eligibility. I checked the reference lists of included articles for additional relevant citations.

QUALITY CRITERIA

For assessing study quality (internal validity), I used the United States Preventive Services Task Force (USPSTF) methods.\textsuperscript{33} I graded the internal validity of each study as "good," "fair," or "poor."\textsuperscript{33} The criteria used to assess individual studies (by design) and descriptions for the overall grade of internal validity are presented in Table 3 and Table 4. Due to the subjectivity of the grading scale, a more detailed description of a study's grade is included where necessary.

<table>
<thead>
<tr>
<th>Table 3. Quality criteria by study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>Systematic reviews</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Case-control studies</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Cross-sectional studies

- Level of selection bias (comparability of groups if comparison done, eligibility criteria)
- Level of measurement bias (equal, reliable, valid)
- Confounding (confounders identified/measured/addressed)

RCTs, NRCTs and cohort studies

- Comparability of groups (randomization, concealment, restriction criteria, measurement of confounders)
- Attrition, loss to f/u, crossover, adherence very large or differing by group
- Measurement (equal, reliable, valid)
- Intervention explicit
- Outcomes relevant
- Adjustment, ITT

*Adapted from USPSTF criteria for grading the internal validity of individual studies*

<table>
<thead>
<tr>
<th>Rating</th>
<th>Appraisal criteria met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Meets all criteria; very low potential for systematic bias</td>
</tr>
<tr>
<td>Fair</td>
<td>Does not meet all criteria, but does not have fatal flaw or bias that completely explains results</td>
</tr>
<tr>
<td>Poor</td>
<td>Has fatal flaw (e.g. results could be explained completely by bias, complete lack of information on important components of study design)</td>
</tr>
</tbody>
</table>

*Adapted from USPSTF criteria for grading the internal validity of individual studies*

**SELECTION OF ARTICLES**

Due to resource limitations, I conducted the steps involved in study selection independently. Ideally, I would have had two reviewers independently assess abstracts and full-text articles. After conducting my search, I began the selection process with a review of relevant abstracts. I applied the eligibility criteria to titles and abstracts and discarded irrelevant studies (some were kept for background). Following abstract review, I applied the eligibility criteria to the full text of the remaining articles. I repeated both the abstract review and full-text review to ensure that no relevant studies were inappropriately excluded.
DATA ABSTRACTION

In the next step, I abstracted evidence from included articles. Again, data extraction was performed independently without double review. I used a standardized abstraction form to collect data from each study, and the following characteristics were extracted from each study: date of data extraction; title; author(s); year of publication; journal; number of studies included in paper; year in which study was conducted; details regarding other relevant papers cited; study characteristics (population; care setting; methodological quality of the study; interventions; outcomes); outcome measures/results (length of follow-up; drop-outs/crossovers; missing data; discrete/continuous results; risk comparisons; and effect measures).

Based on the information extracted from individual studies, I constructed a set of evidence tables to summarize my findings. Each table listed the included studies (author and year) as individual rows. Evidence tables included one descriptive table with information about study characteristics and basic design and another table with quality rating information. This table included information about potential for selection bias, measurement bias, confounding, analysis methods, external validity, and overall internal validity of the study. Finally, I developed a table dedicated to reporting important results, in the form of effect measures, from individual studies.

I synthesized the information in these tables qualitatively. I considered breaking the studies down according to study quality or STI subgroup, butfinally decided to stratify studies according to the risk profile of the study population (see Results below). I did not perform quantitative analysis due to significant heterogeneity in study design and reporting (see Results below).
RESULTS

STUDY IDENTIFICATION

The literature search identified 745 potentially relevant citations. I modeled the search strategies used for EMBASE and the Cochrane Database after my MEDLINE search, using similar search terms, which resulted in duplicate citations. I excluded 75 duplicate citations prior to abstract review. Figure 1 shows the flow of my literature search starting with abstract review. Of the 670 abstracts reviewed, I excluded 628. I excluded 488 abstracts because they did not meet one or more eligibility criteria (see Figure 1). I excluded 68 abstracts that were relevant except that they were international studies. Another 72 abstracts failed to meet eligibility criteria but I kept them as useful background resources (e.g. commentaries on relevant articles, responses by authors of relevant articles, policy recommendations).

I identified one additional relevant citation by hand searching the reference lists of the included abstracts, leaving a total of 43 citations for full-text review. At full-text review, I excluded 31 articles that did not meet one or more of the eligibility criteria (15 with wrong study population; five were not original research; two with wrong outcomes; one with wrong intervention; four with wrong study design; and four either lacked comparison group, were unable in full-text form, or had been updated by a more recent version). This selection process left me with 12 articles to include in the review.26,34-44

TYPES OF STUDIES RETRIEVED

The 12 included articles described 13 observational studies (one article described both a cross-sectional and a cohort study). There were nine cross-sectional studies, one case-control study, and three cohort studies. No RCTs or systematic reviews were included (three African RCTs excluded at abstract review stage; seven systematic reviews excluded at full-text review stage because they included international studies).
Abstracts reviewed (n=670)

Abstracts excluded and reasons (n=628)
- Relevant international studies (n=68)
- Useful background (n=72)
- Irrelevant abstracts (n=488; letter/comment, news article, wrong outcome [e.g. penile cancer, UTI], wrong study type [e.g. case reports, narrative review], wrong intervention [e.g. female circumcision], wrong population [female risk for STI], no comparison group, not published in English)

Hand searching citations of relevant full-text articles (n=1)

Potentially relevant full-text articles reviewed (n=43)

Full-text excluded and reasons (n=31)
- Wrong population/setting (n=15; i.e. not at U.S. study)
- Not original research (n=5; letter to editor, commentary)
- Wrong outcome (n=2; e.g. bacterial vaginosis)
- Wrong intervention (n=1; circumcision not considered)
- Wrong design (n=4; e.g. narrative review)
- Other (n=4; no comparison group, full-text unavailable)

Relevant articles for abstraction and appraisal (n=12)
The studies meeting eligibility criteria assessed outcomes including gonorrhea, chlamydia, syphilis, HIV, genital herpes (or HSV-2 status), genital warts (or HPV status), chancroid, and hepatitis (unspecified type). Five studies (one cohort, one case-control, three cross-sectional) included multiple STI outcomes, with gonorrhea, chlamydia, and syphilis being the most commonly included. One cross-sectional study included all of the outcomes listed above (except chancroid and genital warts/HPV) and also had outcomes for “all bacterial” and “all viral” STIs.26

The included studies investigated populations that differed in their risk profile for STIs. Two studies examined the association between circumcision status and STIs among males in the general U.S. population; seven others looked at high-risk heterosexual males at STD clinics; and four studied MSM in major U.S. cities. The studies, which were stratified by population risk profile, are described below and summarized in Tables 5 through 7 (Appendix A).

CIRCUMCISION EFFECT AMONG GENERAL U.S. POPULATION

Laumann and colleagues identified a nationally representative sample of 1,511 men between 18-59 years-old (with oversampling for African Americans and Hispanics) in the National Health and Social Life Survey (NHSLS) – 1992 and studied the association between circumcision status and an array of bacterial and viral STIs, including: gonorrhea, syphilis, chlamydia, herpes, hepatitis (type unspecified), and HIV.26 75% of the study population was circumcised. Investigators measured circumcision status by participant self-report and confirmed STI status by validated lab tests. The circumcision groups differed with respect to multiple characteristics (with many more unreported). Notably, circumcised men were more educated and less likely to be African American or Hispanic. In this cross-sectional study, they detected no association between circumcision status and any of the specified outcomes (see Table 7 for effect measures by outcome).
Using data from The National Health and Nutrition Examination Survey (NHANES), 1999-2004, Xu and associates studied 4,185 boys and men (14-49 years old) to determine if an association exists between circumcision status and HSV-2 seropositivity. NHANES employed a nationally stratified, multistage probability design that oversampled for adolescents, blacks, and Mexican Americans. 79% of participants were circumcised. All participants identified circumcision status by self-report and underwent serologic testing for HSV-2. In the absence of randomization (cross-sectional design), groups had limited comparability: circumcised participants were younger, more likely to be foreign-born, less likely to be a minority, and had fewer lifetime sex partners compared to uncircumcised participants. Investigators found no association between being uncircumcised and HSV-2 seropositivity (adjusted OR [95% CI] = 1.1 [0.8-1.5]).

Quality of the Studies and Summary of Findings

Both of these cross-sectional studies assessing the association between circumcision status and STIs in the general U.S. population were fair quality studies. For both studies, the circumcision groups being compared differed substantially due to lack of randomization, matching, or restriction. Although both studies measured numerous potential confounders and made appropriate adjustments in their logistic regression analysis, the results may be biased by unknown, unmeasured confounders and limited comparability of study groups. The use of self-report for measuring circumcision status creates potential for misclassification bias in both studies. The possible non-differential misclassification bias in the study by Xu et al. may partially explain the null finding. Despite the moderate potential for bias in both studies, no systematic errors appear to seriously threaten the validity of their findings of no associations between circumcision status and numerous STI outcomes including gonorrhea, syphilis, chlamydia, HSV-2, hepatitis, and HIV.
CIRCUMCISION EFFECT AMONG HIGH-RISK HETEROSEXUAL MALES IN U.S.

Using patients seen at U.S. Naval Hospital venereal clinics in St. Albans, NY, Hand compared 1,391 servicemen without STIs to 1,082 servicemen with gonorrhea, 532 with syphilis, and 138 with chancroid in order to test for an association between circumcision status and STIs. The control group was mostly white with a large proportion of Jewish men. The case groups had much higher proportions of blacks compared with the control group. Hand does not describe his methods of measurement or consider any potential confounders. His analysis is limited to descriptive frequencies of circumcision among the different groups. Using these frequencies, I calculated unadjusted ORs with 95% CIs for each outcome. Hand’s findings suggest strong associations between being uncircumcised and having all three outcomes (gonorrhea - 6.05 [5.03-7.28]; syphilis - 5.47 [4.32 - 6.92]; chancroid - 23.7 [11.5 - 48.8]).

Cook and coworkers reviewed the charts of 2,776 heterosexual men, who sought care for a new problem at an STD clinic in Seattle, WA, to assess whether an association exists between circumcision status and multiple STI outcomes (gonorrhea, syphilis, chlamydia, genital herpes, and genital warts). The sample included 985 men without STIs and 81% of the study population was circumcised. Circumcision status was measured by clinical exam at the time of the visit and all patients consenting for exam underwent STI testing. The comparability of circumcision groups by various cofactors was unreported. Investigators found lack of circumcision to be associated with gonorrhea, syphilis, and genital warts (adjusted ORs [95% CI] = 1.6 [1.2-2.2], 4.0 [1.9-8.4], 0.7 [0.5-0.9], respectively). The results suggest a trend toward protection by circumcision against gonorrhea and syphilis, but increased odds for genital warts.

Diseker and colleagues used data from a randomized controlled trial of HIV prevention counseling, which took place in STD clinics in Baltimore, Denver, Long Beach, Newark, and San Francisco, to study the relationship between circumcision status and STIs (gonorrhea, chlamydia, and syphilis) among 2,021 heterosexual men who came to STD clinics for an
834 of participants did not have the STIs in question and 75% were circumcised. More than half of participants were African American. Investigators did not describe the comparability of circumcision groups. Circumcision status was measured by clinical exam and STI outcomes were lab-confirmed. 1,456 of 2,021 participants followed up after baseline at 6 or 12 months, or both. The article includes both cross-sectional and cohort results, which were similar. Overall, the investigators found no association between circumcision status and STIs except for a marginal finding from the cohort analysis suggesting an association between lack of circumcision and gonorrhea (adjusted OR [95% CI] = 1.6 [1.0-2.6]).

Baldwin and associates studied 443 high-risk men attending a public STD clinic in Tucson, AZ to test for an association between circumcision status and HPV status (any type, non-oncogenic, and oncogenic). 67% of participants were circumcised and 90% self-identified as heterosexual. Participants had a greater prevalence of multiple, concurrent STIs compared to non-participants. Data on group comparability was not reported and HPV outcomes are missing for 50 men (mostly white and circumcised). Circumcision status determined by clinical exam and HPV detected by PCR followed by sub-typing. The investigators detected an association between circumcision and HPV status, suggesting protection by circumcision against any non-oncogenic, oncogenic, and any type of HPV (adjusted ORs [95% CI] = 0.44 [0.23-0.81], 0.44 [0.22-0.90], and 0.34 [0.20-0.57], respectively).

Based on data from the same randomized controlled trial of HIV prevention counseling used by Diseker and colleagues, Gottlieb and coworkers evaluated the relationship between circumcision and HSV-2 seropositivity among 1,120 heterosexual men attending STD clinics in five major U.S. cities (see list above). Participants were followed prospectively for 12 months. More than half the population was African American and 71% of participants were circumcised. All participants tested negative for HSV-2 at baseline. Circumcision groups were not comparable and the investigators report nothing about those lost to follow-up. They measured circumcision status by clinical exam and tested participants for HSV-2 seroconversion at
baseline and follow-up visits (6 and 12 months). After 12 months of follow-up, Gottlieb and coworkers found no relationship between circumcision status and HSV-2 seroconversion (adjusted hazard ratio [95% CI] 1.0 [0.6-1.6]).

Warner and colleagues studied data from 40,571 STD clinic visits made by 26,448 heterosexual African American men who underwent HIV testing at two STD clinics in Baltimore, MD in order to test for an association between circumcision and HIV status. 87% of clinic visits were made by circumcised men. Participants had no previous positive or uncertain HIV tests. 394 and 40,177 visits were made by men with known and unknown HIV exposure, respectively. Uncircumcised participants were older and had a higher proportion of STD (not HIV) diagnoses than circumcised men. Clinicians measured circumcision status by physical exam and determined HIV status by immunoassay screening and Western blot confirmation. Among men with known HIV exposure, investigators detected an association between circumcision and being HIV seropositive (adjusted OR = 0.49 [0.26-0.93]). However, findings from the group with unknown HIV exposure did not suggest a trend towards protection by circumcision (1.00 [0.86-1.15]).

Quality of the Studies and Summary of Findings

This group of articles focusing on high-risk heterosexual populations in the U.S. included two fair quality cohort studies,\(^{37,38}\) one poor quality case-control study,\(^{39}\) and four fair quality cross-sectional studies.\(^{34,36,37,43}\) Both cohort studies had strong potential for selection bias due to limited comparability of circumcision groups (no randomization, matching, or restriction) and moderate potential for confounding resulting mainly from lack of randomization. The study by Diseker and colleagues had differential follow-up by circumcision status, which could bias results toward a protective circumcision effect and potentially explain some of their findings favoring circumcision (see Table 6).\(^{37}\) Given the lack of reporting about participants reasons for not following up, there is significant uncertainty about the presence of such bias.
The case-control study by Hand (from 1949) was rated as poor primarily due to uncertain methodology. He does not state his technique for measuring exposure and outcomes. Cases and controls were significantly different according to reported cofactors like race and religion. His analysis did not include any calculation of effect measure. My calculations of unadjusted ORs do not account for any confounders. Thus, despite the apparently strong association between circumcision and three STIs (gonorrhea, syphilis, and chancroid) detected by Hand, the study's results are not internally valid.

All four cross-sectional studies have large potential for selection bias due to limited comparability of study groups. The study by Baldwin and associates found an association suggesting protection by circumcision against HPV, but their analysis did not adjust for education and socioeconomic status (SES). Both education and SES are likely confounders, which could partially explain this study's results, although their findings are consistent for all HPV types and robust even after adjustment for other cofactors. Additionally, education and SES may also be confounders in the study by Warner and colleagues, whose findings suggest protection by circumcision against HIV among those with known HIV exposure. These factors were not fully addressed and may partially explain their results, unless their study population was homogenous with respect to education and SES (distribution of these factors not reported).

Only one out of seven studies of high-risk heterosexual males had fatal flaws. This poor quality case-control study by Hand also found the strongest association between lack of circumcision and having STIs (gonorrhea, chlamydia, and syphilis). One cohort study and three cross-sectional studies also had findings that suggested a protective effect by circumcision. The other cohort study and cross-sectional study found no association between circumcision status and STIs. Overall, these studies of circumcision among high-risk heterosexual males in the U.S. demonstrate mixed results.

CIRCUMCISION EFFECT AMONG MSM IN MAJOR U.S. CITIES
Kreiss and Hopkins studied the relationship between circumcision and HIV serostatus among 502 MSM in Seattle, WA who were recruited at three study sites (two AIDS comprehensive care clinics and one public health screening center). 85% of participants were circumcised, 90% were white, and 316 were HIV seropositive. All the seronegative men were recruited at the screening center. Uncircumcised men were older, more often non-white, and more likely to have a history of syphilis. Patients self-reported circumcision status and HIV serostatus was measured by ELISA screening and Western blot confirmation. Investigators detected an association between lack of circumcision and being HIV seropositive (adjusted OR [95% CI] = 2.0 [1.0-4.0]).

Using data from the Vaccine Preparedness Study (VPS), an 18 month-long prospective cohort study in Boston, Chicago, Denver, New York, San Francisco, and Seattle, Buchbinder and associates tested for an association between circumcision status and HIV seroconversion among 3,257 high-risk MSM. 88% of participants were circumcised and 75% were white. Investigators did not report participant characteristics by circumcision status and 12% of participants did not complete the study. Circumcision status was measured by self-report and HIV seroconversion was lab confirmed (at 6, 12, and 18 months). The study revealed an association between lack of circumcision and HIV seroconversion after 18 months of follow-up (adjusted OR [95% CI] = 2.0 [1.1-3.7]).

Millet and coworkers evaluated the association between circumcision and HIV in a cross-sectional study of 1,154 black MSM (from New York and Philadelphia) and 1,081 Latino MSM (from New York and Los Angeles). 74% of black participants were circumcised compared to 33% of Latino participants. Investigators found participants through network-based recruiting. Among the black participants, circumcised MSM were older, more educated, and had unprotected anal sex with more partners. In the group of Latinos, circumcised MSM were more likely to be born in the U.S. Participants self-reported circumcision status and investigators screened for HIV by ELISA and patient history with confirmation by Western blot.
Neither black nor Latino MSM groups displayed an association between circumcision and HIV serostatus (adjusted ORs [95% CI] = 1.23 [0.87-1.74] and 1.10 [0.73-1.66], respectively).

Reisen and colleagues studied the association between circumcision and HIV status among 482 immigrant Latino MSM living in New York City (146 Brazilian, 169 Colombian, 167 Dominican). 25% of participants were circumcised and MSM in this population were burdened by a relatively high prevalence of STIs. Circumcision and HIV status were both measured by self-report. Circumcised men reported higher education level and circumcision rate did not vary by country of origin. The investigators analyzed results for the whole sample and by country of origin. They detected an association between lack of circumcision and HIV seropositivity among the whole study population (adjusted OR [95% CI] = 1.9 [1.01-3.59]). Analyses by country of origin showed the same association, but only among the Colombian group (adjusted OR [95% CI] = 4.06 [1.40-11.75]).

Quality of the studies and Summary of Findings

The studies focusing on the urban MSM populations in the U.S. included one fair quality cohort study, two fair quality cross-sectional studies, and one poor quality cross-sectional study. Potential selection bias due to poor comparability of circumcision groups limited the quality of all four studies. The cohort study by Buchbinder and associates does not have a specific bias that could explain their findings, which suggest a protective effect of circumcision against HIV. Both the fair quality cross-sectional studies have moderate potential for non-differential misclassification bias, which could partially explain the null finding in the study by Millet and coworkers and cause an underestimation of the association detected by Reisen and colleagues (see Tables 6 and 7). The poor quality cross-sectional study, by Kreiss and Hopkins, failed to address important potential confounders like SES and education, which could bias their findings in favor of circumcision. This strong potential for confounding and selection bias severely limits the internal validity of the study.
Each of the four studies examining MSM populations focused on HIV status as their outcome. The one poor quality cross-sectional study\textsuperscript{40} found an association suggesting a protective effect by circumcision. Two of the other three studies had findings that pointed to possible protection by circumcision,\textsuperscript{35,42} with the strongest evidence coming from the cohort study by Buchbinder and associates. Reisen and colleagues detected an association between lack of circumcision and self-reported HIV status, but this finding may be attributed to the subgroup of Colombian men in their Latino study population. Overall, the studies among MSM in the U.S. reveal mixed results with regard to the effect of circumcision.

DISCUSSION

Whether circumcision reduces the risk for STIs among adult men in the U.S. is controversial. The literature on this topic consists of studies that suggest protective, mixed, and harmful effects of circumcision. In this systematic review, I identified 13 U.S. observational studies that sought to elucidate the relationship between circumcision status and various STI outcomes. The populations investigated by these studies differed with respect to risk profile. Two studies assessed the general population of U.S. males and neither found an association between circumcision status and various STI outcomes. Seven studies focusing on high-risk heterosexual populations (at STD clinics in major U.S. cities) report mixed results for circumcision, with conflicting or null findings across an array of STI outcomes. The final four studies included urban MSM populations with HIV as their outcome of interest. These four studies presented protective and null findings, suggesting an uncertain effect of circumcision. Taken together, this evidence implies that circumcision does not uniformly reduce the risk for STIs among adult men in the U.S. and that its effect is uncertain in both low risk and high risk populations.
OVERALL FINDINGS BY STI AND STI SUBGROUP

To build a better understanding of the specific effects of circumcision, I looked for trends in the data according to individual STI and STI subgroups. Of the STI outcomes included, HIV had the most consistent relationship with circumcision status across studies. In four out of six studies with HIV outcomes, investigators found a trend towards protection by circumcision. Excluding the results from the one poor quality HIV study, studies that detected an association between circumcision and HIV reported that the odds of having HIV among uncircumcised men doubled the odds of having HIV among circumcised men (see Table 7). The overall evidence for HIV is muddled, however, by the poor quality study and two other studies that found no association. Furthermore, a study among Latino MSM suggested protection by circumcision, but additional analysis demonstrated that the finding was likely attributed only to the Colombian immigrant MSM in the study population, which confuses circumcision’s effect among Latino MSM.

Gonorrhea was a common outcome, appearing in five studies. One of these studies was a poor quality case-control study that demonstrated increased odds for gonorrhea among uncircumcised men relative to circumcised men, but was riddled with potential biases due to unclear methodology and limited analyses. Two other studies suggested that the odds of having gonorrhea among uncircumcised men were one-and-a-half times greater than the odds among circumcised men. One of these studies was a cohort analysis showing only a marginal association (95% CI of 1.0-2.6) that did not match the null findings in the cross-sectional analysis of the same population. Despite some evidence of protection against gonorrhea, inconsistent results and findings of no association make circumcision’s effect less clear.

Chlamydia, the other mucopurulent STI considered along with gonorrhea, was the outcome in four studies. None of these studies demonstrated a meaningful association between circumcision status and chlamydia. Of the ulcerative STIs (syphilis, herpes, and
chancroid) only syphilis appeared to have any association with circumcision, showing a potential protective effect but only in one of four studies. Of the remaining viral STIs, only studies with HPV as an outcome found an association with circumcision. Results of the two HPV studies directly conflict, however, with an apparent protective effect of circumcision among the general population against clinically diagnosed genital warts but a harmful effect of circumcision among high-risk heterosexual men when the outcome was HPV detected by PCR. Only one study looked at hepatitis as an outcome (without specifying type) and found no association.

Overall, the evidence from this review does not suggest a consistently protective or harmful effect of circumcision. Although there were studies suggesting a protective effect against certain STIs (HIV, gonorrhea), there were also several studies of the same STIs reporting no benefit (i.e. no association). Thus, there is insufficient evidence to conclude that circumcision is or is not protective against STIs in the U.S.

OTHER RESEARCH

Previous systematic reviews have assessed the potential protective effects of circumcision. Seven of these systematic reviews were included in the full-text review stage of this study, but were excluded from abstraction and appraisal because they reviewed both U.S. and international studies. Three of these studies considered multiple STI outcomes and four looked solely at HIV as an outcome. In 2007, Van Howe identified 30 articles to help determine the relationship of circumcision status to the risk for genital ulcerative disease (GUD) and sexually transmitted urethritis (caused by gonorrhea and chlamydia). He included observational studies from across the globe and performed meta-analysis by STI subgroup despite the presence of significant qualitative heterogeneity between studies. Although he found that GUD had a trend towards being more common among uncircumcised men and that uncircumcised men were no more likely to have sexually transmitted urethritis than their circumcised counterparts, the heterogeneity (e.g. study location, exposure/outcomes
measurement, risk profile of population) between included studies brings significant uncertainty to the findings.

In another review, Weiss and colleagues identified 26 articles (both U.S. and international observational studies) in order to assess the association between circumcision status and HSV-2, chancroid, and syphilis. Their findings suggested that male circumcision was associated with a reduced risk for syphilis and chancroid, but not HSV-2. Much like the study by Van Howe, the qualitative heterogeneity between studies assessed by Weiss and colleagues limits the sureness of these findings.

To address the relationship between circumcision status and HIV as well as other STIs among MSM, Millet and coworkers performed a systematic review with meta-analysis of available observational data from around the world. They included 18 observational studies and did not detect any statistically significant association between circumcision and HIV among all MSM nor among MSM engaging primarily in insertive anal sex. However, they did uncover a protective association between circumcision and HIV in MSM studies conducted prior to the highly active antiretroviral therapy (HAART) era, which was comparable to the protective effect observed in the three recent circumcision RCTs of African men.

In a systematic review published earlier this year, Siegfried and associates evaluated three large circumcision RCTs of men from the general population in South Africa, Kenya, and Uganda. These trials enrolled a combined 11,054 HIV negative men who were randomized to circumcision or control group and followed for up to 24 months. Together, these RCTs found that medical male circumcision reduced HIV incidence among heterosexual men by between 38% and 66%. In the review, they reported "low to moderate’ potential for biases to explain the studies' results. Previous systematic reviews (2003 and 2005) by Siegfried and associates identified 35 and 37 observational studies, respectively, that tested the association between circumcision and HIV. Both of these prior reviews concluded that there was
insufficient evidence to definitively support the protective role of circumcision against HIV infection in heterosexual men.\textsuperscript{28, 49}

Prior to the 2009 review by Siegfried and colleagues, the systematic reviews exploring the protective role of circumcision against STIs included only observational data. With the exception of the three RCTs from Africa, the literature on this topic appears to echo the uncertainty regarding the risk-lowering role of circumcision against STIs reported in this review.

LIMITATIONS

The evidence base described in this review has significant limitations. The only potentially relevant RCTs come from Africa and they were excluded from this review of U.S. studies. All 13 included studies had strong potential for selection bias due to limited comparability of groups, although it was unclear how this bias affected the results from each study. Investigators consistently attempted to account for unevenly distributed confounders through adjustment in multivariate analysis, but the confounding variables addressed often varied by study, which made comparisons between studies difficult. The methods for assessing circumcision status and measuring outcomes also differed by study with some investigators employing patient self-report and others using clinical exams and lab tests. None of the studies asked about the age at which participants were circumcised.

This review also has limitations. I included cross-sectional studies because they represent the bulk of the evidence on the relationship between circumcision and STIs in the U.S. These cross-sectional designs lacked randomization, matching, or restriction to ensure comparability of groups, which accounted for much of the potential selection bias. Additionally, the cross-sectional data can limit causal inference. Although in the case of circumcision in the U.S., it seems reasonable to assume that nearly all participants without foreskins underwent neonatal circumcision, which would have preceded any exposure to STIs. Another important limitation to my study design was the lack of independent, dual review of abstracts and full-text
articles. In an attempt to redress this reliability issue, I repeated the abstract review and full-text reviews a second time one week after the initial review. Still, I may have inadvertently left out relevant studies.

Another potential caveat of this review is the limitation to U.S. studies. This strategy was based on the fact that circumcision/STI prevalence, transmission patterns, pathogen characteristics (e.g. HIV subtypes), and treatment for STIs in the U.S. do not directly correspond to those seen internationally. Had I not restricted my review to the U.S., I could have included better quality studies from other countries, like the three African RCTs. But the differences listed above could alter the effectiveness of circumcision for STI prevention when translated to the U.S. Thus, I believe that limiting studies to the U.S. was a strength of this study and critical to answering the focused question.

Finally, I did not attempt to pool data from included studies for meta-analysis. Although quantitative findings might have lent support to the conclusions of this review, there was far too much qualitative heterogeneity among the studies in question (e.g. study design, outcomes reported, exposure/outcome measurement). Meta-analysis would have been inappropriate and so its absence should not be considered a limitation.

IMPLICATIONS FOR POLICY AND FUTURE RESEARCH

This systematic review has important implications for clinicians, policymakers, and researchers. I developed my focused question because it addresses a potential preventive role for newborn circumcision --preventing STIs later in life-- that is not yet fully understood. My findings here in this review should further convince stakeholders that the effect of circumcision on STI outcomes in the U.S. is still uncertain. Although the WHO supports male circumcision as an "important strategy for the prevention of heterosexually acquired HIV infection in men," this policy stance is heavily influenced by the findings from the African RCTs and the body of
evidence supporting the biologic plausibility of circumcision's protective effect against HIV.\textsuperscript{4,29} U.S. policies regarding circumcision should be informed by the new evidence from Africa as well as the findings from domestic, observational studies, which point to a need for more information before endorsing circumcision as a panacea against STIs in the U.S.

This review has highlighted the differential risk profiles in the U.S., and described the reported effects of circumcision in the general population, high-risk heterosexual male populations, and MSM populations. For policymakers like the AAP Task Force on Circumcision, the findings among the general male population, rather than those for high-risk populations (heterosexual men attending STI clinics, MSM), should be the most salient. Pediatricians will not know a child's future adult STI risk profile and cannot recommend circumcision based on risk level. A blanket policy statement promoting circumcision for prevention against STIs should be based on evidence from the general population, because the policy would affect all males.

After conducting this review, it is clear that the "evidence regarding the relationship of circumcision to STD in general is complex and conflicting."\textsuperscript{4} In future policy statements on circumcision, the AAP will hopefully continue to acknowledge and publicize the uncertain relationship between circumcision and STIs in the U.S. Likewise, physicians should continue to consider all of the important medical and non-medical factors affecting a parents' decision to circumcise their child, and appropriately inform parents of the risks, benefits, and uncertainties of circumcision.

Considerable gaps exist in the literature of male circumcision in the U.S. For example, certain outcomes like hepatitis B and C are underrepresented. Additionally, there is a conspicuous absence of high-quality prospective studies with comparable groups and methodology that includes genital exams, diagnostic tests for STIs, and appropriate multivariate analysis. Research may be more likely to advance among groups at high-risk for certain STIs, like MSM. In their 2008 systematic review, Millet and colleagues make a strong case for a circumcision RCT for MSM.\textsuperscript{45} Although an RCT in any U.S. population would provide critical
advancement to the current state of evidence, there is limited feasibility for such a study in the U.S. The need for an RCT would need to outweigh recruitment challenges, logistical burden of adequate follow-up, and most importantly, the ethical dilemma posed by randomizing individuals (as adults or children) to be circumcised.

CONCLUSIONS

Using data from 13 observational studies, I attempted to answer the question, "Does the circumcision of newborn males in the U.S. prevent STIs among adolescents and young adults?" The quality of evidence was fair and the overall findings pointed to an uncertain relationship between circumcision and numerous STIs. Some evidence suggesting a protective effect of circumcision came from studies of HIV among MSM. Even these results, however, are limited by biases and conflicting results between studies. Thus, there is insufficient evidence to conclude whether circumcision does or does not protect against STIs. Given the preponderance of cross-sectional studies, there is a need for more high-quality prospective studies among high-risk groups (heterosexual men at STD clinics and MSM) with comparable circumcision groups and methodology that includes genital exams, diagnostic tests for STIs, and appropriate multivariate analysis. In the absence of high quality studies that suggest otherwise, important stakeholders like the AAP and clinicians should continue to acknowledge the uncertain relationship between circumcision and STIs, and translate this knowledge appropriately in their policy statements and recommendations to patients.
REFERENCES


# APPENDIX A – Evidence Tables

## Table 5. Study design and characteristics

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Design</th>
<th>Location*</th>
<th>Study population*</th>
<th>Intervention/exposure</th>
<th>Outcomes*</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of General U.S. Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Laumann et al., 1997 | Cross-sectional | United States | 1,511 men between 18-59 years old  
- 75% circumcised  
- Nationally representative sample from National Health and Social Life Survey (NHSLS) – 1992  
- Excludes those living in group quarters and non-English speakers | Circumcision | - Bacterial STIs: gonorrhea, syphilis, chlamydia, all bacterial  
- Viral STIs: herpes, hepatitis, HIV, all viral | - National probability sample with oversampling for African Americans and Hispanics  
- Did not exclude based on sexual orientation |
| Xu et al., 2007      | Cross-sectional | Mobile examination centers across the United States | 4,185 boys/men (14-49 years old) selected for The National Health and Nutrition Examination Survey (NHANES), 1999-2004  
- National stratified, multistage probability sample with oversampling for adolescents, blacks, and Mexican Americans  
- Excludes non-civilians and institutionalized populations  
- 79% circumcised | Circumcision | Herpes simplex type 2 (HSV-2) positive by serology | - Details of survey methodology published by National Center for Health Statistics[50] |
| **Studies of High-risk Heterosexual Males at STD Clinics**                                                                                                                                                                                    |
| Hand, 1949           | Case-control | St. Albans, NY – U.S. Naval Hospital venereal clinics | U.S. servicemen  
- 1391 without STIs  
- 1082 with gonorrhea  
- 532 with syphilis  
- 138 with chancroid | Circumcision | Gonorrhea, syphilis, chancroid | - Control group mostly white (non-Jewish) and Jewish  
- Case groups with higher proportion of blacks  
- Ages not described |
| Cook et al., 1994    | Cross-sectional | Seattle, WA – King County Public Health STD Clinic at Harborview Medical Center | Heterosexual men seeking care at STD clinic (n=2,776)  
- 80.5% circumcised  
- 965 men without STIs | Circumcision | Gonorrhea, syphilis, chlamydia, genital herpes, genital warts | - Youngest age group 13-19 y  
- Participants visited clinic for new problem in 1988, but did not return (excluded if only presenting for HIV testing) |
| Diseker et al., 2000 | Cross-sectional | STD clinics in 5 U.S. cities (Baltimore, MD; Denver, CO; Long Beach, CA; Newark, | 2,021 heterosexual men who came to STD clinics for an exam  
- 75% circumcised | Circumcision | Gonorrhea, chlamydia, syphilis | - Investigators used data from a randomized controlled trial of HIV prevention counseling (Project RESPECT)[51] |
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Location</th>
<th>Population Characteristics</th>
<th>Sample Size</th>
<th>Data Collection Time</th>
<th>Methodologies</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NJ; San Francisco, CA</td>
<td>Cohort (12 month follow-up)</td>
<td>STD clinics in 5 U.S. cities (Baltimore, MD; Denver, CO; Long Beach, CA; Newark, NJ; San Francisco, CA)</td>
<td>834 men without STIs - &gt;50% of population African American - &gt;15 years-old - Spoke English - Vaginal sex &lt;30 days ago</td>
<td>1,456 of 2,021 men in cross-sectional study</td>
<td>Data from 1993-96</td>
<td>Investigators used data from a randomized controlled trial of HIV prevention counseling (Project RESPECT)51</td>
<td>- Performance of cross-sectional and cohort analyses (see below)</td>
</tr>
<tr>
<td>Baldwin et al., 2004</td>
<td>Cross-sectional</td>
<td>Tucson, AZ – Public STD clinic</td>
<td>1,120 heterosexual men attending STD clinic for any reason - &gt;18 years-old (mean age of 30 years old) - Mostly white and Hispanic, single men - 67% circumcised, 75% US born, 90% heterosexual, 50% spent time in jail</td>
<td>443 high-risk men attending STD clinic for any reason</td>
<td>Data from 2000-01</td>
<td>Investigators used data from a randomized controlled trial of HIV prevention counseling (Project RESPECT)51</td>
<td>Participants self-referred to clinic - Greater prevalence of &quot;several STDs&quot; among study participants compared to those choosing not to participate</td>
</tr>
<tr>
<td>Gottlieb et al., 2004</td>
<td>Cohort (12 month follow-up)</td>
<td>STD clinics in 5 U.S. cities (Baltimore, MD; Denver, CO; Long Beach, CA; Newark, NJ; San Francisco, CA)</td>
<td>1,120 heterosexual men (at least) who came to STD clinics for an exam - &gt;14 years-old (median age of 25 years-old) - 71% circumcised - Vaginal intercourse in last 3 months - No genital herpes (or HSV-2 positive) at baseline - Baseline HSV-2 sample available - &gt;50% African American</td>
<td>2004</td>
<td>Investigators used data from a randomized controlled trial of HIV prevention counseling (Project RESPECT)51</td>
<td>- Data from 1993-96</td>
<td></td>
</tr>
<tr>
<td>Warner et al., 2009</td>
<td>Cross-sectional</td>
<td>Baltimore, MD – two STD clinics</td>
<td>40,871 STD clinic visits by 26,448 heterosexual, African American men who underwent HIV testing - No IVDU; no sex with men; no previous positive or uncertain HIV test; no condom use</td>
<td>40,871</td>
<td>Data from 1993-2000</td>
<td>Investigators used data from a randomized controlled trial of HIV prevention counseling (Project RESPECT)51</td>
<td>- Data from 1993-96</td>
</tr>
</tbody>
</table>
- 87% of visits made by circumcised men; 63% by men > 25 years-old
- 394 and 40,177 visits by men with known and unknown HIV exposure, respectively

### Studies of MSM in Major U.S. Cities

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sites</th>
<th>Recruitment</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreiss and Hopkins, 1993</td>
<td>Cross-sectional</td>
<td>Seattle, WA - Harborview Medical Center AIDS Clinic; University Hospital Virology Clinic; Public Health AIDS Prevention Project</td>
<td>502 MSM recruited to participate at three sites</td>
<td>85% circumcised</td>
<td>HIV positive by serology - Data from 1989-91</td>
</tr>
<tr>
<td>Buchbinder et al., 2005</td>
<td>Cohort (18 month follow-up)</td>
<td>Boston, MA; Chicago, IL; Denver, CO; New York, NY; San Francisco, CA; Seattle, WA</td>
<td>3,257 high-risk MSM enrolled in the Vaccine Preparedness Study (VPS) in 6 major US cities (see notes)</td>
<td>88% of visits by circumcised men; 75% white; mostly &gt; 35 years-old</td>
<td>HIV seroconversion - VPS by HIV Network for Prevention Trials; prospective cohort study of high-risk MSM, women at high risk for HIV, and IVD users 52 - Data from 1995-97</td>
</tr>
<tr>
<td>Millet et al., 2007</td>
<td>Cross-sectional</td>
<td>New York, NY; Philadelphia, PA; Los Angeles, CA - Makeshift study sites at office buildings, community-based organizations and health centers</td>
<td>1,154 black MSM from New York and Philadelphia; 1,091 Latino MSM from New York and Los Angeles - 74% of black MSM and 33% Latino MSM circumcised - &gt;18 years old</td>
<td>HIV positive by serology - Data from 2005-06</td>
<td></td>
</tr>
<tr>
<td>Reisen et al., 2008</td>
<td>Cross-sectional</td>
<td>New York, NY - site not specified (not STD clinic)</td>
<td>482 immigrant Latino MSM living in New York City (146 Brazilian, 169 Colombian, 167 Dominican) - &gt; 18 years-old - 26% circumcised - High STI rates</td>
<td>HIV positive by self-report - Recruited through ads in Latino gay media and by word-of-mouth - Participants compensated $50 for participation plus $15 for transportation</td>
<td></td>
</tr>
</tbody>
</table>

*STI = Sexually transmitted infection; STD = Sexually transmitted disease; IVDU = intravenous drug use; MSM = men who have sex with men
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Potential for Selection Bias</th>
<th>Potential for Measurement Bias</th>
<th>Potential for Confounding</th>
<th>Analysis Methods Assessment</th>
<th>External validity</th>
<th>Overall Internal Validity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laumann et al., 1997</td>
<td>+++</td>
<td>- Not all characteristics</td>
<td>- No randomization</td>
<td>Good</td>
<td>Fair</td>
<td>Potential for differential misclassification bias (those not knowing circumcision and STI status may default to &quot;yes&quot; response for circumcision question AND assume no past/current STI, if unsure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>reported by circumcision group</td>
<td>- No adjustment for significantly associated cofactors in multivariate analysis (age, race/ethnicity, SES/education, religion, residence, sexual attitudes, # of sex partners)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Circumcision status and STI status based on self-report</td>
<td>- Measured and adjusted for potential confounders (demographics, sex behavior)</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lower % of African Americans and Hispanics circumcised</td>
<td>- All participants had lab testing for outcomes</td>
<td>Appropriate adjustment for significantly associated cofactors in multivariate analysis (age, race/ethnicity, SES/education, religion, residence, sexual attitudes, # of sex partners)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Only 1,118 men included in effect measure calculation</td>
<td></td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al., 2007</td>
<td>+++</td>
<td>- Limited comparability of groups</td>
<td>- No randomization</td>
<td>Good</td>
<td>Fair</td>
<td>- Potential for differential misclassification bias (those not knowing circumcision and STI status may default to &quot;yes&quot; response for circumcision question AND assume no past/current STI, if unsure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Compared to circumcision group, uncircumcised group was older, had greater % minorities, was more likely born outside U.S., had fewer lifetime sex partners</td>
<td>- Measured and adjusted for potential confounders (demographics, sex behavior)</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 8% of those examined/surveyed have no HSV-2 result (see notes)</td>
<td></td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand, 1949</td>
<td>+++</td>
<td>- Methods for measuring exposure and</td>
<td>- No confounders considered or accounted for in</td>
<td>Limited; no analysis methods described</td>
<td>Poor</td>
<td>Poor</td>
<td>- Age at circumcision not specified - Methods section</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ethnicity distribution uneven between cases and controls</td>
<td></td>
<td>Poor</td>
<td></td>
<td>Large potential for multiple</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Quality Ratings – Assessment of Bias with Description
<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Outcome Not Explained</th>
<th>Analysis</th>
<th>Demographics Poorly Described</th>
<th>Biases</th>
<th>Very Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook et al., 1994</td>
<td>++ - Participant characteristics not reported by circumcision group - Comparability of groups unknown</td>
<td>++ - Exposure measured by clinical exam - STI outcome lab-confirmed (genital warts diagnosed clinically) - Data from chart review - No report of inter-reviewer reliability</td>
<td>++ - No randomization - Measured for potential confounders (demographics, sex behavior)</td>
<td>Appropriate adjustment for significantly associated cofactors in multivariate analysis (age, race, residence, # sex partners, other STIs)</td>
<td>Poor - Applies best to heterosexual men seeking care at STD clinics - Limited to urban areas because they underwent lab testing for outcomes listed (except genital warts) - Genital warts screening part of standard physical exam</td>
<td>- Age at circumcision not specified - All consenting patients underwent lab testing for outcomes listed (except genital warts) - Genital warts screening part of standard physical exam</td>
</tr>
</tbody>
</table>

| Diseker et al., 2000; Cross-sectional | +++ - Participant characteristics not reported by circumcision group - Comparability of groups unknown | +++ - Exposure measured by clinical exam (see notes) - STI outcome lab-confirmed - Samples for lab testing collected from all participants - Unclear how confounders measured | +++ - No randomization - Uncertain which potential confounders measured (at least age, race/ethnicity, study site, # of sex partners, and new partners) | Appropriate adjustment for significantly associated cofactors in multivariate analysis, but list of factors is limited (age, race/ethnicity, study site) | Fair - Multiple US cities included (geographic variety) - Limited to urban areas - Source population is high-risk: heterosexual men seeking care at STD clinics - Prevalence/incidence of STIs in this group higher than general population - Important for source population - Potential differential misclassification bias if STI at baseline (based on clinical exam) makes clinician more likely to classify as uncircumcised - Measurement still better than self-report |

<p>| Diseker et al., 2000; Cohort    | +++ (see cross-sectional study above) - No reasons reported for loss to follow-up (565 men) - Slightly higher % uncircumcised in group without follow-up (see notes) | +++ (see cross-sectional study above) - Baseline STI status does not affect exposure measurement at follow-up (circumcision) | +++ - No randomization - Uncertain which potential confounders measured (at least age, race/ethnicity, study site, # of sex partners, and new partners) | Appropriate adjustment for significantly associated cofactors in multivariate analysis, but list of factors is limited (age, race/ethnicity, study site) | Fair - Multiple US cities included (geographic variety) - Limited to urban areas - Source population is high-risk: heterosexual men seeking care at STD clinics - Prevalence/incidence - Same selection bias issues as cross-sectional study (above) - Issue of differential follow-up | - If men did not follow-up because they recovered, then differential follow-up (higher % uncircumcised not following up) could bias results toward |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics not reported by circumcision group (nothing reported about group comparability)</th>
<th>Circumcision status by clinical exam by trained clinician</th>
<th>Circumcision status by trained interviewer</th>
<th>- Validation 50-item questionnaire given by trained interviewer</th>
<th>- HPV detection by PCR</th>
<th>- Testing of lab accuracy (+/− controls)</th>
<th>- Exposure measured by clinical exam (see notes)</th>
<th>- STI outcome lab-confirmed</th>
<th>- Samples for lab testing collected from all participants</th>
<th>- Unclear how confounders measured</th>
<th>- No randomization</th>
<th>- Uncertain about which potential confounders assessed (at least race, age, study site, HSV-1 serostatus, and % condom use)</th>
<th>- No randomization</th>
<th>- Associated cofactors in multivariate analysis (sex frequency, genital warts, condom use past 3 months and last anal sex, steady partner)</th>
<th>- Did not adjust for education level or ethnicity despite being independent risk factors for HPV infection</th>
<th>- Important for source population presentation</th>
<th>- Loss to follow-up: Project RESPECT included 2,365 women and men. 25% did not follow up (gender break-down unknown; uncertain &quot;n&quot;.)</th>
<th>- Misclassification bias if misclassification bias is not to check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldwin et al., 2004</td>
<td>++ - Participant characteristics not reported by circumcision group (nothing reported about group comparability)</td>
<td>+ - Circumcision status by clinical exam by trained clinician</td>
<td>+ - Circumcision status by trained interviewer</td>
<td>- Validation 50-item questionnaire given by trained interviewer</td>
<td>- HPV detection by PCR</td>
<td>- Testing of lab accuracy (+/− controls)</td>
<td>+ - Exposure measured by clinical exam (see notes)</td>
<td>- STI outcome lab-confirmed</td>
<td>- Samples for lab testing collected from all participants</td>
<td>- Unclear how confounders measured</td>
<td>+ - No randomization</td>
<td>- Uncertain about which potential confounders assessed (at least race, age, study site, HSV-1 serostatus, and % condom use)</td>
<td>+ - No randomization</td>
<td>- Associated cofactors in multivariate analysis (sex frequency, genital warts, condom use past 3 months and last anal sex, steady partner)</td>
<td>- Did not adjust for education level or ethnicity despite being independent risk factors for HPV infection</td>
<td>- Important for source population presentation</td>
<td>- Loss to follow-up: Project RESPECT included 2,365 women and men. 25% did not follow up (gender break-down unknown; uncertain &quot;n&quot;.)</td>
<td>- Misclassification bias if misclassification bias is not to check</td>
</tr>
<tr>
<td>Gottlieb et al., 2004</td>
<td>+ + - Participant characteristics not reported by circumcision group (nothing reported about group comparability)</td>
<td>+ + - Circumcision status by clinical exam by trained clinician</td>
<td>+ + - Circumcision status by trained interviewer</td>
<td>+ + - Validation 50-item questionnaire given by trained interviewer</td>
<td>+ + - HPV detection by PCR</td>
<td>+ + - Testing of lab accuracy (+/− controls)</td>
<td>+ + - Exposure measured by clinical exam (see notes)</td>
<td>+ + - STI outcome lab-confirmed</td>
<td>+ + - Samples for lab testing collected from all participants</td>
<td>+ + - Unclear how confounders measured</td>
<td>+ + - No randomization</td>
<td>+ + - Uncertain about which potential confounders assessed (at least race, age, study site, HSV-1 serostatus, and % condom use)</td>
<td>+ + - No randomization</td>
<td>+ + - Associated cofactors in multivariate analysis (sex frequency, genital warts, condom use past 3 months and last anal sex, steady partner)</td>
<td>+ + - Did not adjust for education level or ethnicity despite being independent risk factors for HPV infection</td>
<td>+ + - Important for source population presentation</td>
<td>+ + - Loss to follow-up: Project RESPECT included 2,365 women and men. 25% did not follow up (gender break-down unknown; uncertain &quot;n&quot;.)</td>
<td>+ + - Misclassification bias if misclassification bias is not to check</td>
</tr>
<tr>
<td>Warner et al., 2009</td>
<td>++ - Neither circumcision group has any IVDU,</td>
<td>++ - Circumcision status by clinical exam by trained clinician</td>
<td>++ - Circumcision status by trained interviewer</td>
<td>++ - Validation 50-item questionnaire given by trained interviewer</td>
<td>++ - HPV detection by PCR</td>
<td>++ - Testing of lab accuracy (+/− controls)</td>
<td>++ - Exposure measured by clinical exam (see notes)</td>
<td>++ - STI outcome lab-confirmed</td>
<td>++ - Samples for lab testing collected from all participants</td>
<td>++ - Unclear how confounders measured</td>
<td>++ - No randomization</td>
<td>++ - Associated cofactors in multivariate analysis (sex frequency, genital warts, condom use past 3 months and last anal sex, steady partner)</td>
<td>++ - Did not adjust for education level or ethnicity despite being independent risk factors for HPV infection</td>
<td>++ - Important for source population presentation</td>
<td>++ - Loss to follow-up: Project RESPECT included 2,365 women and men. 25% did not follow up (gender break-down unknown; uncertain &quot;n&quot;.)</td>
<td>++ - Misclassification bias if misclassification bias is not to check</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>status constant)</td>
<td>sex partners, and new partners)</td>
<td>of STIs in this group higher than general population</td>
<td>(see notes)</td>
<td>circumcision benefit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hispanics and those with lower education status more likely to be circumcised and have higher risk for HPV infection. These cofactors could influence the results with a bias towards a protective effect of circumcision.
sex with men, previous positive or uncertain HIV test, condom use (all important cofactors restricted from study) - Uncircumcised group older and has greater % of other STD diagnoses - Other demographics not reported by group

- Clinical exam (check box in chart; see notes)
- Cofactors abstracted from charts
- HIV serostatus by standard enzyme immunoassay/Western blot algorithm

(see notes)
- Not addressed: SES/education, sex frequency (with/without HIV+ partner), # of partners, HIV+ partner's stage
- Addressed: age, STDs, visit year, study site

(age, STDs, visit year, study site)
- High-risk group (especially HIV-exposed group)
- Does not generalize to general population or MSM

even with restriction

uncircumcised box, so default is circumcised (non-differential misclassification)
- Self-report may be inaccurate (e.g. lying, poor recall) for cofactors restricted from study; analysis does not adjust for them

---

**Studies of MSM in Major U.S. Cities**

<table>
<thead>
<tr>
<th>Study</th>
<th>Circumcision Status</th>
<th>Cofactors</th>
<th>Randomization</th>
<th>Seroconversion</th>
<th>Other cofactors</th>
<th>Bias/Comparability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreiss Hopkins, 1993</td>
<td>+++</td>
<td>- Differences between circumcision groups - Uncircumcised men older, more often nonwhite, more likely to have syphilis history, less likely to have IVDU history - 3 HIV+ men with unknown circumcision status - All seronegative men recruited at Prevention Project (see notes)</td>
<td>- No randomization - Not addressed: SES, education, age at first sex, religion, travel to high-risk areas - Addressed: age, race, IVDU, prostitute use, # of sex partners, unprotected sex, study site</td>
<td>Adjustment for significantly associated cofactors including age, # of partners, frequency of unprotected anal sex</td>
<td>Limited - Does not apply to heterosexual men in U.S. - Uncertain applicability to wider MSM population in U.S. because limited to predominantly white, urban source population</td>
<td>Poor - Strong potential for selection bias (limited comparability of groups) and confounding</td>
</tr>
<tr>
<td>Buchbinder et al., 2005</td>
<td>+++</td>
<td>- Tested many factors associated with HIV seroconversion; circumcision groups not designed to be similar (participant characteristics not reported by group) - 12% of population did not finish (no comprehensive list of confounders considered and appropriate adjustment for significantly associated cofactors (age, education, insurance, # partners, unprotected sex, STIs, nitrite inhalants,)</td>
<td>- No randomization</td>
<td></td>
<td>Limited - Most risk factors assessed were very specific to high-risk MSM population - Hard to generalize to wider population</td>
<td>Poor - Selection bias due to lack of comparability and loss to follow-up without explanation</td>
</tr>
</tbody>
</table>

---

Notes:
- ELISA = enzyme-linked immunosorbent assay
- IVDU = intravenous drug use
- STIs = sexually transmitted infections
- HIV = human immunodeficiency virus
- SES = socioeconomic status
- Western blot = a test to confirm HIV status
- Nitrite inhalants: Inhaling nitrites, often used as an aphrodisiac, can lead to health issues such as fainting, heart problems, and stroke.
<table>
<thead>
<tr>
<th>Missing Values</th>
<th>6 mo., 12 mo., 18 mo.</th>
<th>Drugs</th>
<th>Limited</th>
<th>Fair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millet et al., 2007</td>
<td>+++ - Used network-based recruiting - Poor comparability of groups - Black MSM: circumcised older, more educated, had more anal sex partners - Latino MSM: circumcised more likely born in U.S., used drugs more</td>
<td>++ - Circumcision status and cofactors by self-report - HIV status screened by ELISA/self-report and confirmed by Western blot - English and Spanish surveys</td>
<td>Comprehensive list of confounders considered and appropriate adjustment for significantly associated cofactors (age, education, income, sexual identity, site, place of birth, unprotected anal sex, sex position, STIs)</td>
<td>Limited - Source population probably a growing population in urban areas (especially Latino group, due to immigration) - May not extrapolate to white MSM and very difficult to extrapolate to heterosexual men</td>
</tr>
<tr>
<td>Reisen et al., 2008</td>
<td>+++ - Uncertainty about comparability of groups - Circumcised men more educated (other factors not reported) - Circumcision rate did not vary by country of origin - Missing data for 55 MSM (did not answer HIV status question); excluded from analysis</td>
<td>++ - Self-report for circumcision status, cofactors, and HIV status - Worry about misclassification bias - Survey in English, Spanish, Portuguese</td>
<td>Appropriate adjustment for significantly associated cofactors (age, income, education, history of sex work, syphilis, receptive role in anal sex)</td>
<td>Limited - Very high-risk group of MSM (immigrants from nations with high HIV seroprevalence and high seroprevalence among peers in U.S.) - Uncertain if applies even to all Latinos because sub-group analysis showed protective effect only for Colombian group</td>
</tr>
</tbody>
</table>

*STI = Sexually transmitted infection; STD = Sexually transmitted disease; IVDU = intravenous drug use; MSM = men who have sex with men
†Definition of internal validity (quality rating), see Table 4
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Results (effect measure)†</th>
<th>Precision (95% CI)</th>
<th>Statistical significance*</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of General U.S. Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laumann et al., 1997</td>
<td>Adjusted OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gonorrhea: 1.42</td>
<td>- Gonorrhea (0.79 - 2.56)</td>
<td>NR</td>
<td>- No association detected between circumcision status and specified outcomes</td>
</tr>
<tr>
<td></td>
<td>- Syphilis: 2.14</td>
<td>- Syphilis (0.41, 11.30)</td>
<td></td>
<td>- Fair quality study</td>
</tr>
<tr>
<td></td>
<td>- Chlamydia: NR</td>
<td>- Chlamydia (NR)</td>
<td></td>
<td>- Moderate potential for bias but uncertain how this affects results (e.g. misclassification bias could be differential or non-differential)</td>
</tr>
<tr>
<td></td>
<td>- All bacterial: 1.61</td>
<td>- All bacterial (0.94,2.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Herpes: 1.18</td>
<td>- Herpes (0.23,5.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hepatitis: 1.22</td>
<td>- Hepatitis (0.43,3.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HIV: NR</td>
<td>- HIV (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- All viral: 1.30</td>
<td>- All viral (0.52,3.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al., 2007</td>
<td>Adjusted OR‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HSV-2 positive: 1.1</td>
<td>- HSV-2 positive (0.8 - 1.5)</td>
<td>p = 0.47</td>
<td>- No association between circumcision status and being HSV-2 seropositive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Null finding could be partially explained by potential non-differential misclassification bias due to self-report of circumcision</td>
</tr>
<tr>
<td><strong>Studies of High-risk Heterosexual Males at STD Clinics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand, 1949</td>
<td>Unadjusted OR‡§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gonorrhea: 6.05</td>
<td>- Gonorrhea (5.03 - 7.26)§</td>
<td>NR</td>
<td>- Unadjusted ORs and CIs not reported in article, but calculated according to reported frequencies</td>
</tr>
<tr>
<td></td>
<td>- Syphilis: 5.47</td>
<td>- Syphilis (4.32 - 6.92)§</td>
<td></td>
<td>- Strong association for all three outcomes</td>
</tr>
<tr>
<td></td>
<td>- Chancroid 23.7</td>
<td>- Chancroid (11.5 - 48.8)§</td>
<td></td>
<td>- Suggest protective trend for circumcision against all three STI outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Results questionable given strong potential for bias and unclear methodology</td>
</tr>
<tr>
<td>Cook et al., 1994</td>
<td>Adjusted OR‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gonorrhea: 1.6</td>
<td>- Gonorrhea (1.2 - 2.2)</td>
<td>NR</td>
<td>- Association detected between circumcision status and gonorrhea, syphilis, genital warts</td>
</tr>
<tr>
<td></td>
<td>- Syphilis: 4.0</td>
<td>- Syphilis (1.9 - 8.4)</td>
<td></td>
<td>- Protective trend for circumcision against gonorrhea and syphilis (limited precision for syphilis result)</td>
</tr>
<tr>
<td></td>
<td>- Chlamydia: 1.0</td>
<td>- Chlamydia (0.7 - 1.6)</td>
<td></td>
<td>- Protective trend for lack of circumcision against genital warts</td>
</tr>
<tr>
<td></td>
<td>- Genital herpes: 1.2</td>
<td>- Genital herpes (0.8 - 1.7)</td>
<td></td>
<td>- No association between circumcision status and chlamydia or genital herpes</td>
</tr>
<tr>
<td></td>
<td>- Genital warts: 0.7</td>
<td>- Genital warts (0.5 - 0.9)</td>
<td></td>
<td>- Fair quality study that does not display definitive benefit of circumcision</td>
</tr>
<tr>
<td>Diseker et al., 2000; Cross-sectional</td>
<td>Adjusted OR‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gonorrhea: 1.3</td>
<td>- Gonorrhea (0.9 - 1.7)</td>
<td>NR</td>
<td>- No association detected between circumcision status and specified outcomes</td>
</tr>
<tr>
<td></td>
<td>- Syphilis: 1.4</td>
<td>- Syphilis (0.6 - 3.3)</td>
<td></td>
<td>- Fair quality study</td>
</tr>
<tr>
<td></td>
<td>- Chlamydia: 1.0</td>
<td>- Chlamydia (0.7 - 1.4)</td>
<td></td>
<td>- Large potential but uncertain role of selection bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Results could be biased slightly away from null by</td>
</tr>
</tbody>
</table>

47
<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted OR/HR</th>
<th>Findings</th>
<th>Potential Differential Misclassification Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseker et al., 2000; Cohort</td>
<td>Adjusted OR‡</td>
<td>- Marginal finding of association between circumcision status and gonorrhea</td>
<td>- Only result differing from cross-sectional study from same source population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Only result differing from cross-sectional study from same source population</td>
<td>- Bias introduced through differential follow-up could explain tendency toward protective effect of circumcision</td>
</tr>
<tr>
<td>Baldwin et al., 2004</td>
<td>Adjusted OR‡</td>
<td>- Associations detected between circumcision status and all three HPV outcomes</td>
<td>- Education and ethnicity are both likely confounders that may at least partially explain the results. Thus, it is possible that true effect is not as dramatic, although their may be homogeneity in this population with regard to education/SES</td>
</tr>
<tr>
<td>Gottlieb et al., 2004</td>
<td>Adjusted HR†</td>
<td>- No association between circumcision status and becoming HSV-2 seropositive over 12 months</td>
<td>- Few studies look at HSV-2 as outcome</td>
</tr>
<tr>
<td>Warner et al., 2009</td>
<td>Adjusted OR‡</td>
<td>- No association between circumcision status and being HIV seropositive among men with unknown exposure (larger segment of population)</td>
<td>- Education and SES are both likely confounders that may at least partially explain the results. Thus, it is possible that true effect is not as dramatic, although their may be homogeneity in this population with regard to education/SES</td>
</tr>
</tbody>
</table>
### Studies of MSM in Major U.S. Cities

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted OR‡</th>
<th>95% CI</th>
<th>Note</th>
</tr>
</thead>
</table>
| Kreiss and Hopkins, 1993 | HIV+: 2.0   | (1.0 - 4.0) | - Association detected between circumcision status and being HIV seropositive among this group of MSM  
- Suggests protective trend against being HIV seropositive among MSM attending these clinics in Seattle  
- Differences between groups by study site a major concern (differential recruitment, confounders)  
- Adjusted OR (95% CI) of 3.2 (0.9-11.7) when limiting to Prevention Project (screening site)  
- Association no longer statistically significant and CI very wide when limiting to this much smaller sample |
| Buchbinder et al., 2005  | HIV seroconversion: 2.0 | (1.1 - 3.7) | - Association detected between circumcision status and HIV seroconversion after 18 months among this group of high-risk MSM  
- Suggests protective trend against HIV seroconversion after 18 months  
- Of factors tested for association, circumcision had second lowest PAR % (10.2); large number of male sex partners, nitrite inhalant use, and younger age all with higher PAR % (28.3 - 30.8) |
| Millet et al., 2007     | HIV+ (Black MSM): 1.23 | (0.87 - 1.74) | - No association detected between circumcision status and being HIV seropositive among black or Latino MSM  
- Authors suggest greater background HIV prevalence in this high-risk groups could diminish any protective effect  
- Non-differential misclassification bias could partially explain null finding |
| Reisen et al., 2008     | HIV+ (whole sample): 1.9 | (1.01 - 3.59) | - Association detected between circumcision status and being HIV seropositive among the whole sample and the Colombian sub-group  
- Absence of association for Brazilian and Dominicans could mean that Colombian group responsible for overall association for the whole sample  
- Uncertain if sub-group size large enough to detect meaningful associations |

*NR = not reported  
† OR = odds-ratio; HR = hazard ratio; PAR % = population attributable risk percentage  
‡ Estimated ratio of odds of uncircumcised men having experienced the outcome relative to odds for circumcised men  
§ Effect measure not reported in study; calculated based on reported frequencies  
¶ Estimated ratio of odds of circumcised men having experienced specified outcome relative to odds for uncircumcised men  
‖ Ratio of incidence of outcome among circumcised men relative to incidence in uncircumcised men