Rapid review

Male non-therapeutic circumcision

ASERNIP-S REPORT NO. 65
ASERNIP-S Rapid Review

Disclaimer

This is a rapid systematic review in which the methodology has been limited in one or more areas to shorten the timeline for its completion. Thus, modifications have been made in at least one of the following areas: search strategy, inclusion criteria, assessment of study quality and data analysis. It is considered that these amendments would not significantly alter the overall findings of the rapid review when compared to a full systematic review.

The methodology used for the rapid review is described in detail, including the limits made for this particular topic. These limitations have been made possible mainly by restricting the specific clinical questions asked. These limits were applied following the requirements of the specific review topic, together with clinical guidance from a protocol surgeon.

Therefore, this rapid review is a limited evidence-based assessment that is based on a simple systematic search of studies published in the peer reviewed literature. As a result, this rapid review may be used to inform certain questions on the specific review topic.
Executive summary

Aim and scope

The objective of this rapid review was to assess the safety and effectiveness of male non-therapeutic circumcision in comparison with no circumcision (i.e. intact genitalia), through a rapid systematic review of the literature. Therapeutic male circumcision is performed to treat an underlying pathological process. Non-therapeutic male circumcision may be performed for prophylactic, religious, cultural, or social reasons.

Eligible studies were those reporting on circumcision in a hospital setting in males of any age with no contraindications to circumcision and no medical indications for circumcision. The main comparator for circumcision was no circumcision (intact genitalia). Outcomes of interest were safety (including removal of excessive or inadequate amounts of skin, haemorrhage, glanular ulceration, wound separation, urinary retention), effectiveness (incidence of urinary tract infection, sexually transmitted infections (STIs), human immunodeficiency virus (HIV) and penile cancer), and patient-reported outcomes such as religious, cultural and social assimilation and acceptance and psychosocial outcomes.

Research papers were excluded if they were not systematic reviews or randomised controlled trials (RCTs), or if they reported solely on cost effectiveness analyses. High quality systematic reviews were considered the best evidence and where there were two or more systematic reviews with the same inclusion and exclusion criteria, the latest and most complete study was included. Where no good-quality recent systematic reviews could be found, RCTs were used to review the safety and effectiveness of male non-therapeutic circumcision. In addition, RCTs published after the search dates of the most recent systematic review were also included to further inform upon male non-therapeutic circumcision.

Methods

Due to the sheer volume of literature on this subject, studies included were restricted to those published from January 1997 onwards, allowing the most recent literature to form the basis of this rapid review. Databases searched included BMJ Clinical Evidence, The York (UK) Centre for Reviews and Dissemination (CRD), The Cochrane Library, PubMed and EMBASE. The medical subject heading (MeSH) search term was circumcision, male and textword search terms included circumcis*, bris, mohel*, khitan*, milah*, dhapi*, djapi*, mandiwa*, and mandiyala*. Bris, mohel and milah are terminologies associated with Jewish religious circumcision, khitan is a terminology for Islamic religious circumcision, and dhapi, djapi, madiwa and mandiyala are terminologies for Australian Aboriginal circumcision.

Summaries of appraisal of the included systematic reviews and RCTs were then presented in Evidence Tables. Results were synthesised and overall conclusions made.
Key results and conclusions

From the search strategy, 1200 potentially relevant articles were identified of which 86 were retrieved. Retrieved papers included primary and secondary research. In total, 74 retrieved articles were excluded. Six systematic reviews were eligible for appraisal and inclusion in this rapid review. Four of the identified systematic reviews on circumcision and STIs, penile cancer or safety outcomes included only non-RCT studies, and did not critically appraise the included studies. However due to the paucity of systematic review and RCT evidence surrounding circumcision and STIs, penile cancer and safety outcomes, it was decided to include these four systematic reviews in this rapid review.

Six RCTs were identified: three on male circumcision and HIV transmission and three on the psychosocial effects of male circumcision. These RCTs were not assessed in any of the included systematic reviews. No systematic reviews or RCTs were identified for the religious, cultural and social issues surrounding circumcision, so the researcher undertook to find key recent literature reviews summarising current knowledge on these topics.

The following findings and conclusions were made:

- One systematic review found that the prevalence of complications reported ranged from 0% to 50.1% in a series of haemophiliacs. Two RCTs reported upon adverse events relating to circumcision and found that the adverse events were generally mild or moderate in severity, including postoperative bleeding and infections, wound disruptions, delayed healing, pain, damage to the penis, haematoma, insufficient skin removed, problems with appearance, swelling at the incision site, anaesthetic-related and erectile dysfunction.

- One systematic review concluded that despite the positive results of a number of observational studies, there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV infection, does more good than harm. However, three subsequent RCTs which assessed the association between circumcision and HIV infection in African men were stopped by their data and safety monitoring boards before their designed completion because of significant reductions in HIV incidence in the circumcision groups.

- Two systematic reviews assessed the association between circumcision and the transmission of sexually transmitted infections. One systematic review concluded that genital ulcerative disease may be more common in uncircumcised men, whereas sexually transmitted urethritis is more common in circumcised men. The other systematic review concluded that there is a strong indication that circumcised men are at lower risk of chancreoid and syphilis. However, the summary relative risk for syphilis should be interpreted cautiously as there was significant heterogeneity between studies. There was less association between circumcision and herpes simplex virus type 2 (HSV-2).

- One systematic review assessed the association between male circumcision and urinary tract infections (UTI). Although all included studies showed benefit of
circumcision to prevent UTI, a table of harms and benefits of circumcision showed that the benefit of circumcision on UTI only outweighs the risk in boys who have had UTI previously and have a predisposition to repeated UTI. This systematic review did not support the routine circumcision of normal boys with standard risk in order to prevent UTI, but suggested that circumcision of boys with higher than normal risk of UTI should be considered.

• One systematic review assessed the association between male circumcision and penile cancer and concluded that the medical literature does not support an association between the prevalence of genital human papillomavirus (HPV) and circumcision status when strict criteria for diagnosis of HPV are applied.

• One RCT reported upon return to work/normal activity. Of the 1333 circumcised men interviewed three days post-surgery, all those who were employed reported that they had resumed working, and 1287 (96%) reported having returned to normal activities by this time. By eight days post-surgery, all but one person had returned to normal activities.

• Two RCTs reported upon satisfaction with circumcision. One RCT reported that 1274 (99.5%) individuals were ‘very satisfied’ and six (0.5%) were ‘somewhat satisfied’ with their circumcision. The other RCT reported that 98.5% of men who were circumcised, including those who were HIV-positive at the time of randomisation, were ‘very satisfied’ with the result of their circumcision at three months post-surgery.

• One RCT reported upon sexual satisfaction and function in circumcised and uncircumcised men and despite uncircumcised men reporting greater sexual satisfaction, which was statistically significant, this RCT concluded that adult male circumcision does not adversely affect sexual satisfaction or clinically significant function in men.

• One RCT noted the reciprocal and synchronous nature of mother-infant interactions during the early postpartum period, and suggested pain control after circumcision to promote neonatal comfort and improve mother-infant interaction.

• One RCT concluded that circumcised infants showed a stronger pain response to subsequent routine vaccination that uncircumcised infants, and recommended analgesia for circumcision pain.
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Introduction

Objective
The objective of this Rapid Review was to assess the safety and effectiveness of male non-therapeutic circumcision in comparison with no circumcision (i.e. intact genitalia), through a rapid systematic review of the literature.

Therapeutic male circumcision is performed to treat an underlying pathological process. Non-therapeutic male circumcision may be performed for prophylactic, religious, cultural, or social reasons. This review is only concerned with male circumcision and does not address female circumcision, which has been legislated against in most States and Territories of Australia (RANZCOG 2001).

Background

The prepuce
The prepuce (or ‘foreskin’) is the simple retractable fold of skin that covers and protects the glans of the penis. At birth, the prepuce is usually unretractable and there is some degree of preputial adherence to the glans (Rickwood 1999). During the first three or four years of life, growth of the penis, accumulation of epithelial dermis (smegma), and erections eventually separate the prepuce from the glans, permitting retraction of the prepuce (Lerman and Liao 2001). The preputial orifice is thought to function like a one way valve, blocking the entry of contaminants while allowing the passage of urine (Fleiss et al 1998).

Procedure
Circumcision involves removal of the prepuce, usually in a day surgery setting. The technique used depends upon any medical indications and the patient’s age. For infants, three devices are generally used for circumcision. The Mogen® (Mogen Instrument Company, Brooklyn, NY, USA) and Gomco® clamps (Gomco Surgical Manufacturing Company, Buffalo, NY, USA) are designed to protect the glans while producing a crush injury to the prepuce, thus inducing haemostasis. The prepuce is then surgically removed. The PlastiBell® device (Hollister Incorporated, Libertyville, IL, USA) is designed to induce necrosis of the prepuce, which is then sloughed off, complete with the device, within approximately one week (Holman et al 1995).

For older boys and men, freehand techniques involving a sleeve resection (Elder 2007) or a dorsal slit surgical technique (Holman and Stussi 1999) are used. The sleeve technique involves a circumferential incision in the penile skin in the midportion of the penile shaft. The prepuce is retracted and a second circumferential incision is made. The two incisions are connected by cutting the dorsal penile skin in the middle and the prepuce is excised circumferentially. The dorsal slit technique involves identifying the corona of the glans and determining the extent of the dorsal slit, thus enabling the removal of the correct amount of prepuce. The preputial skin is then excised at its base (Holman and Stussi 1999).
Until recently, most neonatal circumcisions were performed without analgesia (Paediatrics and Child Health Division 2004). Comfort measures may include sucrose, non-nutritive suckling, and swaddling (Langer and Coplen 1998); however, unanaesthetised circumcision is an invasive and painful procedure which can elicit systemic stress responses in the neonate (Brady-Fryer et al 2004). The type of analgesia used depends upon the age of the patient. General anaesthesia, paracetamol, parenteral opioids, caudal analgesia, dorsal penile nerve block, subcutaneous penile ring block, caudal epidural block, or topical analgesias such as EMLA (Eutectic Mixture of Local Anaesthetic), amethocaine gel or lidocaine may be used (British Association of Paediatric Urologists 2007).

**Status of circumcision in Australia**

In 1970, 70% of all Australian boys and men had been circumcised; however, the rate of circumcision has fallen considerably in recent years (Fetus and Newborn Committee 1996). Currently approximately 10%–20% of male infants in Australia and New Zealand are routinely circumcised (Paediatrics and Child Health Division 2004). In Australia during the 2006–2007 financial year 17,877 males younger than six months, 3,481 males older than six months but younger than 10 years, and 569 males aged 10 years or older were circumcised (Medicare Benefits Schedule Online 2008). It is not clear whether these procedures were performed for therapeutic or non-therapeutic reasons.

**Table 1 Medicare Benefits Scheme (MBS) numbers applicable to male circumcision**

<table>
<thead>
<tr>
<th>MBS Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30653</td>
<td>Circumcision of a male under 6 months of age</td>
</tr>
<tr>
<td>30656</td>
<td>Circumcision of a male under 10 years of age but not less than 6 months of age</td>
</tr>
<tr>
<td>30659</td>
<td>Circumcision of a male 10 years of age or over (GP)</td>
</tr>
<tr>
<td>30660</td>
<td>Circumcision of a male 10 years of age or over (Specialist)</td>
</tr>
<tr>
<td>30663</td>
<td>Haemorrhage, arrest of, following circumcision requiring general anaesthesia</td>
</tr>
</tbody>
</table>

At a local level, the South Australian Department of Health recently produced elective surgery exclusion guidelines highlighting procedures which may not be performed in South Australian public hospitals unless justified on clinical grounds (South Australia Department of Health 2007). Non-therapeutic circumcision is one of these procedures. Victoria, New South Wales and Tasmania have also excluded the public funding of non-therapeutic male circumcision as an elective procedure (Victorian Government Department of Human Services 2007).

**Why is circumcision performed?**

Gatrad et al (2002) estimate that approximately one third of the global male population is circumcised, for therapeutic and non-therapeutic reasons.

**Therapeutic reasons**

The three most commonly cited indications for therapeutic circumcision are recurrent inflammation of the foreskin and glans (balanoposthitis), inability to retract the foreskin (phimosis) and entrapment of the foreskin behind the glans (paraphimosis) (Paediatrics and Child Health Division 2004). Presently, circumcision to treat these conditions is available in
Australian public hospitals. Clinical expert opinion indicates that there are several other indications for therapeutic circumcision, including the treatment of preputial neoplasms, traumatic prepuce injury where the prepuce cannot be salvaged, balanitis xerotica obliterans, and recurrent febrile urinary tract infections (UTIs) in patients with an abnormal urinary tract (F Bridgewater 2008, personal correspondence).

**Non-therapeutic reasons**

By definition, male non-therapeutic circumcision is not clinically necessary as it does not treat an underlying pathological process. It has been suggested that circumcision originated as a hygiene measure for communities in hot, dusty and dry environments (Paediatrics and Child Health Division 2004).

Male non-therapeutic circumcision is performed for a variety of reasons, including religious, cultural, social, and prophylactic. Circumcision has been widely debated as a preventative measure for several conditions, including transmission of sexually transmitted diseases (including cervical cancer) and HIV, and development of penile cancer and UTIs (Task Force on Circumcision 1999). However it has also been suggested that maintaining good penile hygiene can prevent several of these conditions.

Religious circumcision for males is practiced under both Jewish and Islamic law and allows individuals to participate fully in their religion and to uphold family honour and tradition. Circumcision is also integral to the culture of several groups including Australian Aboriginals, Filipinos, Koreans, Turks and Africans, among others. In addition, there are several social factors leading to male circumcision including the desire to resemble other family members (particularly fathers and brothers), a desire to conform to the practices of peers, to please a partner, genital aesthetics, and as a measure of maintaining penile hygiene (Chessler 1997; Waldeck 2003; Queensland Law Reform Commission 1993; Krieger et al 2005).

**Mechanisms for a protective effect of circumcision**

Five biological mechanisms for a protective effect of circumcision against HIV transmission, sexually transmitted infections (STIs), UTIs and penile cancer have been commonly proposed.

1) The prepuce contains a higher density of Langerhans cells, which express HIV-1 receptors, compared with the remainder of the penis (MacDonald et al 2008; Inugu et al 2005; Weiss et al 2006). By removing a rich source of Langerhans cells, circumcision could potentially reduce the risk of HIV acquisition and transmission (Atashili 2006; Weiss et al 2006).

2) Ulcerative STIs, which are more common in uncircumcised men (Inugu et al 2005; MacDonald et al 2008), destroy the mucosal integrity and potentially provide a portal of entry for infection (Weiss et al 2006; Van Howe 1999).

3) The foreskin may be susceptible to mild trauma during intercourse, facilitating transmission of infection (Van Howe 1999).
4) The environment under the prepuce is warm and moist, and conducive to prolonged viral survival (Van Howe 1999).

5) A circumcised penis develops a layer of keratin, which provides additional defence (Inugu et al 2005).

In contrast, three theories supporting a protective effect of the prepuce have been suggested. Firstly, the inner prepuce contains apocrine glands that secrete lysozyme, which reportedly kills HIV-1 in vitro (Siegfried et al 2003). Secondly, sub-preputial flora, secretory immunoglobulins, and lytic secretions from the prostate, urethra, and seminal residues may provide some immunological protection (Van Howe 1999). Thirdly, the prepuce reduces the likelihood of abrasions occurring during intercourse, thereby removing a potential site for viruses to enter the body (Van Howe 1999).

**What are the potential adverse effects associated with male non-therapeutic circumcision?**

**Medical adverse effects**
The potential complications include (Williams and Kapila 1993):

- haemorrhage
- infection
- glanular ulceration
- meatal stenosis
- inadvertent injury of the urethra (fistula)
- too much skin removed
- loss of penis (1 in 1,000,000)
- anaesthetic complications
- secondary chordee.

The incidence of major complications after newborn circumcision is reported to range from between 0.2% and 0.6% to as high as 2% to 10% (Paediatrics and Child Health Division, 2004).

**Psychosocial adverse effects**
Several psychosocial adverse effects may be associated with genital surgery, and may affect individuals receiving either therapeutic or non-therapeutic circumcision. These may include poor cosmetic appearance, sexual dysfunction, castration anxiety, increased susceptibility to pain, interference with maternal-infant bonding, resentment, guilt, shame, adverse reaction to parents, lack of trust, decreased intimacy, and envy of intact males, amongst others (Yılmaz et al 2003; Chessler 1997; Taddio et al 1997; Macke 2001; Waldeck 2003; Silverman 2004; Goldman 1999).
What are the potential adverse effects associated with restricting male non-therapeutic circumcision?

Restricting the availability of circumcision may force it to be performed in non-sterile environments without anaesthesia or analgesia by non-medical practitioners. In addition, if circumcision is an effective preventative measure for conditions such as HIV, STI, penile cancer and UTI, then restricting access could increase their incidence.

Religious adverse effects of restriction

Non-circumcision may suggest lack of religious commitment, and individuals and their families may be stigmatised and ostracised from their religious community. The individual may also be prevented from accessing his religion, leading to psychological trauma or decreased quality of life (Freeman 1999; F Bridgewater 2008, personal correspondence).

Cultural adverse effects of restriction

Non-circumcision may cause an individual to be different to others in their cultural community, and the individual and his family may be stigmatised and ostracised. The individual may also be prevented from accessing his appropriate cultural roles, leading to psychological trauma or decreased quality of life. For example, uncircumcised Walbiri men of central Australia are not permitted to enter into their father’s lodge, participate in religious ceremonies, or legitimately marry (Queensland Law Reform Commission 1993; F Bridgewater 2008, personal correspondence).

Social adverse effects of restriction

Non-circumcision may cause an individual to be different to others in their social network, and the individual and their family may be stigmatised and ostracised. An individual may feel different to others in his family if his siblings and father are circumcised, leading to a lack of family cohesion, adverse parental reaction to the child, or a perceived deficiency in oneself. The individual may experience bullying or teasing by peers or rejection by sexual partners, leading to psychological trauma and decreased quality of life (Chessler 1997; Lee 2006; F Bridgewater 2008, personal correspondence).

Figure 1 illustrates the current practice of circumcision in most Australian public hospitals.
Figure 1: Clinical decision pathway for male circumcision
Research questions

The specific research questions that were addressed in this review are as follows:

- Does male non-therapeutic circumcision confer a benefit, compared with no circumcision?
- What are the adverse effects of male non-therapeutic circumcision, compared with no circumcision?
- What are the adverse effects of restricting male non-therapeutic circumcision?
Methodology

Inclusion criteria
Studies were selected for inclusion in this rapid review on the basis of the criteria outlined below.

Population
Studies of males of any age with the following characteristics were included:

- no contraindications to circumcision
  - congenital anomalies of the penis, including hypospadias, epispadias or chordee
  - buried penis
  - sick and unstable infants
  - bleeding disorder or family history of a bleeding disorder (Paediatrics and Child Health Division 2004)
- no medical indications for circumcision

Intervention
Circumcision in a hospital setting performed with a Mogen clamp, Gomco clamp, PlastiBell device, or by a freehand surgical technique.

Comparator interventions
The main comparator for circumcision was no circumcision (intact genitalia).

Outcomes
Studies were included if they contained information on at least one of the following outcomes:

Safety
Clinical adverse effects associated with the surgery include but are not limited to:

- removal of excessive or inadequate amounts of skin
- haemorrhage
- glanular ulceration
- wound separation
- urinary retention
- time lost from school or work.
Clinical expert opinion advises that further, rare adverse events associated with circumcision include necrotising fasciitis, death, scalded skin syndrome, penile amputation, sepsis, penile necrosis and meningitis, meatitis, chordee, inclusion cysts, retained PlastiBell devices, urethral fistula, meatal stenosis, cutaneous tags, poor cosmetic appearance, psychological trauma, acute renal failure, anaesthetic complications (particularly general anaesthesia), concealed penis, skin bridges, injury to the urethra, and infection (Paediatrics and Child Health Division 2004; Task Force on Circumcision 1999; F Bridgewater 2008, personal correspondence).

**Effectiveness**
Regardless of the motivation for non-therapeutic circumcision, clinical effectiveness outcomes associated with the surgery may include the incidence of UTI, STI, HIV and penile cancer.

**Patient-reported outcomes**
The motivation for non-therapeutic circumcision may have associated patient-reported outcomes:

- Religious assimilation and acceptance, access to religious ritual and community.
- Cultural assimilation and acceptance, ability to perform appropriate cultural roles.
- Social assimilation and acceptance.
- Psychosocial outcomes, including but not limited to psychological trauma, quality of life, cosmetic appearance, satisfaction, sexual function, castration anxiety, susceptibility to pain, maternal-infant bonding, resentment, guilt, shame, reaction to parents, trust, intimacy, and envy of intact males (Yilmaz et al 2003; Chessler 1997; Taddio et al 1997; Macke 2001; Waldeck 2003; Silverman 2004; Goldman 1999).

**Study design**
Recently published, well-conducted systematic reviews, rather than primary studies were selected preferentially for inclusion in the review and critical appraisal. Systematic reviews were defined as those studies that met all the following criteria as defined by Cook et al (1997):

1. Focused clinical question
2. Explicit search strategy
3. Use of explicit, reproducible and uniformly applied criteria for article selection
4. Critical appraisal of the included studies
5. Qualitative or quantitative data synthesis.

Where there were two or more systematic reviews with the same inclusion and exclusion criteria, the latest and most complete study was included. In addition, randomised controlled trials (RCTs) published after the search dates of the most recent systematic review were also included.
If no suitable systematic reviews on the topic were available, RCTs and pseudorandomised controlled trials were considered eligible for inclusion and critical appraisal. A study was deemed to be an RCT if the author(s) stated explicitly (usually by some variant of the term ‘random’ to describe the allocation procedure used) that the groups compared in the trial were established by random allocation (Higgins & Green 2005). Studies in which the method of allocation was known but was not considered strictly random (for example, alternation, date of birth and medical record number) were classified as pseudorandomised controlled trials (Higgins & Green 2005). Where no randomised and pseudorandomised controlled trials were identified, nonrandomised comparative studies were also included in the review.

When overlapping patient groups were reported in studies, only the paper quoting the most complete data set was used.

**Publication date**

Due to the sheer volume of literature on this subject, studies included were restricted to those published from January 1997 onwards, allowing the most recent literature to form the basis of this rapid review.

**Language of publication**

Included studies were restricted to those published in English.

**Literature search strategies**

**Databases searched**

The following databases were searched from January 1997 to 5 March 2008:

- BMJ Clinical Evidence
- The York (UK) Centre for Reviews and Dissemination (CRD)
- The Cochrane Library
- PubMed
- EMBASE.

Extended searching of internet websites and conference abstracts, handsearching of journals, contacting of authors for unpublished data and pearling of references from retrieved articles were not undertaken.

**Search terms**

The search terms used for each of the databases listed above are provided in Appendix A.

**Selection of studies**

The reviewer (CP) applied the inclusion criteria to identify those studies potentially eligible for selection and appraisal based on their abstracts; these studies were retrieved as full text. The
selection criteria were then applied fully to the retrieved studies to identify those to be appraised and included in the review. Full publications subsequently found not to meet the inclusion criteria were excluded and reasons for exclusion were documented.

**Data extraction and appraisal of study methodology**

Data from all included studies were extracted by one reviewer (CP) and checked by a second reviewer (PT) using standardised data extraction tables that were developed a priori. The studies included in the review were classified according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence (Table 2).

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one properly designed randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)</td>
</tr>
<tr>
<td>III-2</td>
<td>Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group</td>
</tr>
<tr>
<td>III-3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from case-series, either post-test or pre-test/post-test</td>
</tr>
</tbody>
</table>

Source: NHMRC 2000

Where systematic reviews were eligible for inclusion in the review, the methodology of these secondary studies was evaluated with respect to the following factors:

- Did the review ask a focused research question that incorporated the elements of the patient population, intervention, comparator intervention and outcomes (PICO)?
- Were the inclusion and exclusion criteria of included studies clearly stated?
- Did the review use a clear and comprehensive search strategy?
- Did the review assess the validity of included studies, and if so which validity criteria were used?
- Was the analysis or synthesis of the results appropriate?
- Did the review include a summary of its main results, including a discussion of its strengths and limitations?

Where primary studies were eligible for inclusion in the review, the following criteria were used to appraise their methodology, where applicable:

- Were the objectives of the study clearly defined?
- Were the inclusion and exclusion criteria clearly described?
- Was there a clear description of the interventions used?
• Were the characteristics of patients included in the study clearly described?

• Were patients randomly assigned to intervention groups, and if so was the method of randomisation described?

• Was the randomised assignment of patients to intervention groups concealed from both patients and staff administering the study until recruitment was complete?

• Was an attempt made to blind both patients and staff responsible for measuring outcomes of the intervention to the interventions patients received?

• Were the number of patients who withdrew or dropped out of the study reported, and the characteristics of these patients described?

• Were the main outcomes of interest adequately reported?

• Were point estimates and measures of variability presented for the primary outcome measures?

Non-randomised studies were also assessed for other features of study design or execution that may have introduced bias, such as comparability of patient groups at baseline, method of patient selection and comparability of timing of outcome assessment.

One reviewer (CP) appraised the studies, which were checked by the second reviewer (PT). Any differences were resolved through discussion.
Results

From the search strategy, 1200 potentially relevant articles were identified of which 86 were retrieved. Retrieved papers included primary and secondary research. In total, 74 retrieved articles were excluded and these are listed in Appendix B.

Six systematic reviews were eligible for appraisal and inclusion in this rapid review (Muula et al 2007; Siegfried et al 2003; Weiss et al 2006; Van Howe 2007; Van Howe 2007a; Singh-Grewal et al 2005). Four of the identified systematic reviews reporting on circumcision and STIs, penile cancer or safety outcomes (Muula et al 2007; Van Howe 2007; Van Howe 2007a; Weiss et al 2006) included only non-RCT studies, and did not critically appraise included studies. However due to the paucity of systematic review and RCT evidence surrounding the associations between circumcision and STI, penile cancer and safety outcomes, it was decided to include these four systematic reviews in this rapid review.

Systematic review evidence was not located for the psychosocial effects of male non-therapeutic circumcision, so it was necessary to search further for any relevant RCTs which may also inform on the topic. Three RCTs were identified (Taddio et al 1997; Macke 2001; Kigozi et al 2008). Three RCTs published after the included systematic reviews were identified (Gray et al 2007; Auvert et al 2005; Bailey et al 2007). These all RCTs all reported on male circumcision and HIV transmission and were not assessed in any of the included systematic reviews. Evidence tables of the included studies are presented in Appendix C. No systematic reviews or RCTs were identified for the religious, cultural and social issues surrounding circumcision, so the researcher (CP) undertook to find key recent literature reviews summarising current knowledge on these topics.

Systematic review evidence

Muula et al (2007)

Appraisal of study methodology

This systematic review assessed the prevalence of complications of male circumcision. Using several sources (abstracts from the International Conference on AIDS, African Journals Online, Medline, Google Scholar and Web of Science), the reviewers identified ten eligible studies; which included conference abstracts, RCTs and reports of routine clinical work in Anglophone Africa. Muula et al (2007) used circumcision as a search term and included only English language studies. They did not search reference lists of included studies or handsearch relevant journals.

Inclusion criteria were studies which reported on any series of patients in Anglophone Africa on whom male circumcision had been conducted and complications reported. No exclusion criteria were provided. Three reviewers participated in the data collection; however, apart from a list of data to be extracted from the studies, no further details on this process were provided. The reviewers used the MOOSE guidelines to construct this systematic review, however it is important to note that there was no critical appraisal of the included studies.
Between-study heterogeneity was not assessed, nor was performance, detection, attrition or selection biases. The included patients ranged from neonates to 54 years of age. Muula et al (2007) did not report the circumcision technique used, pain relief, or postoperative care. Inclusion and exclusion criteria of the included studies were very diverse, with RCTs reporting stringent inclusion criteria and the other studies reporting less restrictive inclusion criteria. Further bias may have been introduced by confounders and the likely higher prevalence of complications in Africa than in countries with well-resourced health systems.

Safety

The prevalence of complications was reported as summed totals for the occurrence of all complications, making it difficult to extract meaningful data on the incidence of particular complications. Overall, the prevalence of complications reported in the various included studies (including RCTs, conference abstracts and reports of routine clinical work) ranged from 0% to 50.1% in a series of haemophiliacs. There was no firm evidence to suggest that circumcisions performed by physician surgeons were associated with lower prevalence of complications when compared with non-physician health professionals.

Effectiveness

Effectiveness outcomes were not addressed as none of the included studies reported on the efficacy of circumcision.

Authors’ Conclusions

Muula et al (2007) concluded that the available data were inadequate to obtain a reasonable assessment of the prevalence of complications of male circumcision in sub-Saharan Africa. The different follow-up times in the included studies may have had an effect upon the complications reported, as studies with short follow-up times may have missed long-term complications such as keloid formation. Complications may not have been reported either because: they did not occur; they were considered relatively minor and hence not ‘worth’ reporting; significant barriers to medical care prevented patients from presenting for treatment of mild to moderate complications; or patients may have presented for management of complications at a different facility from where they obtained circumcision.

Van Howe (2007)

Appraisal of study methodology

This systematic review assessed the association between male circumcision and various STI. The reviewers employed a poor search strategy to locate studies, relying on a very simple search in PubMed and searching of bibliographies of published studies. The search period was not defined, but most likely was between 1966 and 13 March 2006. All included studies were in English and the review followed the recommendations of Stroup et al (2000) for the meta-analysis of observational studies.

Inclusion criteria were publication in a peer-reviewed journal and the presence of data on the circumcision status of men both with and without genital ulcerative disease (GUD), chancroid, various types of sexually transmitted urethritis, or a comparison of GUD versus genital discharge syndrome (GDS).
A total of 30 observational studies were included in this systematic review. It is important to note that Van Howe (2007) did not critically appraise the included studies. The effect of removing outlier studies on the summary effect odds ratio (OR) and between-study heterogeneity were assessed. Van Howe (2007) did not report upon the age range of included patients. Publication bias was likely to have been present in the GUD and chlamydial studies, with no evidence of publication bias in the GDS, non-specific urethritis, chancroid, GUD versus GDS, or gonorrhoea studies. Other possible sources of bias may have included the broad inclusion criteria (which allowed low-quality studies with small patient numbers to be included), confounding factors, selection bias through STD clinic, and self-report of circumcision status. Between-study heterogeneity was assessed, revealing significant heterogeneity for both the GUD and the urethritis analyses ($P<0.05$). Sensitivity analyses were conducted between high risk and general populations.

Two randomised cluster of general population studies (Gray et al 2000; Gray et al 2004) used data from the same cohort in Rakai, with one study used to report on urethritis and the other study used to report on GUD. One study by Diseker et al (2000) included both cohort and cross-sectional data, with only the cohort data used in the Van Howe (2007) review. Van Howe (2007) examined the effects of using the data from the second publication of the Gray et al cohort in place of the first publication, and the effects of using the cross-sectional data from Diseker et al (2000) instead of the cohort data.

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

Van Howe (2007) conducted meta-analyses with uncircumcised men as the group of interest. Aside from non-specific urethritis and gonorrhoea which used the general variance based method, all summary effect ORs were calculated with the Mantel-Haenszel method.

The summary effect OR for genital ulcerative disease was calculated from one case-control, four convenience sample, two randomised cluster of the general population, one random cluster sample survey and two cross-sectional studies. The OR was 1.34 (95% confidence interval [CI] 0.98–1.82), suggesting that uncircumcised men are at greater risk for GUD, especially men in a high-risk population. If the data from the second study of the Rakai cohort were substituted for the first publication, the summary OR for GUD infection was higher (OR 1.63, 95% CI 1.21–2.20). Meta-regression of the GUD studies showed that neither population type nor the method to document circumcision status were significant factors, however combining these two factors in meta-regression was found to be statistically significant ($P=0.03$). When studies were adjusted for this score, the summary OR for GUD infection was 1.07 (95% CI 0.78–1.47).

The summary effect OR for non-specific urethritis was calculated from one chart review, two probability sample survey, three consecutive sample, two convenience sample, and two cross-sectional studies. The OR was 0.80 (95% CI 0.64–1.01), suggesting that circumcised men are at greater risk for sexually transmitted urethritis in general. When the cross-sectional data
from the Diseker et al (2000) study and the first publication of the Rakai data were used, the summary effect ORs for the urethritis studies were little changed.

The summary effect OR for gonorrhoea was calculated from two probability sample, four cross-section, two probability sample, one case-control, two cohort, two randomised cluster of general population, three convenience sample, and four consecutive sample studies. One study did not document its study type, and was included in this analysis. The OR was 1.02 (95% CI 0.82–1.28), suggesting that circumcision status did not affect the risk of gonorrhoea.

The summary effect OR for *Chlamydia* was calculated from one cross-sectional, one chart review, two probability sample, one case-control, one cohort, two randomised cluster of general population, two consecutive sample, and one convenience sample studies. The OR was 0.59 (95% CI 0.23–1.52), suggesting that circumcised men are at an increased risk of chlamydial infection. Van Howe (2007) noted that this became statistically significant when adjusted for publication bias, although no *P* value was provided. When publication bias was adjusted for, the summary effect OR for *Chlamydia* was 0.46 (95% CI 0.22–0.97).

The summary effect OR for chancroid, calculated from two convenience sample studies and one study type which was not documented, was 1.02 (95% CI 0.42–2.44) hence no association was demonstrated between circumcision status and risk for chancroid.

The summary effect OR for genital discharge syndrome was calculated from one case-control, two cross-sectional, one random cluster sample survey, two randomised cluster of general population, and three convenience sample studies. The OR was 0.76 (95% CI 0.59–0.98), suggesting that uncircumcised men are less likely to be diagnosed with GDS or non-specific urethritis; however, there was significant between-study heterogeneity (*P*<0.05) for these analyses. Population type had an adjusted OR for circumcision status of 0.74 (95% CI 0.57–0.96). Meta-regression of the type of population studied was not a significant factor for chlamydial infections, gonorrhoea, or non-gonococcal urethritis.

**Authors’ Conclusions**

Van Howe 2007 concluded that genital ulcerative disease may be more common in uncircumcised men, whereas sexually transmitted urethritis is more common in circumcised men.

**Van Howe (2007a)**

**Appraisal of study methodology**

This systematic review assessed the association between circumcision and genital infection with human papillomavirus (HPV). The reviewers employed a poor search strategy to locate studies, with a very simple search in PubMed and searching of bibliographies of published studies. The search period was not defined, but most likely was between 1966 and 13 March 2006.

Inclusion criteria were cohort, cross-sectional and case-control studies which were published in a peer-reviewed journal, with the presence of data on the circumcision of males both with and without genital HPV infections. Diagnosis of HPV was by culture, biopsy, or HPV DNA detection using polymerase chain reaction (PCR) or Hybrid capture 2. Determination of
circumcision status was by physical examination. Studies included for analysis only measured prevalence of HPV infection. No exclusion criteria were provided; however, there was an explanation of excluded studies. Little information was provided on the methodology, although one reviewer was responsible for data extractions, and the recommendations of Stroup et al (2000) for the meta-analysis of observational studies were followed. When attempting to control for the confounders of patient report/clinical appearance for diagnosis, patient report of circumcision, and sampling, only three studies were identified for inclusion in the review. Van Howe (2007a) elected to include eight further studies which used reliable diagnostic methods, but had incomplete sampling and determination of circumcision status by patient report. A total of eleven observational studies were included in this systematic review.

Van Howe (2007a) did not critically appraise the included studies. The age range of included patients was not reported. The bias of including the eight further studies was minimised using meta-regression and estimation of the number of cases of HPV infection missed by not sampling the penile shaft, using the numbers generated by Weaver et al (2004). Other potential sources of bias were studies with small patient numbers (stabilised with a general variance-based random-effects model using each study’s exact OR and CI), and publication bias, which was not found for the eight additional studies and may not have been assessed for the three original studies. No outlier studies were found.

Safety

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

Effectiveness

Van Howe (2007a) conducted meta-analyses with sensitivity analyses, with uncircumcised men as the group of interest. The results of the three and eight studies were reported separately. The random-effects summary OR of the three studies meeting the inclusion criteria was 1.20 (95% CI 0.80–1.79) with no evidence of between-study heterogeneity. These three studies included two cross-sectional studies and one consecutive sample study. When the eight additional studies were adjusted for the method of determining circumcision and failure to sample the penile shaft, the summary effects OR was 1.25 (95% CI 0.95–1.67). These eight studies included three cross-sectional, two case-control, one chart review, one probability sample survey, four consecutive sample surveys, four convenience sample, and two convenience sample studies. These results suggested that HPV is more common in uncircumcised men. Van Howe (2007a) did not present any $P$ values for a significant association between genital HPV infection and circumcision status, but narratively stated that there was no statistical significance.

The results were challenged by Castellsague et al (2007), who argued that a re-analysis of the data showed that male circumcision was associated with a statistically significant reduced risk of penile HPV and related lesions (OR 0.56, 95% CI 0.39–0.82). Van Howe replied to this challenge, noting the importance of diagnostic methods and sampling of the penile shaft, and re-iterating the original results of the review.
Authors’ Conclusions

Van Howe (2007a) concluded that the medical literature does not support an association between the prevalence of genital HPV and circumcision status when strict criteria for HPV diagnosis are applied.


Appraisal of study methodology

This systematic review assessed the association between circumcision and various sexually transmitted infections (STI). The reviewers employed a rigorous search strategy in PubMed and EMBASE to locate studies published between 1950 and April 2004. A broad range of search terms were used with no language restrictions, and ascertainment bias was minimised by not using the term circumcision in searching. The reference lists of included studies were searched, as were previously published reviews of circumcision and STIs, and authors were contacted for additional information where necessary. Inclusion criteria were studies of patients with the selected outcomes (herpes simplex virus type 2 (HSV-2), syphilis, and chancroid) based on serological evidence of infection, not disease, as circumcision could protect against HSV-2 infection but is unlikely to affect the risk of recurrence of HSV-2 once the patient becomes infected. Extensive exclusion criteria were supplied and both a flow chart of study selection for inclusion and a detailed explanation of excluded studies were provided. A total of 26 papers incorporating 28 observational studies were included in the review. Each abstract was reviewed independently by two authors and data were extracted using a standardised form.

Weiss et al (2006) did not appear to critically appraise the quality of included studies, but did discuss extraction of data relevant to quality assessment such as participation rates, loss to follow-up and confounding. Weiss et al (2006) did not report upon the age range of included patients. Possible sources of bias may have included misclassification of either circumcision status or confirmation of infection, age at circumcision, and the low participation rates in several studies. Weiss et al (2006) noted that residual confounding may have affected the results, although many of the potential biases would tend to underestimate the protective effect of male circumcision on STI transmission.

Safety

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

Effectiveness

One cohort, one nested case-control and one cross-sectional study each found the statistically significant result that circumcised men were at lower risk of HSV-2 seropositivity than uncircumcised men ($P<0.05$). Two cohort, one nested case-control and four cross-sectional studies adjusted for confounding, and presented a random effects summary relative risk (RR) of 0.88 (CI 0.77–1.01), suggesting little association between male circumcision and HSV-2 seropositivity. Similar results were found when studies were restricted to those adjusting for
age and at least one measure of sexual behaviour (summary RR 0.85, CI 0.74–0.98) or those where circumcision occurred before first sexual intercourse (summary RR 0.86, CI 0.74–0.99).

For syphilis infection, eight cross-sectional, one nested case-control and two cohort studies included some adjustment for confounders, with best estimate RR varying from 0 to 1.01 and five reportedly showing a statistically significant reduction in risk. The random effects summary RR for these studies was 0.67 (CI 0.54–0.83), but with significant between study heterogeneity ($P=0.01$). The summary RR was similar for studies that assessed circumcision by genital examination, studies among heterosexual men, and studies that included some adjustment for confounding (summary RR 0.69, CI 0.50–0.94). The effect was stronger among men for whom circumcision occurred before first sexual intercourse (summary RR 0.53, CI 0.34–0.83; $P$ value compared with later circumcision=0.15).

One cohort, one cross-sectional and two case-control studies reported a statistically significant reduced risk of chancroid among circumcised men. No meta-analysis was carried out due to between-study differences regarding definition and ascertainment of chancroid, and variation between the comparison groups. One cross-sectional study with a serological outcome found no association of chancroid with circumcision. One cross-sectional and two case-control studies comparing chancroid or penile ulcer patients with asymptomatic controls found that circumcised men were at much lower risk, with RR ranging from 0.04 to 0.40.

**Authors’ Conclusions**

Weiss et al (2006) concluded that there was a strong association between circumcision and lower risk of chancroid and syphilis, whilst noting the significant heterogeneity between the syphilis studies. They found less association between circumcision and risk of HSV-2.

Further, potential male circumcision interventions to reduce HIV in high risk populations may provide additional benefit by protecting against other STI.

**Singh-Grewal et al (2005)**

**Appraisal of study methodology**

This systematic review assessed the association between male circumcision and urinary tract infection (UTI). The reviewers employed a basic search strategy in Medline, EMBASE and the Cochrane Controlled Trials Register to locate studies published between 1966 and 2004. The search was not restricted by language, and any non-English studies located were translated before assessment. A flow chart outlining the study selection was provided.

Bibliographies of identified publications were searched for further studies, and authors were contacted to obtain details of any further published or unpublished studies.

Inclusion criteria were studies examining the effect of male circumcision on UTI, with no age restriction. Diagnosis of UTI was the only outcome of interest, and studies were only included if they provided sufficient information for a 2x2 contingency table to be constructed. No exclusion criteria were provided. All methods of the review, including literature search, data extraction, and data analysis, were carried out independently by two authors without blinding to authorship. Resolution of discrepancies was by consensus and the involvement of the third author when necessary. A list of extracted data was not provided.
Twelve studies (one RCT, four cohort studies and seven case-control studies) were included in the systematic review. The RCT was assessed using the CONSORT guidelines, and did not provide details about the method of randomisation, allocation concealment, or blinding. No demographic details other than age were available for comparison between the two groups, and ages ranged from less than one year to adults. Observational studies were assessed using the guidelines provided by the MOOSE statement and were deemed to be of variable quality. Differing UTI definitions and methods of ascertaining circumcision status and UTI outcome were used, and exclusion criteria and adjustment for confounding varied between studies. Singh-Grewal et al (2005) also discussed the short length of follow-up reported by the included studies, the poor definition of method of urine collection, and that the majority of studies reported episodes of UTI rather than the number of patients experiencing UTI. Several confounding variables were adjusted for, including age, socioeconomic status, and ethnicity.

Heterogeneity was assessed between and within subgroups, and between individual studies when combined. Possible sources of heterogeneity included study type, setting, study population, and follow-up.

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

The RCT had an odds ratio (OR) of 0.13 (95% CI 0.01–2.63), suggesting that circumcision decreases the risk of UTI. All four cohort studies showed benefit of circumcision with a summary OR of 0.13 (95% CI 0.07–0.23). There was significant heterogeneity between these studies ($P<0.001$), however when the outlier study was excluded the heterogeneity between the cohort studies was not significant ($P=0.64$).

All seven case-control studies showed benefit of circumcision, with a combined OR of 0.13 (95% CI 0.07–0.23) and there was no significant heterogeneity between the case-control studies ($P=0.2$).

The summary OR when all three study types were combined was 0.13 (95% CI 0.08–0.20) and there was no significant heterogeneity between the three subgroups ($P=0.9$). Significant heterogeneity was observed between the individual studies when the outlier was included ($P<0.00001$) and when the outlier was excluded there was no significant heterogeneity between the remaining studies ($P<0.4$). Singh-Grewal et al (2005) suggested that the heterogeneity may have reflected varying methods of circumcision and UTI ascertainment, and differing follow-up periods of the studies.

Estimates of UTI incidence and circumcision complication rate were used to construct a table of harms and benefits of circumcision, which showed that the benefit of circumcision only outweighs the risk in boys who have had UTI previously and have a predisposition to repeated UTI. However, the overall risk benefit of circumcision to prevent UTI is not easily quantifiable, as the incidence of important sequelae of UTI is unknown.
Authors’ Conclusions

Singh-Grewal et al (2005) discussed the homogeneity observed in the effect across a variety of settings and across the three different study designs and suggested that an OR of 0.13 makes residual confounding an unlikely source of the observed association. A table of harms and benefits of circumcision showed that the benefit of circumcision only outweighs the risk in boys who have had UTI previously and have a predisposition to repeated UTI. The review did not support the routine circumcision of normal boys with standard risk in order to prevent UTI and suggested that circumcision of boys with higher than normal risk of UTI should be considered.


Appraisal of study methodology

Siegfried et al (2003) assessed the association between circumcision in heterosexual men and HIV transmission. This systematic review employed a rigorous search strategy to locate studies published between 1966 and 2002. A broad range of search terms (both MeSH and text word) were used, no language restrictions were applied, and studies conducted in any country were included. Databases searched were Medline, EMBASE, AIDSonline/GATEWAY, The Cochrane Library, and databases listing conference abstracts. Reference lists of included studies were examined and authors were contacted in order to identify any further studies. Siegfried et al (2003) also investigated relevant ongoing trials.

Inclusion criteria were studies assessing the association between circumcision and HIV-1 and HIV-2 which reported on heterosexual men 12 years of age or older. Circumcision status was determined by self-or partner-report or by direct observation, and HIV-1 or HIV-2 infection was based on laboratory results. Siegfried et al (2003) searched for RCTs or quasi-RCTs and, in their absence, observational studies. Studies with historical controls and ecological studies were excluded, but no other exclusion criteria were supplied.

The review included 35 observational studies. Two reviewers independently applied the inclusion criteria and differences were resolved by discussions with a third author. Extensive data were extracted independently by two reviewers, using standardised data extraction forms. Where data were incomplete, attempts were made to contact the authors for clarification of important information, which were successful on a number of occasions.

Quality assessment was carried out using standardised quality assessment forms developed specifically for the review. The overall quality of included studies was reported to be highly variable, and Siegfried et al (2003) performed bias assessment. Performance bias may have been present in each of the 15 studies where circumcision status was obtained by self-report rather than by direct observation. Detection bias was rare across all studies, but all five cohort studies were susceptible to attrition bias. Selection bias was problematic in all studies, with confounders including sexual behaviour and religion. Circumcised and uncircumcised groups and HIV-positive and HIV-negative groups were rarely equal for all or most possible
confounders prior to the quality assessment. Age at circumcision varied from at birth to early adulthood.

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

The 35 studies were stratified into general and high risk populations. Odds ratios (OR) greater than one indicated increased of HIV infection with circumcision, and odds ratios less than one indicated decreased risk of HIV infection with circumcision.

For general populations, one cohort study showed a decrease in HIV infection in circumcised men, compared with uncircumcised men (adjusted OR 0.53, 95% CI 0.33–0.87). The odds ratios of the fourteen cross-sectional studies ranged between 0.28 and 1.73, with significant heterogeneity between studies \(P<0.00001\). Although no \(P\) values were provided, four of these studies had statistically significant results for decreased risk of HIV infection after circumcision, and two had statistically significant results for increased risk of HIV infection.

The case-control study found no significant difference in HIV transmission rates between circumcised and uncircumcised men (OR 1.90 95% CI 0.50–7.20).

Although no \(P\) values were provided, two cohort studies were statistically significant in the direction of a protective benefit of circumcision on HIV transmission after circumcision for the high-risk populations, and between-study heterogeneity was not significant \(P=0.16\). Although no figures were provided, eight cross-sectional studies were statistically significant in the direction of benefit from circumcision, and there was heterogeneity between studies \(P=0.0009\). Although no \(P\) values were provided, two case-control studies were statistically significant in the direction of a protective effect of circumcision on HIV status with odds ratios varying from 0.37–0.88 with marginal between-study heterogeneity \(P=0.11\). Studies in high-risk populations were significantly more in favour of circumcision than those in the general populations \(P=0.001\).

**Authors’ Conclusions**

The reviewers concluded that despite the positive results of a number of observational studies there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV infection, does more good than harm. A sensitivity analysis found that, generally, adjustment of crude estimates of treatment effects made little difference to the size, direction or significance of effects.

**Randomised controlled trial evidence**

**HIV**

**Appraisal of study methodology**

Three RCTs have investigated the effect of male circumcision on HIV incidence in Ugandan (Gray et al 2007), Kenyan (Bailey et al 2007) and South African (Auvert et al 2005) men. Two
of these studies employed the forceps-guided method (Bailey et al 2007; Auvert et al 2005), while one study used the sleeve procedure (Gray et al 2007). Circumcision was performed under local anaesthesia by certified physicians in operating theatres (Gray et al 2007), by study clinicians in the study clinic (Bailey et al 2007), and in the surgical offices of local general practitioners experienced in male circumcision (Auvert et al 2005). The circumcision status of patients enrolled in all three trials was confirmed by physical examination and participants in the intervention group were offered to be circumcised within one week of enrolment, while patients in the control group were asked to wait until the end of the study before being offered to be circumcised.

All three studies provided adequate information regarding inclusion and exclusion criteria, and clearly described the characteristics of patients included in the trials. Bailey et al (2007) reported that the treatment and control groups were similar at baseline in terms of demographic characteristics, physical characteristics, prevalence of sexually transmitted infections, and reported sexual history with women, although no P-values were provided. Similarly, Gray et al (2007) reported that the two groups were comparable at baseline in terms of sociodemographic characteristics (age, marital status, religion and education), sexual risk behaviours (number of partners, condom use, alcohol consumption with sex, and sex for money or gifts), and rates of symptoms of sexually transmitted infection, although no P-values were provided. Gray et al narratively stated that at enrolment, previous receipt of voluntary counselling and testing was slightly higher in the intervention group than in the control group, although no figures were provided (Gray et al 2007). Auvert et al (2005) reported that at baseline, most of the participants had completed a primary level of education, very few were married or living as married, and about half were involved in at-risk behaviour. No statistical analysis of comparability of relevant baseline parameters was provided.

Median age for the circumcision and control groups in one RCT was 20 years (Bailey et al 2007). Another RCT reported that the median age was 21.0 years of age (Auvert et al 2005). The third RCT reported various age ranges between 15 to 49 years for both the intervention group and the control groups (Gray et al 2007).

In all three RCTs, patients were randomly assigned to intervention groups using opaque, sealed envelopes which contained the assignment to circumcision or control group. Bailey et al (2007) reported that the nurse-counsellors who did the HIV testing and administered questionnaires on sexual function and behavioural factors associated with HIV infection were blinded to study group allocation. Similarly, in order to ensure blinding of personnel, Auvert et al (2005) reported that the randomisation group information was not available to the personnel in charge of counselling or collecting information during the participants’ visits. Gray et al (2007) did not report any attempts to blind staff responsible for measuring outcomes to treatment allocation.

The length of follow-up in two studies was 24 months (Bailey et al 2007; Gray et al 2007), while a third study reported a follow-up period of 21 months (Auvert et al 2005). Bailey et al (2007) reported that 240 (8.6%) patients were lost to follow-up, 126 (9.1%) in the circumcision group and 114 (8.2%) in the control group. Patients who were lost to follow-up
were more likely to have some secondary education or above, compared with the 2544 patients with complete follow-up information (Bailey et al 2007). Similarly, Gray et al (2007) reported that 229 (10.4%) patients were lost to follow-up, 114 (10.4%) in the circumcision group and 115 (10.4%) in the control group. Auvert et al (2005) reported that 251 (8%) patients were lost to follow-up, 100 (6.5%) in the circumcision group and 151 (9.5%) in the control group ($P$=0.0016). Among the patients lost to follow-up at the 12 or 24 month visit, none (0/124) were HIV positive at their previous completed visit (Auvert et al 2005).

The main outcomes of interest, namely HIV incidence and adverse events associated with circumcision, were adequately reported in all three RCTs.

Safety

One RCT (Bailey et al 2007) reported that 21 adverse events, which were probably or definitely related to surgery, occurred in 20 of the 1334 patients who underwent circumcision (1.5%, 95% CI 0.9–2.3). These adverse events were mild or moderate in severity and included five cases each of postoperative bleeding and infections, four cases of wound disruptions, three cases of delayed healing, two cases of swelling at the incision site, one anaesthetic-related adverse event and one case of erectile dysfunction (Bailey et al 2007). With the exception of erectile dysfunction, all adverse events resolved with treatment within hours or days. At three days post-surgery 643 patients (48%) reported no pain, 690 (52%) reported very mild pain, and none reported mild to severe pain (Bailey et al 2007). By eight days post-surgery 1179 patients (89%) reported no pain and 148 (11%) reported very mild pain. At thirty day post-surgical wound examinations which were performed in 1282 of the 1334 men who were circumcised (96%), the wound was judged to be completely healed in all but 16 (1%) patients, and by the three month examination all wounds had healed completely (Bailey et al 2007).

One RCT reported 60 adverse events during surgery or in the first month following surgery in 1,568 South African men who underwent circumcision, including those who were HIV-positive at the time of randomisation (Auvert et al 2005). The range of adverse events reported included pain (31.7%), excessive bleeding (15%), infection (5%), damage to the penis (6.7%), swelling or haematoma (16.7%), anaesthesia related events (1.7%), insufficient skin removed (6.7%), delayed wound healing (3.3%), problems with appearance (15%) and other causes (8.3%) (Auvert et al 2005). A higher rate of adverse events was observed among patients who were HIV-positive at the time of randomisation, however this difference was not statistically significant ($P$=0.056). In the 1,131 patients examined at 21 months post-surgery, 11 adverse events were reported, including problems with urinating (three patients), dissatisfaction with the appearance of the penis (four patients), and mild or moderate erectile dysfunction (four patients) (Auvert et al 2005).

Effectiveness

Gray et al (2007) reported that the cumulative HIV incidence over the 24 month study period in men who underwent circumcision was 0.66 cases per 100 person-years, compared with 0.33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%, 95% CI 16–72; $P$=0.006). The unadjusted incidence rate ratio (IRR) was 0.49 (95% CI 0.28–0.84;
After adjustment for age, marital status, and sexual risk behaviours at enrolment, the IRR was 0.49 (0.29–0.81; \(P=0.003\)) (Gray et al 2007). The as-treated Poisson analysis demonstrated a cumulative HIV incidence of 0.61 cases per 100 person-years in men who were circumcised (20 events in 3268.1 person-years), compared with 1.35 cases per 100 person-years in the control group (47 events in 3481.6 person-years) (estimated efficacy of intervention 55%, 95% CI 22–75; \(P=0.002\)). The as-treated IRR was 0.45 (95% CI 0.25–0.78; \(P=0.0022\)) (Gray et al 2007). In addition, HIV incidence was lower in circumcised men than it was in the control group in all sociodemographic (age, marital status, religion and education), behavioural (number of sexual partners, non-marital relationships, condom use, consumption of alcohol before sexual intercourse, and transactional sexual intercourse), and sexually transmitted disease symptom (genital ulcer disease, urethral discharge and dysuria) subgroups examined.

Bailey et al (2007) reported that the two year incidence of HIV in Kenyan men who underwent circumcision was 2.1% (95% CI 1.2–3.0), compared with 4.2% (3.0–5.4) in the control group (\(P=0.0065\)). In addition, the relative risk of HIV infection in men who were circumcised was 0.47 (0.28–0.78), which equates to a 53% reduction in the risk of acquiring a HIV infection (22–72). After the study had commenced, further testing by polymerase chain reaction (PCR) revealed that three patients (two in the circumcision group and one in the control group) who had originally been classed as HIV positive at one month were found to be positive at baseline, while one patient from the circumcision group who had originally been classed as HIV positive at six months was confirmed as being positive at baseline (Bailey et al 2007). An as-treated analysis, which adjusted for these four men who were found to be HIV positive at enrolment, as well as for individuals who did not adhere to the randomisation assignment, revealed that the risk ratio (RR) of circumcision was 0.40 (0.23–0.68), which translates to a 60% reduction in the risk of acquiring a HIV infection (32–77) (Bailey et al 2007).

Auvert et al (2005) reported that the HIV incidence over the 21 month study period in South African men who underwent circumcision was 0.85 cases per 100 person-years, compared with 2.1 cases per 100 person-years in the control group. This corresponded to a rate ratio (RR) of 0.40 (95% CI 0.24–0.68), \(P<0.001\), which translates to a protection against HIV infection of 60% (95% CI 32–76). The protective effect of circumcision against HIV infection after behavioural characteristics were adjusted for was 61% (95% CI 34–77), suggesting that the protective effect of circumcision is not attributable to the observed changes in these behaviours following circumcision (Auvert et al 2005).

It is important to note that all three studies described here were stopped by their data and safety monitoring boards before their designed completion because of significant reductions in HIV incidence in the circumcision groups, making it unethical to continue following control group participants without offering them circumcision.

Further information on effectiveness

One RCT which primarily reported on HIV infection also reported on the association between circumcision and STI (Gray et al 2007). Over each of the visits during this study, the
prevalence of self-reported genital ulcers was lower in the circumcision group than in the uncircumcised group (3.1% vs 5.8%; prevalence risk ratio 0.53, 95% CI 0.43–0.64; P<0.0001). Circumcision reduced the rate of self-reported symptoms of GUD, with a cumulative efficacy of 48% over all follow-up visits. Gray et al (2007) could not determine whether circumcision reduced the incidence of ulcerative infections due to syphilis, herpes simplex virus 2, or *Haemophilus ducreyi*, or whether circumcision reduced the severity, duration, or recurrence of ulceration. This may have led to lower recognition of STI symptoms. Circumcision did not have an effect on symptoms of discharge or dysuria.

**Authors’ Conclusions**

All three RCTs concluded that male circumcision reduced HIV acquisition in men. Bailey et al (2007) and Auvert et al (2005) noted that where appropriate, voluntary, safe and affordable, circumcision should be offered with other HIV preventive interventions in sub-Saharan Africa.

Gray et al (2007) concluded that the observed effect of circumcision on GUD was comparable with the effects of circumcision on GUD reported in observational studies, and that the lack of an effect of circumcision on gonorrhoea or *Chlamydia* prevalence was also consistent with observational studies. Gray et al (2007) suggested a biological explanation for this effect, noting that circumcision could be protective against cutaneously acquired infections, but does not appear to protect against urethral infections.

**Mother-infant interaction**

**Appraisal of study methodology**

One RCT (Macke 2001) investigated the pain distress (cry and heart rate) and behaviours (clarity of cues and responsiveness) of infants undergoing circumcision. Macke (2001) reported on the effect of acetaminophen on pain distress during and after circumcision, and on behavioural changes during a mother-infant feeding interaction after circumcision. Patients were recruited at the convenience of the investigator and all infants received circumcision; however, one group received pre-circumcision analgesia whilst the other group received a placebo.

Macke (2001) stated that infants were randomised into groups but did not provide any detail on the method of randomisation, other than that infants were assigned to groups by pharmacy staff. Birth characteristics (complications, maternal drug influence, prolonged labour, or trauma from forceps or vacuum extraction) were similar between the two groups. There were no significant differences between the groups for maternal/newborn variables including marital status, number of siblings, planned pregnancy, labour anaesthesia used, type of feeding, maternal age, gestational age of newborn, and birth weight of newborn.

All infants received a circumcision with the Gomco method and group one (29 infants) received acetaminophen one hour pre-circumcision while group two (31 infants) received a placebo one hour pre-circumcision. Physicians, mothers, nurses, and the investigator were blinded to participant groups.
Groups were compared on circumcision-related variables, with no significant differences found except for type of physician performing the circumcisions \((P<0.05)\). Twelve private physicians and 17 resident physicians performed the circumcisions in the analgesia group, while twenty one private physicians and 10 resident physicians performed the circumcisions in the placebo group. All physicians had performed at least 10 circumcisions before the study. A second analysis showed that there were no significant differences between time, group and physician.

Length of follow-up was one hour post-circumcision and one investigator conducted all observations. Pain distress was observed for 10 minutes during a nappy change one hour pre-circumcision, in order to establish baseline characteristics. Pain distress was then observed during the circumcision and for 10 minutes during a nappy/dressing change one hour post-circumcision. Infant and parent behaviours, along with infant alertness, were observed during feeding 20 minutes post-circumcision and the time taken to initiate feeding was recorded. Pain distress was measured by cry and heart rate and behavioural changes were indicated by clarity of cues and responsiveness to parent and measured by the Nursing Child Assessment Feeding Scale (NCAFS).

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

Both the heart rate and percentage of cry increased significantly \((P<0.01)\) for both groups from the pre-circumcision nappy change observation to the circumcision, reflecting the pain experienced by the infants during circumcision. No significant differences were found between the groups during the circumcision. For heart rate, no significant difference between the groups was found from the first to the second nappy change. Percentage of cry increased from the first to the second nappy change for both groups. When the Wilcoxon statistic was used for this period, cry percentage was significant for the placebo group at the second nappy change \((P<0.01)\), suggesting pain distress for this group. When analyses were repeated with a repeated multivariate analysis of covariance (ANCOVA), a significant effect was also noted \((P<0.05)\). Before the second nappy change, all infants were either drowsy, alert or sleeping, and none demonstrated crying or irritability until the nappy change commenced. At the second change, crying was significantly higher in the placebo group than at the first change \((P<0.01)\), suggesting an effect from the analgesia.

Infant behaviour scores decreased in both groups from before to after the circumcision, with the analgesia group demonstrating a smaller decrease in cue clarity and responsiveness \((P=0.01)\). Mothers of infants in the analgesia group demonstrated an increase in their social and emotional growth-fostering behaviours score, and the score for the mothers of infants in the placebo group declined \((P<0.05)\). Infants in the analgesia group demonstrated clearer cues and were more responsive to their mothers during feeding after the circumcision, but there was no group difference in the ability of infants to initiate feeding 20 minutes after the circumcision. Alertness at the first feeding was compared with alertness at the second and 13
of the 22 infants in the analgesia group who were alert at the pre-circumcision feeding were also alert at the post-circumcision feeding, compared with nine of the 22 infants in the placebo group. All infants in the analgesia group who were not alert at the first feeding were subsequently alert at the second feeding, compared with two of the nine infants in the placebo group who were not alert at the first feeding and were subsequently alert at the second feeding ($P=0.01$).

**Authors’ Conclusions**

Macke (2001) noted the reciprocal and synchronous nature of mother-infant interactions during the early postpartum period, and suggested pain control after circumcision to promote neonatal comfort and improve mother-infant interaction.

**Subsequent pain response**

**Appraisal of study methodology**

One RCT (Taddio et al 1997) reported on the differences between circumcised and uncircumcised infants in subsequent pain response at four-month or six-month vaccination, and also investigated whether pre-treatment with lidocaine-prilocaine cream (EMLA) affected the subsequent vaccination response for the circumcised infants. A prospective cohort of 87 infants formed three groups: uncircumcised infants ($n=32$); and infants who, aged five days or less, had been randomised in a previous clinical trial to receive EMLA ($n=29$) or placebo ($n=26$) for their circumcision. Taddio et al (1997) did not provide details as to the randomisation procedure, and only the research assistant who assessed pain response appeared to be blinded. There were no significant demographic differences among the three groups at the time of vaccination and infant temperament and birth characteristics were similar in all groups. Three infants in the uncircumcised group were circumcised after study initial contact. Two of these infants were circumcised within five days of birth and the other at 20 days. As none of these infants received analgesia, their results were added to the group circumcised with placebo.

No inclusion criteria were provided, however Taddio et al (1997) noted that uncircumcised infants were recruited by the same inclusion criteria as the circumcised infants, but their parents had chosen not to have their infants circumcised. Vaccination took place at four or six months in the clinic of the infant’s primary care physician and the vaccination procedure was standardised across settings. All infants were physically examined before the vaccination, and an intramuscular injection of the vaccine was administered by a physician or nurse. The infant’s face was recorded with a video camera for a minimum of 20 seconds before, during and for up to 1 minute after vaccination. To minimise bias during data collection, Taddio et al (1997) standardised the infants’ position before vaccination and waited for infants unsettled by the physical examination to calm down. Five infants were held by a parent during the vaccination procedure, and 76 were vaccinated with a 25-gauge needle. No details were provided on the remaining vaccinations.

Infant pain response was assessed from the videotape by a research assistant who was blinded to the purpose of the study and also to the treatment-group status of the infants. Infant pain
reactions were scored using the neonatal facial coding system and cry duration (infant facial action, cry duration and visual analogue scale scores). The overall facial action pain score ranged from 0–100% and visual analogue scale pain scores were rated with a 10 cm pain ruler.

Taddio et al (1997) identified several confounders including genetic attributes, socioeconomic status, and parent-infant interactions. They noted that race and socioeconomic status did not differ between groups in this study and that there were no observable qualitative differences in the way parents interacted with their infants during the vaccination.

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

Multivariate analysis of variance (ANOVA) showed a significant difference in pain scores between circumcised and uncircumcised groups ($P<0.001$). Significant group effects were found with univariate ANOVAs for percentage facial action ($P=0.04$), percentage cry duration ($P=0.01$), and visual analogue scale pain scores ($P=0.02$). Post-hoc analysis showed that the group circumcised with placebo had a higher difference between scores ($P<0.05$) than the uncircumcised group for percentage facial action, percentage cry duration and visual analogue scale pain scores.

Taddio et al (1997) also investigated the effects of EMLA cream in reducing post-circumcision pain responses. Of the circumcised infants, visual analogue scale pain scores were significantly higher in infants who received placebo than in those who received EMLA ($P<0.05$). Facial action scores, cry duration and visual analogue scale pain scores all increased significantly from the uncircumcised group to the circumcised with EMLA group, and then to the placebo group ($P<0.05$). Univariate analysis of covariance (ANCOVAs) reported similar main results with vaccination pain scores as the outcome and baseline value as the covariate.

Potential confounders such as age, weight, temperament, ingestion of paracetamol, time of last feeding and time of last sleep before vaccination, did not correlate significantly with pain response.

**Authors’ Conclusions**

Taddio et al (1997) concluded that circumcised infants showed a stronger pain response to subsequent routine vaccination that uncircumcised infants, and recommended analgesia for circumcision pain.

**Sexual satisfaction and function**

**Appraisal of study methodology**

One RCT (Kigozi et al 2008) investigated the relationship between adult male circumcision and sexual satisfaction and function in men. A conflict of interest was declared by one author.

No inclusion or exclusion criteria were provided, and all participants were HIV-negative men aged between 15 and 49 years. A total of 4996 males were enrolled into this RCT and of these
2474 were randomised to receive immediate circumcision and 2522 were randomised to receive circumcision delayed for 24 months. There were no details provided on the method of randomisation or on blinding of the outcome assessors, aside from the fact that circumcision status did not appear to have been concealed from the interviewers and that interviewer bias therefore may have been present. There were no statistically significant differences between groups in socio-demographic characteristics (age \(P=0.56\), religion \(P=0.81\), marital status \(P=0.31\), education \(P=0.67\), number of sexual partners in the past year \(P=0.57\)) or sexual behaviours at enrolment. At the time of enrolment, there were no statistically significant differences between the study arms in the frequency of low sexual desire (\(P=0.26\)), lack of sexual satisfaction (\(P=0.37\)), ability to achieve or maintain an erection (\(P=0.07\)), vaginal penetration (\(P=0.2\)), ejaculation (\(P=0.9\)), and penile pain during or after sexual intercourse (\(P=0.9\)).

No comorbidities were reported and there was no investigation of confounders. All circumcisions were performed by trained medical officers using the sleeve procedure, in fully equipped outpatient theatres located in a central facility. Men were followed up at six, 12 and 24 months and information on sexual desire, satisfaction and erectile dysfunction was collected. Of the participants, 89.3% of those who received immediate circumcision and 89.1% of those who received delayed circumcision were sexually experienced, and thus could provide information on their sexual experiences before and after circumcision. Only these sexually active men were included in the analysis, to enable comparisons before and after circumcision in the intervention arm. At baseline and all follow-up visits, information on sexual experience was collected by male interviewers using a standardised questionnaire, with questions derived from the International Index of Erectile Function. Men who reported any problem with sexual satisfaction or function were seen by medical officers for management, with referral to a urologist when necessary.

Throughout the RCT, it appeared that Kigozi et al (2008) gave undue prominence to the intervention arm, rather than to the control arm which observed statistically significant effects. Further, they did not adequately account for the differences seen between the circumcised and uncircumcised groups, noting only that they may have occurred by chance. No further exploration of these differences was provided.

**Safety**

Safety outcomes were not addressed as none of the included studies reported on the adverse effects of circumcision.

**Effectiveness**

Overall, the frequency of most problems related to sexual desire, satisfaction and function either did not change, or diminished over follow-up. At enrolment 0.8% of the circumcised group and 1.6% of the uncircumcised group reported erectile problems. At the two year follow-up 0.3% of circumcised men and 0.1% of uncircumcised men reported such problems. This change was statistically significant within the uncircumcised group (\(P<0.001\)), but there was no significant difference between the two groups at two year follow-up.
At enrolment 1.5% of the circumcised group and 2% of the uncircumcised group reported difficulties with penetration. At the two year follow-up only 0.6% of circumcised men and 0.1% of uncircumcised men reported such problems. This change was statistically significant within both groups ($P<0.001$), but there was no significant difference between the two groups at two year follow-up. At the six month follow-up there was a statistically significant difference between the circumcised and uncircumcised groups ($P=0.02$).

At enrolment 1.2% of both circumcised and uncircumcised groups experienced dyspareunia. At the two year follow-up this declined to 0.1% for circumcised men and 0.4% for uncircumcised men. This change was statistically significant for the circumcised group ($P<0.001$), but there was no statistically significant difference between the two groups at two year follow-up. At the six month follow-up there was a statistically significant difference between the two groups, with circumcised men experiencing more pain during or after intercourse compared with uncircumcised men ($P=0.05$). Kigozi et al (2008) suggested that the effects seen at the six month follow-up for difficulties with penetration and dyspareunia were transient, as they were confined to the first six months after surgery.

Problems with sexual satisfaction and function were rare (<2%) at all time points. The uncircumcised men reported a statistically significant increase in sexual satisfaction over time from 98.0% at enrolment to 99.9% at the 24 months follow-up ($P<0.001$). There was no statistically significant change in sexual satisfaction in the circumcised men. The differences in self-reported sexual satisfaction between the intervention and control arms were statistically significant at 12 months ($P=0.007$) and at 24 months ($P=0.004$) in favour of uncircumcised men.

Although the differences were minor (0.8%), a significantly higher proportion of men in the circumcision group reported difficulty with penetration in the first six months after circumcision. This may have been a transient problem due to incomplete keratinization of the scar, as there were no differences between the study arms at 12 and 24 months after surgery.

**Authors’ Conclusions**

Despite a statistically significant difference in sexual satisfaction between the circumcised and uncircumcised men, Kigozi et al (2008) concluded that adult male circumcision does not adversely affect sexual satisfaction or clinically significant function in men.

**Time to return to work or normal activity**

One RCT reported on the association between circumcision and time to return to work or normal activity. The appraisal of study methodology for this RCT (Bailey et al 2007) has been described above, together with the relevant safety and efficacy outcomes. While the focus of this paper was HIV the authors also briefly reported on the time to return to work or normal activity.

Of the 1333 circumcised men interviewed three days post-surgery, all those who were employed reported that they had resumed working, and 1287 (96%) reported having returned to normal activities by this time. By eight days post-surgery, all but one person had returned to normal activities (Bailey et al 2007).

RESULTS
Satisfaction with circumcision

Two RCTs reported on satisfaction with circumcision (Bailey et al 2007; Auvert et al 2005). The appraisals of study methodology for these studies have been described above, together with their relevant safety and efficacy outcomes. While the focus of these papers was HIV the authors also briefly reported on satisfaction with circumcision.

Bailey et al (2007) reported that 1274 (99.5%) individuals were ‘very satisfied’ and six (0.5%) were ‘somewhat satisfied’ with their circumcision. One patient who reported being ‘somewhat dissatisfied’ at one month post-surgery complained of weak erections; however this complaint resolved at subsequent visits (Bailey et al 2007). Similarly, in the South African study, 98.5% of men who were circumcised, including those who were HIV-positive at the time of randomisation, were ‘very satisfied’ with the result of their circumcision at three months post-surgery (Auvert et al 2005).
Summary of review findings

Overview
This rapid review identified a total of six eligible systematic reviews, one published in 2003, one published in 2005, one published in 2006, and three published in 2007. Four of the systematic reviews included meta-analyses and two provided narrative analyses. Additional relevant RCTs that were not assessed in any of the included systematic reviews were also examined.

Safety
One systematic review Muula et al, 2007) assessed the prevalence of complications of male circumcision and reported that overall, the prevalence of complications reported ranged from 0% to 50.1% in a series of haemophiliacs. In addition, there was no firm evidence to suggest that circumcisions performed by physician surgeons were associated with a lower prevalence of complications when compared with non-physician health professionals. Muula et al (2007) concluded that the available data were inadequate to obtain a reasonable assessment of the prevalence of complications of male circumcision in sub-Saharan Africa.

Two RCTs (Bailey et al 2007; Auvert et al 2005) reported upon adverse events relating to circumcision. The adverse events were generally mild or moderate in severity, including postoperative bleeding and infections, wound disruptions, delayed healing, pain, damage to the penis, haematoma, insufficient skin removed, problems with appearance, swelling at the incision site, anaesthetic-related and erectile dysfunction.

HIV
One systematic review (Siegfried et al 2003) concluded that despite the positive results of a number of observational studies, there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV infection, does more good than harm. Three subsequent RCTs which assessed the association between circumcision and HIV infection in African men (Gray et al 2007; Bailey et al 2007; Auvert et al 2005) have shown a strong protective effect of circumcision for HIV transmission in African men.

STI
Two systematic reviews assessed the association between circumcision and the transmission of sexually transmitted infections. Van Howe (2007) concluded that genital ulcerative disease may be more common in uncircumcised men, whereas sexually transmitted urethritis may be more common in circumcised men. This conclusion was also supported by studies that did not meet the inclusion criteria. Weiss et al (2006) concluded that there is a strong indication that circumcised men are at lower risk of chancroid and syphilis, however the summary relative risk for syphilis should be interpreted cautiously as there was significant heterogeneity between studies. There was less association between circumcision and HSV-2. Potential male circumcision interventions to reduce HIV in high risk populations may provide additional benefit by protecting against other STI.
UTI
Singh-Grewal et al (2005) reported on the association between male circumcision and UTI. Although all included studies showed benefit of circumcision to prevent UTI, a table of harms and benefits of circumcision showed that the benefit of circumcision on UTI only outweighs the risk in boys who have had UTI previously and have a predisposition to repeated UTI. The review did not support the routine circumcision of normal boys with standard risk in order to prevent UTI, but suggested that circumcision of boys with higher than normal risk of UTI should be considered.

Penile cancer
Van Howe (2007a) assessed the association between male circumcision and penile cancer and concluded that the medical literature does not support an association between the prevalence of genital human papillomavirus (HPV) and circumcision status when strict criteria for diagnosis of HPV are applied.

Other outcomes
Return to work/normal activity
One RCT (Bailey et al 2007) reported upon return to work/normal activity. By eight days post-surgery, all but one person had returned to normal activities.

Satisfaction with circumcision
Two RCTs (Bailey et al 2007; Auvert et al 2005) reported upon satisfaction with circumcision. Bailey et al (2007) reported that 1274 (99.5%) individuals were ‘very satisfied’ and six (0.5%) were ‘somewhat satisfied’ with their circumcision. Auvert et al (2005) reported that 98.5% of men who were circumcised, including those who were HIV-positive at the time of randomisation, were ‘very satisfied’ with the result of their circumcision at three months post-surgery.

Sexual satisfaction and function
One RCT (Kigozi et al 2008) reported upon sexual satisfaction and function in circumcised and uncircumcised men and suggested that studies of dissatisfaction or dysfunction should allow time for scar formation to be completed, with participants warned that they may experience some transient difficulty with penetration. Despite uncircumcised men reporting greater sexual satisfaction, which was statistically significant, Kigozi et al (2008) concluded that adult male circumcision does not adversely affect sexual satisfaction or clinically significant function in men.

Mother-infant interaction
One RCT (Macke 2001) noted the reciprocal and synchronous nature of mother-infant interactions during the early postpartum period, and suggested pain control after circumcision to promote neonatal comfort and improve mother-infant interaction.
Subsequent pain response
One RCT (Taddio et al 1997) concluded that circumcised infants showed a stronger pain response to subsequent routine vaccination that uncircumcised infants, and recommended analgesia for circumcision pain.

Issues in interpreting the results
When interpreting the included systematic reviews and RCTs, it is important to consider the applicability of research conducted in other countries to the Australian context. It is not clear whether results from African trials can be extrapolated to countries with developed market economies (Inugu et al 2005) for several reasons, including ready access to condoms, which offer greater protection against STIs than circumcision (Jenkins 2007).

Another important factor is the intangible benefits and risks which circumcision may confer on Australians of particular cultural or religious backgrounds. Between 2005 and 2006 2.9% of all permanent immigrations to Australia were Sudanese and 3.0% were South African (Australian Bureau of Statistics 2008). Between 1996 and 2001, the numbers of Australian who identified themselves as Jewish increased by 5.2%, and as Islamic increased by 40.2% (Australian Bureau of Statistics 2006). Although these people reside in Australia, it may be culturally appropriate to allow them to access circumcision (MacDonald et al 2008).

The introduction of circumcision may have an impact upon current health promotion efforts to promote sexual behaviour change. Circumcision may inadvertently expose men to the risk of contracting HIV or STIs, as circumcised men may engage in subsequent sexual experimentation and risk-taking behaviours (Kamau et al 2006). If men believe that circumcision affords protection against STIs, including HIV, behavioural disinhibition may lead them to forgo the use of condoms. However, two RCTs that briefly assessed the change in behavioural disinhibition in circumcised and uncircumcised men (Gray et al 2007; Bailey et al 2007) did not find any significant changes in sexual behaviour after circumcision.

Social and Ethical Implications - Summary of the literature
Despite the fact that some psychosocial outcomes were reported in three RCTs, a number of the clinical outcomes highlighted by the protocol surgeon were not adequately covered in these studies. As a result, this rapid review includes a concise literature review covering these remaining topics.

Genital alteration, particularly when involuntary, may lead to several psychosocial sequelae, including significant anger, sadness, feeling incomplete, cheated, hurt, concerned, frustrated, abnormal, and violated (Boyle 2003). Recently there has been increasing awareness of the possibility of foreskin restoration through a process of stretching and skin expansion, which may go some way towards attenuating the psychosocial adverse effects of circumcision (Boyle et al 2002).
The age at which a male is circumcised may be important to whether or not psychosocial side effects are felt. Expert opinion advises that there is not an optimal age at which to perform circumcision, particularly as social motivations may not become apparent until later in life (F Bridgewater 2008, personal correspondence). The ‘phallic period’ of childhood, where awareness of the phallic structure and gender identity develops, occurs between the ages of three and six years. Circumcision at this time may affect the psychological status of the child and eventually cause psychological and behavioural disturbances. Castration anxiety may develop during the phallic period and child psychiatrists do not recommend operating on the penis while children are in this stage (Sahin et al 2003; Yilmaz et al 2003). It is unclear from the literature whether there are more or less adverse medical and psychosocial effects when circumcision is performed on a neonate or on an adult male.

**Religious issues**

Religious circumcision for males is practiced under both Jewish and Islamic law. Jewish male infants are usually circumcised at eight days of age, often outside of the hospital setting by a mohel. A mohel is an observant Jew who is not necessarily medically trained or qualified but is trained to perform circumcisions (Chesser 1997). Jewish circumcision may be seen as an emblem of faith and a symbol of the fight for freedom against oppression (Chesser 1997; Goodman 1999).

Islamic male infants are usually circumcised at seven days of age, with circumcision required before they are ten years old (Gatrad et al 2002). Of the six schools of Islamic law, only the Shafiite considers circumcision to be mandatory, with the others regarding circumcision as Sunnah (Prophet’s tradition) and therefore as recommended (Rizvi et al 1999).

Religious circumcision allows individuals to participate fully in their religion and to uphold family honour and tradition. Early circumcision allows a child to immediately identify with his culture, giving him a sense of belonging (Gatrad et al 2002). To delay circumcision could result in the individual becoming non-compliant due to fear of the procedure, resulting in a dilution of religious values (Gatrad et al 2002). Non-circumcision may suggest a lack of religious commitment, and individuals and their families may be stigmatised and ostracised from their religious community. An uncircumcised individual may be prevented from accessing their religion and religious community, leading to psychological trauma and decreased quality of life (Freeman 1999; F Bridgewater 2008, personal correspondence).

**Cultural issues**

Male circumcision is integral to the culture of several groups including Australian Aboriginals, Filipinos, Koreans, Turks and Africans, among others. Circumcision rituals can help males to identify with their culture and gain a sense of belonging (Gatrad et al 2002), and can ensure the acceptance of a male and his family within a particular community. Cultural circumcision may represent an expected and anticipated step into adulthood, with the initiates gaining new identity and respect in their society (Kamau et al 2006). In some cultures circumcision is a rite of passage, leading to socially recognised manhood (Bonner 2001), and it is unacceptable not to be circumcised (Sahin et al 2003). Circumcision ceremonies are also an important social
event for the family (Sahin et al 2003). If a child is rejected by the community because of an omission to carry out the circumcision, the child and their family will be disadvantaged and possibly ostracised (Gatrad et al 2002).

An uncircumcised male may be prevented from accessing his appropriate cultural roles, leading to psychological trauma and decreased quality of life. Uncircumcised Walbiri men of central Australia are not permitted to enter into their father’s lodge, participate in religious ceremonies, take the role of tribal elder, or legitimately marry (Queensland Law Reform Commission 1993; F Bridgewater 2008, personal correspondence). Uncircumcised men in many African communities are seen by their community as undeveloped and are thought to be inclined to poor sexual or reproductive performance (Hellsten 2004).

**Social issues**

There are several social motivations for male circumcision including the desire to conform to the practices of peers, to please a partner, and as a measure of maintaining penile hygiene, as circumcised penises are popularly believed to be cleaner (Chessler 1997; Waldeck 2003; Queensland Law Reform Commission 1993; Krieger et al 2005; Bonner 2001). The desire to resemble other family members (particularly fathers and brothers) is a strong motivator, and being circumcised oneself is the only significant predictor for a man who would circumcise a male child (Kebaabetswe et al 2003). Genital aesthetics is another social reason for circumcision. A circumcised penis is unambiguously phallic and resembles an erect penis even when flaccid, thus appearing more symbolically expressive of its purpose (Richters 2006).

An uncircumcised male may feel different to others in their family if their siblings and father are circumcised, leading to a lack of family cohesion, adverse parental reaction to the child, or a perceived deficiency in oneself. The individual may experience bullying or teasing by peers, rejection by a sexual partner or ostracism from his social network, leading to psychological trauma and decreased quality of life (Chessler 1997; Lee 2006; F Bridgewater 2008, personal correspondence).

**Ethical considerations**

The ethics of male circumcision concern the issues of permanently altering an individual’s body, possibly causing avoidable pain, or physical or psychological harm, for no proven benefit (Hellsten 2004). Issues of consent are particularly important in neonatal and child circumcision. Further, if circumcision is performed on a healthy child with a view to preventing disease (STI, cervical cancer, HIV) in a third party in the future, this will be on the assumption that the individual will go on to have a partner of the opposite sex (Warren 2004).

Some suggest that circumcision exposes a child to potential harm in order to gratify his parents and that the child’s interests should supersede those of his parents (Svoboda et al 2001). Further, there is potential harm in denying a male the opportunity to choose not to be circumcised, which may impact upon the individual’s relationship with his parents and the medical profession if he feels that he has been harmed by the circumcision (British Medical Association 2008).
It is important to also consider the child’s social and cultural circumstances, as circumcision may confer a strong intangible benefit for children living in a culture in which male circumcision is required for all males (British Medical Association 2008). Indeed, to deny a Jewish or Muslim child a circumcision may undermine that child’s right to cultural heritage and identity (Freeman 1999). It may be appropriate to consider the best interests of Jewish and Muslim boys separately to children in general (Freeman 1999). If a child will be circumcised regardless (due to religious, cultural or social factors), a decision not to circumcise in the hospital setting may result in the procedure being performed in unhygienic conditions or by an unskilled practitioner (British Medical Association 2008).
Conclusions

Six systematic reviews and six RCT’s, published between 1997 and 2008 were eligible for inclusion in this review. These studies assessed the effect of male non-therapeutic circumcision on a range of outcomes, including transmission of HIV and STI and development of UTI and penile cancer. Few safety outcomes were reported. Conclusions based on the included systematic reviews and RCTs are summarised below.

Safety

- In the appraised studies, the adverse effects of circumcision were infrequent, suggesting that circumcision can be performed safely. The reported rates of adverse effects associated with circumcision ranged from 1.5% to 8%, and a rate of 50% was reported in a group of haemophiliacs.

- Complications were generally mild to moderate and resolved within hours or days. Serious, permanent adverse effects, such as erectile dysfunction (reported in five patients, 0.17%) occurred infrequently.

Effectiveness

HIV

- A systematic review of observational studies found that there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV infection, does more good than harm.

- Three subsequent good quality RCTs have shown a strong protective effect of circumcision for HIV transmission in African men. When confounders such as sexual behaviour and sociodemographic factors were controlled for, the protective effect of circumcision was still present.

- The three RCTs were cancelled early as such a strong effect was seen that it was considered unethical to continue the trials.

STI

- One systematic review of observational studies has shown that circumcised men are at a lower risk of developing chancroid and GUD. One RCT reported similar results for GUD.

- One systematic review of observational studies suggested little association between male circumcision and HSV-2 seropositivity.

- There was insufficient evidence to determine the effect of circumcision on syphilis infection, as circumcised men appear to be at a lower risk, but this was reported from studies which had significant heterogeneity.
• One systematic review of observational studies did not show an association between circumcision status and gonococcal urethritis.

• One systematic review of observational studies suggested that circumcised men are at an increased risk of chlamydial infection.

• One systematic review of observational studies found that uncircumcised men were less likely to be diagnosed with GDS or non-specific urethritis; however there was significant between-study heterogeneity for these analyses.

UTI

• One systematic review comprising one RCT and several observational studies suggested that circumcision reduced the incidence of UTI, although this evidence was not sufficient to recommend routine circumcision of normal boys with standard risk of UTI. The circumcision of boys with higher than normal risk of UTI should be considered.

Penile cancer

• One systematic review of observational studies did not support an association between the prevalence of genital HPV and circumcision status.

Other outcomes

Psychosocial issues

• One RCT reported that uncircumcised men reported higher sexual satisfaction than circumcised men, but this effect could not be definitively attributed to circumcision.

• One RCT found that circumcision had an adverse effect on mother-infant interactions. Infant behaviour scores decreased following circumcision, but the degree of change was significantly smaller in the infants who had received pre-circumcision analgesia.

• One RCT found that circumcised infants are more sensitive to pain than uncircumcised infants at subsequent vaccination.

Religious, social, cultural and ethical issues

There was a lack of primary studies on these topics. However, the consensus from the literature is that these issues are important and must be considered in any decision on the provision of access to circumcision.
Acknowledgements

The authors wish to acknowledge Dr Prema Thavaneswaran and Dr Ann Scott for their assistance during the preparation of this review.
References


Bonner K Male circumcision as an HIV control strategy: not a “natural condom”. *Reproductive Health Matters* 2001; 9(18): 143–155


Boyle GJ. Issues associated with the introduction of circumcision into a non-circumcising society. *Sexually Transmitted Infections* 2003; 79(5): 427–428


Freeman MDA. A child’s right to circumcision. *BJU International* 1999; 83(Suppl 1): 74–78


Hellsten SK. Rationalising circumcision: from tradition to fashion, from public health to individual freedom – critical notes on cultural persistence of the practice of genital mutilation. *Journal of Medical Ethics* 2004; 30(3): 248–253


Jenkins R. To cut or not to cut. *Australian Doctor* July 6 2007; 21


MacDonald A, Humphreys J, Jaffe H. Prevention of HIV transmission in the United Kingdom: what is the role of male circumcision? Sexually Transmitted Infections published online 18 Feb 2008

Macke JK. Analgesia for circumcision: effects on newborn behaviour and mother/infant interaction. JOGNN 2001; 30(5): 507–514


NHMRC. How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra, Australia 2000.


Rickwood AM. Medical indications for circumcision. BJU International 1999; 83(Suppl 1): 45–51

Rizvi SAH, Naqvi SAA, Hussain M, Hasan AS. Religious circumcision: a Muslim view. BJU International 1999; 83(Suppl 1): 13–16


REFERENCES 45

Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, Meyer C, Stern M, Koutsky LA. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. *Journal of Infectious Diseases* 2004; 189(4); 677–685


Appendix A: Search terms

Cochrane Library:
MeSH Circumcision, male
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* [limit to systematic reviews, RCTs, English language, 1997-2008]

York CRD:
MeSH Male circumcision
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* [limit to systematic reviews, RCTs, English language, 1997-2008]

PubMed:
MeSH Circumcision, male
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* [limit to systematic reviews, RCTs, English language, 1997-2008]

EMBASE:
MeSH Circumcision
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* [limit to systematic reviews, RCTs, English language, 1997-2008]

In order to adequately address the religious, cultural and social factors of male non-therapeutic circumcision, three additional social sciences databases were searched:

PsycINFO:
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* limit to English language, 1997-2008]

CINAHL:
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* limit to English language, 1997-2008]

AustHEALTH:
Textwords circumcis* or bris or mohel* or khitan* or milah* or dhapi* or djapi* or mandiwa*or mandiyala* limit to English language, 1997-2008]

Bris, mohel and milah are terminologies associated with Jewish religious circumcision, khitan is a terminology for Islamic religious circumcision, and dhapi, djapi, madiwa and mandiyala are terminologies for Australian Aboriginal circumcision.
Appendix B: Excluded studies

**Excluded systematic reviews**

**Pain relief**

Cyna AM, Jha S, Parsons JE. Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database of Systematic Reviews* 2003

Brady-Fryer B, Wiebe N, Lander JA. Pain relief for neonatal circumcision. *Cochrane Database of Systematic Reviews* 2004

Stevens B, Yamada J, Ohlsson A. et al. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database of Systematic Reviews* 2004


Taddio A, Ohlsson K, Ohlsson K. Lidocaine-prilocaine cream for analgesia during circumcision in newborn boys. *Cochrane Database of Systematic Reviews* 1999

**Not relevant**

Puckett RM & Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. *Cochrane Database of Systematic Reviews* 2000

**Not a systematic review**


**Updated systematic review included**


**Excluded RCTs**

**Pain relief**


Guillet R & Butler-O’Hara M. Efficacy of anesthesia during neonatal circumcision. *Pediatric Research* 1997; 41: 152A


Lehr VT, Cepeda E, Fratarelli DAC, Thomas R, LaMothe J, Aranda JV. Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. *American Journal of Perinatology* 2005; 22(5): 231–7

Lenbart JG. Local anesthesia for circumcision: which technique is most effective? *Journal of the American Board of Family Practice* 1997; 10(1): 13–9


Woodman PJ. Topical lidocaine-prilocaine versus lidocaine for neonatal circumcision: a randomized controlled trial. *Obstetrics and Gynecology* 1999; 93(5 Pt 1): 775–9


**Surgical technique**


**Not comparative**


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*APPENDIX B*


**Clinical trial simulation**


**Already included**

Nayir A. Circumcision for the prevention of significant bacteriuria in boys. *Pediatric Nephrology* 2001; 16(12): 1129–34
## Appendix C: Evidence tables

### Table C1: Evidence table of appraised secondary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and search method</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Results and author conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muula AS, Prozesky HW, Mbitaya RH, Ikechelobu JL, 2007, Africa and US.</td>
<td><strong>Aim:</strong> What has been the reported prevalence of complications of male circumcision in Sub-Saharan Africa? Who is conducting male circumcision in Africa?</td>
<td><strong>Study Design:</strong> Systematic review of RCTs and observational studies (not NHMRC Level 1 evidence)</td>
<td><strong>10 studies were included (4 RCTs, 2 conference abstracts, reports of routine clinical work). Studies were conducted in Kenya, Nigeria, South Africa and Tanzania.</strong></td>
<td>• no exclusion criteria defined</td>
</tr>
<tr>
<td></td>
<td><strong>Search Period:</strong> 1980 to August 2006.</td>
<td><strong>Inclusion Criteria:</strong> studies were included for analysis if they reported on any series of patients in Anglophone Africa on whom male circumcision had been conducted and complications reported.</td>
<td><strong>Safety:</strong> Bleeding: reported in 6 studies; 50.1% occurrence rate reported in Shittu and Shokunbi; no data reported for other studies.</td>
<td>• no handsearching of reference lists of included studies</td>
</tr>
<tr>
<td></td>
<td><strong>Databases Searched:</strong> African Journals Online (AJOL), Medline, CMD, Google Scholar, Web of Science, abstracts from the International Conference on AIDS (2004 and 2006).</td>
<td><strong>Exclusion Criteria:</strong> none specified.</td>
<td>Other adverse events were reported; however, no data on occurrence were provided.</td>
<td>• no date restrictions</td>
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<tr>
<td></td>
<td><strong>Additional Information:</strong> only studies published in English were included, irrespective of study design.</td>
<td><strong>Study Selection and Appraisal Methods:</strong> three authors participated in the data collection. A list of the data to be extracted from the studies was included.</td>
<td>Infection: reported in 5 studies.</td>
<td>• no handsearching of relevant journals</td>
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<tr>
<td></td>
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<td></td>
<td>Redundant foreskin: reported in 1 study.</td>
<td>• limited description of excluded studies</td>
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<td></td>
<td></td>
<td></td>
<td>Excessive skin removal: reported in 2 studies.</td>
<td>• data extraction and appraisal methodology inadequately described</td>
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<td></td>
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<td></td>
<td>Insufficient skin removal/incomplete circumcision: reported in 2 studies.</td>
<td>• no information provided on how data extraction took place</td>
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<td></td>
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<td>Skin bridges: reported in 1 study.</td>
<td>• inadequate appraisal of included studies</td>
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<td></td>
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<td></td>
<td>Amputation of glans: reported in 1 study.</td>
<td>• used Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines to construct systematic review</td>
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<td></td>
<td></td>
<td></td>
<td>Buried penis: reported in 1 study.</td>
<td>no discussion of excluded studies</td>
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<td></td>
<td>Haemorrhage: reported in 2 studies.</td>
<td>poor reporting of incidence of complications; occurrence of all complications summed together to give mean percentage of overall complications per study; prevalence rates provided for each study were a summation of all complications, no reporting on individual categories of complication.</td>
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<td></td>
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<td></td>
<td>Pain: reported in 1 study.</td>
<td>• did not discuss confounders</td>
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<td></td>
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<td></td>
<td>Damage to penis/glans: reported in 2 studies.</td>
<td>Statistical Methods Used: NR</td>
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<td></td>
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<td>Anaesthetic complications: reported in 1 study.</td>
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<td>Delayed healing: reported in 2 studies.</td>
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<td>Cosmetic concerns: reported in 1 study.</td>
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<td></td>
<td>Problems with urination: reported in 2 studies.</td>
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<td></td>
<td>Disrupted wound: reported in 2 studies.</td>
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<td></td>
<td>Swelling/penile oedema: reported in 2 studies.</td>
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<td>Erectile dysfunction: reported in 1 study.</td>
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<td>Meatal stenosis: reported in 2 studies.</td>
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<td>Urethral laceration: reported in 2 studies.</td>
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<td></td>
<td>Haematomas: reported in 2 studies.</td>
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<td></td>
<td>Scrotal laceration: reported in 1 study.</td>
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<td></td>
<td>Overall, the prevalence of complications ranged from 0% to 50.1% (in a series of haemorrhages). There was no firm evidence to suggest that male circumcisions performed by physician surgeons were associated with lower prevalence of complications when compared with non-physician health professionals. As the length of follow-up differed between studies, some studies reported on possible late complications of circumcision; and in included studies with short follow-up, long-term complications may have been missed. Four of the 10 studies did not report follow-up time. Generally, most of the studies included in the review reported on bleeding and infection. In virtually all of the included studies, the majority of complications reported were of minor clinical consequence.</td>
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<td></td>
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<td></td>
<td>Effectiveness: NR</td>
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<td></td>
<td>Conclusion: the literature on the prevalence of complications following male circumcision in Sub-Saharan Africa is limited. Most of the complications reported have been of minor clinical consequence. Varying reporting practices make it difficult to compare studies with regards to patient age, indications for circumcision, duration of follow-up of complications, and categories of circumcisers. The available data are inadequate to obtain a reasonable assessment of the prevalence of complications of male circumcision in sub-Saharan Africa.</td>
<td></td>
</tr>
</tbody>
</table>
### Study details

- **Aim:** 1). To assess the evidence of an interventional effect of male circumcision for preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. 2). To examine the feasibility and value of performing individual person data meta-analysis.

- **Search Period:** Medline and EMBASE: 1986–2002, AIDSONLINE: (presumably from inception to 2001), Cochrane Library: (presumably from inception to 2002).

- **Databases Searched:** Medline, EMBASE, AIDSONLINE/GATEWAY, The Cochrane Library, databases listing conference abstracts.

- **Additional Information:** reference lists of included studies were examined in order to identify any further studies. Contacted authors of included studies to identify any further results. No language restrictions, studies performed in any country were included.

### Study design and inclusion/exclusion criteria

- **Study Design:** systematic review (not NHMRC Level 1 evidence).

- **Inclusion Criteria:** heterosexual men 12 years of age or older included in studies assessing the association between circumcision and HIV-1 and HIV-2. Circumcision status determined by self- or partner-report or by direct observation. HIV-1 or HIV-2 infection (incidence or prevalence) in men, based on laboratory results. Studies performed in general of specific populations and in hospitals or clinics. RCTs or quasi-RCTs or in their absence, observational studies (e.g. cohort, case-control and cross-sectional).

- **Exclusion Criteria:** studies with historical controls and ecological studies, as these provide unreliable data for determining causation and/or association.

### Study Selection and Appraisal Methods:

- 2 authors independently applied the inclusion criteria, differences were resolved by discussions with a third author. Data were extracted independently by 2 authors, using standardised data extraction forms (one for cohort/cross-sectional studies, one for case-control studies). A list of the data extractions was provided.

Performance, detection, attrition and selection bias were assessed. Performance bias may be present in all studies where circumcision status was obtained by self-report (15 studies) rather than direct observation (20 studies). Detection bias was rare as 33/35 studies used blinded methods for assessing and confirming HIV status. All 5 cohort studies were susceptible to attrition bias as loss-to-follow-up was greater than 20%, unequal between circumcised and uncircumcised groups, or unclear. Selection bias was problematic in all studies, and the results were potentially confounded by other risk factors for HIV transmission.

### Results and author conclusions

35 studies were included (16 in general population settings, 19 in high-risk population settings: where the HIV infection rate is either known to be high or the setting provides conditions conducive to the spread of HIV). For reporting, studies were stratified according to the population setting and further stratified according to study type (cohort, cross-sectional, case-control).

- **Safety:** no studies reported on the adverse effects of circumcision, in most studies exposure to circumcision had taken place during childhood or adolescence, before the studies commenced.

- **Effectiveness:** odds ratio (OR) was used to compare results of cross-sectional and cohort studies with those of case-control studies. OR >1 indicate increased risk of HIV infection with circumcision, odds ratio <1 indicate decreased risk of HIV infection with circumcision. Some studies reported crude and adjusted OR. 17 studies reported both crude and adjusted effects. In general, adjustment made little difference in the size, direction or significance of effects in 11 studies.

- **General population study results:** 1 cohort study, 14 cross-sectional studies, 1 case-control study. The cohort study showed a significant difference in HIV transmission rates between circumcised and uncircumcised men, with an adjusted OR of 0.53 (95% CI: 0.33 to 0.87). Of the 14 cross-sectional studies, 8 were in the direction of benefit (4 of these were statistically significant) and 6 were in the direction of harm (2 were statistically significant). Point estimates of OR varied between 0.28 and 1.73. The test for heterogeneity was highly significant ($P=0.001$). 9 studies reported adjusted OR, 8 in the direction of benefit ranging from 0.26 to 0.80. The small (N=51) case-control study found no significant difference in HIV transmission rates between circumcised and uncircumcised men (OR 1.90, 95%CI: 0.50 to 7.20). High-risk population study results: 4 cohort studies, 12 cross-sectional studies, 3 case-control studies. The cohort studies were all in the direction of benefit from circumcision, with 2 statistically significant. Point estimates varied from OR of 0.10 to 0.39. Between-study heterogeneity was not significant ($P=0.16$), however 42% of the variability in results was not explainable by chance. Of the 12 cross-sectional studies, 11 were in the direction of benefit, eight being statistically significant. Estimates of effect varied from OR of 0.10 to 0.66. Four of the cross-sectional studies report OR ranging from 0.20 to 0.59, and all were significant. One additional study only reported an adjusted OR in the direction of benefit which was statistically significant (no OR provided). Of the 3 case-control studies, all were in the direction of a protective effect of circumcision on HIV status, two being statistically significant. Point estimates varied from OR of 0.37 to 0.88.

- **Sub-group analyses were conducted. Studies in high-risk groups were significantly more in favour of circumcision than those in general populations (P=0.001). Differences were observed between study designs for the high-risk studies (P=0.03 for cross-sectional compared with case-control, P=0.06 for cohort compared with case-control).

### Conclusion:

Despite the positive results of a number of observational studies, there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV-infection, does more good than harm.

### Comments

- search terms specified for each database
- no date restrictions
- no language restrictions
- handsearching of reference lists of initial included studies
- authors contacted where necessary
- list of excluded studies
- appraisal methodology detailed and tables included
- sensitivity analyses carried out
- discussion of potential confounders
- discussion of possible indexing, publication and reporting biases
- meta-analysis not performed due to heterogeneity

### Statistical Methods Used:

Meta-analyses were not conducted due to the heterogeneous results, so a narrative description of the differences between crude and adjusted results was undertaken. Between-study heterogeneity was assessed and quantified using the I-squared statistic. Siegfried et al (2003) used the odds ratio (OR) to compare the results of cross-sectional and cohort studies with those of case-control studies, with an OR greater than 1 indicating an increased risk of HIV infection with circumcision, and an OR less than 1 indicating a decreased risk of HIV infection with circumcision.

---

**A P P E N D I X  C**
Table C1 continued: Evidence table of appraised secondary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and search method</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Results and author conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss HA, Thomas SL, Munabi SK, Hayes RJ, 2006, UK</td>
<td>Aim: to review systematically the evidence for an association between male circumcision and infection with ulcerative STIs, herpes simplex virus type 2 (HSV-2), Treponema pallidum, and Haemophilus ducreyi (the causative agents of syphilis and chancroid).</td>
<td></td>
<td>Safety: NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Search Period: 1950 to April 2004.</td>
<td></td>
<td>Effectiveness:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Databases Searched: PubMed and EMBASE.</td>
<td></td>
<td>• Male circumcision and HSV-2 seropositivity: 10 studies, 6 studies were among men at low risk of STIs, 4 were among men at higher risk of STIs. Circumcised men were at lower risk of HSV-2 seropositivity than uncircumcised men on univariable analysis in 6 studies, and the association was statistically significant (P&lt;0.05) in 3 of these. 7 studies included RR with some adjustment for confounding and best estimate RRs ranges from 0.30 to 1.20, random effects estimate summary RR was 0.88 (CI=0.77 to 1.01), P=0.57, suggesting that there is no association between male circumcision and HSV-2 seropositivity. Results were similar for studies that adjusted for age and at least one measure of sexual behaviour (summary RR=0.85, CI=0.74 to 0.98) or those where circumcision occurred before first sexual intercourse (summary RR=0.96, CI=0.74 to 0.99). 6 studies assessed the effect of circumcision on both HIV and HSV-2. The magnitude of association between circumcision and HIV (summary RR 0.34) was about twice that for HSV-2 (summary RR=0.69 CI=0.46–1.03).</td>
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<tr>
<td></td>
<td>Additional Information: Additional information was sought where necessary from authors. No language restrictions were included. The reference lists of all relevant papers were searched, as were previously published reviews of circumcision and STIs.</td>
<td></td>
<td>• Male circumcision and syphilis seropositivity: 14 studies, 14 studies compared chancroid patients (diagnosed by clinical diagnosis or microbiology) or penile ulcer patients with asymptomatic controls, found that circumcised men were at much lower risk (RR 0.04–0.40).</td>
<td></td>
</tr>
<tr>
<td>Study Selection and Appraisal Methods:</td>
<td>study populations that appeared in more than one publication were included only once, choosing the publication with the more informative study design or that controlled most fully for confounders. Flow chart of study selection for inclusion was provided and explanation of included/excluded studies. Each identified abstract was reviewed independently by 2 authors. Data was extracted using a standardised form.</td>
<td></td>
<td>Conclusion: this systematic review strongly indicates that circumcised men are at lower risk of syphilis and chancroid. There is less association with HSV-2. Potential male circumcision interventions to reduce HIV in high risk populations may provide additional benefit by protecting against other STI.</td>
<td></td>
</tr>
<tr>
<td>Study Design: systematic review (not NHMRC Level I evidence)</td>
<td>Inclusion Criteria: studies were restricted in the first instance to those with the selected outcomes based on serological evidence of infection, not disease. Studies in which the comparison groups were asymptomatic clinic attenders or seronegative individuals. Studies whose abstracts indicated analysis of risk factors for either HSV-2 seropositivity or past/recent infection with syphilis or chancroid. HIV risk factor studies that mentioned male circumcision.</td>
<td></td>
<td>• Male circumcision and chancroid: 7 studies, six found a reduced risk of chancroid among circumcised men, and this was statistically significant in four studies. Study heterogeneity prevented meta-analysis from being carried out. The single study with a serological outcome found no association with circumcision. 3 of the 7 studies that compared chancroid patients (diagnosed by clinical diagnosis or microbiology) or penile ulcer patients with asymptomatic controls, found that circumcised men were at much lower risk (RR 0.04–0.40).</td>
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<td>Exclusion Criteria: studies among women, studies from countries where overall prevalence of circumcision is either extremely high or low (&lt;5% or &gt;95% prevalence), more than 99% of the population is Muslim, case-series of genital ulcer disease (GUD) patients or HIV positive individuals, and studies of syphilis without confirmed treponemal tests, individuals who were circumcised after first intercourse or after the age of 11, however this information was not available for all studies.</td>
<td></td>
<td>• losses to follow-up reported</td>
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<tr>
<td></td>
<td>Study Selection and Appraisal Methods:</td>
<td></td>
<td>many search terms used</td>
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<td>all included studies are observational</td>
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<td>potential biases may underestimate an association, indicating that the true association may be stronger than the summary RRs presented</td>
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<td>significant heterogeneity between the studies on syphilis</td>
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<td>explanations for study heterogeneity</td>
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<td>discussed publication bias</td>
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<td>discussed confounders</td>
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<td>low participation rates in several studies</td>
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<td>sensitivity analyses were conducted</td>
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</table>

Statistical Methods Used: effect sizes (relative risk, RR) were estimated with rate ratios for cohort studies, prevalence ratios or odds ratios for cross sectional studies, and odds ratios for case-control studies. Where the RR was not presented but raw data were available, the RR and 95% confidence interval were calculated. Sensitivity analyses were carried out and publication bias was assessed.
<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and search method</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Results and author(s) conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Howe RS, 2007, USA</td>
<td>Aim: to determine the relationship of circumcision status to the risk for genital ulcerative disease (GUD) and sexually transmitted urethritis.</td>
<td><strong>Study Design</strong>: systematic review (not NHMRC Level I evidence) <strong>Inclusion Criteria</strong>: Inclusion criteria were published in a peer-reviewed journal and the presence of data on the circumcision status of men both with and without GUD, chancroid, various types of sexually transmitted urethritis, or a comparison of GUD versus genital discharge syndrome (GDS).</td>
<td>30 studies were included (10 on GUD, 4 on GUD versus GDS, 3 on chancroid, 9 on GDS, 10 on non-gonococcal urethritis (NGU), 10 on <em>C</em>. <em>trachomatis</em>, and 19 on gonococcal infections).</td>
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<tr>
<td><strong>Study Selection and Appraisal Methods</strong>: no critical appraisal of included studies.</td>
<td><strong>Safety</strong>: NR <strong>Effectiveness</strong>: GUD: • uncircumcised men are at greater risk for GUD, especially men in a high-risk population. • if the data from the second publication of the Rakai data were used in place of the first publication, the summary OR for GUD infection was higher (OR=1.63, 95% CI=1.21–2.20 using GVB method with exact ORs). • neither population type (high-risk versus general) or the method to document circumcision status (physical exam versus other methods) were significant factors, but combining these two factors in meta-regression was found to be statistically significant (P=0.03). When studies were adjusted for this score, the summary OR (using exact ORs from each study) was 1.07 (95% CI=0.78–1.47). Sexually transmitted urethritis: • circumcised men are at greater risk for sexually transmitted urethritis in general. • uncircumcised men were less likely to be diagnosed non-specific urethritis. Gonorrhoea: • circumcision status had no impact on the risk of gonorrhea. <em>C</em>. <em>trachomatis</em>: • circumcised men showed a trend towards an increased risk of chlamydial infection that became statistically significant when adjusted for publication bias. Chancroid: no association could be demonstrated between circumcision status and risk for chancroid.</td>
<td><strong>Other reporting</strong>: • when the cross-sectional data from Diseker et al and the first publication of the Rakai data were used, the summary effect ORs were little changed (chlamydial infection OR=0.66, 95% CI=0.36–1.18, gonorrhoea OR=1.03, 95% CI=0.62–1.72, GDS OR= 0.82, 95% CI=0.65–1.02). • no association between circumcision status and gonococcal urethritis, or <em>C</em>. <em>trachomatis</em> infections. • uncircumcised men were less likely to be diagnosed with GDS. • type of population studied (general versus high-risk) was not a significant factor for chlamydial infections, gonorrhea, and NGU.</td>
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<tr>
<td>Databases Searched: PubMed</td>
<td>Authors were contacted where necessary to obtain further data.</td>
<td><strong>Additional Information</strong>: NR</td>
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</tbody>
</table>
Table C1 continued: Evidence table of appraised secondary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and search method</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Results and author(s) conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh-Grewal D, Macdessi J, Craig J, 2005, Cochrane Collaboration</td>
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<td>12 studies were included (1 RCT, 4 cohort studies, 7 case-control studies). Most of the included studies examined UTI in infants. Studies generally reported episodes of UTI rather than patients with UTI. Most originated from North America and relied on hospital inpatient and outpatient data.</td>
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<td><strong>Safety:</strong> NR, the authors note that while circumcision is protective for UTI, the overall risk-benefit derived from circumcision in preventing UTI is not easily quantifiable, as the incidence of important sequelae of UTI (sepsis, permanent renal damage, hypertension, and chronic renal failure) are not known.</td>
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<td><strong>Effectiveness:</strong> All 4 cohort studies showed benefit with a summary OR of 0.13 (95% CI=0.07 to 0.23). There was significant heterogeneity between the cohort studies (<strong>P</strong>=0.001), and when the outlier study (To) was excluded, the heterogeneity between cohort studies was non-significant (<strong>P</strong>=0.04). The reasons for the observed heterogeneity may reflect varying methods of circumcision and UTI ascertainment, and the differing follow-up periods of the studies. All 7 case-control studies included showed benefit, with a combined OR of 0.13 (95% CI=0.07-0.23). There was no significant heterogeneity between the studies within this group (<strong>P</strong>=0.2). The summary OR across study types included showed benefit, with a combined OR of 0.13 (95% CI=0.07-0.23). There was no significant heterogeneity between the studies within this group (<strong>P</strong>=0.2). The summary OR across study types when all three were combined was 0.13 (95% CI=0.08-0.20). There was no significant heterogeneity between the three subgroups (<strong>P</strong>=0.9). Significant heterogeneity was observed between the individual studies when the To study was included (<strong>P</strong>=0.00001), and when the To study was excluded there was no significant heterogeneity between the remaining studies (<strong>P</strong>=0.4). The odds of UTI in uncircumcised boys are about 0.1 when compared with those in the uncircumcised group.</td>
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<td><strong>Conclusion:</strong> the authors conclude that the systematic review does not support the routine circumcision of normal boys with standard risk in order to prevent UTI. However, they suggest that circumcision of boys with higher than normal risk of UTI should be considered.</td>
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</table>

**Statistical Methods Used:** an odds ratio (OR) with 95% CI was calculated for each study and a summary OR using a random effects model was first calculated for subgroups based on study type and then an overall OR was calculated across all study types if no heterogeneity was present.
Table C1 continued: Evidence table of appraised secondary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
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<th>Results and author(s) conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Howe RS, 2007a, USA</td>
<td>Aim: clarify the impact of circumcision status on sexually transmitted HPV infections and indirectly on the female partner’s risk of cervical cancer.</td>
<td>Study Design: systematic review (not NHMRC Level I evidence)</td>
<td>11 studies were included and analysed. The sets of 3 and 8 studies are reported separately.</td>
<td>• recommendations of Stroup et al for the meta-analysis of observational studies were followed</td>
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<td>Search Period: undefined, presumably from 1966 to 13 March 2008.</td>
<td>Inclusion Criteria: publication of a cohort, cross-sectional, and case-control study in a peer-reviewed journal, the presence of data on the circumcision status of males both with and without genital HPV infections, diagnosis by culture, biopsy, or HPV DNA detection using polymerase chain reaction (PCR) or Hybrid capture 2, determination of circumcision status by physical examination.</td>
<td>The studies included for analysis only measured prevalence of HPV infection and did not describe the relationship between circumcision status and persistent HPV infection or penile cancer.</td>
<td>• poor search strategy</td>
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<td>Databases Searched: PubMed.</td>
<td>Exclusion Criteria: NR. 16 studies identified, however 4 made the diagnosis of genital warts clinically, one relied on patient report, 4 lacked documentation of the diagnostic method, 2 failed to sample the penile shaft, and 3 relied on patient report to determine circumcision status. These studies were excluded, as they introduced various forms of bias.</td>
<td>Safety: NR.</td>
<td>• assessed methodological quality of included studies</td>
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<td>Additional Information: bibliographies of published articles were also searched.</td>
<td>Study Selection and Appraisal Methods: because of the small number of included studies, the author also analysed 8 of the excluded studies which had sufficient diagnostic methods, and attempted to minimise the bias introduced by incomplete sampling and determination of circumcision status by patient report. The sets of 3 and 8 studies are reported separately.</td>
<td>Effectiveness: the random-effects summary effect OR of the 3 studies meeting the inclusion criteria was 1.20 (95% CI=0.80–1.79). If the 8 studies using accurate diagnostic methods are adjusted for the method of determining circumcision status and failure to sample the penile shaft using meta-regression the summary effects OR is 1.25 (95% CI=0.95–1.67).</td>
<td>• considered confounding factors</td>
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<td>For the 3 studies, there was no evidence of significant between-study heterogeneity, and this was not clearly reported for the 8 studies.</td>
<td>• extensive discussion on methods used to minimise bias</td>
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<td>For the 8 studies, publication bias was assessed using 3 tests (Egger’s regression model, Begg’s adjusted rank correlation test, Macaskill’s funnel plot regression) and was not significant, and did not appear to be tested for the 3 studies. Adjustment for publication bias was performed using the “trim and fill” method described by Duval and Tweedie.</td>
<td>• extensive inclusion criteria</td>
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<td>To stabilise the impact of studies containing small numbers, a general variance-based random-effects model was run using each study’s exact OR and CI. To test for potential outliers, the dataset from each study group was individually excluded from the analysis to measure the impact on between-study heterogeneity. None of the 3 studies were identified as outliers.</td>
<td>• no exclusion criteria, although reasons for study exclusions were given</td>
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<td>A meta-analysis was performed with sensitivity analyses.</td>
<td>• no date restrictions</td>
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<td>Conclusion: the medical literature does not support an association between the prevalence of genital HPV and circumcision status when strict criteria for diagnosis are applied.</td>
<td>• no language restrictions</td>
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<td>• no handsearching of relevant journals</td>
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<td></td>
<td>• one reviewer responsible for data extractions</td>
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<td>explanation for excluded studies</td>
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</table>

Statistical Methods Used: meta-regression adjusted for incomplete sampling and method of ascertaining circumcision status using a regression model. The second method estimated the number of cases of HPV infection missed by not sampling the penile shaft using the numbers generated by Weaver and colleagues. The author states that knowing that these biases exist and not adjusting for them would generate results known to be biased.

Table C2: Evidence table of appraised primary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and Intervention</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Study Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al, 2007, USA and Uganda.</td>
<td><strong>Aim:</strong> to investigate the effect of male circumcision on HIV incidence in men.</td>
<td><strong>Study Design:</strong> RCT (NHMRC Level II evidence)  <strong>Method of Randomisation:</strong> participants randomly allocated to their treatment assignment (control or intervention) by selecting an envelope out of a box (the no. of envelopes 20 remained constant).  <strong>Allocation Concealment:</strong> participants / researcher were unaware of treatment allocation until after selection had been drawn (via concealed envelope method above).  <strong>Blinding:</strong> NR  <strong>Duration of Follow-up:</strong> 6, 12, and 24 months.  <strong>Losses to Follow-up:</strong> 114/1092 (10%) in circumcision group, and 115/1110 (10%) in control group.</td>
<td><strong>Sample Size:</strong> Total: 4996  Intervention group (receiving circumcision): 2474  Control Group (circumcision delayed for 24 months): 2522  <strong>Median Age [range]</strong>: 32 [15–49]  <strong>Comorbidities:</strong> those with contraindications were treated and re-screened for eligibility.  <strong>Ethnicity/race:</strong> African.  <strong>Surgical Setting:</strong> central study facility and mobile rural facilities. Well-equipped operating theatre.  <strong>Geographical Location:</strong> Rakai District, Uganda.</td>
<td><strong>General Findings:</strong> the study notes a significant reduction in HIV incidence among circumcised men compared with uncircumcised control participants, although no P-value was provided  <strong>Safety:</strong> wound infection, haematomas, wound disruption, postoperative herpetic ulceration. Moderate or severe adverse events occurred in 84 (3.6%) of circumcisions, and resolved following treatment  <strong>Efficacy:</strong> HIV incidence over 24 months was 0.66 cases per 100 person-years in the circumcision group and 1.33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%, 95% CI=16–72; P=0.006). HIV incidence was lower in the intervention group than it was in the control group in all sociodemographic, behavioural, and sexually transmitted disease symptom subgroups.  <strong>Statistical Methods Used:</strong> the Kaplan-Meier estimation, based on analyses of time-to-detection of HIV infection at the visit at which positive serology or PCR was first identified. The as-treated Poisson analysis, which assigns person-time according to the actual circumcision status of participants.</td>
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<tr>
<td>Study details</td>
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<td>Bailey et al, 2007, USA and Kenya.</td>
<td><strong>Aim:</strong> to determine whether circumcision had a protective effect against HIV infection and to assess safety and changes in sexual behaviour related to this intervention.</td>
<td><strong>Study Design:</strong> RCT (NHMRC Level II evidence) <strong>Method of Randomisation:</strong> participants randomly assigned to either the intervention (circumcised) or control (delayed circumcision) group. An opaque envelope draw from box was used. Allocation ensured equal sample sizes across two age strata (18–20 years) and (21–24 years). <strong>Allocation Concealment:</strong> participants / researcher were unaware of treatment allocation until after selection had been drawn (via concealed envelope method above). <strong>Blinding:</strong> nurse-counselors performing HIV testing / counselling were blinded. <strong>Duration of Follow-up:</strong> post circumcision follow-up at 3, 8 and 30 days. Study visit at 1,3,6,12,18, and 24 months. <strong>Losses to Follow-up:</strong> 240 participants (8.6%) <strong>Study Period:</strong> February 2005–December 2006. <strong>Screening Tools Used:</strong> medical examination, blood and urine test, penile swabs, haemoglobin concentration, questionnaire, counselling. <strong>Inclusion Criteria:</strong> uncircumcised, HIV negative, sexually active, 18–24 years, resident of district, no plans to move for 2 years, haemoglobin 90g/L or more. <strong>Exclusion Criteria:</strong> foreskin covers less than half the glans, haemophiliac or other bleeding disorder, high Prothrombin time index, other medical condition contraindicating surgery. <strong>Potential Confounders Reported:</strong> age, race, presentation at time of study and general previous STI history.</td>
<td>Sample size: 2784 participants Intervention (circumcision) group=1391 Control=1393 <strong>Median Age [range]</strong> 20 [18–28] <strong>Comorbidities:</strong> infection with herpes simplex virus 2 was considered independently for association. <strong>Ethnicity/Race:</strong> most (98%) identify as Luo (do not traditionally practice circumcision). <strong>Surgical Setting:</strong> study clinic. <strong>Geographical Location:</strong> Kisumu District, Kenya.</td>
<td><strong>General Findings:</strong> male circumcision significantly reduces the risk of HIV acquisition in young men in Africa. <strong>Safety:</strong> 24 adverse events were recorded as possibility, probability or definitely related to the circumcision (most common being post op bleeding and infections). Other adverse events included delayed healing, wound disruption, swelling, erectile dysfunction, and anaesthetic complication. <strong>Efficacy:</strong> the 2-year HIV incidence was 2.1% (95% CI=1.2–3.0) in the circumcision group and 4.2% (3.0–5.4) in the control group (P=0.0065). The relative risk of HIV infection in circumcised men was 0.47 (0.28–0.78), which corresponds to a reduction in the risk of acquiring HIV infection of 53%. <strong>Statistical Methods Used:</strong> the Kaplan-Meier method was used to estimate the HIV event distribution over time. Estimates of 2 year HIV were obtained by Greenwood’s formula. Cox regression models with fixed covariates were used to consider the various baseline adjustments to the treatment effect.</td>
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<td>Study details</td>
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<td>Auvert et al, 2005, France and South Africa.</td>
<td><strong>Aim:</strong> to determine the impact of circumcision on the acquisition of HIV by young men.</td>
<td><strong>Study design:</strong> RCT (NHMRC Level II evidence) <strong>Method of Randomisation:</strong> participants randomly assigned to either the intervention (circumcised) or control (delayed circumcised) group. An opaque envelope draw from box was used. <strong>Surgical Technique:</strong> forceps-guided method, each circumcision. <strong>Circumcision Performed By:</strong> three local GPs in their surgical offices. <strong>Was Circumcision Confirmed:</strong> yes, self-reported and confirmed by physical examination. <strong>Anaesthesia:</strong> not reported. <strong>Postoperative Care:</strong> not reported.</td>
<td><strong>Sample Size:</strong> Total: 3274 uncircumcised men <strong>Median Age [range]</strong> 21 [19.6–22.5] <strong>Comorbidities:</strong> NR <strong>Ethnicity/Race:</strong> African (Zulus n=1109 and Sothos n=1506) <strong>Surgical Setting:</strong> local public clinic. <strong>Geographical Location:</strong> Gauteng province, South Africa.</td>
<td><strong>General Findings:</strong> male circumcision provides a degree of protection against acquiring HIV, thereby reducing the spread of HIV in sub-Saharan Africa. <strong>Safety:</strong> adverse events included pain, excessive bleeding, infection, swelling, haematoma erectile dysfunction, problems with appearance. <strong>Efficacy:</strong> there were 20 HIV infections (incidence rate=0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to an RR of 0.40 (95% CI=0.24%–0.68%, P&lt;0.001). This RR corresponds to a protection of 60% (95% CI=32%–76%). When controlling for behavioural factors, including sexual behaviour that increased slightly in the intervention group, condom use, and health-seeking behaviour, the protection was 61% (95% CI=34%–77%). <strong>Statistical Methods Used:</strong> Poisson log-linear model, to provide an incidence rate and incidence rate ratio of HIV infection among men of the intervention group compared with men of the control group.</td>
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Table C2 continued: Evidence table of appraised primary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Aim and Intervention</th>
<th>Study design and inclusion/exclusion criteria</th>
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<tbody>
<tr>
<td>Study design: RCT (NHMRC Level II evidence)</td>
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<tr>
<td>Method of Randomisation: Pharmacy staff randomly assigned newborns to groups (no further explanation of process given)</td>
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<td>Allocation Concealment: NR</td>
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<td>Blinding: Physicians, mothers, nurses, and the investigator were blind to participant groups</td>
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<td>Duration of Follow-up: feeding interaction was 20 minutes post-circumcision; nappy/dressing change was 1 hour post-circumcision.</td>
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<td>Losses to Follow-up: NR</td>
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<tr>
<td>Study Period NR</td>
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<td>Screening Tools Used: NR</td>
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<td>Inclusion Criteria: Infants had to meet the inclusion criteria adapted from the Littman and Parmelee Obstetrical Complications Scale. This ensured that infants had Apgar scores of 8, 9 or 10 at 1 and 5 minutes, and no complications, maternal drug influence, prolonged labour, or trauma from forceps or vacuum extractions</td>
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<tr>
<td>Exclusion Criteria: NR</td>
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<td>Potential Confounders Reported: NR</td>
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</table>

| Sample Size: 60 full-term newborns |
| Analgesia: 29 |
| Placebo: 31 |
| Mean Age (hours): 29.57 (SD 9.18) for analgesia, 26.82 (SD 6.37) for placebo |
| Comorbidities: NR |
| Ethnicity/Race: NR. Most mothers in the study were white: 93% analgesia and 90% placebo. |
| Surgical Setting: a designated area of the nursery. |
| Geographical Location: NR |

**General Findings:** There is a need for pain control after circumcision to promote neonatal comfort and improve mother-infant interaction.

**Safety:** NR

**Effectiveness:**
- Between first nappy change and circumcision:
  - Both the heart rate and percentage of cry increased significantly from the first diaper change observation to the circumcision.
  - Analyses were repeated with ANCOVA, and although time remained significant, no significant differences were found between the treatment groups during the circumcision.
- Between first to the second nappy change:
  - A significant group difference was found.
  - Percentage of cry increased for both the analgesia and the placebo group.
  - When the Wilcoxon statistic was used, cry percentage was significant for the placebo group at the second change. When analyses were repeated with a repeated ANCOVA, a treatment effect was also noted (P=0.05).
  - At the second nappy change, crying was significantly higher for the placebo group than at the first nappy change (P=0.01).

**Cue clarity and responsiveness:**
- Neonates in the analgesia group demonstrated a smaller decrease in cue clarity and responsiveness.
- A significant group difference was also found in their mothers' behaviours (P=0.05).
- Mothers of newborns in the acetaminophen group demonstrated an increase in the score on their social and emotional growth-fostering behaviours, whereas the score for the control mothers declined.

**Infant behaviour:**
- Scores in both groups of newborns decreased from before to after the circumcision.
- Thirteen of the 22 drug group who were alert at the precircumcision feeding interaction remained alert at the postcircumcision feeding interaction, compared with only 9 of the 22 newborns in the placebo group.
- All newborns in the drug group who were not alert at the first feeding were alert at the second feeding, compared with only 2 of the 9 newborns in the placebo group (P=0.01).

**Statistical Methods Used:**
A multivariate analysis of covariance (ANCOVA) was used to test the means of the two groups on the NOAFS. A repeated ANCOVA was used to test heart rates and percentage of cry. Multiple regression analysis, including discriminate analysis, was used to analyse and differences within and between groups and assess any confounding. The Wilcoxon nonparametric test was used to test the means of heart rates and cry. The Cochran-Mantel-Haenszel statistic was used to determine whether groups differed on post-alertness, controlling for pre-alertness. Homogeneity was analysed with the chi square test used for frequency variables and t tests for continuous variables.
<table>
<thead>
<tr>
<th>Study details</th>
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</table>
| Kigozi et al., 2008, Uganda and USA. | **Aim:** to investigate the relationship between adult male circumcision and sexual satisfaction and function in men, as observational studies show conflicting results. | **Study Design:** RCT (NHMRC Level II evidence)  
**Method of Randomisation:** NR  
**Allocation Concealment:** NR  
**Blinding:** NR. Circumcision status could not be completely concealed from the interviewers. | **Sample size:** 4996 originally included  
Only the results for men who were sexually active at the time of enrolment were reported, as they could provide information on their sexual experiences before and after circumcision. Circumcision group: 2210 (89.3%). Delayed circumcision: 2246 (89.1%). | **General Findings:** Adult male circumcision does not adversely affect sexual satisfaction or clinically significant function in men. |
| | **Surgical Technique:** All circumcisions were performed using the sleeve procedure. | **Circumcision Performed By:** Medical officers | **Age:** | **Safety:** NR |
| | **Was Circumcision Confirmed:** NR | **Anaesthesia:** NR | **Losses to Follow-up:** NR | **Effectiveness:** Erectile problems: At enrolment, 0.8% of the circumcised group and 1.6% of the uncircumcised group reported erectile problems, at 2-year follow-up, 0.3% of circumcised men and 0.1% of uncircumcised men reported such problems. This change was statistically significant within the uncircumcised group (**P**<0.001), but there was no significant difference between the two groups at 2-year follow-up. Difficulties with penetration: At enrolment, 1.5% of the circumcised group and 2.1% of the uncircumcised group reported difficulties with penetration. At 2-year follow-up, 0.6% of circumcised men and 0.1% of uncircumcised men reported such problems. This change was statistically significant within both groups (**P**<0.001), but there was no significant difference between the two groups at 2-year follow-up. At 6-month follow-up, there was a statistically significant difference between the groups (**P**=0.02). Dyspareunia: At enrolment, 1.2% of both circumcised and uncircumcised groups experienced dyspareunia. At 2-year follow-up, this decreased to 0.1% for circumcised men and 0.4% for uncircumcised men. This change was statistically significant for the circumcised group (**P**<0.001), but there was no statistically significant difference between the two groups at 2-year follow-up. At 6-month follow-up, there was a statistically significant difference between the two groups (**P**=0.05). Sexual satisfaction: Uncircumcised men reported a statistically significant increase in sexual satisfaction from 98.0% at enrolment to 99.9% at the 24-month follow-up (**P**<0.001). There was no statistically significant change in sexual satisfaction in the circumcised men. The differences in self-reported sexual satisfaction between the intervention and control arms were statistically significant at 12 months (**P**<0.007) and at 24 months (**P**<0.004). | **Duration of Follow-up:** 24 months after enrolment | **Effectiveness:** Erectile problems: At enrolment, 0.8% of the circumcised group and 1.6% of the uncircumcised group reported erectile problems, at 2-year follow-up, 0.3% of circumcised men and 0.1% of uncircumcised men reported such problems. This change was statistically significant within the uncircumcised group (**P**<0.001), but there was no significant difference between the two groups at 2-year follow-up. Difficulties with penetration: At enrolment, 1.5% of the circumcised group and 2.1% of the uncircumcised group reported difficulties with penetration. At 2-year follow-up, 0.6% of circumcised men and 0.1% of uncircumcised men reported such problems. 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There was no statistically significant change in sexual satisfaction in the circumcised men. The differences in self-reported sexual satisfaction between the intervention and control arms were statistically significant at 12 months (**P**<0.007) and at 24 months (**P**<0.004). | |
| | **Postoperative Care:** Intervention group strongly advised to abstain from sexual intercourse until the wound was certified by a clinician to be fully healed. | **Losses to Follow-up:** NR | **Study Period:** NR | **Statistical Methods Used:** Tests of statistical inference were based on chi-square or the Fisher’s exact tests for proportions and chi-square for trend in analyses of changes over time. | |
| | **Comparator:** Immediate circumcision after randomisation. | **Study Period:** NR | **Screening Tools Used:** NR | | |
| | **Exclusion Criteria:** NR. All included males were uncircumcised, HIV negative men aged between 15–49 years. | | **Inclusion Criteria:** NR | | |
| | **Potential Confounders Reported:** NR | | | | |
| | **Sample size:** 4996 originally included  
Only the results for men who were sexually active at the time of enrolment were reported, as they could provide information on their sexual experiences before and after circumcision. Circumcision group: 2210 (89.3%). Delayed circumcision: 2246 (89.1%). | | | | |
| | **Age:** | | | | |
| | 15–19 | 21.0% | 21.7% |
| | 20–24 | 29.1% | 28.9% |
| | 25–29 | 19.6% | 20.1% |
| | 30–49 | 30.2% | 28.6% |
| | **Comorbidities:** NR | | | | |
| | **Ethnicity/race:** Ugandan. | | | | |
| | **Surgical Setting:** Fully equipped outpatient theatres located in a central facility. | | | | |
| | **Geographical Location:** Rakai, Uganda. | | | | |
Table C2 continued: Evidence table of appraised primary studies relating to male circumcision

<table>
<thead>
<tr>
<th>Study details</th>
<th>Study design and inclusion/exclusion criteria</th>
<th>Study population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taddio et al, 1997, Canada.</strong></td>
<td><strong>Aim:</strong> the objectives of the study were to investigate prospectively whether neonatal circumcision affects infant pain response to routine vaccination 4–6 months after surgery and whether vaccination is affected by pre-treatment of neonatal circumcision pain with EMLA.</td>
<td><strong>Sample size:</strong> 87 newborns Circumcision with placebo: 26 Circumcision with Emla: 29 Non-circumcision: 32</td>
<td><strong>General Findings:</strong> circumcised infants showed a stronger pain response at subsequent vaccination compared with uncircumcised infants. The authors recommended treatment to prevent neonatal circumcision pain.</td>
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<tr>
<td><strong>Surgical Technique:</strong> the vaccination procedure was standardised across settings. Infant was physically examined before vaccination and was placed supine on the examination table. The infants received an intramuscular injection in the thigh.</td>
<td><strong>Method of Randomisation:</strong> NR</td>
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<tr>
<td><strong>Vaccination Performed By:</strong> a physician or nurse.</td>
<td><strong>Allocation Concealment:</strong> NR.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Was Circumcision Confirmed:</strong> NR</td>
<td><strong>Blinding:</strong> assessments were performed by a blinded assessor.</td>
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<tr>
<td><strong>Anaesthesia:</strong> one intervention group received EMLA for circumcision. One intervention group received placebo for circumcision.</td>
<td><strong>Duration of Follow-up:</strong> vaccinations were performed either 4 or 6 months after circumcision. Infants were assessed for up to one minute after vaccination.</td>
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<tr>
<td><strong>Postoperative Care:</strong> NR</td>
<td><strong>Losses to Follow-up:</strong> 4 (9%) uncircumcised, 1 (3%) circumcised with Emla, 3 (10%) circumcised with placebo.</td>
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<td><strong>Study Period:</strong> NR</td>
<td><strong>Study Period:</strong> NR</td>
<td></td>
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<tr>
<td><strong>Screening Tools Used:</strong> parents were sent copies of the revised infant temperament questionnaire for infants aged 4–8 months.</td>
<td><strong>Inclusion Criteria:</strong> NR</td>
<td></td>
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<tr>
<td><strong>Inclusion Criteria:</strong> NR</td>
<td><strong>Exclusion Criteria:</strong> NR</td>
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<tr>
<td><strong>Potential Confounders Reported:</strong> genetic attributes, socioeconomic status, parent-infant interactions, age, weight, temperament, ingestion of paracetamol, time of last feeding and time of last sleep before vaccination.</td>
<td><strong>Mean Age (days):</strong> Circumcision with placebo: 143 (SD 28.4) Circumcision with Emla: 140 (SD 23.7) Uncircumcised: 133 (SD 12.9)</td>
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<td></td>
</tr>
<tr>
<td><strong>Ethnicity/race:</strong> NR</td>
<td><strong>Comorbidities:</strong> NR</td>
<td></td>
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<tr>
<td><strong>Surgical Setting:</strong> vaccinations took place at 4–6 months at the clinic of the infant’s primary care physician.</td>
<td><strong>Ethnicity/race:</strong> NR</td>
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<td><strong>Geographical Location:</strong> Canada</td>
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