Circumcision and Lifetime Risk of Urinary Tract Infection: A Systematic Review and Meta-Analysis

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Abbreviations and Acronyms

UTI = urinary tract infection

VUR = vesicoureteral reflux

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Nothing to disclose.

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See Editorial on page 2022.

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Purpose: Urinary tract infection is common in infant males who are uncircumcised and can lead to renal parenchymal disease of the still growing pediatric kidney. Although the rate of urinary tract infection is highest in the first year of life, the cumulative incidence during the rest of the lifetime is under-recognized, but is expected to be nontrivial. Thus, any intervention that might prevent urinary tract infection would be expected to reduce suffering and medical costs.

Materials and Methods: We conducted a meta-analysis of 22 studies examining the single risk factor of lack of circumcision, then determined the prevalence and relative risk of urinary tract infection in different age groups (0 to 1, 1 to 16 and older than 16 years). From these data we estimated the lifetime prevalence.

Results: For age 0 to 1 year the relative risk was 9.91 (95% CI 7.49–13.1), for age 1 to 16 years RR was 6.56 (95% CI 3.26–13.2) and for older than 16 years it was 3.41-fold (95% CI 0.916–12.7) higher in uncircumcised males. We then calculated that 32.1% (95% CI 15.6–49.8) of uncircumcised males experience a urinary tract infection in their lifetime compared with 8.8% (95% CI 4.15–13.2) of circumcised males (RR 3.65, 95% CI 1.15–11.8). The number needed to treat was 4.29 (95% CI 2.20–27.2).

Conclusions: The single risk factor of lack of circumcision confers a 23.3% chance of urinary tract infection during the lifetime. This greatly exceeds the prevalence of circumcision complications (1.5%), which are mostly minor. The potential seriousness of urinary tract infection supports circumcision as a desirable preventive health intervention in infant males.

Key Words: circumcision, male; foreskin; urinary tract infections; meta-analysis; male

Urinary tract infections are common in infancy[1] and can lead to significant morbidity.[2] The younger the infant, the more likely and severe will be the UTI, and the greater the risk of sepsis and death.[3] By the age of 7 years 2% (definitely) and another 5% (probably) of boys have had at least 1 UTI.[4] Apart from severe pain and fever, the infant kidney is still growing, thus increasing susceptibility to renal injury and scarring from UTI.[5,6] This exposes half to serious, life threatening conditions later in life.[7]

Rushton and Majd found that 50% to 86% of children with febrile UTI and presumed pyelonephritis had renal parenchymal defects which persisted.[8] Others reported pyelonephritis in 34% to 70% of febrile UTI cases in the first year of life[9] and another estimate was 90%.[10] Nuclear scans in febrile infants after treatment for UTI noted scarring in 10% to 30%.[11] Acute pyelonephritis is a major cause of renal scarring[12] and the likelihood of renal scarring after acute pyelone-

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phritis is 36% to 52%.[10,13–15] The majority with renal scarring do not have VUR.[16] Moreover, recurrent UTI can occur in the absence of VUR with an incidence of 36%.[17] It is the parenchymal infection with inflammation rather than the VUR that is the prerequisite for renal scarring.[14–16] Roberts estimated that infant circumcision prevents 20,000 cases of acute pyelonephritis annually.[18] A 27-year followup study of pyelonephritis in childhood noted a 10% to 20% risk of hypertension associated with hyperreninemia and hypernatremia, consistent with renal involvement.[19] Post-infection scarring may occasionally progress to renal insufficiency and end stage renal disease. As a result, measures that can be put in place to prevent UTI would seem worthy of consideration.

The first evidence that infant male circumcision might protect against UTI emerged in the early 1980s,[20] although the association had been suspected since 1972.[21] The studies that followed, involving a variety of designs including a small randomized controlled trial,[22] attested to the protection afforded by circumcision against UTI in infancy. The Pediatric Research in Office Settings Febrile Infant Study of 219 United States practices found that being uncircumcised was the strongest multivariate predictor of UTI (OR 11.6, 95% CI 5.9–22.6).[23] Among boys with UTI one study demonstrated that 19% experienced recurrent UTIs if not circumcised compared with zero for the circumcised.[24] In another study recurrent UTI was seen in 34% of those with nonretractile foreskins compared with 18% of those whose foreskin could be retracted.[17] Acute pyelonephritis increased the likelihood of recurrent UTI by 4.6,[17] nonretractile foreskin and acute pyelonephritis being the greatest risk factors for recurrent UTI. In premature uncircumcised boys whose risk of UTI was increased elevenfold, Cason et al found that circumcision eliminated the risk of recurrence.[25]

Previously published meta-analyses have noted a consistent protective effect of circumcision against UTIs of approximately tenfold.[26–28] Most studies have been of infants, with only a few examining the prevalence of UTIs in children. Studies in men are scarce.[29] To our knowledge an estimate of the prevalence of UTI by circumcision status during the entire lifetime has never been done. This deficit poses particular difficulties for evidence-based decision making. Authors attempting to weigh risks vs benefits have tended to use the cumulative incidence in infancy as an approximation of the lifetime risk. Typical estimates of the risk of UTI among uncircumcised males have been 1% to 2%,[27] 1.4% to 1.6%[30] and 2.5%.[31] Although the risk of UTI in males is greatest during the first month of life,[32] the risk after infancy is not zero and, therefore, such analyses would inevitably have underestimated the absolute risk reduction attributable to circumcision. Moreover, not only is the prevalence of UTI highest in infancy, but it is a much more severe and generalized disease at this age, with fever the predominant sign due to pyelonephritis.

Therefore, we generated estimates of the protective effect of circumcision against UTI during the lifetime of a male. We devised a strategy to 1) generate best estimates of the relative risk among uncircumcised males through a meta-analysis of published data, and 2) use these figures, in addition to estimates of lifetime risk and circumcision rates for populations in which these were known, to generate projected risk of UTI by circumcision status.

MATERIALS AND METHODS

The inclusion criteria for our meta-analysis were publication in a peer reviewed journal, publication before September 9, 2011, the presence of an adjusted RR or odds ratio or sufficient data to allow the calculation of crude or adjusted RR or OR for UTI by circumcision status. Articles were identified by searching the PubMed® database and by hand searching the bibliographies of published reports, including those of previously published meta-analyses. We searched for articles matching 1 or more of the keywords circumcision, circumcised or uncircumcised plus 1 or more of the keywords UTI, urinary tract infection or bacteriuria. The abstracts of papers were used to judge whether they met our inclusion criteria (for convenience, the "Limits" facility was used to exclude articles without abstracts).[33] We retrieved the full text of every article except when this was not possible or it was in a language other than English. Previously published meta-analyses and systematic reviews of circumcision and UTIs were examined in full. No attempt was made to contact authors to identify additional studies they might have performed or of which they might have been aware.

We performed random effects inverse variance meta-analyses using the natural logarithm of the OR as the effect size. Adjusted measures were considered more reliable than crude effect estimates since they partially controlled for confounding factors and, therefore, were used in our analysis where available. Otherwise we calculated the appropriate crude measure and CI from published frequencies. When frequencies of zero were shown we added 0.5 to the relevant cell. For one study we estimated RR using the quotient of published means and standard error of the mean for UTI incidence.[34] When data in 1 report represented a subset of data reported in another, we used the most complete report.

To assess the impact of age we created 3 binary valued variables representing participant age, namely 0 to 1 year, 1 to 16 years and 16+ years. These particular boundaries were chosen largely for convenient analysis rather than for any biological reason. When studies presented data for current UTI and history of UTI, we preferred the former as this facilitated classification of participant age. The age ranges for some studies included 2 of these categories, meaning that age groups were poorly isolated.

We estimated lifetime risk by circumcision status using meta-regression results for the 3 previously mentioned age groups. This analysis provided RR estimates by age groups, which were then used as inputs in the model described. For the first age group (subjects age 0 to 1 year) we obtained incidence by circumcision status through meta-analysis of the 4 cohort studies following infants during this period.[26,35–37] A random effects inverse variance model was used, using the logit function for normal approximation of rate data. Data for later groups were

Table 1. *Characteristics of studies included in analysis*

References	Location	Design	Population Age Range	UTI Definition	Circumcision Classification
Wiswell et al[36]	USA Army hospitals	Cohort 1975–1984	Birth-1 yr	Not stated (92% of cultures suprapubic)	Birth records
Herzog[41]	Boston Children's Hospital	Case-control 1985–1986	Birth-1 yr	10^5 cfu/ml or Greater	Medical records letter to parents
Kashani and Taradag[51]	UCSD Medical Center	Case-control 1980–1985	1 Mo-2 yrs	10^5 cfu/ml or Greater (catheter or suprapubic aspiration)	Medical records
Crain and Gershel[42]	New York	Case-control 1982–1987	Younger than 8 wks	10^4 cfu/ml or Greater (bag/catheter), greater than 10^2 (suprapubic)	Medical records
Rushton and Majd[5]	Washington, DC	Case-control 1987–1988	2 Wks–6 mos	10^5 cfu/ml or Greater (clean catch), greater than 10^4 (catheterized)	Medical records (prospectively for circumcised)
Spach et al[29]	Seattle, WA	Case-control (sexually transmitted disease clinic urine culture)	Adult (median age pts 30, controls 32)	10^5 cfu/ml or Greater mid stream plus 1 or more symptoms	Examination
Wiswell and Hachey[26]	USA Army hospitals	Cohort 1985–1990	Birth-1 yr	Not stated	Birth records
Craig et al[43]	Sydney, Australia	Case-control 1993–1994	Birth-4 yrs	10^5 or Greater (suprapubic or catheter), greater than 10^8 (midstream urine)	Parents or examination
Kim[44]	Seoul, Korea	Case-control	Younger than 15 yrs	10^5 cfu/ml or Greater	Examination
Shaw et al[45]	Philadelphia, PA	Case-control 1995–1996 (1 yr)	1 yr or younger (84% African-American)	10^5 cfu/ml or Greater (sterile urethral catheterization)	Not stated
To et al[35]	Ontario, Canada	Cohort 1993 (fiscal yr)	Birth-3 yrs	ICD-9 codes 590, 595, 597, 599	Canadian Classification Code 76.0 (in 1st month)
Herndon et al[46]	USA, 3 sites	Case-control 1993–1998	"Boys"	Society for Fetal Urology data sheets	Society for Fetal Urology data sheets
Schoen et al[37]	Kaiser Hospitals, CA	Retrospective cohort 1996–1997	Birth-1 yr	ICD-9 coding or outpatient clinic record	ICD-9 coding
Nayir[22]	Istanbul, Turkey	Randomized controlled trial	3 Mos-10 yrs who had UTI	10^5 cfu/ml or Greater + symptoms	Performed as part of trial
Newman et al[23]	USA, 219 sites	Case-control 1995–1998	Birth-98 days	10^2 cfu/ml or Greater (suprapubic), 2×10^4 or greater (catheter), 10^5 or greater (bag, clean voided)	Not stated
Kwak et al[47]	Seoul, Korea	Cohort 1985–1993	4.2–174 Mos	10^5 cfu/ml or Greater	Performed during study
Zorc et al[48]	USA, 8 sites	Cross-sectional	60 Days or younger	10^3 cfu/ml or Greater (suprapubic), 5×10^4 or greater (catheter), 10^5 or greater (catheter) + pos urinalysis)	Examination
Ghaemi et al[49]	Isfahan, Iran	Case-control July 2001–February 2002	Neonates (mean age 10.8 days)	Any cfu in suprapubic specimen, or 10^4 or greater in clean voided specimen	Examination
Mukherjee et al[34]	Birmingham Children's Hospital, UK	Retrospective cross-sectional case-note review	1–18 Yrs (mean age 6.7)	Proven pure bacterial culture (organisms tabulated)	Not stated
Roth et al[50]	Children's Hospital of Oklahoma	Retrospective analysis	1–11 Mos (mean age 6.1)	Pos urine culture	Not stated
Alsaywid et al[52]	Children's Hospital Westmead, Sydney	Prospective cohort study 1995–2006	1 Day–8.8 yrs	Urine culture, organisms identified	Performed during study
Simforoosh et al[53]	Tehran, Iran	Prospective cohort study 2004–2008	Neonatal followed for 15 mos	10^5 cfu/ml or Greater if pos or equivocal rechecked by suprapubic catheter	Performed neonatally as part of study

derived from published figures for cumulative incidence to age 16 years and during a lifetime.[38–40] To combine these figures it was necessary to first adjust them for hypothetical populations with standardized circumcision rates. We did this by creating a simple mathematical model using the formula, p = Cc + (1-C)Rc, where p is the overall risk for a population, C the proportion of circumcised males, R is the relative risk for uncircumcised vs circumcised males and c is the risk among circumcised males. We were then able to estimate risk by circumcision status for each age group using the same model. The sum of these figures was used as an estimate of lifetime risk. Monte Carlo simulations (using 10,000 samples) were used to find 95% CIs.

All statistical analyses were performed using the R statistical language and environment version 2.14.1 (http://www.r-project.org/). The metafor package (version 1.6–0) was used to perform meta-analyses and meta-regressions.

RESULTS

Our PubMed search resulted in 163 articles. Most were reviews or opinion pieces but 19 met the inclusion criteria.[5,22,23,26,29,34–37,41–50] Another article was identified by a review of bibliographies[51] and 2 further articles were identified from the authors' libraries.[52,53] Table 1 shows the characteristics of the studies included in the analysis.

Table 2 shows the frequencies of UTIs in circumcised and uncircumcised boys, together with RR, ARR or OR as reported in each study. The figure is a forest plot of these data as ORs. An analysis by different age groups indicated that for ages 0 to 1 year, RR of UTI was 9.91-fold (95% CI 7.49–13.1) higher for uncircumcised boys, for age 1 to 16 years the RR of UTI was 6.56-fold higher (95% CI 3.26–13.2) and for males older than 16 years the RR was 3.41-fold higher (95% CI 0.916–12.7, table 3). We then used these data to estimate risk during the entire lifetime according to circumcision status, finding RR to be 3.65 (95% CI 1.15–11.8) higher for uncircumcised (32.1%, 95% CI 15.6–49.8) vs circumcised males (8.8%, 95% CI 4.15–13.2). The difference, 23.2 (ie 32.1 minus 8.8), represents the percentage of UTIs during the lifetime attributable to the single risk factor of lack of circumcision. From our data we calculated that the number needed to treat was 4.29 (95% CI 2.20–27.2).

DISCUSSION

Our analysis shows that during the entire lifetime the adjusted risk of UTI is 3.7 times higher in uncircumcised vs circumcised males. Infant males had a 9.9 times higher risk of UTI if uncircumcised. This decreased to 6.6-fold for age 1 to 16 years and 3.4-fold beyond age 16 years. Lifetime UTI risk was 32% in uncircumcised males and 8.8% in circumcised males.

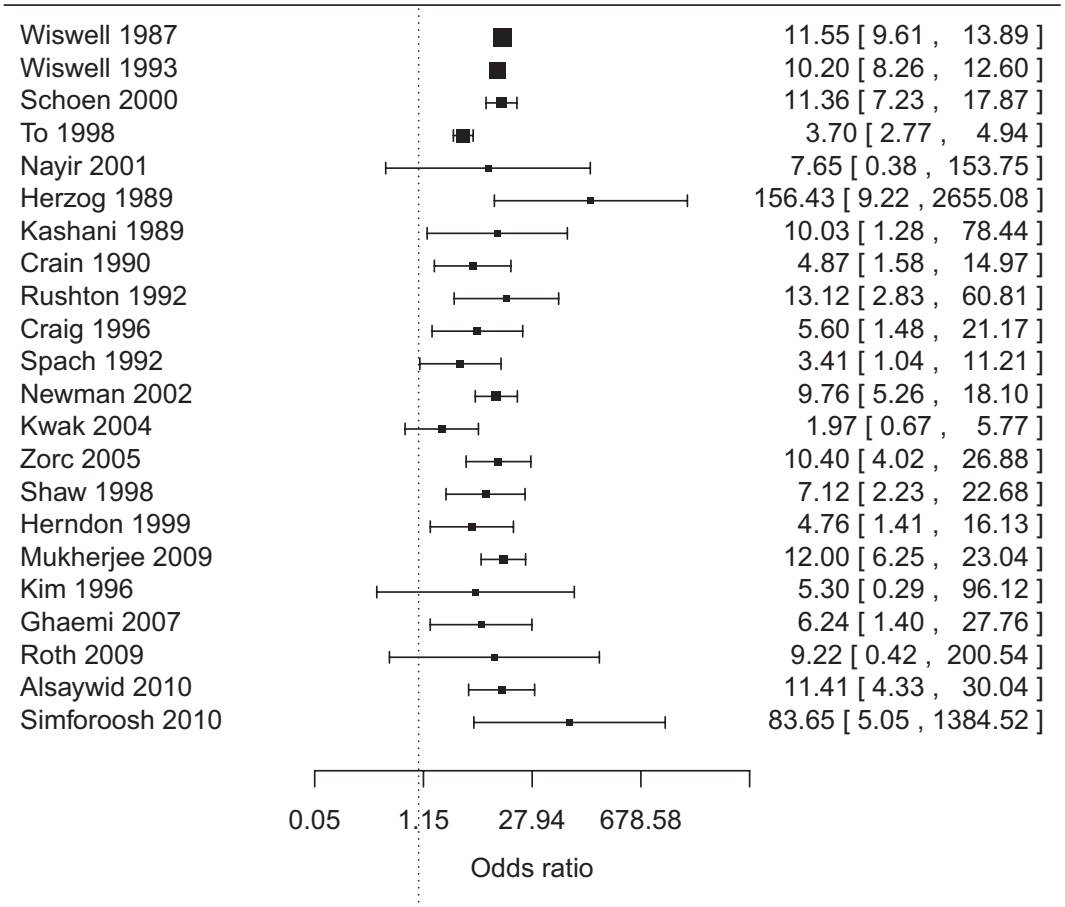
Previous meta-analyses found risk of UTIs in uncircumcised boys to be twelvefold (95% CI 11–14, range 5 to 89-fold)[26] and eightfold (95% CI 5–13)[27] greater than in circumcised boys. UTI is especially

Table 2. *The included studies showing frequency of UTI*

References	No./Total No. Circumcised	No./Total No. Uncircumcised	AOR,[a] ARR,[b] OR[c]*	Notes*
Wiswell et al[36]	151/173,663	459/46,112	11.4 (9.53–13.8)	e h i j
Herzog[41]	0/52	36/60	156 (9.22–26.60)	c d e h i j
Kashani and Faraday[51]	1/43	16/83	10 (1.28–78.4)	c e f h i
Crain and Gershel[42]	4/96	18/103	4.87 (1.58–15)	c e h i
Rushton and Majd[5]	2/37	21/49	13.1 (2.83–60.8)	c e h i
Spach et al[29]	18/64	8/14	3.41 (1.04–11.2)	c g h i
Wiswell and Hachey[26]	112/80,279	384/27,319	10.1 (8.17–12.4)	e h i j
Craig et al[43]	2/49	142/837	5.6 (1.4–20)	a e f h i
Kim[44]	0/19	8/70	5.3 (0.293–96.1)	c d e f i
Shaw et al[45]	6/497	6/75	7.12 (2.23–22.7)	c e i
To et al[35]	55/29,217	205/29,217	3.7 (2.8–5)	b e f h i
Herndon et al[46]	7/37	10/19	4.76 (1.41–16.1)	c e i
Schoen et al[37]	22/9,668	132/5,225	11.1 (7.08–17.4)	e h i j
Nayir[22]	0/35	3/35	7 (0.375–131)	d e f i
Newman et al[23]	15/572	41/197	9.76 (5.26–18.1)	c e i
Kwak et al[47]	6/27	18/50	1.97 (0.672–5.77)	c f i
Zorc et al[48]	6/262	62/291	10.4 (4.7–31.4)	a e i
Ghaemi et al[49]	2/105	16/148	6.24 (1.4–27.8)	c e i
Mukherjee et al[34]	–/Not available	–/Not available	12 (6.4–23.6)	a f i
Roth et al[50]	0/41	2/24	9.22 (0.424–201)	c d e i
Alsaywid et al[52]	5/74	62/137	11.4 (4.33–30)	c e f i
Simforoosh et al[53]	0/2,000	20/1,000	83.7 (5.05–1,380)	c d e f h i

The studies are listed in chronological order.

* a, adjusted odds ratio. b, adjusted relative risk. c, odds ratio. d, small sample correction. e, infant. f, child. g, adult. i, systematic search. j, USA. When a, b or c does not appear, the study did not report one of these.



Forest plot showing odds ratios derived from studies included in meta-analysis. Mean is shown as square symbol and as first number in column on right. Horizontal bars and numbers in brackets depict 95% CIs.

common in uncircumcised boys with underlying urinary tract abnormalities.[34,54] The conservative recommendation by Singh-Grewal et al[27] that circumcision should only be recommended in boys with recurrent UTI or VUR is flawed.[3] Moreover, it ignores other disorders that circumcision protects against.[55,56] Although the overall UTI rate of 1.1% was stated in that particular meta-analysis,[27] the cumulative incidence was 2.2% by age 2 years in a Swedish study,[57] 6% in uncircumcised and 1% (sample size of 2) in circumcised boys younger than 5 years old in Western Sydney,[43] and 3.6% to age 16 years in a United Kingdom study.[38]

There were 3 major limitations of our analysis. 1) Inclusion of circumcision (and related terms) as keywords may have introduced bias since authors might have been more likely to mention circumcision in the abstracts of papers in which associations were found. However, if we had searched by UTI and related terms and had not included circumcision and related terms, our search would have returned approximately 47,000 articles. Scrutiny of all of these was unrealistic. 2) Bag specimens or clean catch urine samples were used in several studies. The organisms identified in these samples were typically pure cultures of known pathogens in great quantities (cfu/ml).

Table 3. *UTI risk estimates for circumcised and uncircumcised males of different age groups*

Age Group (yrs)	RR (95% CI)	% Circumcised Risk (95% CI)	% Uncircumcised Risk (95% CI)
0–1	9.91 (7.49–13.1)	0.127 (0.072–0.223)	1.26 (0.737–2.14)
1–16	6.56 (3.26–13.2)	0.409 (0.221–0.704)	2.68 (1.67–4.13)
16+	3.41 (0.916–12.7)	8.26 (3.61–12.7)	28.2 (11.6–45.7)
Lifetime	3.65 (1.15–11.8)	8.8 (4.15–13.2)	32.1 (15.6–49.8)

Does not include results for meta-regression and stratified meta-analysis models, nor an analysis of various subsets such as studies of a general population vs those with VUR.

However, the findings were similar to those of studies in which the majority of samples were obtained by suprapubic aspiration or bladder catheterization. 3) In our estimates of lifetime risk we relied on combining risk data from dissimilar populations. While we adjusted for different circumcision rates, it is likely that other differences among countries limited the accuracy of such calculations. Cumulative rates from a British study were for specialist referrals[38] and, thus, may have underestimated the true risk since many UTIs may be treated by a general practitioner. There are relatively few studies of UTI incidence in males, and most focus on infancy and early childhood. A 1974 study reported a minimum risk of 1.1% by age 11 years,[58] but more recent studies reported 2.2% by age 2,[57] 1.9% by age 5[59] and 1.8% by age 6 years.[60] Lifetime prevalence data in a nationally representative American sample relied on self-reported history of UTI diagnosis.[39,40] These might underestimate or overestimate the true rate of UTI. Although our lifetime risk estimates were based on the best available data, they remain projections based on mathematical models.

A previous meta-analysis noted significant differences among studies,[27] primarily from 1 large cohort study. That study was notable for its long followup period (to 3 years). RR among uncircumcised males was greatest in infancy, decreasing from 4.5 in the first month to 3.0 during the first 3 years.[35] A comparable association with age was reported in one[37] but not in another[43] cohort study. Phimosis may be a risk factor for UTI,[17,61–64] supporting the view that pathogenesis involves pathogens ascending from the preputial sac.[65–67] Retractability of the foreskin is low among newborns but common in adolescence.[68] Although the prevention of phimosis has been invoked in explaining the protective effect of circumcision, a recent Canadian study found a similar UTI prevalence in uncircumcised boys with a completely, partially or nonvisible urethral meatus.[69]

The circumcision rate is 71% for United States men born in the 1940s and 78% for those born in the 1980s.[70] However, we did not break down UTI risk in adulthood by age. We believe that further age adjustments would have introduced an excess of complexity into the analysis without a sufficient increase in accuracy.

Our ability to fully explore the influence of age was limited by the fact that some studies included wide age ranges. Future studies of UTI and circumcision in populations with wide age ranges, particularly when younger children are included, should be careful to stratify by age.

Our analysis is the first to estimate the lifetime prevalence of UTI by circumcision status and, thus, may represent the most realistic estimate of the number needed to treat to date. A previous systematic review compared the risk of complications from circumcision with the absolute reduction in UTI risk during the first year of life.[27] Since circumcision must be performed once but its benefits last for a lifetime, complications should be compared with the sum of all benefits and not just a reduction in UTI. When data for UTIs are combined with data on protection against balanoposthitis, phimosis, paraphimosis, various sexually transmitted infections, penile cancer, and other conditions and infections, the benefits were found to exceed the risks by more than 100 to 1.[56,71]

CONCLUSIONS

The present meta-analysis is the first to estimate the lifetime risk of UTI in circumcised and uncircumcised males. Our finding that the single risk factor of lack of circumcision accounts for 23% of UTIs during the lifetime of males compares favorably with the 1.5% complication rate associated with infant circumcision in a meta-analysis.[72] While most complications are minor, UTIs can be associated with long-term morbidity and potential mortality.[1] By protecting against UTIs the cost savings are considerable.[73] Prevention of UTIs in infancy was emphasized in the 2012 American Academy of Pediatrics policy recommendations.[55] Coupled with other lifetime benefits, the circumcision of all infant males would seem desirable. Newborn circumcision is as protective against UTIs as are many vaccines given to children to prevent other infections and diseases.[37] For example, the level of protection deemed acceptable against influenza vaccines[74,75] justifies claims that infant male circumcision be regarded as a surgical vaccine.[71,76,77]

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