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Effect of confounding in the association between circumcision status and urinary tract infection

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Summary *Objectives*. To estimate the impact of confounding in the association between circumcision status and urinary tract infection from epidemiological factors, sample collection, and health-seeking behaviors in the first year of life.

Methods. Beginning with the assumption that true urinary tract infection occurred equally regardless of circumcision status, a Markov model incorporating the differences in the rates of prematurity, of urine collection, of false positive urine specimens, and of health-seeking behaviors in infant boys based on circumcision status was developed. Using this model, the rates of false-positive urine cultures, asymptomatic bacteriuria, and true urinary tract infection detected in the first year of life were estimated and contrasted. Error of the model was estimated using Monte Carlo simulations.

Results. Keeping the incidence of true urinary tract infection constant between groups, the factors included in the model could account for urinary tract infection being diagnosed 4.27 times more frequently in non-circumcised males under a year of age.

Conclusions. Previously reported differences in the rate of urinary tract infection by circumcision status could be entirely due to sampling and selection bias. Until clinical studies adequately control for sources of bias, circumcision should not be recommended as a preventive for urinary tract infection.

Introduction

Since the publication of a brief report in 1985 implicating the foreskin of infants as a risk factor for urinary tract infection,[1] much of the American medical community has adopted the premise that circumcision has a role in preventing urinary tract infection in boys in the first year of life. These early studies, based on a database of discharge diagnoses, failed to control for a number of confounding factors. Subsequent studies, which have provided less dramatic findings, have, for the most part, also failed to control for known confounding variables. This study will incorporate these confounding variables into a theoretical model to determine

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their potential impact on the frequency of the diagnosis of urinary tract infection in boys less than a year of age, and to determine whether these variables can explain the difference in urinary tract infection incidence noted between circumcised and intact boys as reported in observational studies.

Methods

To assess the impact of confounding factors, it was necessary to begin with the assumption that true urinary tract infection occurred at the same frequency regardless of circumcision status. A decision tree was developed, using a Markov model that cycled monthly, to assess the impact of confounding factors on urinary tract infection incidence for boys in the first year of life. A decision tree allows the calculation of overall risk based on the probabilities of each set of circumstances and the risk associated with each circumstance. Overall risk becomes the sum of the risk of each circumstance multiplied by the probability of that circumstance. Since the probability of circumstances affecting urinary tract infection risk differs based on circumcision status, the difference in risk based on circumcision status can be estimated using a decision tree. A Markov model allows you to use the decision tree repeatedly and to adjust the variables that may change with time. In this model, the decision tree is used 12 times, once for each month of the first year of life. In the first month, the risks associated with neonates, both those born at and before term, are used to determine the overall risk of detecting a urinary tract infection, an episode of asymptomatic bacteriuria, or a false positive urine culture result. For the second and subsequent months, the risk of these events is estimated based on whether an infant was born at or before term and the other factors associated with detection of a urinary tract infection. After running the decision tree twelve times, the total number of events is tabulated and the relative risk, based on circumcision status, is determined.

The variables, their values, and their ranges as incorporated into the model are listed in Table 1.

Model assumptions were made based on the medical literature.

Prematurity. In the database of hospitalizations from US Army Hospitals worldwide, one-third of boys who were not circumcised at birth because they were too sick to undergo the procedure.[2]

Table 1 Values for the variables used in the model to explain the difference in the urinary tract infection rates

Variable	Baseline	Range
Probabilities		
Of febrile illness each month	0.20	0.1-0.30
Urinalysis in non-circumcised	0.20	0-0.40
Of non-circumcised being preterm	0.33	0.15-0.4
Urinalysis by bag specimen	0.80	0-0.85
Of urinary tract infection	0.10	0.04-0.15
Positive culture in bag specimen for non-circumcised	0.17	0.10-0.35
Suprapubic aspirate following bag specimen	0.05	0-0.20
Catheter specimen following bag specimen	0.05	0-0.20
False positive culture in term infant	0.05	0.02-0.10
False positive culture in catheter specimen	0.07	0-0.1
Neonatal urinary tract infection in term infant	0.01	0-0.04
Urinalysis by catheter specimen	0.15	0-0.2
False positive culture in preterm infant	0.1	0-0.2
Neonatal urinary tract infection in preterm infant	0.04	0.01-0.08
Asymptomatic bacteriuria	0.025	0.01-0.05
False positive culture from suprapubic aspiration	0.001	0-0.02
Urinalysis performed in circumcised	0.05	0-0.20
Positive culture from bag specimen in circumcised	0.05	0.01-0.07
Urinary tract infection in positive bag specimen	0.25	0.2-0.5
Circumcised preterm neonates	0.001	0-0.1
Multipliers		
Health seeking behavior of non-circumcised	1.25	0.5-2.5
Health seeking behavior of former preterm infants	1.25	0.5-2.5
Risk of former preterm infants for urinary tract infection	1.80	1-4
Risk of asymptomatic bacteriuria in neonatal period	1	0.5-2

Preterm infants have a higher risk of urinary tract infection than term babies, both in the initial neonatal period and through the first year of life.[3,4] One study found the preterm infants to be nearly nine times more likely to develop a urinary tract infection after discharge from the hospital than term infants (OR = 8.93, 95%CI = 2.13-37.48).[4] It is also well established the preterm infants are more susceptible to the "vulnerable child syndrome" and more likely to brought for consultation for minor complaints.

Urine collection. The reliability and accuracy of urine cultures depends heavily on the method of urine collection. A suprapubic aspiration is the most accurate collection, but the least used. Catheterized specimens are slightly less accurate. The most commonly used method to collect urine is in a bag. The accuracy of this method differs with circumcision status, with this method being more accurate in circumcised infants.[5]

Health-seeking behavior. Infants that are born prematurely are more likely to seek medical care for minor medical problems. This behavior has also been documented in Hispanic infants,[6] who are also much more likely to be non-circumcised. Since a third of non-circumcised boys in some American populations were preterm and Hispanic boys make up a sizable portion of non-circumcised American boys, non-circumcised boys on average will be more likely to seek medical care for minor medical problems than circumcised boys.

Collection rate. Because it is commonly believed that non-circumcised male infants are more likely to have urinary tract infection, it has resulted in non-circumcised boys being tested for urinary tract infection more commonly. This was seen in a prospective study (OR = 1.32, 95%CI = 1.04-1.68) in which urine sampling was to have taken place in all subjects.[7] This difference, as our model assumptions shows, would be expected to be greater outside of a study setting in which urine specimens were encouraged on all presenting febrile infants.

Collection method. Despite repeated calls to abandon the use of bagged specimens, this method is still the most widely used. The baseline assumption was a high rate of bagged specimens, but the certainty of the assumption should be offset by the wide confidence interval used. The positive culture rate from a bagged specimen (17%) is consistent with that reported by Schlager et. al.[5] and Nelson and Peters.[8] A review of the rates and accuracy of different urine collections methods is shown in Tables A1 and A2. The rates of confirmatory urine collection and the collection methods used has not been reported in the medical literature. Estimates of these behaviors with wide confidence intervals were made on a best guess basis after discussion with colleagues.

Febrile illnesses. The average infant has three febrile illnesses in the first year of life.

Sources of a positive urine culture. (1) False positive culture. (2) Asymptomatic bacteriuria with fever from another source. (3) Urinary tract infection. Any of these can be interpreted as being a urinary tract infection. The model estimated the rate at which each of these would be detected.

Rate of urinary tract infection. The rate of urinary tract infection in term infants was held constant throughout the model, regardless of circumcision status. The model is designed to measure any differences in urinary tract infection detection rates. The rate of 10% for a febrile infants was taken from Shaw et al. [9] and reflects other studies in the medical literature (Table A3).

Rate of asymptomatic bacteriuria. The estimate of 2.5% is based on the extensive study by Wettergren et al.[10] and consistent with other reports in the medical literature (Table A2).

Sensitivity analysis was performed on each of the variables within their likely ranges to determine the impact of the variable on the overall outcome of the model. A comparison of the relative impact of the variables over their range of values on the overall outcome of the model was made using a tornado diagram. In a tornado diagram, the most influential variables are stacked atop the less influential variables giving the diagram the appearance of a tornado. Two-way sensitivity analysis was also performed on the most influential variables. In this analysis the values of two variables are varied over their respective ranges to determine the impact on the outcome of the model depending on the combination of values of the two variables.

A Monte Carlo simulation with 1000 samples was performed using the expected ranges of six influential variables. In each simulation, a value for each variable is chosen from its range following its likelihood distribution. The model is run using these variable values. The simulation is run 1000 times choosing new variable values each time. The model outcome (relative risk) for each simulation is converted to its natural logarithm. The average and standard deviation of the logarithm is determined and 95% confidence intervals calculated, providing a confidence interval for the model.

Results

The model predicted the incidence of detected false-positive urine cultures would be 5.4% in circumcised infants and 13.4% in non-circumcised infants (relative risk (RR) = 2.47). For detected asymptomatic bacteriuria the incidence would be 1.07% for circumcised boys and 2.50% for non-circumcised boys (RR = 2.33). For detected urinary tract infection the incidence would be 1.34% for circumcised boys and 5.72% in non-circumcised boys (RR = 4.27). If the numbers for urinary tract infection and asymptomatic bacteriuria are combined the relative risk is 3.41, and 2.76 if all positive urine cultures are combined.

The results of the sensitivity analysis are depicted in a tornado diagram (Fig. 1). The model was most sensitive to the frequency of febrile illness, the frequency in which urine specimens were collected in non-circumcised infants, the health-seeking behavior of non-circumcised boys, the rate of positive culture in bagged specimens in non-circumcised boys, and rate at which bagged urine specimens with positive urine cultures were confirmed by suprapubic aspiration. More frequent diagnosis of urinary tract infection in non-circumcised infants dominated the analysis. Equal diagnostic rates of urinary tract infection could not be demonstrated in one-way sensitivity for any of the variables. Using two-way sensitivity, equal diagnostic rates could only be demonstrated the urinalysis was sampled more than 15 times more frequently in circumcised boys than non-circumcised boys (Fig. 2).

Using a Monte Carlo simulation with 1000 samples the relative risk for diagnosing a true urinary tract infection in an non-circumcised boy was 3.95 (95%CI = 2.59–6.04), for detecting asymptomatic bacteriuria the relative risk was 2.29 (95%CI = 2.02–2.60).

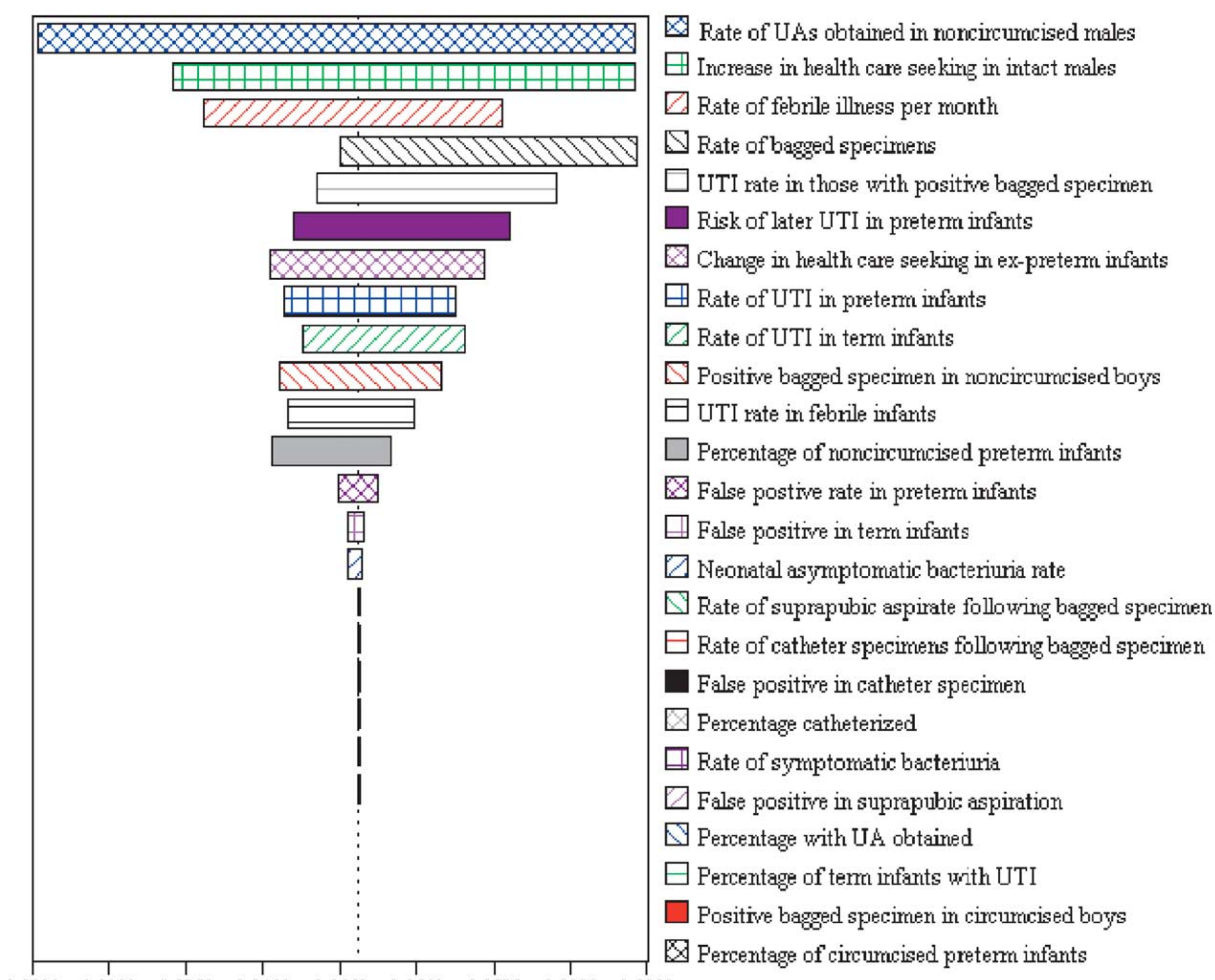

Figure 1 Tornado diagram of the variables used in a model to assess the impact of confounding on the ability to diagnose urinary tract infection in boys based on circumcision status.

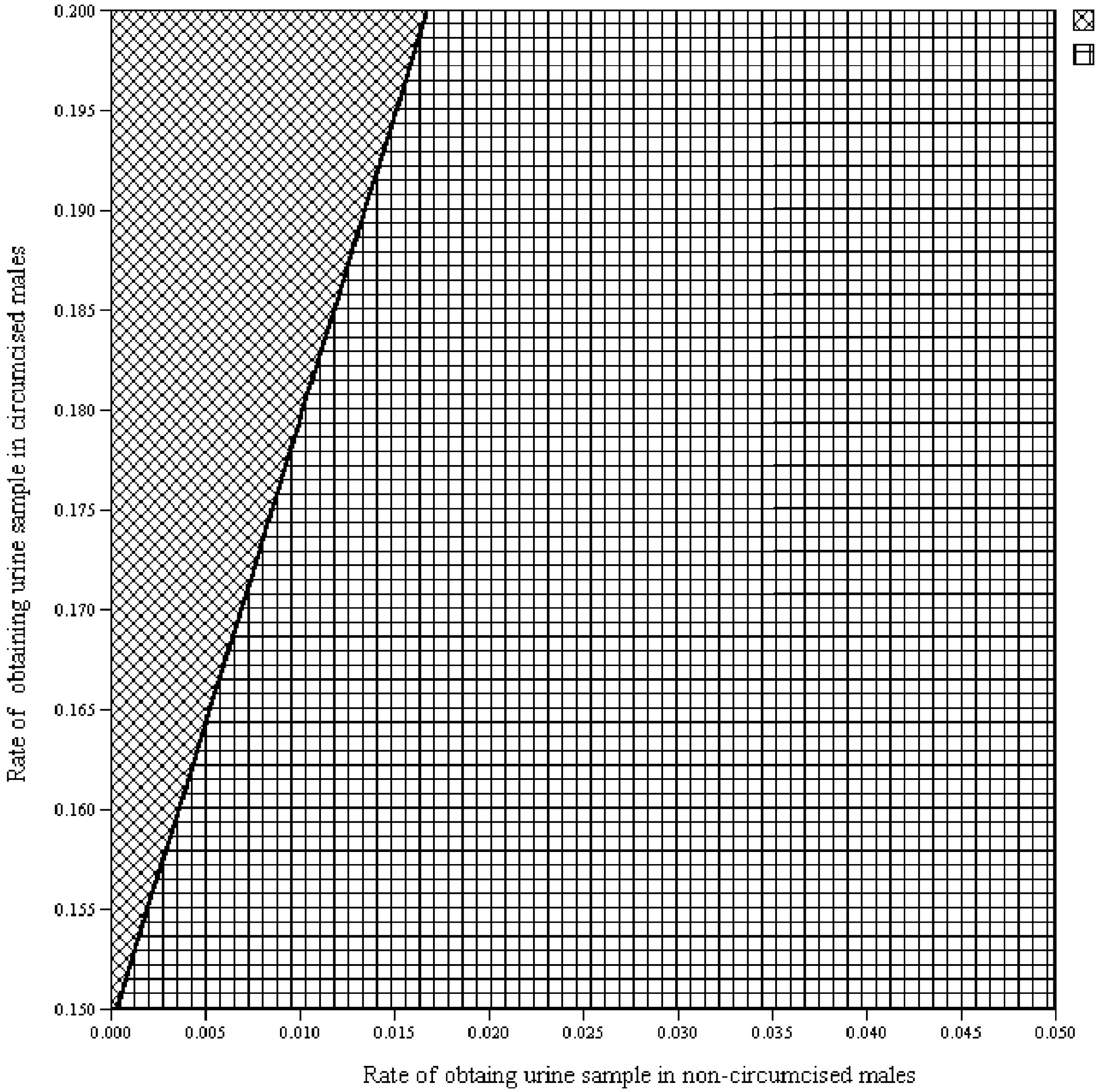

Figure 2 Two-way sensitivity analysis of the rate at which urine is sampled in circumcised males compared and the rate at which urine is sampled in non-circumcised males. Circumcised males are more likely to be diagnosed with a urinary tract infection in the situations represented by the diagonal cross-hatched pattern, while the cross-hatched area represents the situations where a urinary tract infection is more likely to be diagnosed in non-circumcised males.

Discussion

This model indicates that non-circumcised infants boys are four times more likely to be diagnosed with urinary tract infection and circumcised infant boys, despite the assumption of identical rates of true urinary tract infection. Sensitivity analysis and Monte Carlo simulation confirmed that the over-diagnosis of urinary tract infection in the non-circumcised is within the variation of the variables and the model. The ranges for the variables were purposely wide. Despite this, the underlying assumption of no difference in the rate of urinary tract infection based on circumcision status was nearly impossible to detect. It was only in the highly unlikely situation of circumcised boys having their urine sampled at 15 times or greater the sampling rate of intact boys that the true neutral risk would be determined. The model clearly demonstrated that factors other than the rate of urinary tract infection may be responsible for differences seen in diagnostic rates.

Several confounding factors affecting the incidence of urinary tract infection in the first year of life have been well-documented in the medical literature. These include prematurity, low birth weight,[3,11,12] perinatal anoxia,[13] lack of breast-feeding,[14,15] low parental education and social status,[16] poor hygienic practices,[17] race,[9] prenatal maternal urinary tract infection,[18] maternal fever at the time of delivery, history of urinary tract infection in a first-degree relative, previous bacterial or viral infection, previous course of antibiotics,[15] rooming-in,[19] the method of urine collection, the diagnostic standard employed, and health-seeking behavior.[20]

Of these potential confounders, this model focused on those for which a clear differential effect has been demonstrated between circumcised and non-circumcised infants. The effects of the other confounders may be differential by circumcision status, but further research is needed to demonstrate this.

This model is based on 10% of infants with a febrile illness having a urinary tract infection and thus generated more children diagnosed with urinary tract infection and bacteriuria than is generally seen in clinical practice. Most instances of urinary tract infection and bacteriuria in the first year of life are not identified. Surprisingly, this rate of febrile infants with urinary tract infection had less impact on the model than ten other variables.

This model did not attempt to estimate the effect of differential classification bias, although this may be a substantial source of bias in large studies reliant on databases for information. For example, if the US Army hospital data from 1974 to 1983[21] is adjusted for potential differential misclassification, such as the 15.7% of circumcised boys who were not identified as such on hospital face sheets,[22] the odds ratio drops from 10.27 to 4.13 (95%CI = 3.34-5.11). When the US Army hospital data from 1984 to 1988[23] is adjusted, the odds ratio drops from 9.43 to 4.07 (95%CI = 3.28-5.05).

Appendix A

Table A1 Accuracy of diagnosing urinary tract infection using different specimen gathering techniques

Author	Gender[a]	Ages[b]	Method[c]	TP[d]	FP[d]	FN[d]	TN[d]	Sens[d]	Spec[d]	PPV[d]	NPV[d]
Kunin[24]	F	5-18	CC	15	188	0	1207	1.00	0.87	0.07	1.00
Kunin	M	5-18	CC	0	15	0	1632	NA	0.99	0.00	1.00
Kunin	F	5-18	CC	58	304	0	4770	1.00	0.94	0.16	1.00
Schlager[25]	M	<3 yr	Bag	0	16	0	74	0.00	0.82	0.00	1.00
Saez-Llorens[26]	M	2-15	NCC	2	7	0	90	1.00	0.93	0.22	1.00
Saez-Llorens	M	2-15	CC	2	3	0	94	1.00	0.97	0.40	1.00
Edelmann[27]	B	Preterm	Bag	5	71	0	130	1.00	0.65	0.07	1.00
Edelmann	B	Term	Bag	6	43	0	787	1.00	0.95	0.12	1.00
McCarthy[28]	M	nn	CC	1	17	0	82	1.00	0.83	0.06	1.00
McCarthy	F	nn	CC	1	27	0	72	1.00	0.73	0.04	1.00
Boehm[29]	M	nn	Bag	2	38	0	47	1.00	0.55	0.05	1.00
Boehm	F	nn	Bag	6	38	0	22	1.00	0.37	0.14	1.00
Abbott[e,30]	B	nn	CC	10	281	0	1055	1.00	0.79	0.03	1.00
Abbott[f]	B	nn	CC	6	48	4	1288	0.60	0.96	0.11	1.00
Lincoln[f,31]	B	nn	CC	2	22	0	46	1.00	0.68	0.08	1.00
Lincoln[f]	B	nn	CC	6	13	0	209	1.00	0.68	0.32	1.00
Cohen[32]	B	<2 yr	Diaper	5	2	0	31	1.00	0.94	0.71	1.00
Monzon[33]	B	Adult	Cath	7	4	0	27	1.00	0.87	0.64	1.00
Ramage[34]	B	Infants	CC	16	2	2	38	0.89	0.95	0.89	0.95
Gower[35]	B	nn	Bag	2	9	0	23	1.00	0.72	0.18	1.00
Saccharow[36]	B	Infants and children	CC	10	48	0	96	1.00	0.67	0.17	1.00

[a] F, female; M, male; B, both.
[b] nn, neonatal.
[c] CC, clean catch; NCC, neonatal clean catch.
[d] TP, true positive; FP, false positive; FN, false negative; TN, true negative; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.
[e] Using 10^4 CFU/ml as criteria for bacteriuria.

Table A2 Random population surveys for incidence of incidental bacteriuria

Author	Gender	Ages	No. infected	Total patients	Percentage
Kunin[37]	Male	5-18	0	1824	0.00
Kunin	Female	5-18	15	1768	0.85
Kunin[38]	Male	5-18	2	7731	0.026
Kunin	Female	5-18	58	5132	1.13
Edelmann[39]	Both	Term nns	6	836	0.72
Edelmann	Both	Preterm nns	5	206	2.43
Abbott[40]	Both	nns	6	1346	0.45
Lincoln[a,41]	Both	nns	7	70 000	0.01
Lincoln[b]	Male	nns	8	298	2.68
Drew[42]	Male	nns	54	6471[c]	0.83
Drew	Female	nns	10	6471[c]	0.15
Littlewood 1950-1963[43]	Both	nns	20	27 025	0.00074
Littlewood 1964[44]	Both	nns	4	2633	0.0015
Littlewood 1965-1967	Both	nns	41	8443	0.0049
Littlewood	Male	nns	5[d]	309	1.62
Littlewood	Female	nns	1	291	0.34
Wettergren[45]	Female	<1 year	14	1899	0.9
Wettergren	Male	<1 year	36	1682	2.5
Mårild[46]	Female	0-6 years	231	3705	6.23
Mårild	Male	0-6 years	68	3877	1.75
Randolph[47]	Female	0-2 years	29	800	3.63
Davies[48]	Female	1 month-5 years	4	507	0.79
Davies	Male	1 month-5 year	1	528	0.15
Saccharow[49]	Male	Children	8	272	2.94
Saccharow	Female	Children	7	178	3.93
Maherzi[50]	Male	Neonatal	36	1006	3.58
Maherzi	Female	Neonatal	7	756	0.93
Randolph[51]	Female	<2 years	29	800	3.63
Siegel[52]	Female	Infants	15	420	3.57
Siegel	Male	Infants	7	391	1.79
Siegel	Female	Preschool	7	375	1.87
Siegel	Male	Preschool	0	285	0.00
Hansson[53]	Female	<2 years	1198	68 978	1.74
Hansson	Male	<2 years	1111	72 660	1.53
Dogunro[54]	Both	School children	28	1000	2.80
Fargason[55]	Female	Up to 7 years	295	43 441	0.68
Fargason	Male	Up to 7 years	85	43 966	0.19
Wettergren[e,56]	Female	2 week-15 months	14	1696	0.83
Wettergren[e]	Male	2 week-15 months	36	1502	2.40
Wettergren[f]	Female	2 week-15 months	20	1696	1.18
Wettergren[f]	Male	2 week-15 months	20	1502	1.33
Saxena[57,58]	Female	4 week-5 year	3	440	0.68
Saxena	Male	4 week-5 year	2	560	0.36
Brundtland[59]	Girls	8-12 years	35	1035	3.38
Randolph[60]	Female	0-24 months	9	200	4.50
Randolph	Male	0-24 months	1	200	0.50
Airede[61]	Both	Neonates	22	8391	0.26
Eliakim[62]	Both	Premies	27	333	8.10
Macauley[63]	Female[g]	3 week-4.5 year	22	1533[h]	1.44
Macauley	Male[g]	3 week-4.5 year	10	1533[h]	0.65
Jakobsson[64]	Females	<1 year	827	68 978	1.20
Jakobsson	Males	<1 year	967	72 660	1.33
Jakobsson	Females	12-24 months	371	68 978	0.54
Jakobsson	Males	12-24 months	144	72 660	0.20
Pead[65]	Males	0-12 years	553	45 727	1.21

(*continued on next page*)

Table A2 (*continued*)

Author	Gender	Ages	No. infected	Total patients	Percentage
Pead	Males	Under 1 year	243	7221	3.37
Pead	Males	2-5 years	171	14 873	1.15
Pead	Males	6-12 years	139	23 737	0.59
Pead	Females	0-12 years	1332	43 359	3.07
Pead	Females	Under 1 year	193	6959	2.77
Pead	Females	2-5 years	513	14 223	3.61
Pead	Females	6-12 years	626	22 177	2.82
Eliakim[66]	Both	Premies	27	333	8.10

[a] 1961 Annual report of the National Board of Health in Sweden.
[b] Combination of pyuria and bacteriuria.
[c] Assumed a 50/50 split in gender of newborns.
[d] Littlewoood included one boy who grew a mixed culture and one boy who grew *Staphylococcus albus*, which I excluded from this number.
[e] Patients with ABU.
[f] Patients with symptomatic urinary tract infections.
[g] Assumes a 50/50 split in population.
[h] Among hospitalized children.

Table A3 Rate of urinary tract infection in febrile children

Author	Gender	Ages	No. infected	Total patients	Percentage
Krober[67]	Female	<3 months	6	83	7.23
Krober	Male	<3 months	14	99	14.14
Bonadio[a,68]	Female	<1 year	12	119	10.08
Bonadio[a]	Male	<1 year	0	146	0.00
Roberts[69]	Female	<2 year	9	242	3.72
Roberts	Male	<2 year	0	263	0.00
Bauchner[70]	Female	<5 year	6	268	2.24
Bauchner	Male	<5 year	5	396	1.26
Buys[71]	Male		27	291	9.28
Buys	Female		19	254	7.48
Hoberman[72]	Both	=1 year	50	945	3.89
North[73]	Both	Children	82	1	1.22
Kadish[74]	Both	=28 days	32	372	8.60
Hoberman[75]	Female	<1 year	37	419	8.83
Hoberman	Male	<1 year	13	526	2.47
Shaw[76]	Female	<2 years	63	1469	4.29%
Shaw	Male	<1 year	17	942	1.84%
Crain[77]	Both	<8 weeks	33	442	7.47

[a] Infants with no apparent source of infection on physical examination.

These odd ratios are nearly the same as the relative risks generated by this model and indicate that the differences demonstrated in the US Army studies may be entirely attributed to confounding factors. Similarly, the summary effect of meta-analysis using a random-effects model of studies comparing urinary tract infection rates by circumcision status is an odds ratio of 4.30 (95% confidence interval 2.25–8.22).(unpublished data) This also indicates that the differences seen in urinary tract infection rates in infant boys by circumcision status may be completely attributable to confounding factors.

In summary, a model demonstrates that differences in urinary tract infection incidence between circumcised and non-circumcised boys can be attributed to factors other than a true difference in incidence. The impact of these differential factors needs to be considered when determining the importance of studies that have not controlled for them. It is quite possible that the differences noted in the incidence of urinary tract infection between circumcised and non-circumcised boys are entirely due to confounding factors.

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