



The Relationship between Neonatal Circumcision, Urinary Tract Infection, and Health

Michael L. Eisenberg^{1,2}, Deron Galusha³, William A. Kennedy¹, Mark R. Cullen⁴

Departments of ¹Urology and ²Obstetrics/Gynecology, Stanford University School of Medicine, Stanford, CA, ³Statistician, Yale Occupational and Environmental Medicine Program, Yale University School of Medicine, New Haven, CT, ⁴Department of Internal Medicine, Stanford University School of Medicine, Stanford, CA, USA

The risk-benefit profile of neonatal circumcision is not clear. Most studies have focused on urinary tract infections but other health sequelae have not been evaluated. While evidence supports benefits of circumcision, a lack of randomized trials has been cited as a weakness. National guidelines provide mixed recommendations regarding neonatal circumcision. We review the weight of evidence and utilize current statistical methodology on observational data to examine the risks and benefits of neonatal circumcision.

Keywords: Foreskin; Hypertension; Penis; Pyelonephritis; Urinary tract infections

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Circumcision is the most common procedure performed on newborns. While it has been performed for thousands of years for religious and medical reasons, its use is still controversial. Regional and cultural discrepancies in circumcision rates exist nationally and internationally. Indeed, national medical panels from different countries have arrived at different conclusions and recommendations when reviewing the literature. While circumcision rates in the United States are around 65% to 75% with the American Academy of Pediatrics concluding 'health benefits of newborn male circumcision outweigh the risks', England has circumcision rates around 15% with the NHS website stating 'Most health professionals in England would

argue that there are no medical reasons why an otherwise healthy baby boy should be circumcised' [1]. Similarly, recent Canadian Pediatric Society recommended circumcision in only certain circumstances; however, the methodology of the evidence evaluation has been questioned [2,3]. The Royal Dutch Medical Association recommends deterrence [4].

Nevertheless, many health benefits of circumcision have been suggested, including lower rates of urinary tract infection (UTI), human immunodeficiency virus acquisition, herpes simplex virus acquisition, syphilis transmission, penile cancer, balanitis, phimosis, bacterial vaginosis in female partners, human papilloma virus transmission and cervical cancer in female partners [1]. Indeed, the Centers for Disease Control (CDC) recently released proposed recommendations for counsel-

Received: Jan 13, 2018 **Revised:** Jan 22, 2018 **Accepted:** Jan 28, 2018 **Published online** Mar 22, 2018

Correspondence to: Michael L. Eisenberg <https://orcid.org/0000-0001-5482-0141>

Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, USA.

Tel: +1+650-723-5700, **Fax:** +1+650 724-9609, **E-mail:** eisenberg@stanford.edu

ing parents and uncircumcised adolescents and adult males about the benefits of circumcision [5]. However, the low overall rate of UTIs in the infant population demonstrated in several large cohort studies, suggested that the number needed to circumcise to prevent one hospitalization for UTI was between 100 and 200 [6,7]. Importantly, pediatric studies of UTI and circumcision have been restricted to UTI alone, thus other health sequelae, such as renal or hypertensive disease, have not been evaluated [8-11]. While some studies reported complication rate of up to 10%, most contemporary

series report complications rates well below 0.5% [1,12]. While most complications are minor, several societies have voiced concerns about the risk to benefit ratio. Even the American Academy of Pediatrics, which acknowledges the benefits of circumcision, has stopped short of recommending neonatal circumcision and instead has suggested the procedure should be offered to the parents of healthy children so that an informed decision can be made [1]. In contrast, the CDC's detailed report on circumcision calculates the benefits of circumcision outweigh the risks by 100 to 1 [13].

Table 1. Characteristics of the cohort based on circumcision status^{a,b}

| | Unmatched | | | Matched | | |
|------------------------------|--------------|-----------------|---------|-------------|-----------------|---------|
| | Circumcised | Non-circumcised | p-value | Circumcised | Non-circumcised | p-value |
| No. of subject | 2,334 | 573 | | 944 | 472 | |
| Age (y) | 32.5±6.3 | 33.7±7.4 | <0.01 | 33.5±6.5 | 33.5±7.3 | 0.95 |
| Race/ethnicity | | | <0.01 | | | 0.05 |
| White | 1,897 (81.3) | 316 (55.2) | | 632 (69.9) | 293 (62.1) | |
| Black | 205 (8.8) | 63 (11.0) | | 102 (10.8) | 46 (9.7) | |
| Other | 232 (9.9) | 194 (33.9) | | 210 (22.2) | 133 (28.2) | |
| Length of stay (newborn) (d) | | | <0.01 | | | 0.96 |
| 1 | 572 (24.5) | 193 (33.7) | | 296 (31.4) | 145 (30.7) | |
| 2 | 1,159 (49.7) | 182 (31.8) | | 332 (35.2) | 162 (34.3) | |
| 3 | 388 (16.6) | 99 (17.3) | | 169 (17.9) | 89 (18.9) | |
| ≥4 | 215 (9.2) | 99 (17.3) | | 147 (15.6) | 76 (16.1) | |
| Delivery | | | <0.01 | | | 0.84 |
| Vaginal | 1,632 (71.6) | 347 (63.7) | | 615 (65.1) | 305 (64.6) | |
| Caesarean section | 646 (28.4) | 198 (36.3) | | 329 (34.9) | 167 (35.4) | |
| Employee type | | | 0.48 | | | 0.42 |
| Salary | 913 (39.1) | 215 (37.5) | | 359 (38.0) | 190 (40.3) | |
| Hourly | 1,421 (60.9) | 358 (62.5) | | 585 (62.0) | 282 (59.7) | |
| Region | | | <0.01 | | | 0.12 |
| Northeast/MidAtlantic | 403 (17.3) | 101 (17.6) | | 166 (17.6) | 87 (18.4) | |
| East North Central | 674 (28.9) | 108 (18.9) | | 215 (22.8) | 98 (20.8) | |
| West North Central | 158 (6.8) | 40 (7.0) | | 65 (6.9) | 39 (8.3) | |
| South Atlantic | 260 (11.1) | 55 (9.6) | | 91 (9.6) | 26 (5.5) | |
| East South Central | 262 (11.2) | 59 (10.3) | | 123 (13.0) | 56 (11.9) | |
| West South Central | 377 (16.2) | 119 (20.8) | | 184 (19.5) | 106 (22.5) | |
| West | 112 (4.8) | 22 (3.8) | | 30 (3.2) | 21 (4.4) | |
| Pacific | 88 (3.8) | 69 (12.0) | | 70 (7.4) | 39 (8.3) | |
| Year of birth | | | <0.01 | | | 0.05 |
| 2003–2004 | 728 (31.2) | 154 (26.9) | | 292 (30.9) | 132 (28.0) | |
| 2005–2006 | 589 (25.2) | 143 (25.0) | | 223 (23.6) | 120 (25.4) | |
| 2007–2008 | 508 (21.8) | 126 (22.0) | | 207 (21.9) | 103 (21.8) | |
| 2009–2010 | 268 (11.5) | 57 (9.9) | | 119 (12.6) | 44 (9.3) | |
| 2011–2012 | 241 (10.3) | 93 (16.2) | | 103 (10.9) | 73 (15.5) | |

Values are presented as mean±standard deviation or number (%).

^aUnmatched and propensity matched cohorts are listed. p-values represent chi squared test for categorical variables (race/ethnicity, delivery, employee type, region) and ANOVA for continuous variables (age, length of stay). ^bIndividual totals vary based on missing data for covariates.

A meta-analysis in 2013, which included data on 407,902 children (19 studies) as well as older boys and men, concluded that there is a lifetime benefit to circumcision which prevents UTI [14]. A recent systematic review published in 2017 concluded that early infant circumcision should not be considered controversial and suggested that a decline in national rates of circumcision were a threat to public health [4]. However, the most recent Cochrane review identified no randomized or quasi-randomized controlled trials (RCTs) examining circumcision and UTI [15]. The authors concluded that further data was needed before circumcision could be recommended [1]. Indeed, there are significant sociodemographic and economic differences between families utilizing circumcision which may also influence relevant outcomes [16]. However, limiting the analysis to only RCT, excludes the wealth of data provided by observational studies over the past several decades.

TECHNIQUES BEYOND RANDOMIZED CONTROLLED TRIALS

There are significant financial, ethical, and logistical challenges to performing RCTs. In such instances, investigators have used observational data to attempt to guide policies. Yet observational data may be biased as differences in baseline characteristics may impact both the treatment and outcome. However, with detailed clinical data, many confounding factors can be adjusted for using analytical models. Moreover, several analytic techniques can help account for overt or hidden biases

especially when unmeasured patient characteristics can affect the disease and outcome. We used data from an ongoing study of a geographically and demographically diverse cohort of industrial workers and their families to determine the association between circumcision and the incidence of UTIs and surgical complications to simultaneously assess risks and benefits of neonatal circumcision.

The design of the parent study has been previously described [17-23]. Briefly, as part of continuing monitoring of employee health and safety, employee medical, insurance, and workplace records are compiled. Data on over 120K employees from around the US (*i.e.*, 24 states) is available with complete medical claims and pharmacy records as well as insurance claims data for all covered spouses and dependents.

Using insurance claims data, we identified boys that underwent neonatal circumcision prior to 1 month of age. The circumcised group was compared to uncircumcised boys. Diagnosis and treatment codes were used to identify urinary infections, surgical complications, or urologic imaging.

In all, we identified 2,334 boys who underwent neonatal circumcision and 573 who did not during the study period. Method of delivery and length of stay were also associated with circumcision status (Table 1). Propensity-based matching produced 944 circumcised boys and 472 uncircumcised boys matched 2:1 with similar patient characteristics, indicating a high degree of similarity in the distributions of prognostic variables (Table 1).

Table 2. Incidence of UTI, vesicoureteral reflux, kidney disease, pyelonephritis, and hypertension and radiologic urological evaluation stratified by circumcision status^a

| Outcomes | Within 1st 2 weeks | | | | | Within 1st 2 years | | | | |
|--------------------------------------|--------------------|-------------------|-----------------|-------------------|---------|--------------------|-------------------|-----------------|-------------------|---------|
| | Circumcised | | Non-circumcised | | p-value | Circumcised | | Non-circumcised | | p-value |
| | Number | Rate ^b | Number | Rate ^b | | Number | Rate ^b | Number | Rate ^b | |
| UTI | 0 | 0.0 | 0 | 0.0 | NA | 19 | 0.59 | 20 | 2.7 | <0.001 |
| Vesicoureteral reflux | 0 | 0.0 | 0 | 0.0 | NA | 4 | 0.13 | 2 | 0.27 | NA |
| Kidney disease | 1 | 1.1 | 1 | 4.6 | NA | 2 | 0.063 | 1 | 0.13 | NA |
| Pyelonephritis | 0 | 0.0 | 0 | 0.0 | NA | 0 | 0.0 | 5 | 0.67 | NA |
| Hypertension | 0 | 0.0 | 0 | 0.0 | NA | 1 | 0.031 | 2 | 0.27 | NA |
| Medical diagnoses (any of the above) | 1 | 1.1 | 1 | 4.6 | NA | 21 | 0.65 | 26 | 3.5 | <0.001 |
| Hospitalization | 41 | 45.8 | 17 | 77.4 | 0.0022 | 217 | 6.8 | 67 | 9.0 | 0.0037 |

UTI: urinary tract infection, NA: not available.

^aCircumcised males (n=1,146) and non-circumcised males (n=573). p-value represents analysis of propensity matched analysis. Comparisons represent cox regression models after adjustment for age, race, method of delivery, length of birth hospitalization, employee type, location of the factor, and year of birth. ^bIncidence rate per 100 person years.

A total of 39 boys were diagnosed with a UTI during 3,945.5 person-years of follow-up. The hazard ratio (HR) for UTI of circumcised boys was 0.29 (95% confidence interval [CI], 0.15–0.58) compared to uncircumcised boys. Using the propensity-matched control, circumcision was associated with a 75% lower rate of UTI (HR, 0.23; 95% CI, 0.10–0.54) comparing the propensity matched cohort. Similar results were also seen for propensity score risk adjustment (HR, 0.29; 95% CI, 0.15–0.59) (Table 2).

Importantly, no difference in the rate of UTI was identified in the first two weeks of life. However, up to 2 years of age, uncircumcised boys had a higher rate of UTIs compared to circumcised boys (2.68 per 100 person-years *vs.* 0.59 per 100 person-years), the difference was statistical significant ($p=0.0005$). The number needed to treat (NNT) with circumcision to prevent one UTI was 37. This number decreased to 25 when we included other sequelae (*i.e.*, vesicoureteral reflux, renal disease, pyelonephritis, and hypertension) into the avoided outcomes. The overall rate of hospitalization was also significantly higher for uncircumcised boys (Table 2). Importantly, the incidence of other diseases not associated with urologic disease did not vary based on circumcision status such as bronchiolitis, respiratory syncytial virus infections, and ear infections were similar across all time periods examined. Similar results were seen with propensity matching or propensity score adjusted models.

In addition, a significantly higher rate of radiologic procedures (*i.e.*, renal ultrasounds) occurred in uncircumcised boys (Table 3). Unlike UTIs, the difference in radiologic evaluation between circumcised and uncircumcised boys began in the first 2 weeks of life. Over the first two years, uncircumcised boys had a significantly higher rate of radiologic evaluation of urinary organs compared to circumcised boys (2.2% *vs.* 0.8%). The number needed to treat with circumcision to prevent one radiologic evaluation was 17.

When examining surgical complications, no differences were seen at each time point for composite endpoints when comparing circumcised and uncircumcised boys. Hemorrhage, infection, meatal stenosis, need for repeat interventions, or unspecified complications were similar between groups ($p>0.05$).

Table 3. Incidence of urological radiologic procedures^a

| Scans | Within 1st 2 weeks | | | | | | Within 1st 2 years | | | | | |
|----------------------------|--------------------|-------------------|---------|-----------------|-------------------|---------|--------------------|-------------------|---------|-----------------|-------------------|---------|
| | Circumcised | | | Non-circumcised | | | Circumcised | | | Non-circumcised | | |
| | Number | Rate ^b | p-value | Number | Rate ^b | p-value | Number | Rate ^b | p-value | Number | Rate ^b | p-value |
| Cystogram | 0 | 0.0 | NA | 0 | 0.0 | NA | 1 | 0.031 | NA | 0 | 0.0 | NA |
| Renal US | 13 | 14.5 | <0.001 | 16 | 72.9 | <0.001 | 19 | 0.59 | <0.001 | 13 | 1.7 | <0.001 |
| Renal nuclear scan | 0 | 0.0 | NA | 0 | 0.0 | NA | 0 | 0.0 | NA | 0 | 0.0 | NA |
| Scans (any of the 3 above) | 13 | 14.5 | <0.001 | 16 | 72.9 | <0.001 | 19 | 0.59 | <0.001 | 13 | 1.7 | <0.001 |

MV: multivariate analysis, pr mtch: propensity score matching, prop: proportion test, US: ultrasound, NA: not available.

^aCircumcised males (n=2,334) and non-circumcised males (n=573). Model a represents addition of propensity score to multivariable model for entire cohort. Model b is model a+propensity score adjustment. Model b represents propensity matched cohort. Comparisons represent cox regression models after adjustment for age, race, method of delivery, length of birth hospitalization, employee type, location of the factor, and year of birth. ^bIncidence rate per 100 person years.

DISCUSSION

Prior reports have demonstrated a lower UTI rate in boys after circumcision. The American Academy of Pediatrics Ad Hoc Task Force on Circumcision reported on data from 427,698 infants born in all US Army hospitals between [24]. They noted an 11-fold increased UTI rate among uncircumcised boys compared to circumcised boys which was reflected in the decline prevalence of neonatal circumcision over this time period. A cohort study from Canada reported a risk reduction of 3.7 fold among 69,100 eligible boys born in 1993 to 1994, but given the low rate of UTIs, the authors estimated that 195 circumcisions must be performed to prevent on UTI [7]. While socioeconomics were estimated with geocoding, the homogeneity of the population limits generalizability. An analysis of members of the Kaiser Permanente Northern California system in 1996 identified 28,812 infants. A 10-fold higher cost for managing UTIs in uncircumcised boys was noted reflecting higher rates of hospitalization [6]. Moreover, the odds of a UTI declined 90%. However, the study represents a single region of the country and was unable to account for race/ethnicity, socioeconomic factors, and delivery characteristics which may impact circumcision and UTI rates.

UTIs early in life can lead to renal and hypertensive disease, thus it is important to consider these diseases as well. Moreover, a UTI in a male often prompts evaluation including urologic imaging. In addition to UTIs, circumcised boys also experience a lower utilization of diagnostic imaging with its associated costs (financial and emotional).

As with all observational data, it is important to note the important baseline sociodemographic differences among boys utilizing and not utilizing circumcision as this can lead to bias. However, application of multivariable, propensity score risk adjustment, and propensity score matching can minimize the impact of overt bias in patient characteristics [25,26].

The mechanism whereby circumcision may lower urinary infection rates has been studied. Studies demonstrate an accumulation of urinary pathogens under the prepuce and in the urethra of uncircumcised boys [27]. While severity of infection, including renal involvement or need for hospitalization, is affected by the specific urinary pathogen as well as the patient's anatomy, a urinary predisposition will increase a pa-

tient's rate of urologic complications. Consistent with existing data, the risk reduction of UTI associated with circumcision is greatest early in life [28]. As chronic renal disease may predispose to additional lifelong health impairments, it is possible early circumcision may prove more beneficial with longer follow-up into the early and middle adulthood [10,11].

It is important to note that estimates using observational data can be subject to unmeasured selection bias. However, given that RCTs cannot guide all clinical decisions, in certain cases, observational data can be useful. Current data identified a consistent reduction in UTI of circumcision and a NNT of 25 to 100 which implies that circumcision demonstrates a higher efficacy than infant influenza vaccination with an estimated number needed to vaccinate of >1,000 [29].

ETHICS STATEMENT (FOR HUMAN STUDY)

The present study protocol was reviewed and approved by the Institutional Review Board of Stanford University School of Medicine (Reg. No. IRB 16281).

ACKNOWLEDGEMENTS

The work was supported in part by NIA grant 2R01AG026291-11A1 Disease, Disability and Death in an Aging Workforce. A portion of salary support for DG was provided by Alcoa.

Disclosure

Dr. Eisenberg is an adviser of the Sandstone Diagnostics and Glow, but he made no influence on this work in relation with the company or its products. Other authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: Eisenberg ML, Cullen MR. Data curation: Cullen MR, Galusha D. Formal analysis: Galusha D. Funding acquisition: Cullen MR. Investigation: Eisenberg ML, Cullen MR, Galusha D. Methodology: Eisenberg ML, Cullen MR, Galusha D, Kennedy WA. Project administration: Cullen MR. Resources: Cullen MR. Software: Galusha D, Cullen MR. Supervision: Cullen MR, Eisenberg ML. Validation: Eisenberg ML, Cullen MR, Galusha D. Visualization: N/A. Writing (original draft): Eisen-

berg ML. Writing (review & editing): Eisenberg ML, Cullen MR, Galusha D, Kennedy WA.

REFERENCES

1. American Academy of Pediatrics Task Force on Circumcision. Male circumcision. *Pediatrics* 2012;130:e756-85.
2. Sorokan ST, Finlay JC, Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee, Infectious Diseases and Immunization Committee. Newborn male circumcision. *Paediatr Child Health* 2015;20:311-20.
3. Morris BJ, Klausner JD, Krieger JN, Willcox BJ, Crouse PD, Pollock N. Canadian Pediatrics Society position statement on newborn circumcision: a risk-benefit analysis revisited. *Can J Urol* 2016;23:8495-502.
4. Morris BJ, Kennedy SE, Wodak AD, Mindel A, Golovsky D, Schrieber L, et al. Early infant male circumcision: systematic review, risk-benefit analysis, and progress in policy. *World J Clin Pediatr* 2017;6:89-102.
5. Centers for Disease Control and Prevention (CDC). Recommendations for providers counseling male patients and parents regarding male circumcision and the prevention of HIV infection, STIs, and other health outcomes. Atlanta (GA): CDC; 2014.
6. Schoen EJ, Colby CJ, Ray GT. Newborn circumcision decreases incidence and costs of urinary tract infections during the first year of life. *Pediatrics* 2000;105:789-93.
7. To T, Agha M, Dick PT, Feldman W. Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. *Lancet* 1998;352:1813-6.
8. Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. *Pediatr Nephrol* 1998;12:727-36.
9. Goonasekera CD, Dillon MJ. Hypertension in reflux nephropathy. *BJU Int* 1999;83 Suppl 3:1-12.
10. Hellerstein S. Long-term consequences of urinary tract infections. *Curr Opin Pediatr* 2000;12:125-8.
11. Jacobson SH, Eklöf O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. *BMJ* 1989;299:703-6.
12. El Bcheraoui C, Zhang X, Cooper CS, Rose CE, Kilmarx PH, Chen RT. Rates of adverse events associated with male circumcision in U.S. medical settings, 2001 to 2010. *JAMA Pediatr* 2014;168:625-34.
13. Centers for Disease Control and Prevention (CDC). Recommendations for providers counseling male patients and parents regarding male circumcision and the prevention of HIV infection, STIs, and other health outcomes. Docket Number CDC-2014-0012. Atlanta (GA): CDC; 2014.
14. Morris BJ, Wiswell TE. Circumcision and lifetime risk of urinary tract infection: a systematic review and meta-analysis. *J Urol* 2013;189:2118-24.
15. Jagannath VA, Fedorowicz Z, Sud V, Verma AK, Hajebrahimi S. Routine neonatal circumcision for the prevention of urinary tract infections in infancy. *Cochrane Database Syst Rev* 2012;11:CD009129.
16. Introcaso CE, Xu F, Kilmarx PH, Zaidi A, Markowitz LE. Prevalence of circumcision among men and boys aged 14 to 59 years in the United States, National Health and Nutrition Examination Surveys 2005-2010. *Sex Transm Dis* 2013;40:521-5.
17. Clougherty JE, Eisen EA, Slade MD, Kawachi I, Cullen MR. Workplace status and risk of hypertension among hourly and salaried aluminum manufacturing employees. *Soc Sci Med* 2009;68:304-13.
18. Sakr CJ, Taiwo OA, Galusha DH, Slade MD, Fiellin MG, Bayer F, et al. Reproductive outcomes among male and female workers at an aluminum smelter. *J Occup Environ Med* 2010;52:137-43.
19. Kubo J, Goldstein BA, Cantley LF, Tessier-Sherman B, Galusha D, Slade MD, et al. Contribution of health status and prevalent chronic disease to individual risk for workplace injury in the manufacturing environment. *Occup Environ Med* 2014;71:159-66.
20. Cullen MR, Checkoway H, Alexander BH. Investigation of a cluster of pituitary adenomas in workers in the aluminum industry. *Occup Environ Med* 1996;53:782-6.
21. Cullen MR, Vegso S, Cantley L, Galusha D, Rabinowitz P, Taiwo O, et al. Use of medical insurance claims data for occupational health research. *J Occup Environ Med* 2006;48:1054-61.
22. Pollack KM, Agnew J, Slade MD, Cantley L, Taiwo O, Vegso S, et al. Use of employer administrative databases to identify systematic causes of injury in aluminum manufacturing. *Am J Ind Med* 2007;50:676-86.
23. Rabinowitz PM, Galusha D, Slade MD, Dixon-Ernst C, O'Neill A, Fiellin M, et al. Organic solvent exposure and hearing loss in a cohort of aluminium workers. *Occup Environ Med* 2008;65:230-5.
24. Wiswell TE, Enzenauer RW, Holton ME, Cornish JD, Hankins CT. Declining frequency of circumcision: implications for changes in the absolute incidence and male to female sex ratio of urinary tract infections in early infancy. *Pediatrics* 1987;79:338-42.
25. D'Agostino RB Jr. Propensity score methods for bias reduc-

- tion in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81.
26. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. *Ann Intern Med* 2002;137:693-5.
 27. Hallett RJ, Pead L, Maskell R. Urinary infection in boys. A three-year prospective study. *Lancet* 1976;2:1107-10.
 28. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J* 2008;27:302-8.
 29. Lewis EN, Griffin MR, Szilagyi PG, Zhu Y, Edwards KM, Poehling KA. Childhood influenza: number needed to vaccinate to prevent 1 hospitalization or outpatient visit. *Pediatrics* 2007;120:467-72.