Published in final edited form as:

Pediatrics. 2010 November ; 126(5): 865–871. doi:10.1542/peds.2010-0744.

Costs and Consequences of Universal Sibling Screening for Vesicoureteral Reflux: Decision Analysis

Jonathan C. Routh, MD, MPH^{a,b}, Frederick D. Grant, MD^c, Paul Kokorowski, MD, MPH^a, Richard S. Lee, MD^a, Frederic H. Fahey, PhD^c, S. Ted Treves, MD^c, and Caleb P. Nelson, MD, MPH^a

^a Department of Urology, Children's Hospital Boston, Boston, Massachusetts

^c Division of Nuclear Medicine and Molecular Imaging, Children's Hospital Boston, Boston, Massachusetts

^b Harvard Pediatric Health Services Research Fellowship Program, School of Medicine, Harvard University, Boston, Massachusetts

Abstract

OBJECTIVE—Our objective was to evaluate screening for vesicoureteral reflux (VUR) among siblings of patients with VUR, in terms of cost, radiation exposure, and number of febrile urinary tract infections (fUTIs) averted.

METHODS—We constructed a Markov model to evaluate 2 competing management options, that is, universal screening (cystographic evaluation of all siblings without symptoms) and usual care (cystographic evaluation of siblings only after fUTIs). Published data were used to inform all model inputs. Costs were estimated by using a societal perspective.

RESULTS—Universal screening yielded 2980 fUTIs, whereas usual care yielded 6330. Therefore, universal screening for VUR in a cohort of 100 000 siblings 1 year of age without symptoms resulted in the prevention of 1 initial fUTI per 3360 siblings, at an excess cost of \$55 600 per averted fUTI, in comparison with usual care. These estimates were heavily dependent on screening age and the effectiveness of antibiotic prophylaxis; prevention of a single fUTI would require screening of 166 siblings 5 years of age and 694 siblings 10 years of age. Similarly, if prophylaxis was ineffective in preventing fUTIs, then up to 10 000 siblings would need to be screened for prevention of a single fUTI.

CONCLUSIONS—Prevention of a single fUTI would require screening of 30 to 430 siblings 1 year of age without symptoms, at an estimated excess cost of \$56000 to \$820000 per averted fUTI. These estimates are heavily dependent on screening age and the effectiveness of antibiotic prophylaxis.

Keywords

vesicoureteral reflux; screening; siblings

Vesicoureteral reflux (VUR) is a familial, polygenic disorder of the genitourinary tract.¹ Despite a reported prevalence of VUR of ~1% in the general pediatric population, the

prevalence of VUR has been shown to be 27% among siblings of patients with VUR. The prevalence of VUR among siblings decreases with age but is not significantly associated with sibling or proband gender.²

Because of the association of VUR with urinary tract infections (UTIs) and renal scarring, many practitioners recommend screening siblings (without symptoms) of patients with VUR. Such screening is based on the assumption that, if VUR in the siblings can be diagnosed early, then measures (eg, antimicrobial prophylaxis) can be implemented to prevent future febrile UTIs (fUTIs) and renal scarring.³ This is controversial, however, because the clinical significance of sibling VUR is unclear⁴⁻⁷ and the effectiveness of antibiotic prophylaxis in preventing fUTIs has been questioned.^{8,9}

There is a relative lack of observational data on this topic, and an adequate, randomized, controlled trial of sibling screening would be difficult to perform.⁶ This implies that the decision to screen siblings without symptoms for VUR will be made on the basis of currently available information. In the application of imperfect information to population-level decisions (such as screening), the use of decision analysis techniques can be helpful, both to determine the decision most likely to result in favorable outcomes and to identify the parameters with particular influence over those outcomes. Therefore, the objective of this study was to examine the population-level economic and radiation-related consequences of a screening regimen for all siblings without symptoms of patients with VUR, compared with a strategy of performing imaging only for siblings with symptoms (ie, those who develop fUTIs).

METHODS

Model Design

We constructed a Markov model to evaluate 2 competing VUR sibling screening regimens, that is, universal sibling screening, in which all siblings undergo cystography, or usual care, in which only siblings who experience an initial fUTI undergo cystography (Fig 1). Markov models function by cycling a population of theoretical patients through discrete health states. In this case, siblings were cycled through 4 possible states, namely, VUR with fUTI, VUR without fUTI, no VUR with fUTI, and no VUR without fUTI. We chose a Markov model because of that method's particular ability to model long-term costs and outcomes, to forecast beyond the follow-up period of published studies, and to consider multiple relevant end points or comparators simultaneously.¹⁰ A societal perspective was used,¹¹ and the analysis time horizon was truncated at the age of 18 years. A 1-year-old child was used as our index (or base case) patient.

All siblings undergoing VUR screening were assumed to undergo an initial outpatient physician visit, pulsed-fluoroscopy voiding cystourethrography (pVCUG) study, and renal ultrasonography study, according to American Academy of Pediatrics guidelines.¹² Siblings who were found to have VUR began to receive daily antibiotic prophylaxis with orally administered trimethoprim-sulfamethoxazole at a daily dose of 2 mg/kg trimethoprim. A physician visit, pVCUG study, and renal ultrasonography study were repeated on an annual basis until the VUR resolved. Siblings who experienced fUTIs underwent an additional urine culture, physician visit, pVCUG study, and renal ultrasonography study and were treated with 24 hours of parenteral antibiotic therapy (75 mg/kg ceftriaxone), followed by a 14-day course of orally administered trimethoprim-sulfamethoxazole at a daily dose of 8 mg/kg trimethoprim, according to American Academy of Pediatrics guidelines.¹² After fUTI treatment, patients resumed antibiotic prophylaxis.

Parameter Estimates

Probability estimates were based on a systematic review of Medline and Embase databases for English-language articles published before September 2009. Reference lists of identified studies were hand-screened for any missed studies. Probability estimates were then based on the pooled results of all pertinent studies. Data were abstracted by a single author (Dr Routh). We decided a priori that, if a methodologically sound meta-analysis had been performed recently for a particular parameter estimate, then we would base our parameter estimates on those results. A notable exception to this policy was the effectiveness of antibiotic prophylaxis for the prevention of fUTIs. For this parameter, 2 high-quality systematic reviews were identified. Williams et al⁹ estimated the pooled relative risk of fUTIs during prophylaxis to be 0.44 (95% confidence interval: 0.19–1.00). However, a more-recent meta-analysis by Mori et al⁸ estimated the pooled relative risk to be 0.96 (95% confidence interval: 0.69–1.32). Because of this significant difference between 2 analyses using apparently sound methods, the 2 parameter estimates for the effectiveness of antibiotic prophylaxis were modeled separately. Parameter values are detailed in Table 1.

Model Outcomes

Model outcomes were the number of UTIs averted, the population-level direct medical costs, and the average per-patient radiation dose associated with each screening regimen. All model outcomes were based on identical stochastic cohorts of 100 000 hypothetical siblings undergoing each screening regimen (universal screening and usual care).

Radiation dosage estimates for each diagnostic test were based on previously published methods.¹³ For each test, the effective dose expressed in millisieverts was calculated. The effective dose represents the overall detrimental biological effect of an exposure to radiation and is calculated by weighting the radiation dose to each organ from a radiation exposure according to the radiosensitivity of that organ. This representation allows for population-level comparisons across different types of radiation exposures.¹⁴

Cost estimates were based on a nationally weighted average of Medicare reimbursements, including both technical and professional fees.¹⁵ Governmental reimbursement data were noted previously to approximate medical costs closely, as determined from a societal perspective.¹⁶ Antibiotic costs were estimated on the basis of 2009 average wholesale prices.¹⁷ Indirect medical costs were calculated on the basis of the average hourly wage of a worker in the United States, by assuming that diagnostic testing and physician consultation would require 1 parent to miss 1 half-day (4 hours) of work and that a fUTI would require 1 parent to miss 2 days (16 hours) of work.¹⁸ All costs were calculated in 2009 US dollars by using a 3% annual discounting rate, as shown in Table 1.¹¹

Sensitivity Analyses

The probability of both VUR and UTIs is highly dependent on the patient's age at the time of screening, and effective radiation doses vary according to children's body sizes. Therefore, we modeled 3 additional age categories (3 months, 5 years, and 10 years) for all simulations, along with our index case analysis of a 1-year-old child. Similarly, both costs and effective doses vary according to the particular type of cystography performed. Therefore, we modeled 2 additional types of cystography (continuous-fluoroscopy voiding cystourethrography [cVCUG] and radionuclide cystography [RNC]), along with our index case analysis using pVCUG.

One-way sensitivity analyses were performed for all model parameters (Table 1). All analyses and model simulations were performed by using TreeAge Pro Suite 2009 (TreeAge, Williamstown, MA).

RESULTS

UTI Outcomes

Universal screening resulted in a decrease in the expected number of fUTIs (Table 2). With a universal screening regimen, 3000 initial fUTIs would be expected to develop in a cohort of 100 000 siblings 1 year of age without symptoms, whereas usual care would be assumed to result in 6300 fUTIs (a net difference of 3300 fUTIs). Therefore, the number needed to screen (NNS), or the number of children who would need to be screened for prevention of a single initial fUTI in a 1-year-old sibling without symptoms, would be 29.8 children in our base case analysis, with the assumption of effective antibiotic prophylaxis. With the assumption of ineffective prophylaxis, however, only 230 fUTIs would be prevented within the same cohort with universal screening versus usual care, and the NNS among 1-year-old siblings without symptoms would be 429.2 children.

Radiation Dose Outcomes

The overall effective radiation dose for universal sibling screening was markedly higher than that for usual care (Table 3). Universal screening of 100 000 siblings 1 year of age without symptoms by using pVCUG would result in a population-level, effective radiation dose of 13 500 mSv (0.13 mSv per child). By comparison, usual care would result in a population-level, effective dose of 1250 mSv (0.013 mSv per child), a 10-fold reduction. The effective radiation doses did not differ significantly on the basis of the effectiveness of antibiotic prophylaxis (mean difference: 0.6%).

Cost Outcomes

The cost of universal sibling screening was markedly higher than the cost of usual care at all ages studied (Table 4). For a cohort of 100 000 siblings 1 year of age without symptoms, the cost of universal VUR screening would be expected to be \$210 600 000. By comparison, the cost of usual care for the same cohort would be expected to be \$23 900 000, with an absolute savings of \$186 700 000. On a per-patient basis, the universal screening strategy cost \$55 600 per averted fUTI. The absolute costs for either management strategy did not differ significantly according to the effectiveness of antibiotic prophylaxis (mean difference: 1.5%), although the cost per averted fUTI for the universal screening strategy did increase to \$819 000 if antibiotic prophylaxis was assumed to be ineffective in preventing fUTIs.

Sensitivity Analyses

In sensitivity analyses, altering the probabilities of UTIs or VUR among the screened populations did not alter model outcomes meaningfully. With any combination of model assumptions, universal screening was more expensive and resulted in higher radiation doses than usual care. Similarly, varying the cost of any single parameter or the effective radiation dose of any cystographic technique did not alter the relative model outcomes meaningfully.

The type of cystography (cVCUG, pVCUG, or RNC) used for screening did influence the effective radiation dose, with RNC providing a much lower dose than pVCUG or cVCUG (600, 12 100, and 111 800 mSv, respectively, for a cohort of 100 000 children 1 year of age). This reduced radiation came at a premium, because RNC also was associated with a significantly increased cost, compared with pVCUG (\$253 vs \$187 million, also for a 1-year-old cohort). Regardless of the type of cystography, however, universal sibling screening was uniformly more expensive and had higher radiation doses than did usual care (Table 3).

Similarly, the age at which siblings were screened and the effectiveness of antibiotic prophylaxis altered significantly the absolute differences between the 2 management

strategies, in terms of number of averted fUTIs, although universal screening remained consistently more expensive than usual care for all patient ages. As the effectiveness of antibiotic prophylaxis decreased, so did the effectiveness of universal screening to avert an initial fUTI among screened siblings (Fig 1). Similarly, as the age at which patients were screened increased, the effectiveness of universal screening over usual care decreased.

DISCUSSION

There is a relative lack of observational data on the outcomes or effectiveness of screening programs for siblings of patients with VUR, and an adequate, randomized, controlled trial of sibling screening seems unlikely.⁶ Therefore, any decision regarding VUR screening programs for siblings without symptoms must be made on the basis of imperfect information. In the absence of large clinical trials or observational studies, clinicians must base their decisions to screen siblings without symptoms on the potential benefits and risks of screening a given patient. In the application of imperfect information to population-level decisions such as screening regimens, decision analysis models such as ours can be helpful for identifying the decision that is most likely to result in favorable patient outcomes and the parameters that may influence those outcomes significantly. This is of significance to pediatric practitioners, given the ubiquity of VUR among children and the likelihood that children with VUR will have ≥ 1 sibling without symptoms.

In this model of 2 hypothetical cohorts of siblings (without symptoms) of patients with VUR, we found that a universal VUR screening program was associated invariably with increased medical costs and increased radiation doses for the screened siblings. However, the effectiveness of such a program (ie, its ability to reduce the number of fUTIs among screened siblings) varied significantly according to the presumed effectiveness of antibiotic prophylaxis in preventing fUTIs and the age at which siblings were screened. In our base case analysis of 100 000 siblings 1 year of age without symptoms, universal screening would prevent ~3400 fUTIs, on the basis of the assumption that antibiotic prophylaxis is effective. That is, 30 siblings without symptoms would need to be screened for prevention of an initial fUTI in a single patient.

Unfortunately, the true effectiveness of antimicrobial prophylaxis in fUTI prevention for patients with VUR is uncertain. One systematic review found a statistically significant 56% reduction in UTI rates with prophylaxis,⁹ whereas another found only a nonsignificant 4% reduction in the likelihood of UTI.⁸ Importantly, although both reviews were performed by using acceptable methods, they both included heterogeneous populations, which indicates that neither review may reflect accurately the true effectiveness of antibiotics.

In this case, the prevention of fUTIs, and thus the reduction in risk of renal damage, is the obvious goal of a screening regimen for siblings without symptoms. This is a laudable goal, and the costs of screening must be balanced against the benefits. If it is assumed that antibiotic prophylaxis is effective in preventing fUTIs (as indicated by Williams et al⁹), then the NNS would be 30 patients 1 year of age and the conservatively estimated costs of screening would be \$187 million, or \$55 600 per averted fUTI. If the effectiveness of prophylaxis was reduced, however, then the number of fUTIs would be increased proportionately, whereas the cost of the overall screening regimen would increase because of the cost of treating those infections. If antibiotic prophylaxis is ineffective (as indicated by Mori et al⁸), then the NNS would increase to 429 children, whereas the screening costs would increase to \$191 million, or \$819 000 per averted fUTI. As the effectiveness of antibiotic prophylaxis decreases, so does the cost-effectiveness of universal sibling screening. Future randomized trials, such as the ongoing Randomized Intervention for Children With Vesicoureteral Reflux study,¹⁹ should provide more-robust estimates of the

effectiveness of prophylaxis. Until then, clinicians must rely on imperfect data to decide whether the true cost of VUR screening for siblings without symptoms is justified, knowing that the true NNS lies some where between 30 and 430 children and that the true cost of screening likely lies somewhere between \$56 000 and \$820 000 per averted fUTI.

Among the potential risks of screening, the radiation-associated outcomes bear mention. Cystourethrography, particularly cVCUG, is associated with a relatively high per-patient dose of ionizing radiation, compared with a low-dose testing method such as RNC.¹³ Although the long-term risks of low-dose radiation are small, they are not immaterial.^{14,20} This increased ionizing radiation exposure can be translated in to a small but measurable increase in long-term risk of radiation-related cancer development, particularly as applied to large populations, as estimated by the National Research Council.²¹ With the assumption of a linear, no-threshold model of cancer risk as a result of low-dose ionizing radiation, the risk of contracting a lethal cancer is ~1 in 20 000 per mSv for an adult. However, children exposed to radiation are presumed to be at higher risk than adults, because of the greater radiosensitivity of growing tissues and children's longer life expectancy. Screening 100 000 siblings 1 year of age without symptoms for VUR would be expected to result in 1.7 radiation-induced lethal solid abdominal tumors. In terms of the natural incidence of cancer, this number is tiny; by comparison, ~42 000 of the 100 000 children in our cohort would be expected to develop a lethal cancer resulting from other causes during the course of their lifetimes.²¹ Therefore, the question to be considered is whether the clinical information gained through the use of a universal screening regimen is great enough to offset the low but measurable risks of the increased radiation dose, particularly in the context of increased medical use of ionizing radiation throughout the nation.^{14,22,23}

Similarly, the risks of treatment, including those of antibiotic prophylaxis, must be considered. The risk of cutaneous reactions among children taking trimethoprim-sulfamethoxazole is 1.4% to 7.4% per year of prophylaxis.²⁴ In our analysis, a screened cohort of 100 000 siblings 1 year of age without symptoms, monitored for 18 years, would be expected to accrue 181 571 person-years of antibiotic prophylaxis, and between 2500 and 13 400 dermatologic reactions over that time span would be expected. Although the overwhelming majority of these complications would be self-limited urticaria or maculopapular rash, more-significant problems, such as Stevens-Johnson syndrome, have been reported. As with cost and radiation exposure, these rare risks of screening must be weighed against a possible decreased risk of renal scarring, hypertension, and renal insufficiency among siblings with VUR.

In evaluating any screening program, it is important to examine the effects of lead-time, length-time, and overdiagnosis biases. Lead- and length-time biases refer to the likelihood of screening programs to overestimate survival benefits of screening and to detect preferentially slowly progressive disease. Because VUR resolves over time, these biases seem unlikely to be pertinent to VUR. Overdiagnosis bias is the screening-related detection of subclinical disease that would not otherwise have become clinically apparent, as reflected in the NNS (30–430 siblings would need to be screened to avert 1 fUTI).

The results of this analysis must be interpreted in light of its limitations. All parameter estimates were based on the existing urological literature; therefore, they reflect any methodological limitations and biases present in that literature. Similarly, all of our cost estimates (particularly for physician time and imaging studies) were based on nationally weighted averages.¹⁵ Although this method has many advantages and is recommended by many authors,¹⁶ national values may not be generalizable to all geographic areas, particularly those outside the United States. Lastly, our analysis extended only to 18 years of age and focused on the more-proximal outcomes of fUTIs. We did not include costs and

outcomes associated with renal scarring and renal failure, which might be prevented through an aggressive VUR screening program.

CONCLUSIONS

Prevention of a single fUTI would require screening of 30 to 430 siblings 1 year of age without symptoms for VUR, at an estimated cost of between \$56 000 and \$820 000 per averted fUTI, depending on the effectiveness of antibiotic prophylaxis in fUTI prevention. Universal sibling screening also would result in increased effective radiation doses among screened siblings, with the magnitude of the increase being dependent on the particular type of cystography used. Importantly, older siblings are much less likely to benefit from screening, and the number of fUTIs averted is proportional to the relative risk of fUTIs with antibiotic prophylaxis. Because of its relatively high cost and relatively low benefit, screening for VUR in siblings without symptoms may not be a worthwhile use of resources, when considered from a population perspective. If siblings are to be screened, however, then screening is most likely to be cost-effective when performed at a younger age (<1 year) and in the context of an effective program of antibiotic prophylaxis.

Acknowledgments

Dr Routh is supported by grant T32-HS000063 from the Agency for Health-care Research and Quality.

We thank Dr Tracy A. Lieu, who proofread and provided critical feedback on the manuscript.

ABBREVIATIONS

VUR	vesicoureteral reflux
fUTI	febrile urinary tract infection
pVCUG	pulsed-fluoroscopy voiding cystourethrography
cVCUG	continuous-fluoroscopy voiding cystourethrography
NNS	number needed to screen
RNC	radionuclide cystography
UTI	urinary tract infection

References

1. Briggs CE, Guo C-Y, Schoettler C, et al. Ageneome scan in affected sib-pairs with familial vesicoureteral reflux identifies a locus on chromosome 5. *Eur J Hum Genet.* 2010; 18(2):245–250. [PubMed: 19690587]
2. Skoog SJ, Peters CA, Arant BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. *J Urol.* 2010; 184(3):1145–1151. [PubMed: 20650494]
3. Ferrer FA, McKenna PH, Hochman HI, Herndon A. Results of a vesicoureteral reflux practice pattern survey among American Academy of Pediatrics, Section on Pediatric Urology members. *J Urol.* 1998; 160(3):1031–1037. [PubMed: 9719272]
4. Bonnin F, Lottmann H, Sauty L, et al. Scintigraphic screening for renal damage in siblings of children with symptomatic primary vesicoureteric reflux. *BJU Int.* 2001; 87(6):463–466. [PubMed: 11298035]
5. Connolly LP, Treves ST, Zurakowski D, Bauer SB. Natural history of vesicoureteral reflux in siblings. *J Urol.* 1996; 156(5):1805–1807. [PubMed: 8863620]

6. MacNeily AE, Afshar K. Screening asymptomatic siblings for vesicoureteral reflux: sound science or religious rhetoric? *Can J Urol*. 2006; 13(6):3309–3316. [PubMed: 17187693]
7. Parekh DJ, Pope JC, Adams MC, Brock JW. Outcome of sibling vesicoureteral reflux. *J Urol*. 2002; 167(1):283–284. [PubMed: 11743340]
8. Mori R, Fitzgerald A, Williams C, Tullus K, Verrier-Jones K, Lakhanpaul M. Antibiotic prophylaxis for children at risk of developing urinary tract infection: a systematic review. *Acta Paediatr*. 2009; 98(11):1781–1786. [PubMed: 19627258]
9. Williams G, Lee A, Craig J. Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. *J Pediatr*. 2001; 138(6):868–874. [PubMed: 11391331]
10. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993; 13(4):322–338. [PubMed: 8246705]
11. Gold, MR.; Siegel, JE.; Russell, LB.; Weinstein, MC., editors. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
12. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics*. 1999; 103(4):843–852. [PubMed: 10103321]
13. Ward VL, Strauss KJ, Barnewolt CE, et al. Pediatric radiation exposure and effective dose reduction during voiding cystourethrography. *Radiology*. 2008; 249(3):1002–1009. [PubMed: 18941159]
14. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med*. 2009; 361(9):850–857.
15. Centers for Medicare and Medicaid Services. Physician fee schedule. Available at: www.cms.gov/PhysicianFeeSched/PFSNPAF/itemdetail.asp?filterType=none&filterByDID=99&sortByDID=2&sortOrder=ascending&itemID=CMS1217859&intNumPerPage=1
16. Lund JL, Yabroff KR, Ibuka Y, et al. Inventory of data sources for estimating health care costs in the United States. *Med Care*. 2009; 47(7 suppl 1):S127–S142. [PubMed: 19536009]
17. Red Book. 2009: Pharmacy's Fundamental Reference. 113. Ann Arbor, MI: Thomson Reuters; 2009.
18. Bureau of Labor Statistics. National Compensation Survey: Occupational Earnings in the United States. Washington, DC: US Department of Labor; 2009.
19. Keren R, Carpenter MA, Hoberman A, et al. Rationale and design issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study. *Pediatrics*. 2008; 122(Suppl 5):S240–S250. [PubMed: 19018048]
20. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med*. 2007; 357(22):2277–2284. [PubMed: 18046031]
21. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. *Health Risks From Exposure to Low Levels of Ionizing Radiation: BEIR VII, Phase 2*. Washington, DC: National Academies Press; 2006.
22. Ellison JS, Maxfield CM, Wiener JS. Voiding cystography practices and preferences of North American pediatric urologists. *J Urol*. 2009; 182(1):299–304. [PubMed: 19450821]
23. Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging in a large integrated health system. *Health Aff (Millwood)*. 2008; 27(6):1491–1502. [PubMed: 18997204]
24. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol*. 2004; 172(2):448–453. [PubMed: 15247700]
25. Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. *J Urol*. 2010; 184(3):1134–1144. [PubMed: 20650499]
26. Estrada CR Jr, Passerotti CC, Graham DA, et al. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol*. 2009; 182(4):1535–1541. [PubMed: 19683762]
27. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med*. 2002; 113(suppl 1A):5S–13S. [PubMed: 12113866]

28. Sureshkumar P, Jones M, Cumming RG, Craig JC. Risk factors for urinary tract infection in children: a population-based study of 2856 children. *J Paediatr Child Health*. 2009; 45(3):87–97. [PubMed: 19210605]
29. Waddle E, Jhaveri R. Outcomes of febrile children without localising signs after pneumococcal conjugate vaccine. *Arch Dis Child*. 2009; 94(2):144–147. [PubMed: 18539684]
30. Wan J, Greenfield SP, Ng M, Zerlin M, Ritchey ML, Bloom D. Sibling reflux: a dual center retrospective study. *J Urol*. 1996; 156(2):677–679. [PubMed: 8683758]
31. Jequier S, Jequier JC. Reliability of voiding cystourethrography to detect reflux. *AJR Am J Roentgenol*. 1989; 153(4):807–810. [PubMed: 2773738]
32. Paltiel HJ, Rupich RC, Kiruluta HG. Enhanced detection of vesicoureteral reflux in infants and children with use of cyclic voiding cystourethrography. *Radiology*. 1992; 184(3):753–755. [PubMed: 1509062]
33. Unver T, Alpay H, Biyikli NK, Ones T. Comparison of direct radionuclide cystography and voiding cystourethrography in detecting vesicoureteral reflux. *Pediatr Int*. 2006; 48(3):287–291. [PubMed: 16732797]

FIGURE 1.
Numbers of averted fUTIs according to age at screening and effectiveness of prophylaxis.

TABLE 1**Model Parameter Values for 1-Year-Old Siblings Without Symptoms**

Parameter	Value	Sensitivity Analysis Range	Ref. No(s).
Annual probability, %			
Probability of sibling VUR	50.2	0–100	25
Probability of sibling VUR resolution	26.3	0–100	26
Probability of fUTI	5.8	0–100	5, 7, 27–30
Probability of false-negative cystographic findings	6.4	0–30	31–33
Relative risk of fUTI with prophylaxis ^a	0.44	0–1	9
	0.96	0–1	8
Radiation dose, mSv			
Renal ultrasonography	0		
cVCUG	0.6	0.3–1.2	13
pVCUG	0.06	0.03–0.12	
RNC	0.003	0.001–0.006	
Costs, 2009 US\$			
New patient office visit (CPT 99213)	63	30–120	15
Renal ultrasonography	226	100–1000	
pVCUG	366	100–1000	
RNC	687	100–1000	

CPT indicates Current Procedural Terminology.

^aTwo values were separately modeled because of the presence of 2 systematic reviews with significantly different results.

Comparison of Universal Screening Versus Usual Care in Terms of Expected Number of fUTIs Diagnosed Among 100 000 Siblings Without Symptoms and NNS to Prevent Single Initial fUTI

Patient Age	Assuming Effective Prophylaxis ⁹		Assuming Ineffective Prophylaxis ⁸			
	No. of fUTIs Diagnosed With Universal Screening	No. of fUTIs Diagnosed With Usual Care	NNS to Prevent 1 Initial fUTI	No. of fUTIs Diagnosed With Universal Screening	No. of fUTIs Diagnosed With Usual Care	NNS to Prevent 1 Initial fUTI
3 mo	3900	8200	23.3	7900	8200	337.8
1 y	3000	6300	29.8	6100	6300	429.2
5 y	500	1100	166.1	1000	1100	2381.0
10 y	120	260	694.4	250	260	10 000.0

TABLE 3
Comparison of Effective Radiation Doses for Universal Screening Versus Usual Care Among 100 000 Siblings Without Symptoms

Patient Age	pVCUG			RNC		
	Effective Dose With Universal Screening, mSv	Effective Dose With Usual Care, mSv	Excess Dose With Universal Screening, mSv (% Increase)	Effective Dose With Universal Screening, mSv	Effective Dose With Usual Care, mSv	Excess Dose With Universal Screening, mSv (% Increase)
3 mo	14 300	1600	12 700 (810)	910	60	850 (1500)
1 y	13 300	1300	12 000 (970)	600	40	560 (1400)
5 y	10 200	200	10 000 (5000)	330	5	325 (6600)
10 y	7200	40	7100 (17 800)	140	1	140 (14 200)

TABLE 4
Comparison of Societal Costs of Universal Screening Versus Usual Care Among 100 000 Siblings Without Symptoms, With pVCUG

Patient Age	Assuming Effective Prophylaxis ⁹			Assuming Ineffective Prophylaxis ⁸		
	Cost of Universal Screening, \$	Cost of Usual Care, \$	Cost per Averted FUTI, \$	Cost of Universal Screening, \$	Cost of Usual Care, \$	Cost per Averted FUTI, \$
3 mo	197 200 000	29 000 000	39 000	202 400 000	29 000 000	586 000
1 y	210 600 000	23 900 000	56 000	214 800 000	23 900 000	819 000
5 y	194 800 000	4 500 000	316 000	195 700 000	4500 000	4 551 000
10 y	162 700 000	1 000 000	1 123 000	162 900 000	1 000 000	16 195 000