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Incidence of urinary tract infection among siblings of children with vesicoureteral reflux

Caleb P. Nelson, MD, MPH¹, Jonathan A. Finkelstein, MD, MPH², Tanya Logvinenko, PhD³, and Mark A. Schuster, MD, PhD⁴

¹Assistant Professor of Surgery and Pediatrics, Department of Surgery, Harvard Medical School; and Department of Urology, Boston Children's Hospital, Boston, MA

²Associate Professor of Pediatrics, Department of Pediatrics, Harvard Medical School; and Vice-Chair for Quality and Outcomes, Division of General Pediatrics, Department of Medicine, Boston Children's Hospital, Boston, MA

³Senior Biostatistician, Clinical Research Center, Boston Children's Hospital, Boston, MA

⁴Professor of Pediatrics, Department of Pediatrics, Harvard Medical School; and Chief, Division of General Pediatrics, Department of Medicine, Boston Children's Hospital, Boston, MA

Abstract

Background—Siblings of children with vesicoureteral reflux (VUR) are at elevated risk of VUR. Screening siblings may identify VUR prior to a clinical illness such as a urinary tract infection (UTI), but the benefit of screening has not been demonstrated. We sought to determine the incidence of UTI among siblings, and hypothesized that the sibling UTI rate is similar between screened and unscreened siblings.

Methods—We performed a retrospective cohort analysis using insurance claims data (1/1/00–12/31/09). Within each family, we identified the index VUR patient and siblings, and included siblings who were enrolled in the insurance plan from birth for at least 1 year. We

Address Correspondence to: Caleb P. Nelson, MD, MPH, Department of Urology, Boston Children's Hospital, 300 Longwood Avenue, HU-355, Boston, MA 02115, (617) 355-3776, FAX (617) 730-0474, caleb.nelson@childrens.harvard.edu.

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Author Contributions:

Caleb P. Nelson, MD, MPH: Dr. Nelson conceptualized and designed the study, developed the database and directed the analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Jonathan A. Finkelstein, MD, MPH: Dr. Finkelstein contributed to the design of the study, reviewed the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Tanya Logvinenko, PhD: Dr. Logvinenko devised the statistical analytic plan, performed the data analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Mark A. Schuster, MD, PhD: Dr. Schuster contributed to the design of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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identified siblings who were screened for VUR and/or had UTI. We investigated the association of screening and UTI, controlling for patient characteristics and clustering within families.

Results—Among 617 siblings (associated with 497 index patients), 317 (51%) were female. Median insurance enrollment time was 53.0 months, with 424 enrolled ≥ 3 years. Among those with 1 or 3 years of enrollment, proportion of siblings who experienced UTI was 8.4% (52/617) and 10.4% (44/424), respectively. Median age at initial UTI was 32.7 months. 223 siblings (36.0%) underwent sibling screening. There was no significant difference in UTI between screened and unscreened siblings (OR [95%CI]: 1.57 [0.87-2.85]; $p=0.14$). In multivariate analysis, screening was not associated with sibling UTI incidence (OR [95%CI]: 1.33 [0.68-2.60]; $p=0.40$).

Conclusions—Although UTI is relatively common among siblings of VUR patients, there was no statistically significant difference in UTI incidence between screened and unscreened siblings.

Keywords

Vesicoureteral reflux; urinary tract infection; siblings; screening

INTRODUCTION

It has been recognized for decades that vesicoureteral reflux (VUR) is common among relatives of patients with VUR, particularly siblings. Published studies report that 11% to 67% of screened siblings have VUR, with overall incidence using pooled data of 32%, and up to 46% among siblings < 2 years old.¹⁻⁵ However, while it is clear that VUR is more common among siblings than among the general population (usually estimated at 1-2%),⁶ the clinical significance of sibling VUR, and the potential benefit of screening siblings to identify it, remains uncertain.

Sibling screening for VUR has been widely promoted in the literature⁷⁻⁹, and has in the past been common practice among pediatric urologists, as indicated in a 1998 survey.¹⁰ However, it is unclear how widespread the practice is currently. Furthermore, the evidence in support of routine sibling screening is weak,¹¹ and the 2010 American Urological Association guidelines cited the lack of evidence in not recommending screening for VUR among siblings with a normal renal ultrasound.¹² Aside from VUR resolution rates in siblings with VUR,^{2,13} few data exist regarding the long-term clinical outcomes of siblings. In particular, observational data on UTI incidence among siblings (screened or unscreened) have not been reported. Since the primary benefit of sibling screening would be to prevent UTI (through identification of VUR and initiation of antimicrobial prophylaxis, surgery, or other interventions), knowledge of the incidence of UTI among the sibling population is needed if we are to assess the effectiveness of sibling screening.

In this study we sought to determine the incidence of UTI among siblings of children with VUR during the sibling's first 3 years of life, and to determine the association of screening for VUR with UTI among these siblings.

PATIENTS AND METHODS

Data source

This study was a retrospective cohort analysis of health insurance claims data. The claims data were obtained from Harvard Pilgrim Health Care (HPHC), a large nonprofit health plan in New England, currently serving over 1 million members in Massachusetts, New Hampshire, and Maine. Claims files include ambulatory visits, hospitalizations, procedures completed, and medication dispensed to insured members. We examined claims over the time period of 1/1/2000 through 12/31/2009. Institutional Review Board approval was obtained from Boston Children's Hospital to which HPHC ceded IRB oversight.

Identification of index patients, family units, and siblings

The initial step was to identify all HPHC-enrolled patients born after 1/1/1995 with VUR, defined as presence of both an ICD-9 diagnostic code for VUR (593.7, 593.70, 593.71, 593.72, 593.73) and a CPT procedure code for cystography (74455 or 78740), at any time during the enrollment period. Each patient meeting this definition was assigned a "diagnosis date" based on the earliest date that a VUR ICD9 code appeared in the claims data. We then excluded those with secondary VUR (concurrent codes for neurogenic bladder and spina bifida [ICD-9 596.5, 741], posterior urethral valves [ICD-9 753.6], bladder exstrophy [ICD-9 753.5], renal transplant [ICD-9 V42], and prune belly syndrome [ICD-9 756.71]). We further identified (but did not exclude) those patients with VUR who had a history of prenatal hydronephrosis (ICD-9 code 591, appearing within 6 months of DOB). VUR patients were then grouped into family units, defined as all those enrolled under a single enrollment identification number (usually that of one parent). In family units with only one VUR patient, that patient was identified as the index patient. In family units with 2 VUR patients, the index patient was the one with the earliest chronological VUR diagnosis date. All other enrolled patients within the family unit born after 1/1/2000 (with or without VUR diagnosis) were defined as siblings. The diagnosis date for the index patient was considered the index diagnosis date for all other siblings in that family.

To further validate the sample, the medical records of index patients who underwent imaging at our institution (n=407) were reviewed to confirm that the claims-based diagnosis of VUR was accurate; the review included medical records within our institution, but not outside records (unless these were incorporated into our records).

Characterization of siblings

Siblings were included in the analysis if they were continuously enrolled in HPHC for at least 1 year after birth, and sibling follow-up time included the entire period of continuous enrollment, from birth to the end of enrollment. Siblings were considered enrolled from birth if their enrollment date was within 90 days of birth, and at least one medical claim was filed within 45 days of life. As is common in claims-based studies, we ignored apparent gaps of < 45 days in determining continuous enrollment. Siblings born prior to the index patient's diagnosis date were called "pre-dx-sibs," and could be categorized based on their age at the time of the index date. Siblings born after the index diagnosis date were called "post-dx-sibs" (and therefore had no age at the index date). We excluded siblings with evidence of

prenatal hydronephrosis (see above) or diagnoses associated with secondary VUR (see above), since both of these groups have reasons for undergoing cystography other than sibling screening. Siblings were further characterized by gender, index patient age at diagnosis, and socioeconomic status (using census geocoding based on median household income).

Diagnosis of VUR among siblings was based on appearance of a new diagnosis code for VUR (ICD-9 593.7, 593.70, 593.71, 593.72, 593.73) and cystography (CPT 74455 or 78740) less than 90 days apart. Occurrence of surgical treatment for VUR among siblings was assessed by open surgical (CPT 50780, 50782, 50785, 50783), laparoscopic (CPT 50947, 50948), or endoscopic codes (CPT 52327). Utilization of antimicrobial prophylaxis (AMP) was defined as dispense records for two 30-day antibiotic prescriptions (or four 14-day prescriptions for penicillins or cephalosporins, as these classes typically require refills every 14 days). Antibiotics were grouped into five categories: trimethoprim/sulfonamides, penicillins, cephalosporins, antiseptics (nitrofurantoin and methenamine mandelate), and other (macrolides, quinolones, and tetracyclines). For purposes of analyzing the association of prophylaxis utilization with UTI, only siblings started on prophylaxis prior to their first UTI diagnosis were considered to have been given prophylaxis.

Characterization of sibling screening—Pre-dx-sibs were considered to have undergone sibling screening for VUR if they underwent initial cystography (VCUG CPT 74455 or RNC CPT 78740) within 12 months after the index patient diagnosis date, and if they did not have a UTI in the 6 months prior to the cystogram. Post-dx-sibs were considered to have undergone sibling screening for VUR if they underwent initial cystography (VCUG CPT 74455 or RNC CPT 78740) within 12 months after the sibling's date of birth, and if they did not have a UTI in the 6 months prior to the cystogram.

Definition of UTI

UTI (for outpatient encounters) was defined by the combined presence of 3 separate elements: 1) ICD-9 UTI diagnosis codes (590.0, 590.1, 590.2, 590.3, 590.8, 590.9, 595.0, 595.2, 595.9, 599.0, or 771.82); and 2) performance of urine culture (CPT codes 87086, 87088); and 3) presence of a claim for a dispensed antibiotic, all occurring within a 7 day window. For inpatient encounters, an inpatient hospitalization with an ICD-9 diagnosis code for UTI as the primary diagnosis (see above code list) was sufficient for UTI definition. For patients with multiple UTI events, the initial event was used for time-to-event calculations.

Data analysis

Association of demographic and clinical variables with UTI incidence and sibling birth timing was investigated using generalized estimating equations with logit link and exchangeable working correlation structure to account for families with more than one sibling. Proportional hazards models accounting for clustering of siblings within a family were used to investigate UTI-free survival time in the sibling cohort. The proportional hazards assumption was satisfied. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary NC, USA) and packages *base*, *survival*, and *plotrix* of statistical software R¹⁴⁻¹⁷.

RESULTS

The initial query of the health plan claims identified 2789 patients with a diagnosis of primary VUR, grouped into 2438 family units, of which 1965 family units had more than one child. Within these 1965 family units, there were 3324 siblings. We excluded 1590 siblings who were born prior to the start of the study period (1/1/2000), leaving 1644 siblings. Of these, 958 were excluded because they were not enrolled continuously from birth for at least 1 year, 47 for diagnosis of prenatal hydronephrosis, and 1 for codes consistent with secondary VUR. This left 638 siblings associated with 517 index patients. Further validation via medical record review identified 20 index patients who were incorrectly classified as having VUR, leaving 497 index patients associated with 617 siblings for the final analysis (297 “pre-dx-sibs” and 320 “post-dx-sibs”)

The siblings in the analysis are characterized in Table 1. Median enrollment time among siblings was 53 months (IQR: 32-80), with 424 (68.7%) enrolled for at least 3 years. Overall, 223 siblings (36.0%) underwent sibling screening at a median age of 18.5 months for “pre-dx-sibs” and 3.0 months for “post-dx-sibs.” Of those siblings who underwent screening, 124/223 (55.6%) were diagnosed with VUR; in contrast, among the 394 siblings who did not undergo screening, only 9 (2.3%) were diagnosed with VUR ($p<0.0001$). Prophylaxis was used in 66 siblings: 57/223 (25.6%) of those who were screened, vs. 9/394 (2.3%) of those not screened ($p<0.0001$). Among those who were screened and diagnosed with VUR, prophylaxis was used in 50/124 (40%). Only 7 siblings (1.1%) underwent anti-reflux surgery during the study period: 2.7% (6/223) of screened and 0.3% (1/394) of unscreened siblings ($p=0.029$).

Overall, 8.4% of siblings (52/617) had at least one UTI (10.8% [24/223] among screened siblings vs. 7.1% [28/394] among unscreened siblings [$p=0.16$]; 10.1% [30/297] of pre-dx-sibs vs. 6.9% [22/320] of post-dx-sibs [$p=0.15$])(Tables 1 and 2). Among the 424 siblings with at least 3 years of enrollment, UTI occurred in 44 (10.4%). Median sibling age at initial UTI was 32.7 months. Most sibling UTI episodes were managed as outpatients; only 9/52 (17%) had inpatient hospitalization associated with UTI.

Use of prophylaxis was not associated with UTI incidence among the sibling group, with or without adjusting for screening status and VUR status. Overall, 15.1% (10/66) of those who received prophylaxis experienced UTI, while 7.6% (42/551) of those who did not receive prophylaxis experienced UTI ($p=0.10$). Limiting the analysis to those screened AND diagnosed with VUR, UTI occurred in 8/50 (16%) of those receiving prophylaxis and 8/74 (10.8%) of those not receiving prophylaxis ($p=0.81$).

There was no significant difference in odds of UTI (at any time) among screened siblings vs. unscreened siblings (OR = 1.57; 95% CI: 0.87-2.85; $p=0.14$). On multivariate analysis, controlling for index patient gender, index patient age at diagnosis, index patient history of UTI, sibling gender, sibling birth pre- or post-index diagnosis, and adjusting for the family clustering, screening was not associated with UTI incidence among siblings (OR=1.47; 95% CI: 0.79-2.73; $p=0.23$). If use of prophylaxis is included in this multivariable model (based

on biological plausibility, despite the lack of association on bivariate analysis), screening was still not associated with UTI incidence (OR=1.33; 95%CI:0.68-2.60; p=0.40).

Similarly, using survival analysis to examine the time to initial UTI among siblings (Figure 1), screening was not associated with UTI-free survival comparing screened siblings versus unscreened siblings (hazard ratio 1.61 [95% CI: 0.93-2.78], p=0.09). On multivariate survival analysis (controlling for the same covariates as in the prior model above), screening was still not significant (HR 1.37 [95%CI: 0.73-2.57], p=0.33).

DISCUSSION

Clinicians have long recognized that family members of VUR patients are more likely to have VUR themselves. Approximately one-third of siblings of children with VUR will have VUR when screened,^{1-5,13,18-23} although the genetic mechanisms of VUR inheritance are unclear. Genetic studies have identified numerous candidate loci but no consistent single gene or gene product²⁴⁻²⁶. Despite the uncertainty, the high prevalence might suggest that screening of siblings for VUR would facilitate early diagnosis and treatment, potentially averting negative sequelae of VUR such as recurrent pyelonephritis and renal scarring. Unfortunately, the screening literature is limited by small sample sizes, differing inclusion and exclusion criteria, and varying diagnostic criteria, and - most crucially - a lack of data regarding outcomes among unscreened siblings.

Furthermore, the clinical significance of sibling VUR remains uncertain. Most of the existing literature focuses on VUR prevalence among these children, and few outcome data exist apart from VUR resolution rates. In general, sibling VUR tends to be low grade; two-thirds of sibling VUR cases are grade I-II, and only 2% of sibling VUR is grade IV-V VUR^{4,8,13,18,20,22,23}. In contrast, grade IV-V comprises 5-7% of VUR diagnosed among infants with UTI²⁷ (up to 30% in some series²⁸), and ~36% of VUR diagnosed among infants with prenatal hydronephrosis.²⁸ Sibling VUR may also be more likely to spontaneously resolve than VUR diagnosed after UTI.^{2,13,29} Similarly, it appears that renal scarring is uncommon among siblings. Most studies have reported renal cortical anomalies on ultrasound or DMSA scan in less than 3% of VUR-positive siblings^{2,5,13,21,23}. Recent data from one cohort conflicts with these general findings; Hunziker et al. found that 46% of screened siblings had Grade IV-V VUR, and 15% had defects seen on renal scintigraphy³⁰. However, this series was limited to siblings of index patients with dilating VUR (Grade III-V), and 37% of index patients had renal scarring; this sample may reflect a more severe end of the VUR spectrum than most sibling series. Our study was not able to differentiate VUR grades, but it is possible that there may be subpopulations (e.g. siblings of index patients with grade IV-V VUR) who may benefit from screening if their risk of high-grade VUR (and associated UTI) is higher.

Despite the multiple published series of siblings with VUR, the key question of whether such siblings are at increased risk for UTI and associated renal injury remains unanswered. Presumably, many siblings with VUR simply outgrow their VUR without ever developing clinical illness. If this proportion is high enough, then screening for VUR is unlikely to be of benefit and may actually be harmful. Until now, observational data on UTI incidence among

unscreened siblings have never been reported. Two studies reported that 6% of those siblings who underwent screening had a history of UTI.^{4,5} However, these studies did not include unscreened siblings, or siblings who underwent clinical imaging after UTI, so these estimates may be biased. The cohort assembled for this study is unique in that it represents all siblings irrespective of VUR or screening status. This, in turn, allows estimation of UTI incidence among all siblings, irrespective of VUR or screening status.

In our cohort, 8.4% of siblings had at least one UTI (10.4% among those followed for >3 years). By comparison, the annual incidence of UTI in children has been estimated at 2.4-2.8% of all children,³¹ and cumulative incidence of UTI during the first 6 years of life has been estimated at 2-8%³²⁻³⁴. Thus, our findings suggest that, if siblings are at increased risk of UTI during childhood compared to the general population, the increase is relatively small.

What, if anything, do our findings suggest about the utility of screening among siblings? There did not appear to be any difference in UTI incidence between screened and unscreened siblings. In theory, the primary benefit of sibling screening is to prevent clinically significant UTI and its sequelae (through early identification of VUR and initiation of antimicrobial prophylaxis). However, there did not appear to be any such benefit of screening in this cohort (if anything, there was a non-significant trend toward more UTIs in the screened group). Of course, this study was not a randomized trial of screening among siblings, and there may be unobserved differences between the screened and unscreened siblings that may confound any true benefit of screening with respect to UTI. Such benefit, however, is likely to be small.

Because sibling screening for VUR directs asymptomatic children into a care pathway involving invasive tests with potentially adverse effects, long-term follow-up requiring repeated genitourinary imaging, prolonged antimicrobial prophylaxis, and possible surgery (as well as significant time and cost), recommendations for such a screening program should be based on evidence of direct benefit, when possible. Most existing data, and the current findings from this study, suggest that sibling VUR is a largely benign condition in most siblings, and that the benefits of screening are likely to be small.

This study should be interpreted in light of its limitations. This claims-based retrospective cohort study is subject to the limitations inherent in use of administrative data sources, such as miscoding, loss to follow-up, incorrect patient identification, and clerical errors. For example, to differentiate testing related to a known clinical condition (as opposed to sibling screening), we relied on presence or absence of diagnostic codes for UTI or hydronephrosis; missing codes in such circumstances could result in misclassification of clinically-indicated VCUG/RNC as a screening test. Other potentially useful variables, such as the screening preferences and practices of the ordering physician, or the rationale for not prescribing prophylaxis in a screened sibling with VUR, cannot be assessed from these data.

A significant number of potential subjects were excluded as they did not meet our criteria for timing and duration of HPHC enrollment; we were unable to analyze these excluded persons to determine whether they differed systematically from the included subjects. However, we

have no *a priori* reason to believe that enrollment status would be associated with the outcome.

Our chart validation effort confirmed that greater than 95% of index patients had VUR, and among VUR-negative siblings (according to the claims), 97% were confirmed negative. However among VUR-positive siblings, we were able to confirm a VUR diagnosis in just 65%; it therefore appears that while claims data are highly reliable for VUR diagnosis among certain subgroups (including, most importantly, the index patients), such claims may be less reliable for siblings. It should also be noted that not every index patient underwent chart validation, as we only had access to medical record information for those index patients who had imaging at our institution (407/638, 63.8%); this could introduce bias if the index patients whose imaging occurred elsewhere differed systematically from those who underwent validation. Furthermore, some index patients with secondary reflux may have been erroneously included, if the diagnosis codes for this designation (e.g. posterior urethral valves) were absent during the study period.

With respect to UTI diagnosis, claims data for UTI (our primary outcome) have previously been shown to be reliable in the inpatient setting³⁵, but the situation is less clear for outpatient coding. It is possible that our requirements for three separate coding elements for UTI diagnosis led to misclassification in some cases. It is possible that we missed some UTI's (low sensitivity), and may have misclassified others because we lacked clinical details from the medical record (e.g. lack of pyuria indicating asymptomatic bacteriuria and not UTI). Furthermore, this was not a randomized trial of sibling screening, limiting our ability to draw definitive conclusions about the efficacy of sibling screening in preventing adverse outcomes. There may be differences between screened and unscreened siblings for which we were unable to control, such as severity of index patient UTI or index patient renal scarring, which may have prompted a lower threshold for sibling screening. If siblings at higher risk for UTI were more likely to undergo screening, then the observed lack of association between screening and UTI may actually have reflected a successful reduction in UTI incidence in this group, bringing the UTI frequency in the higher risk group down to that of the lower risk (unscreened) group. To the extent that we were able to control for such risk factors among index patients and siblings, we did so; however, this study clearly was not able to control for all such factors. Use of prophylaxis is a similar confounding factor, one made more complex since not all screened siblings diagnosed with VUR received prophylaxis; although prophylaxis may plausibly be assumed to reduce the incidence of UTI in general, prophylaxis utilization in this cohort may well have been differentially utilized (e.g. higher utilization in subgroups at higher risk of UTI). We have controlled for prophylaxis use in our model, and screening was still not associated with decreased risk of UTI. Power may also be an issue; given the number of subjects, we would have had to observe a UTI incidence in the screening group of approximately 14% (vs. 7% in the unscreened group) to reach statistical significance. Our study was not planned to have statistical power to detect differences in the range actually observed.

CONCLUSION

UTI is common among siblings of VUR patients, although probably not greatly increased over that of the general pediatric population. Within the limitations of a claims data study such as this, we did not observe a statistically significant difference in UTI incidence between screened and unscreened siblings. Performing cystography of asymptomatic siblings as part of a systematic screening strategy (including antimicrobial prophylaxis of siblings with VUR, early recognition and treatment of UTI, and correction of bowel and bladder dysfunction) could theoretically result in decreased incidence of UTI and associated morbidity among siblings, but we were unable to show such an association in this real-world population.

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What's New

The benefit of screening siblings for vesicoureteral reflux remains unproven. We determined sibling UTI incidence, and observed no difference in UTI risk between screened and unscreened siblings, suggesting (given study limitations) that universal sibling screening may not reduce UTI risk.

Figure 1. UTI-free survival time (months) among screened (black line) and not screened (gray line) siblings. (Hazard ratio 1.61 (95% CI: 0.93-2.78))

Table 1

Association of sibling characteristics with sibling birth timing (relative to index diagnosis) as well as with incidence of urinary tract infection among siblings.

	All siblings	Siblings born prior to index diagnosis (Pre-dx-sibs)	Siblings born after index diagnosis (Post-dx-sibs)	P-value (Pre-dx-sibs vs. Post-dx-sibs)	Siblings With UTI	Siblings Without UTI	P-value (With UTI vs. Without UTI)
N	617	297	320	--	52	565	--
Total Enrollment Time after birth (months, median (IQR))	52.96 (31.59, 79.66)	67.2 (45.30, 93.73)	38.47 (23.75, 63.63)	<0.0001	73.22 (53.08, 96.59)	51.22 (30.77, 78.61)	0.0004
Enrollment time after index diagnosis (months, median (IQR))	37.55 (22.42, 60.99)	37.02 (21.76, 59.05)	38.47 (23.75, 63.63)	0.19	55.51 (32.78, 74.60)	35.90 (22.16, 59.47)	0.006
Sibling age at index diagnosis (years)				--			0.13
Born <u>after</u> index diagnosis (post-dx-sibs)	320 (52%)	--	320 (100%)		22 (42%)	298 (53%)	
Born <u>before</u> index diagnosis (pre-dx-sibs) : age <1 year at index diagnosis	74 (12%)	74 (25%)	--		5 (10%)	69 (12%)	
Born <u>before</u> index diagnosis (pre-dx-sibs): age 1-3 years at index diagnosis	179 (29%)	179 (60%)	--		19 (37%)	160 (28%)	
Born <u>before</u> index diagnosis (pre-dx-sibs): age 4-6 years at index diagnosis	44 (7%)	44 (15%)	--		6 (12%)	38 (7%)	
Gender				0.12			0.0002
Male	300 (49%)	154 (52%)	146 (46%)		12 (23%)	288 (51%)	
Female	317 (51%)	143 (48%)	174 (54%)		40 (77%)	277 (49%)	
Index patient diagnoses				0.016			0.004
Urinary tract infection (UTI)	444 (72%)	208 (70%)	236 (74%)		45 (87%)	399 (71%)	
Prenatal hydronephrosis (PHN)	46 (7%)	30 (10%)	16 (5%)		2 (4%)	44 (8%)	
PNH and UTI	30 (5%)	19 (6%)	11 (3%)		1 (2%)	29 (5%)	
Neither	97 (16%)	40 (13%)	57 (18%)		4 (8%)	93 (16%)	
SES (census block median income, quartile)				0.66			0.23
Quartile 1 (<= \$64,306)	154 (25%)	73 (25%)	81 (25%)		12 (23%)	142 (25%)	
Quartile 2 (\$64,307-\$77,537)	154 (25%)	76 (26%)	78 (24%)		12 (23%)	142 (25%)	
Quartile 3 (\$77,538-\$94,075)	155 (25%)	79 (27%)	76 (24%)		8 (15%)	147 (26%)	
Quartile 4 (>\$94,076)	152 (25%)	67 (23%)	85 (27%)		20 (38%)	132 (23%)	
Sibling Screened for VUR				0.016			0.16
Yes	223 (36%)	93 (31%)	130 (41%)		24 (46%)	199 (35%)	
No	394 (64%)	204 (69%)	190 (59%)		28 (54%)	366 (65%)	
Diagnosed with VUR				0.0496			0.09
Yes	133 (22%)	54 (18%)	79 (25%)		17 (33%)	116 (21%)	

	All siblings	Siblings born <u>prior</u> to index diagnosis (Pre-dx- sibs)	Siblings born <u>after</u> index diagnosis (Post-dx- sibs)	P-value (Pre-dx- sibs vs. Post-dx- sibs)	Siblings With UTI	Siblings Without UTI	P-value (With UTI vs. Without UTI)
N	617	297	320	--	52	565	--
No	484 (78%)	243 (82%)	241 (75%)		35 (67%)	449 (79%)	
Antimicrobial prophylaxis (started prior to any UTI diagnosis)				0.64			0.097
Yes	66 (11%)	30 (10%)	36 (11%)		10 (19%)	56 (10%)	
No	551 (89%)	267 (90%)	284 (89%)		42(81%)	509 (90%)	
Anti-reflux surgery				0.78			0.13
Yes	7 (1%)	3 (1%)	4 (1%)		3 (6%)	4 (1%)	
No	610 (99%)	294 (99%)	316 (99%)		49 (94%)	561 (99%)	

Table 2

Characteristics of urinary tract infections among siblings

	All Siblings with UTI	Unscreened Siblings with UTI	Screened Siblings with UTI	p-value
N	52	28	24	
Age at Initial UTI				0.80
<1	12 (23%)	6 (21%)	6 (25%)	
1-3	24 (46%)	12 (43%)	12 (50%)	
4-6	13 (25%)	8 (29%)	5 (21%)	
6-12	3 (6%)	2 (7%)	1 (4%)	
Treatment setting				
Outpatient	43 (83%)	22 (79%)	21 (88%)	0.39
Inpatient	9 (17%)	6 (21%)	3 (13%)	
Time to UTI from start of enrollment (months; median (IQR))	32.5 (13.5, 51.0)	40.5 (13.5, 52.5)	27.5 (13.0, 47.0)	0.51