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Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

The RIVUR Trial Investigators*

ABSTRACT

BACKGROUND

Children with febrile urinary tract infection commonly have vesicoureteral reflux. Because trial results have been limited and inconsistent, the use of antimicrobial prophylaxis to prevent recurrences in children with reflux remains controversial.

METHODS

In this 2-year, multisite, randomized, placebo-controlled trial involving 607 children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection, we evaluated the efficacy of trimethoprim–sulfamethoxazole prophylaxis in preventing recurrences (primary outcome). Secondary outcomes were renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance.

RESULTS

Recurrent urinary tract infection developed in 39 of 302 children who received prophylaxis as compared with 72 of 305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74) and was particularly

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"Early randomized, controlled trials that compared antireflux surgery with antimicrobial prophylaxis showed no significant differences in the rates of recurrent urinary tract infection (recurrences) and renal scarring; however, the lack of a placebo or observation group precluded a determination that either surgery or prophylaxis was effective."

randomized,
double blind,
placebo controlled trial
of prophylaxis with trim–sulfa

Randomized children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection (index infection).

Randomized children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection (index infection).

- 19 clinical sites across the United States
- 2–71 months of age
- Grade I to IV vesicoureteral reflux

- exclusion criteria
  - Index infection more than 112 days before randomization
  - Children with coexisting urologic anomalies
  - Contraindications for the use of trimethoprim– sulfamethoxazole
  - Certain medical conditions

- Followed the children for 2 years to Primary outcome
  - Febrile or symptomatic recurrence
- Secondary outcome
  - Renal scarring
  - Failure of prophylaxis
  - Antimicrobial resistance

- Urine specimens from children who were not toilet trained were obtained by means of cathe terization or suprapubic aspiration;
- Bag collected specimens were not permitted.
- Clean, voided specimens were collected from toilet trained children.

Index and outcome infections met stringent diagnostic criteria that included evidence of pyuria on urinalysis, culture proven infection, and fever (≥38°C) or urinary tract symptoms within 24 hours before or after urine collection.

Renal scanning with technetium 99m–labeled dimercaptosuccinic acid was performed at:

- baseline
- after one year
- after two years

10,871 children with screening data available

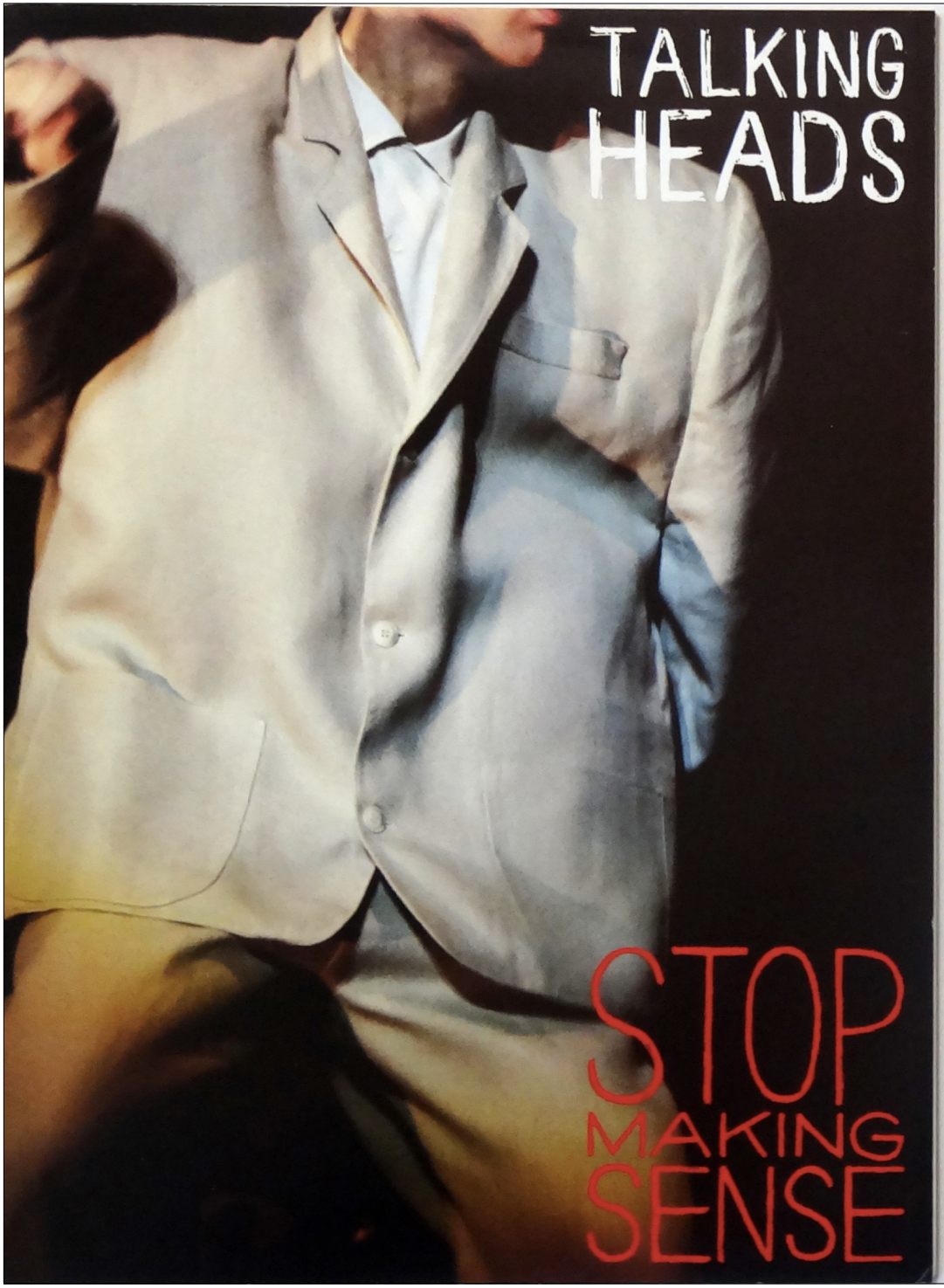
1,426 (13.1%) met the eligibility criteria

607 (42.6%) were enrolled

No significant differences in sex, race, or ethnic group were apparent between enrolled children and those who were screened but not enrolled. The study groups did not differ significantly with respect to any baseline characteristic (Table 1).

For 115 of the 607 children enrolled who met all the eligibility criteria in the course of the study, corresponding screening data for those not enrolled were not available.

Another sentence that does not make any sense.



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STOP MAKING SENSE

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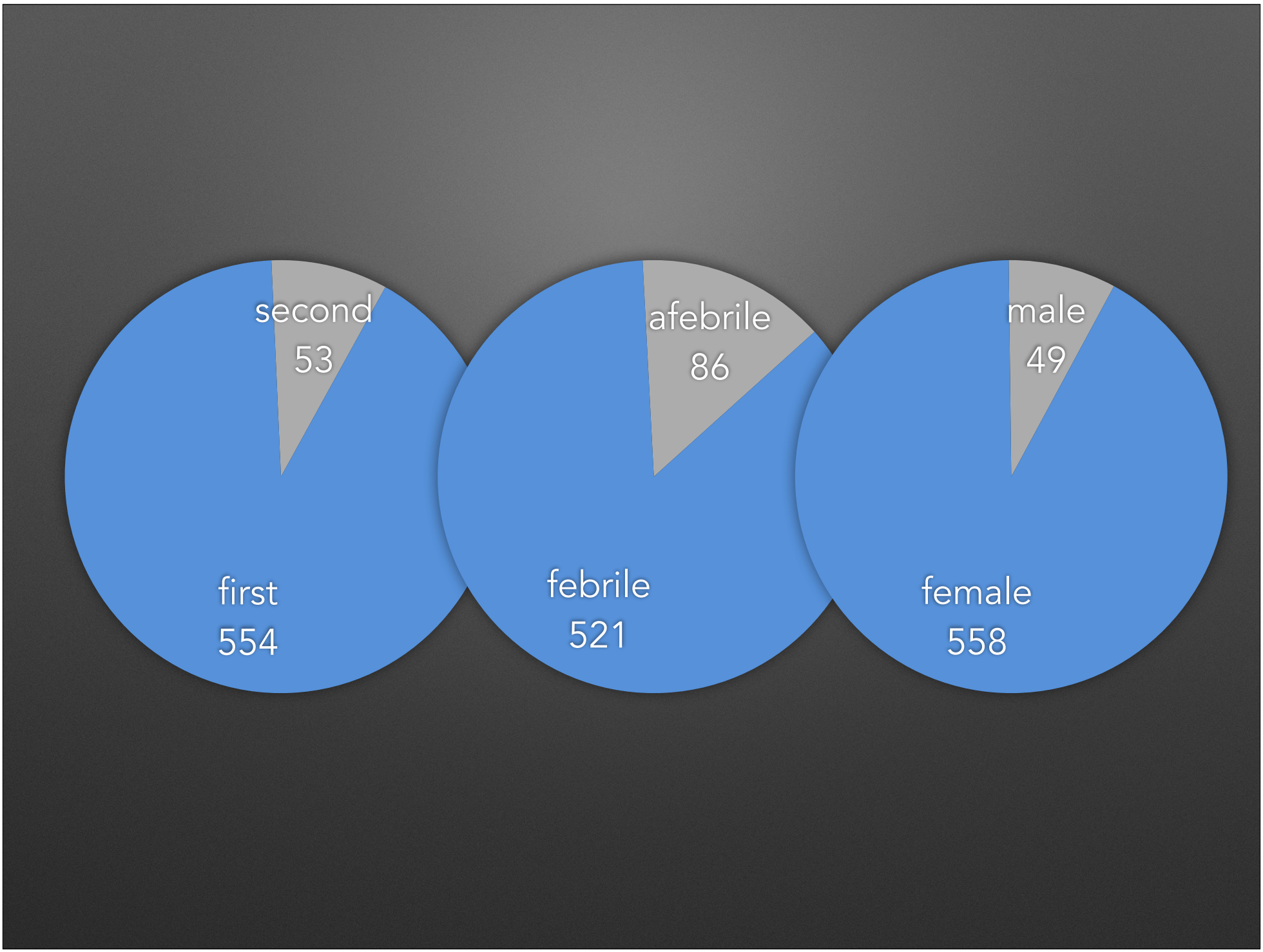
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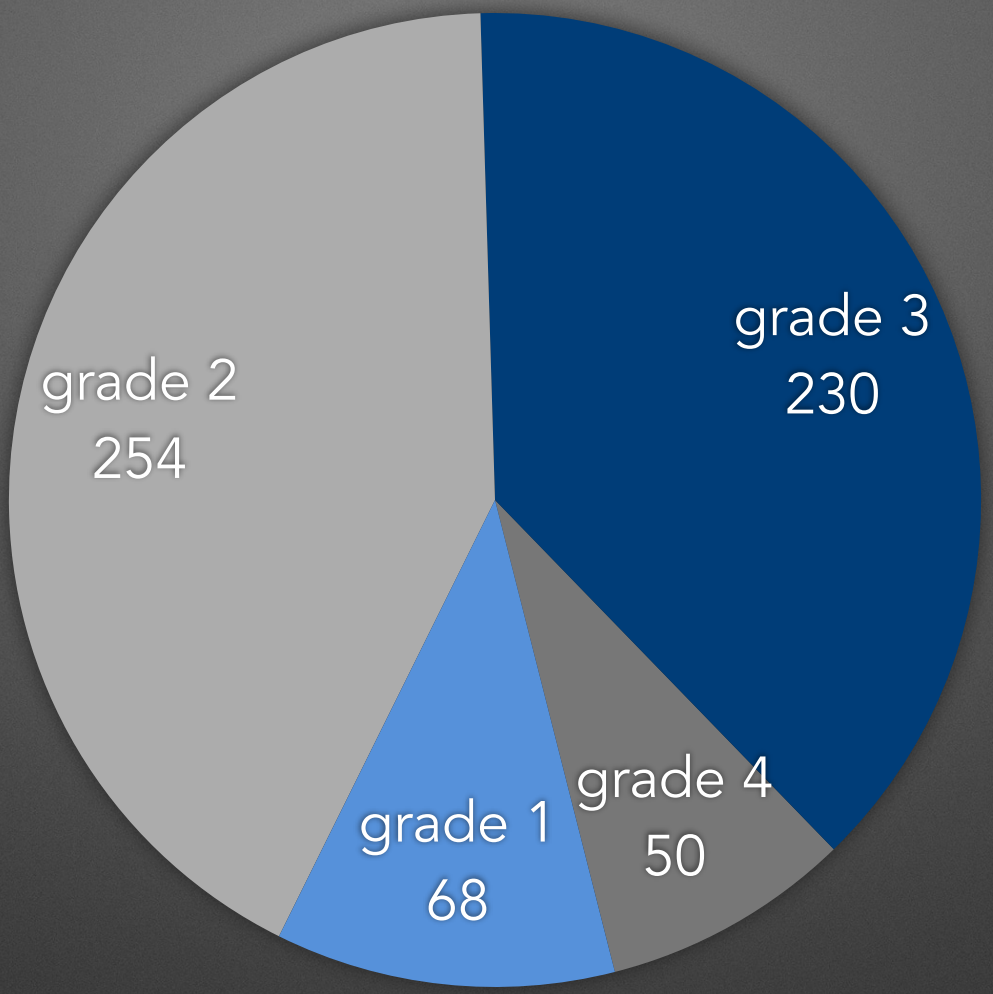
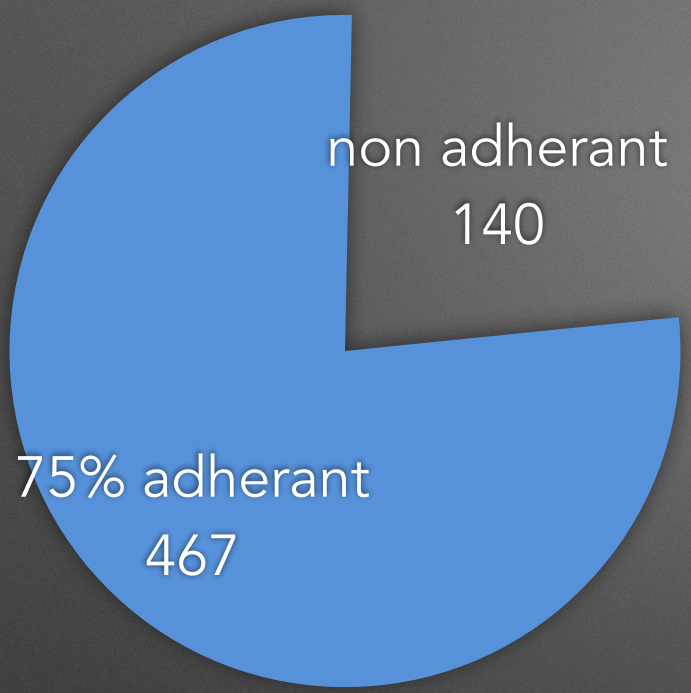
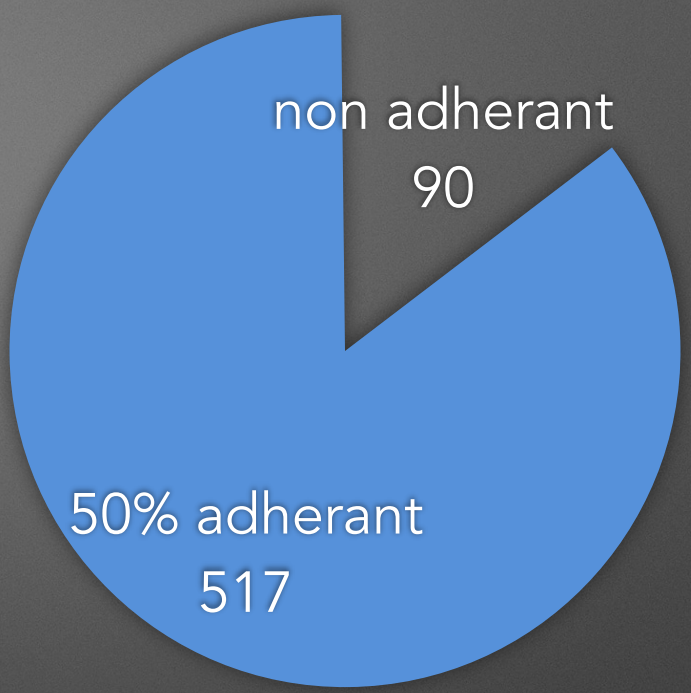


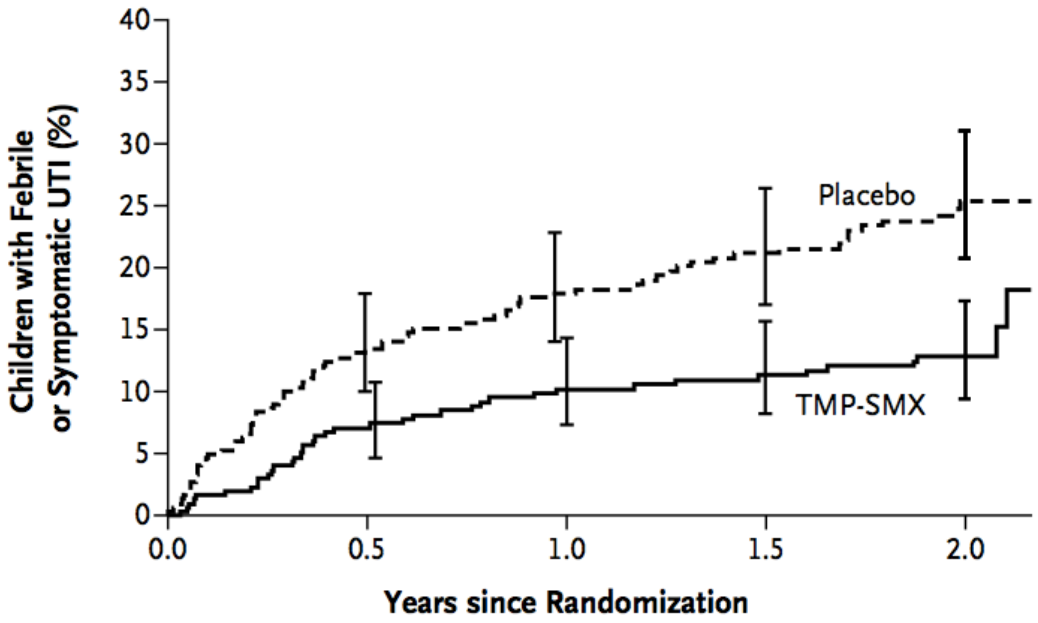
Highest degree of vesicoureteral reflux — no./total no. (%)††			
Grade I	35/301 (11.6)	33/301 (11.0)	68/602 (11.3)
Grade II	123/301 (40.9)	131/301 (43.5)	254/602 (42.2)
Grade III	118/301 (39.2)	112/301 (37.2)	230/602 (38.2)
Grade IV	25/301 (8.3)	25/301 (8.3)	50/602 (8.3)
Bilateral vesicoureteral reflux — no./total no. (%)	146/300 (48.7)	141/300 (47.0)	287/600 (47.8)





Parents of 467 of the children (76.9%) reported having administered the study medication at least 75%

parents of 517 children (85.2%) reported having administered it at least 50% of the time



No. at Risk					
TMP-SMX	302	270	252	244	128
Placebo	305	253	234	214	98

Figure 2. Time to First Recurrent Febrile or Symptomatic UTI.

Shown are Kaplan–Meier estimates of the cumulative percentage of children who had a recurrent febrile or symptomatic UTI according to study group. Fewer children assigned to TMP-SMX prophylaxis had a UTI than children assigned to placebo ($P<0.001$ by log-rank test). I bars indicate 95% confidence intervals.

The risk of febrile or symptomatic recurrences was reduced by half among children who received prophylaxis as compared with those who received placebo

NNT 8 to prevent one febrile infection

NNT 8 to prevent one febrile infection

In separate Cox models, the study group effect remained unchanged after we controlled for age, whether the index urinary tract infection was the child's first or second episode, the degree of baseline reflux, and the presence or absence of baseline renal scarring

Subgroup	No. of Patients with UTI	Total No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Overall	111	607	0.50 (0.34–0.74)	
Sex				0.59
Female	107	558	0.51 (0.34–0.76)	
Male	4	49	0.27 (0.03–2.61)	
Age				0.72
<24 mo	65	405	0.52 (0.31–0.87)	
≥24 mo	46	202	0.45 (0.25–0.83)	
VUR at baseline				0.08
Grade I or II	46	322	0.32 (0.16–0.61)	
Grade III or IV	64	280	0.66 (0.40–1.09)	
VUR at 2 yr				0.93
Resolved	34	218	0.42 (0.20–0.88)	
Improved	17	100	0.52 (0.20–1.37)	
Not improved	25	110	0.49 (0.21–1.11)	
Index UTI				0.11
First episode	94	554	0.43 (0.28–0.66)	
Second episode	17	53	1.01 (0.39–2.65)	
Index UTI type				0.04
Febrile	94	521	0.41 (0.26–0.64)	
Nonfebrile	17	86	1.28 (0.47–3.46)	
Index UTI resistance				0.99
Sensitive to TMP-SMX	77	451	0.49 (0.31–0.79)	
Resistant to TMP-SMX	24	120	0.49 (0.20–1.20)	
BBD at baseline				0.02
Present	25	71	0.21 (0.08–0.58)	
Absent	12	55	1.40 (0.43–4.58)	
BBD during study				0.18
Present	41	154	0.36 (0.18–0.73)	
Absent	24	164	0.76 (0.34–1.70)	
Constipation at baseline				0.78
Present	5	16	0.34 (0.04–3.31)	
Absent	33	113	0.48 (0.23–0.99)	
Constipation during study				0.82
Present	11	51	0.44 (0.12–1.66)	
Absent	58	280	0.52 (0.30–0.90)	

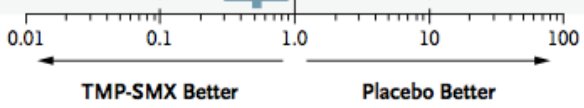
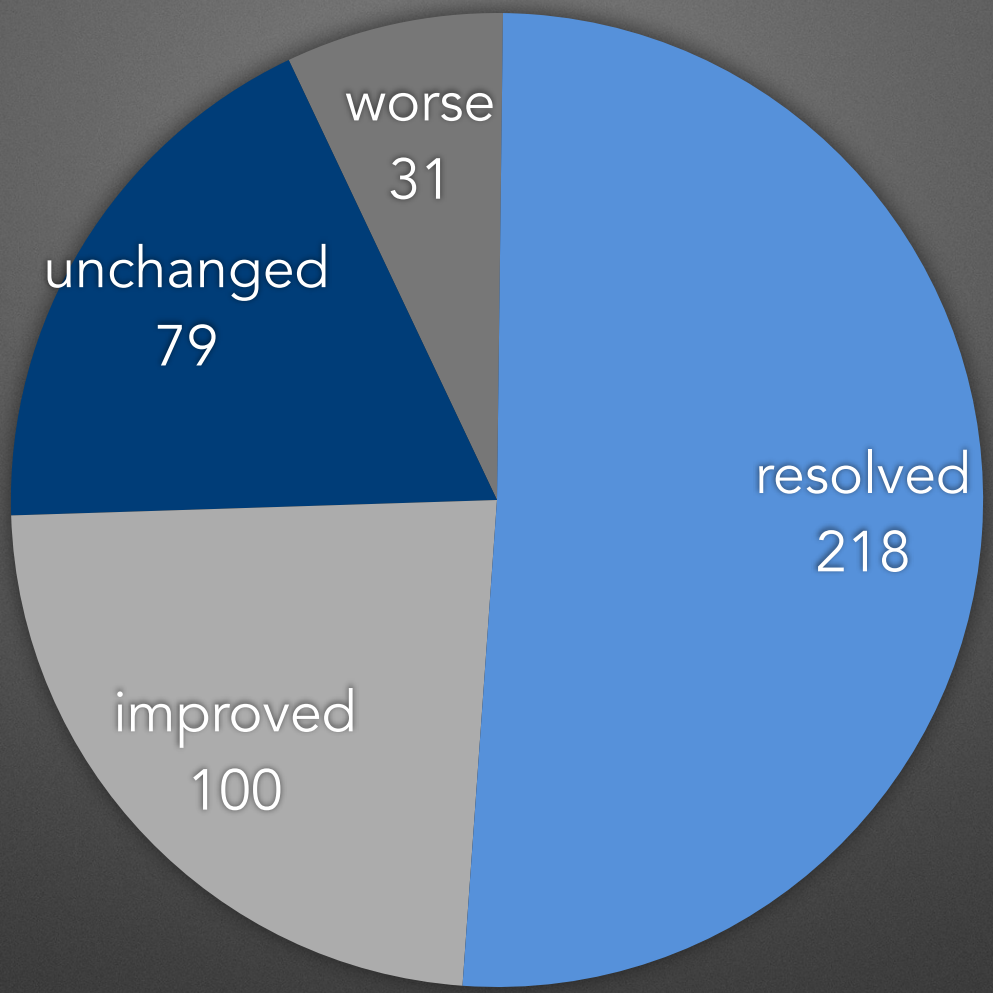


Figure 3. Effect of Antimicrobial Prophylaxis on the Risk of Febrile or Symptomatic UTI.

Depicted are hazard ratios (rectangles) and 95% confidence intervals (horizontal lines) for a first recurrent febrile or symptomatic UTI overall and for subgroups. P values are based on Wald tests for the interaction of subgroup with study-group assignment. Hazard ratios of less than 1.00 indicate that the risk of a recurrent febrile or symptomatic UTI was lower among the children randomly assigned to antimicrobial prophylaxis than among those assigned to placebo. BBD denotes bladder and bowel dysfunction.

Table 2. Clinical Outcomes According to Study Group.

Outcome	Trimethoprim–Sulfamethoxazole	Placebo	Absolute Difference in Risk (95% CI)
	no. of children/total no. (%)		*percentage points*
Recurrent febrile or symptomatic UTI*			
Children with missing 2-yr data classified as having had an event (intention-to-treat analysis)	77/302 (25.5)	114/305 (37.4)†	11.9 (4.6 to 19.2)
Children with missing 2-yr data classified as not having had an event (intention-to-treat analysis)‡	39/302 (12.8)	72/305 (25.4)§	12.6 (6.1 to 19.0)
Children with missing 2-yr data omitted	39/264 (14.8)	72/263 (27.4)§	12.6 (5.7 to 19.5)
Treatment failure‡¶	14/302 (5.0)	27/305 (9.6)‖	4.5 (0.2 to 8.8)
Renal scarring**			
Overall	27/227 (11.9)	24/235 (10.2)	−1.7 (−7.4 to 4.0)
Severe††	9/227 (4.0)	6/235 (2.6)	−1.4 (−4.7 to 1.8)
New‡‡	18/220 (8.2)	19/227 (8.4)	0.2 (−4.9 to 5.3)
Any cortical defect	29/227 (12.8)	25/235 (10.6)	−2.1 (−8.0 to 3.7)
Antimicrobial resistance			
Resistant *Escherichia coli* in stool	56/203 (27.6)	41/210 (19.5)	−8.1 (−16.2 to 0.1)
First recurrent febrile or symptomatic UTI with resistant *E. coli*	19/30 (63.3)§§	11/57 (19.3)	−44.0 (−64.1 to −24.0)
First recurrent febrile or symptomatic UTI with any resistant pathogen	26/38 (68.4)§§	17/69 (24.6)	−43.8 (−61.7 to −25.8)



Voiding cystourethrography was performed at 2 years in 428 children. Reflux was considered to be resolved in 218 children (50.9%), improved in 100 (23.4%), unchanged in 79 (18.5%), and worse in 31 (7.2%).

As long as evidence supporting the benefit of prophylaxis was dubious, the recommendation of a watchful waiting approach, without performance of a voiding cystourethrographic study, seemed reasonable, because the imaging findings would not affect the nature of treatment. However, our finding that antimicrobial prophylaxis was associated with a reduced risk of recurrence may warrant reconsideration of that recommendation.