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## ORIGINAL ARTICLE

# Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

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## ABSTRACT

**BACKGROUND**

From the Screening and Test Evaluation Program (J.C.C., G.J.W., L.M.I.) and the School of Public Health, (J.C.C., J.M.S., E.M.H., L.M.I.), University of Sydney; the Centre for Kidney Research, Children's Hospital at Westmead (J.C.C., G.J.W., A.L., E.M.H., P.H.Y.C., S.H., L.P.R.); and the Department of Urology and Surgery, Children's Hospital at Westmead (G.S.) — all in Sydney; the Department of Paediatrics and Child Health, Australian National University Medical School, Canberra (G.J.R.); Queensland Child and Adolescent Renal Service and the University of Queensland, Brisbane (S.J.M.); Menzies School of Health Research, Charles Darwin University, Darwin (J.R.C.); and Murdoch Children's Research Institute and Royal Children's Hospital, University of Melbourne, Melbourne (N.E.C.) — all in Australia. Address reprint requests to Dr. Craig at the Children's Hospital at Westmead, Centre for Kidney Research, Locked Bag 4001, Westmead, Sydney NSW 2145, Australia.

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Antibiotics are widely administered to children with the intention of preventing urinary tract infection, but adequately powered, placebo-controlled trials regarding efficacy are lacking. This study from four Australian centers examined whether low-dose, continuous oral antibiotic therapy prevents urinary tract infection in predisposed children.

**METHODS**

We randomly assigned children under the age of 18 years who had had one or more microbiologically proven urinary tract infections to receive either daily trimethoprim-sulfamethoxazole suspension (as 2 mg of trimethoprim plus 10 mg of sulfamethoxazole per kilogram of body weight) or placebo for 12 months. The primary outcome was microbiologically confirmed symptomatic urinary tract infection. Intention-to-treat analyses were performed with the use of time-to-event data.

**RESULTS**

From December 1998 to March 2007, a total of 576 children (of 780 planned) underwent randomization. The median age at entry was 14 months; 64% of the patients were girls, 42% had known vesicoureteral reflux (at least grade III in 53% of these patients), and 71% were enrolled after the first diagnosis of urinary tract infection. During the study, urinary tract infection developed in 36 of 288 patients (13%) in the group receiving trimethoprim-sulfamethoxazole (antibiotic group) and in 55 of 288 patients (19%) in the placebo group (hazard ratio in the antibiotic group, 0.61; 95% confidence interval, 0.40 to 0.93;  $P=0.02$  by the log-rank test). In the antibiotic group, the reduction in the absolute risk of urinary tract infection (6 percentage points) appeared to be consistent across all subgroups of patients ( $P\geq 0.20$  for all interactions).

**CONCLUSIONS**

Long-term, low-dose trimethoprim-sulfamethoxazole was associated with a decreased number of urinary tract infections in predisposed children. The treatment effect appeared to be consistent but modest across subgroups. (Australian New Zealand Clinical Trials Registry number, ACTRN12608000470392.)

**U**RINARY TRACT INFECTION IS A VERY common illness in children, affecting 2% of boys and 8% of girls by the age of 7 years.<sup>1</sup> Urinary tract infection is associated with long-term morbidity, with renal damage reported in about 5% of affected children.<sup>2</sup> The observation that urinary tract infection and vesicoureteral reflux are associated with renal damage<sup>3-5</sup> led to the standard clinical practice of assessment with voiding cystourethrography for the presence of vesicoureteral reflux in children who had had urinary tract infection<sup>6,7</sup> and the administration of daily low-dose antibiotics for many years<sup>8</sup> to prevent further urinary tract infections and renal damage in these children. It has been recognized that other children without reflux are also at risk for recurrent urinary tract infection and sequelae, and the use of long-term antibiotics has also been recommended for such children.<sup>9</sup> However, since adequately powered and well-designed, placebo-controlled trials of long-term antibiotics for the prevention of urinary tract infection in children are lacking,<sup>10,11</sup> current clinical practice has been widely questioned.<sup>12,13</sup> Our study, called the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT), was designed to determine whether the long-term use of low-dose antibiotics prevents recurrent urinary tract infection in children.

## METHODS

### PATIENTS

At four centers in Australia, we recruited children from birth to 18 years of age who had had at least one symptomatic urinary tract infection.<sup>14</sup> Children with all grades of vesicoureteral reflux or recurrent infection were potentially eligible. Symptomatic urinary tract infection was defined as symptoms consistent with such an infection together with a positive urine culture, which was defined as any growth of a pathogenic organism from a suprapubic bladder tap or a colony-forming-unit count of  $10^7$  or more of a single organism per liter from a catheter sample or of  $10^8$  or more of a single organism per liter from a mid-stream voided urine sample. Children with a known neurologic, skeletal, or urologic predisposing cause or with a known contraindication to trimethoprim-sulfamethoxazole therapy were ineligible.

### STUDY DESIGN

Children who had completed short-term treatment, had undergone renal tract imaging (if such a study was recommended), and had been clinically asymptomatic before recruitment were randomly assigned to receive either trimethoprim-sulfamethoxazole (Bactrim, Roche) (antibiotic group) or placebo (matched for color, taste, and texture) during 12 months of follow-up. The administration of the study drug ceased when a symptomatic urinary tract infection occurred. Trimethoprim-sulfamethoxazole was chosen as the study drug because it is consistently recommended as the first-line agent for the prevention of urinary tract infection worldwide.<sup>6,7,15,16</sup>

Investigators, patients, pharmacy staff, outcome assessors, and the trial biostatistician were all unaware of study-group assignments. The randomization sequence was computer-generated and stratified according to center, referral source, frequency of previous urinary tract infection, reflux status, age, and sex, according to the method of minimization.<sup>17</sup> Randomization was performed centrally by telephone by an independent clinical trials center after parents of all patients provided written informed consent.

The study was funded by the National Health and Medical Research Council of Australia and the Financial Markets Foundation for Children of Australia. All drugs that were used in the trial were purchased. PRIVENT investigators were responsible for all aspects of the trial.

### URINARY TRACT IMAGING

No requirement for urinary tract imaging was mandated for participation in the trial. This protocol decision reflected the uncertainty surrounding the place of renal tract imaging in pediatric patients with urinary tract infection worldwide.<sup>18</sup> Using local protocols at each center, we performed renal tract ultrasonography, radiologic voiding cystourethrography, and renal scintigraphy with technetium-99m-labeled dimercaptosuccinic acid, with 89% of studies centrally reviewed. When central review was not possible, the routine clinical report was used. Vesicoureteral reflux was graded according to the International Reflux Study,<sup>19</sup> and renal damage was graded according to the criteria of Goldraich et al.<sup>20</sup>

### STUDY MEDICATION

After consent but before randomization, all children received trimethoprim-sulfamethoxazole for

2 weeks during a single-blind run-in period. After randomization, and at every 3-month visit, the study drug was dispensed, with the single daily dose calculated by volume according to body weight (2 mg of trimethoprim plus 10 mg of sulfamethoxazole per kilogram of body weight or 0.25 ml of suspension [containing 40 mg of trimethoprim and 200 mg of sulfamethoxazole per 5 ml] per kilogram,<sup>9</sup> to the nearest 0.5 ml). Adherence was assessed by comparisons of observed and expected volumes remaining in the bottles every 3 months and by direct questioning during study visits.

#### FOLLOW-UP PROCEDURES

Children were seen at 3-month intervals during the 12-month follow-up. At each visit, weight, height, and blood pressure were measured, adherence assessed, and primary and secondary outcomes ascertained with the use of patient diaries and medical records.

#### PRIMARY AND SECONDARY OUTCOMES

The primary outcome was symptomatic urinary tract infection within 12 months, with the use of the same definition as the entry criteria. In the event of infection, the study drug was discontinued, and routine clinical care was provided for the child by the family physician or pediatrician. Children were not followed for longer than 12 months.

Secondary outcomes were urinary tract infection with fever (measured temperature,  $>38.0^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ], or a history of fever), hospitalization for urinary tract infection, hospitalization for causes other than urinary tract infection, antibiotic administration for concomitant illness, and deterioration in cortical scintigraphy at 12 months. Scintigraphy was recommended at the completion of the study in children who had had an abnormal scan at entry or who had a further urinary tract infection. During editorial review, urinary tract infection from bacteria with resistance to trimethoprim-sulfamethoxazole was added as a secondary outcome.

#### STATISTICAL ANALYSIS

We aimed to recruit 780 children (390 in each study group) on the basis of a clinically important reduction in the absolute risk of recurrent symptomatic urinary tract infection of approximately 10 percentage points between the two groups during 12 months of follow-up, with an estimated event rate of 29% in the placebo group. We determined that

#### Figure 1 (facing page). Enrollment and Outcomes.

A total of 13 children (6 in the antibiotic group and 7 in the placebo group) did not fulfill eligibility criteria but underwent randomization and were subsequently identified through central data-validation procedures; 29 children (14 in the antibiotic group and 15 in the placebo group) stopped and restarted a study drug. The numbers of patients who stopped taking a study drug at each time point may not total the number in the final analysis because some subsequently restarted a study drug. UTI denotes urinary tract infection.

this number of patients would provide the study with a power of 80%, with a two-sided type I error of 5% and a nonadherence rate of 10%. An on-treatment risk of 20% was based on trials of antibiotics in children with and without vesicoureteral reflux.<sup>10,11</sup> All analyses were performed on the basis of the intention-to-treat principle.

We compared the proportions of children with primary and secondary outcomes in the two groups using time-to-event analysis for outcomes with respect to urinary tract infection and the chi-square test for other outcomes. The primary outcome was analyzed with the use of the log-rank test. Cox proportional-hazards regression was used to obtain unadjusted hazard ratios and to adjust for significant stratifying variables and to test for effect modification in all secondary analyses. Data from children who were lost to follow-up were regarded as censored at the time of the last contact. Data from children who did not have a urinary tract infection were censored at 365 days. We used Kaplan-Meier estimates of the proportion of children with urinary tract infection throughout. We calculated the number of children who would need to be treated to prevent one urinary tract infection from the hazard ratio and its 95% confidence interval.<sup>21</sup>

To determine whether the treatment effect varied according to the children's reflux status, a priori subgroup analysis was planned with children stratified according to the presence and severity of reflux, and a test of interaction was performed in a Cox model. Post hoc subgroup analyses were also conducted with the use of other stratifying variables, including whether the index infection was sensitive or resistant to trimethoprim-sulfamethoxazole. Treatment effects were described in terms of hazard ratios and absolute risk differences with 95% confidence intervals. All reported P values are two-sided and have not been adjusted for multiple testing.

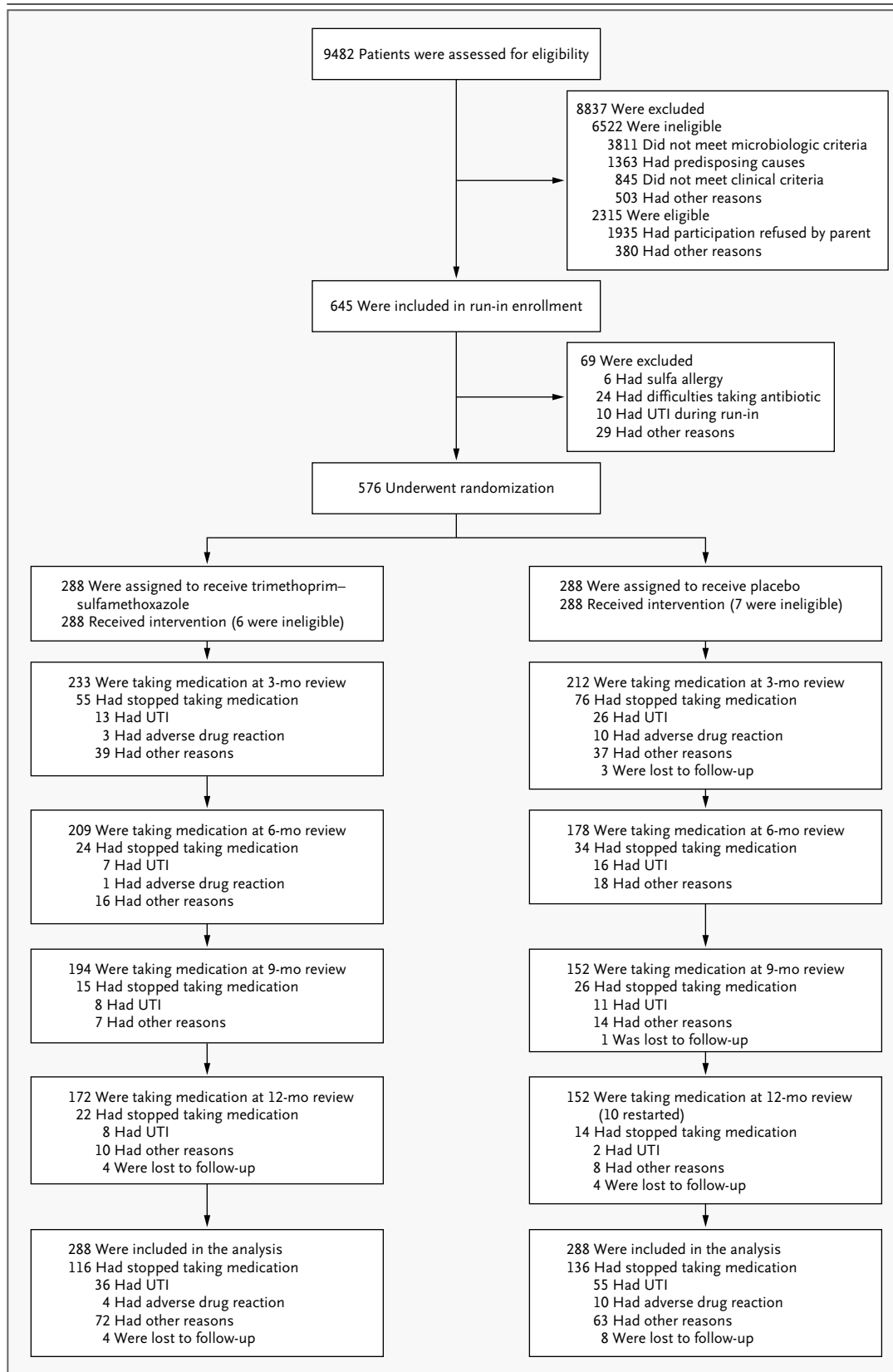


Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	Antibiotic Group (N=288)	Placebo Group (N=288)
Age		
Median — mo	13.1	14.5
Group — no. (%)		
0 to <0.5 yr	61 (21)	53 (18)
0.5 to <1 yr	78 (27)	70 (24)
1 to <2 yr	46 (16)	55 (19)
2 to <4 yr	41 (14)	43 (15)
4 to <10 yr	55 (19)	62 (22)
10 to <15 yr	6 (2)	4 (1)
≥15 yr	1 (<1)	1 (<1)
Female sex — no. (%)	183 (64)	186 (65)
Circumcised — no./total no. (%)		
Yes	4/105 (4)	5/102 (5)
No	94/105 (90)	83/102 (81)
Unknown	7/105 (7)	14/102 (14)
History of urinary tract infection — no. (%)†		
Index infection only	204 (71)	206 (72)
2 infections	26 (9)	35 (12)
≥3 infections	54 (19)	44 (15)
Index urinary tract infection		
With fever‡	219 (76)	235 (82)
With pyuria§		
Yes	191 (66)	197 (68)
No	96 (33)	89 (31)
Unknown	1 (<1)	2 (<1)
Infecting organism — no. (%)		
<i>Escherichia coli</i>	251 (87)	252 (88)
<i>Proteus</i>	11 (4)	15 (5)
<i>Klebsiella</i>	9 (3)	11 (4)
<i>Enterococcus</i>	8 (3)	5 (2)
<i>Pseudomonas</i>	4 (1)	1 (<1)
<i>Staphylococcus</i>	2 (1)	0
Other	3 (1)	4 (1)
Bacterial susceptibility to trimethoprim–sulfamethoxazole — no. (%)		
Sensitive	243 (84)	236 (82)
Resistant¶	42 (15)	44 (15)
Not tested	3 (1)	8 (3)
Maximum grade of vesicoureteral reflux		
None	119 (41)	115 (40)
I or II	57 (20)	57 (20)
III to V	65 (23)	64 (22)
Unknown	47 (16)	52 (18)

**Table 1. (Continued.)**

Characteristic	Antibiotic Group (N=288)	Placebo Group (N=288)
Results of renal scanning — no. (%)		
Abnormal	73 (25)	73 (25)
Normal	160 (56)	162 (56)
Not performed	55 (19)	53 (18)
Study center — no. (%)		
Sydney	179 (62)	181 (63)
Canberra	69 (24)	68 (24)
Brisbane	25 (9)	25 (9)
Melbourne	15 (5)	14 (5)
Referral source — no. (%)		
Emergency department	163 (57)	158 (55)
General pediatrician	59 (20)	58 (20)
Family physician	35 (12)	40 (14)
Nephrologist	22 (8)	27 (9)
Urologist or other	9 (3)	5 (2)

\* Percentages may not total 100 because of rounding.

† Among children who were known to have had at least one previous urinary tract infection, the number of previous infections was not known for four children in the antibiotic group and three in the placebo group.

‡ The number of children who had urinary tract infection with fever was not known for three children in the antibiotic group and four in the placebo group.

§ Pyuria was defined as the presence of at least 100 white cells per cubic millimeter.

¶ Included in this category were nine children (six in the antibiotic group and three in the placebo group) whose index infection was caused by enterococcus or pseudomonas. These bacteria were not tested for susceptibility to trimethoprim-sulfamethoxazole but were assumed to be resistant. Also included were 20 children (12 in the antibiotic group and 8 in the placebo group) whose index infection was caused by bacteria that were resistant to trimethoprim but that were not tested for resistance to sulfamethoxazole.

## RESULTS

### RECRUITMENT AND FOLLOW-UP

From December 1998 through March 2007, we reviewed the results of urine testing for 9482 patients. Of these patients, only 2960 were deemed to be eligible to participate in the study. Of the eligible patients, consent was provided for 645 (22%), and 576 children (89% of those who provided consent) underwent randomization after the 2-week run-in period. Reasons for ineligibility, lack of consent, and exclusion before randomization are provided in Figure 1.

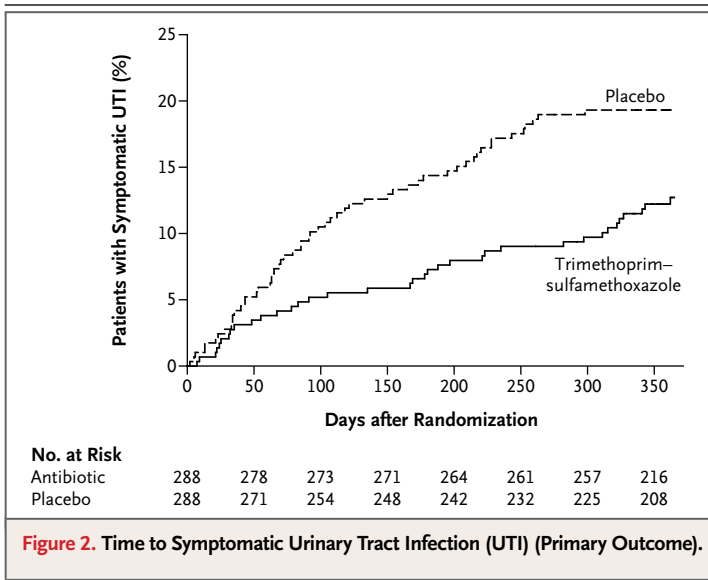
Enrollment ceased at 576 patients, rather than at 780 patients as planned, because of slow recruitment in some centers. The decision to cease recruitment was made without any knowledge of the outcomes and was based solely on the accrual rate. Of the 576 patients who underwent randomization, complete follow-up data were obtained for 564 (98%). A total of 12 children (4 in the anti-

biotic group and 8 in the placebo group) were lost to follow-up; 13 children (6 in the antibiotic group and 7 in the placebo group) did not fulfill eligibility criteria but underwent randomization and were subsequently identified through central data-validation procedures. Reasons for ineligibility were an unconfirmed urinary tract infection (one patient), asymptomatic infection (two patients), a lack of pure bacterial growth (two patients), sample collection from a urine bag (three patients), and bacterial growth below threshold (five patients).

### BASELINE CHARACTERISTICS AND ADHERENCE

Equal numbers of children (288) were randomly assigned to each study group, and baseline characteristics were well matched (Table 1). Overall, the median age at entry was 14 months; 64% of the patients were girls, 42% had known reflux (at least grade III in 53%), and 71% enrolled after the first diagnosis of a urinary tract infection. In the two





**Figure 2. Time to Symptomatic Urinary Tract Infection (UTI) (Primary Outcome).**

groups, approximately 87% of the index infections were caused by *Escherichia coli*, and 15% of the infecting bacteria were resistant to trimethoprim-sulfamethoxazole.

During the study period, a number of patients stopped taking a study drug for reasons other than the diagnosis of symptomatic urinary tract infection: 90 of 576 patients (16%) at 3 months, 122 of 514 patients (24%) at 6 months, 141 of 495 patients (28%) at 9 months, and 151 of 485 patients (31%) at 12 months. A total of 29 children (15 in the antibiotic group and 14 in the placebo group) stopped and restarted a study drug during the 12-month period. Fourteen children (4 in the antibiotic group and 10 in the placebo group) (2%) permanently discontinued a study drug because of a mild adverse drug reaction. There was no difference in the frequency of reported nonadherence between the antibiotic group and the placebo group.

#### PRIMARY OUTCOME

During the study period, urinary tract infection was diagnosed in 36 of 288 patients (13%) in the antibiotic group and in 55 of 288 (19%) in the placebo group (hazard ratio in the antibiotic group, 0.61; 95% confidence interval [CI], 0.40 to 0.93;  $P=0.02$  by the log-rank test), a difference of 6 percentage points (95% CI, 1 to 13) (Fig. 2). Thus, at 12 months, 14 patients (95% CI, 9 to 86) would need to have been treated to prevent one urinary tract infection. Half the events in the placebo group occurred within 3 months after randomization; an

additional 25% occurred during the next 3 months. The spectrum of infecting bacteria was similar in the two groups, with *Escherichia coli* identified as the causative bacterium in 30 of 36 patients (83%) in the antibiotic group and in 46 of 55 patients (84%) in the placebo group.

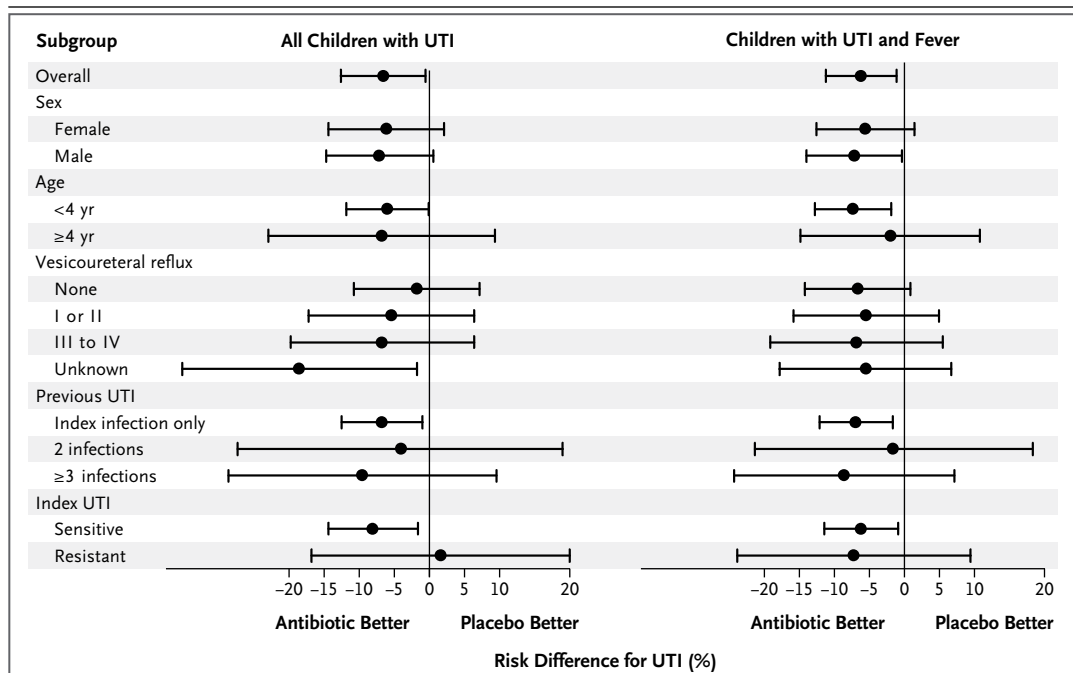
The effect of trimethoprim-sulfamethoxazole on the prevention of symptomatic urinary tract infection did not vary significantly according to any stratifying variable: age, sex, reflux status, history of more than one urinary tract infection, or susceptibility of the causative organism for the index infection to trimethoprim-sulfamethoxazole. The relative hazard did not vary significantly, and the absolute risk difference was 6 to 8 percentage points across all subgroups (Fig. 3, and Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The point estimates favored trimethoprim-sulfamethoxazole for all subgroups except for the group of children who had an index urinary tract infection caused by an organism that was resistant to trimethoprim-sulfamethoxazole.

#### SECONDARY OUTCOMES

The frequency of secondary outcomes was numerically lower, but generally not significantly lower, in the antibiotic group than in the placebo group, with the exception of urinary tract infection from bacteria that were resistant to trimethoprim-sulfamethoxazole, which occurred more frequently in the antibiotic group (Table 2). During the study period, urinary tract infection with fever developed in 19 of 288 patients (7%) in the antibiotic group and in 36 of 288 patients (13%) in the placebo group (hazard ratio, 0.49; 95% CI, 0.28 to 0.86;  $P=0.01$ ), a difference of 6 percentage points (95% CI, 1 to 11) (Fig. 4). The effect of trimethoprim-sulfamethoxazole on the prevention of symptomatic febrile urinary tract infection did not vary significantly according to any stratifying variable in either relative or absolute terms (Fig. 3, and Table 2 in the Supplementary Appendix).

The progression of abnormal results on renal scanning from baseline to follow-up did not differ significantly between the antibiotic group and the placebo group, although, as expected, very few patients had a worsening of scanning results at 12 months, as compared with baseline. Fewer hospitalizations and adverse drug reactions occurred in the antibiotic group than in the placebo group, but the differences were not significant. Although





**Figure 3. Effect of Trimethoprim–Sulfamethoxazole on the Risk of Symptomatic Urinary Tract Infection (UTI) with and without Fever.**

The differences in risk rather than hazard ratios are shown for subgroups of patients receiving either trimethoprim–sulfamethoxazole (antibiotic group) or placebo because the risk difference appeared to be a more consistent measure and more clinically applicable. No significant interactions were identified among the various subgroups of patients. The horizontal bars represent 95% confidence intervals.

the number of children who received at least one course of antibiotics for a cause other than urinary tract infection was not significantly lower in the antibiotic group, a test for trend showed that children in the placebo group were more likely to receive more courses of antibiotics than were children in the antibiotic group (Table 2).

## DISCUSSION

Long-term, low-dose trimethoprim–sulfamethoxazole was associated with a modest decrease in the number of symptomatic urinary tract infections in predisposed children, with a reduction in absolute risk of 6 percentage points. This finding means that 14 children would need to be treated to prevent one case of urinary tract infection. The absolute treatment effect appeared to be consistent across a wide range of risk factors for further urinary tract infection. The pattern of recurrence suggested that the benefit of antibiotic therapy was greatest during the first 6 months of treatment, the most likely time for recurrent in-

fection. Although trimethoprim–sulfamethoxazole prevented urinary tract infection overall, our data suggest that prolonged administration resulted in changes in the susceptibility of pathogenic bacteria, with an increased risk of symptomatic urinary tract infection caused by bacteria that were resistant to trimethoprim–sulfamethoxazole. The results indicated that children with an index infection that was resistant to trimethoprim–sulfamethoxazole might not benefit from such prophylaxis.

Any benefits of long-term antibiotic use in reducing the risk of new kidney damage from pyelonephritis remain speculative, since our study was not powered to analyze this outcome. However, given the modest reduction in the risk of urinary tract infection in the antibiotic group and the low risk of new damage (5%) occurring with a single infection,<sup>2</sup> the magnitude of the benefits is likely to be small at best. Our findings are strengthened by the finding that there was a reduced risk of febrile urinary tract infection among children in the antibiotic group. Concern that the long-term

**Table 2. Secondary Outcomes.**

Outcome	Antibiotic Group (N=288) no. (%)	Placebo Group (N=288) no. (%)	Risk Difference (95% CI)*	P Value
Urinary tract infection with fever†	19 (7)	36 (13)	6 (1 to 11)	0.01
Hospitalization for urinary tract infection	23 (8)	29 (10)	2 (-3 to 7)	0.38
Urinary tract infection with organism resistant to trimethoprim–sulfamethoxazole‡	24 (67)	13 (25)	-42 (-61 to -22)	<0.001
Adverse drug reaction	4 (1)	10 (3)	2 (0 to 5)	0.10
Use of antibiotic for other infectious disease				
Any episode	123 (43)	141 (49)	6 (-2 to 14)	0.13
No. of episodes				
0	165 (57)	147 (51)		0.04§
1	66 (23)	65 (23)		
2	37 (13)	42 (15)		
3	12 (4)	18 (6)		
4	3 (1)	11 (4)		
≥5	5 (2)	5 (2)		
Renal scan at 1 yr¶				
No. of patients	71	83		
Normal results				
Unchanged as compared with baseline	36 (51)	45 (54)	4 (-12 to 19)	0.87
Resolved as compared with baseline	12 (17)	28 (34)		
No baseline scan	19 (27)	15 (18)		
Abnormal results				
Improved as compared with baseline	5 (7)	2 (2)		
Unchanged as compared with baseline	35 (49)	38 (46)		
Improved as compared with baseline	9 (13)	12 (14)		
Unchanged as compared with baseline	18 (25)	19 (23)		
Worse as compared with baseline	5 (7)	7 (8)		
No baseline scan	3 (4)	0		

\* Positive numbers indicate higher risk in the placebo group, and negative numbers increased risk in the antibiotic group. Values may not equal the numerical between-group differences because of rounding.

† The number of children who had a urinary tract infection with fever was not known for five children in each group. For this outcome, P values were calculated with the use of the log-rank test, and percentages are Kaplan–Meier estimates.

‡ The percentages in this category are the proportions of patients with resistant bacteria in whom urinary tract infection was diagnosed and for whom the susceptibility to either trimethoprim or trimethoprim–sulfamethoxazole was known (36 in the antibiotic group and 52 in the placebo group). Two children (one in the antibiotic group and one in the placebo group) had one or more subsequent urinary tract infections that were caused by enterococcus or pseudomonas; these organisms were not tested for susceptibility to trimethoprim–sulfamethoxazole but were assumed to be resistant. Eight children (six in the antibiotic group and two in the placebo group) had infections caused by bacteria that were resistant to trimethoprim but that were not tested for resistance to sulfamethoxazole. Resistance was not tested in three children in the placebo group. The P value for this comparison was calculated with the chi-square test.

§ The P value was calculated with the use of the Mantel–Haenszel test for trend.

¶ The percentages in this category are the proportions of patients with various results who underwent renal scanning at 1 year. Results of renal scanning at 1 year were not known for 22 children in the antibiotic group and 17 in the placebo group who had abnormal results at baseline. The P value for this comparison was calculated with the chi-square test of proportions with a normal scan at 1 year.

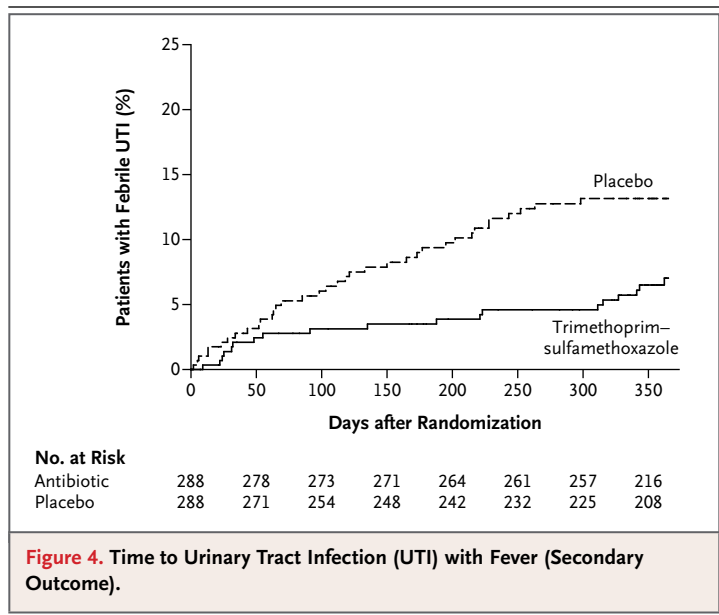
use of antibiotics in such patients may predispose to infections other than urinary tract infection was probably unfounded, since the rate of such infections that were severe enough to warrant the use of antibiotics was lower in the antibiotic group than in the placebo group.

Data from randomized, controlled trials to inform the treatment of children with urinary tract infection have been sparse.<sup>22</sup> In the 1970s, four trials of the prophylactic use of antibiotics tended to favor the antibiotic group.<sup>23–26</sup> However, the combined studies involved only 171 children, of

whom only 32 had reflux, and methodologic limitations and the reporting of positive urine cultures rather than clinically important, symptomatic urinary tract infection limited the applicability of those trials.

Despite such weak evidence, a 20-year hiatus in trials followed, during which time antibiotic prophylaxis was considered to be good clinical practice, making the use of placebo in a trial unethical. During the past decade, as a reflection of the growing uncertainty regarding the efficacy of antibiotic prophylaxis for urinary tract infection, the results of five randomized, controlled trials of antibiotics in children with and without reflux have been published.<sup>27-31</sup> However, none of these trials were placebo-controlled or reported adherence. Furthermore, all the trials were underpowered, with sample sizes of between 100 and 218 patients.<sup>10,11,32</sup> These trials did not show a benefit for prophylactic antibiotics, with the absolute difference in the risk of symptomatic urinary tract infection in the antibiotic group ranging from a reduction of 0.9 percentage points to an increase of 6.0 percentage points. The discordance of these results with our findings may be explained by the lack of adherence to long-term antibiotic use, a lack of statistical power, and unbalanced co-interventions in the earlier trials. We await with interest the results of the ongoing, placebo-controlled Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study (ClinicalTrials.gov number, NCT00405704),<sup>33</sup> which is being funded by the National Institutes of Health. A recent data-linkage cohort study<sup>34</sup> showed no benefit for antibiotic prophylaxis, but the observational nature of the study creates the potential for residual selection bias, and reliance on linked data for outcomes ascertainment renders the validity of these findings uncertain.

Our study had potential limitations. We planned to recruit 780 children but recruited only 576, largely because of a changing attitude away from using prophylactic antibiotics during the nearly 10-year recruitment period. However, our study was adequately powered to show a reduction in the rate of symptomatic urinary tract infection, and these analyses are valid because the study was terminated without regard for outcomes. Our study was not designed to estimate the effect of trimethoprim-sulfamethoxazole on the progression of renal damage, as seen on renal scans.



Given the very low rate of persistent kidney damage after a single urinary tract infection and the modest benefit of antibiotics, a trial would need to enroll at least two to three times the number of patients in our study to show benefit in such patients. Only 4% of boys in the study were circumcised, which reflects the current rate of circumcision among boys in Australia. Accordingly, the study was not designed to address the incremental effect of trimethoprim-sulfamethoxazole over circumcision.<sup>35</sup>

Since the rate of adverse events did not differ between the two study groups and the risk of infections other than urinary tract infection that were severe enough to require the use of antibiotics was lower in the antibiotic group, it would be reasonable for clinicians to recommend the use of trimethoprim-sulfamethoxazole in children who are at high risk for infection or whose index infection was severe. Established risk factors for urinary tract infection are female sex, vesicoureteral reflux, and, particularly, recurrent urinary tract infection.<sup>34,36</sup> In children who have had a single symptomatic urinary tract infection, prophylaxis with trimethoprim-sulfamethoxazole should be considered but not routinely recommended. The modest size of the benefit and the possibility of rare but serious complications from the use of trimethoprim-sulfamethoxazole, such as the Stevens-Johnson syndrome,<sup>37</sup> suggest that the drug should not be used prophylactically in children who have never had a symptomatic uri-

nary tract infection (e.g., those with congenital hydronephrosis or siblings with reflux).

In conclusion, our results indicate that long-term, low-dose antibiotic use was associated with a modest reduction (7 percentage points) in the absolute risk of symptomatic urinary tract infection in predisposed children, regardless of age, sex, frequency of previous urinary tract infection, and concomitant reflux, and may reduce the likelihood that antibiotics will be required for other infections.

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