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ORIGINAL ARTICLE

# Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial

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**Abstract**
*Background* The benefits of long-term low-dose antibiotics in preventing urinary tract infection (UTI) and renal damage in children with primary vesicoureteric reflux (VUR) are unclear.
*Methods* Children aged between 1 and 12 years with VUR grade I–IV and a microbiologically proven UTI were randomized into two groups to receive either antibiotic prophylaxis [2 mg/kg trimethoprim + sulfamethoxazole (TMP-SMX)] daily or placebo, respectively, for 12 months. Primary outcome was microbiologically confirmed symptomatic UTI. Intention-to-treat analysis using time-to-event data was performed.
*Results* A total of 93 children (66.7 % boys) with a median age of 4.6 years were enrolled in this study; VUR grade III–IV was present in 73.1 % of these children. At least one symptomatic UTI occurred in ten (21.3 %) patients receiving antibiotic prophylaxis and in three (6.5 %) patients receiving placebo [hazard ratio in antibiotic group 3.9; 95 % confidence interval (CI) 1– 14; log rank test $P$=0.02). Compared to the group receiving placebo, the antibiotic group had a 14.8 % increased risk for developing UTI (95 % CI 1–28; $P$=0.03). Of the total number of episodes of UTI, 58.3 % of those in the antibiotic group were caused by TMP-SMX-resistant bacteria compared to 20 % in the placebo group ($P$=0.15). A renal scan at 12 months revealed that six of 37 (16.2 %) patients in the antibiotic group and seven of 43 (16.3 %) patients in the placebo group had new or worsening of pre-existing scar.
*Conclusions* Long-term antibiotic prophylaxis with TMP-SMX is associated with increased risk of symptomatic UTI compared to placebo in children with grade I–IV VUR.

**Keywords** Urinary tract infection · Trimethoprim–sulphamethoxazole · Asymptomatic bacteriuria · Bacterial resistance · DMSA scan · Renal scar

**Trial registration** This trial is registered with the Cochrane Renal Group, number CRG110600097

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## Introduction

Urinary tract infection (UTI) occurs in about 2 % of boys and 8 % of girls [1], and one-third of children with proven UTI have vesicoureteric reflux (VUR) [2]. Data from early human and animal studies suggested that UTI in the presence of VUR may cause renal scarring [3]. Various studies subsequently reported that 7–17 % of end-stage renal disease (ESRD) is associated with VUR [4–6], attributable chiefly to renal dysplasia rather than postnatal scarring. Based on the assumption that long-term antibiotic prophylaxis or surgical reimplantation would prevent UTI and subsequent renal scarring, these interventions became the standard clinical practice for the treatment of VUR. In a Cochrane review, Wheeler et al. [7] concluded that there was no difference in the incidence of UTI and renal scarring in children treated with either surgery or

long-term antibiotic prophylaxis. Being non-invasive, the latter became the corner stone of therapy for VUR [8].

A decade ago, Williams et al. [9] in a systematic review found that the evidence to support long-term antibiotic prophylaxis for prevention of UTI was weak. Although generally safe and well tolerated, antibiotic prophylaxis, in addition to its financial costs, can potentially increase the risk of antibiotic-resistant infections in children receiving them. Given this questionable efficacy and potential risk of bacterial resistance, several studies subsequently evaluated antibiotic prophylaxis in children with VUR. While most initial studies failed to show any significant reduction in UTI and scarring [10–12], one study demonstrated an increase incidence of UTI and antibiotic resistance in children with VUR receiving antibiotic prophylaxis [13]. In the study reported here, we conducted a double-blind placebo-controlled trial to determine whether the long-term use of low-dose antibiotics prevents recurrent UTI in children with VUR in a developing country.

## Patients and methods

Children of either sex aged <12 years who were diagnosed with VUR on micturating cystourethrogram (MCU) following a febrile UTI at a tertiary care hospital were eligible for entry into the study. Children aged < 1 year, those with grade V VUR or VUR secondary to urinary tract obstruction, including posterior urethral valves, neurogenic bladder and primary megaureter, were not included in the trial. Children with a history of voiding dysfunction or drug sensitivity to sulphonamides or with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 $m^2$ were also excluded [14]. Symptoms of voiding dysfunction were examined in detail; no scoring was used to define bladder bowel dysfunction. A trained nurse assisted in obtaining urine samples in young children. The study was approved by the Institute Ethics Committee and permission was obtained from the patients and/or parents who participated.

Positive urine culture was defined by the presence of $>10^5$ colony forming units of a single organism per millilitre from a clean catch urine sample. Symptomatic UTI was diagnosed by positive urine culture in a child with isolated fever (>100.4 °C) or urinary symptoms suggestive of UTI. Asymptomatic bacteriuria was defined as positive urine culture in the absence of symptoms, irrespective of leukocyturia.

### Baseline investigations

All children underwent renal function test, urine examination, culture, renal ultrasound, MCU and technetium-99 m-labelled dimercaptosuccinic acid ($^{99m}$Tc-DMSA) scintigraphy to detect renal scarring. VUR was graded on the MCU by a single radiologist according to the International Reflux Study [15]. The baseline and end of study nuclear scans were compared by a single nuclear physician according to the criteria of Goldraich et al. [16]. $^{99m}$Tc-DMSA scans were done at least 12 weeks after the UTI.

### Randomization and intervention

After informed consent, children were randomly assigned to receive either trimethoprim–sulfamethoxazole (TMP-SMX; antibiotic group) or placebo (matched for color, taste and texture) during 12 months of follow-up. Permuted-blocked randomization was done using a fixed block size of four. The randomization sequence was computer-generated. Opaque sealed envelopes containing the identity of the groups were arranged according to the serial number. Patients and investigators, including the radiologist and microbiologist, were blinded to the allocation. The allocation of the patients to the groups was revealed after the statistical analysis was completed. The study medication was dispensed as a suspension containing 40 mg of trimethoprim and 200 mg of sulfamethoxazole per 5 ml or placebo. The daily dose was calculated according to body weight (2 mg of trimethoprim + 10 mg of sulfamethoxazole per kilogram of body weight or 0.25 ml of suspension per kilogram, to the nearest 0.5 ml).

### Follow-up

Children were seen every month during the 12-month follow-up. At each visit, weight and blood pressure were measured and a urine sample was obtained for culture irrespective of symptoms. Parents were instructed to bring the bottle containing the medication to assess compliance, and at each visit the volume of suspension remaining in the returned bottle was measured. A urine specimen for culture and routine and microscopic examination was obtained from all patients suspected of having UTI. All patients with UTI were treated with either cefixime or ofloxacin orally in appropriate doses for 10 days. On completion of therapy for UTI, study medication was restarted. Patients in either group who developed more than two episodes of UTI within 6 months during the follow-up period were considered to be treatment failures and withdrawn from the study. Intercurrent illnesses in the two groups were managed by the Principal Investigator who decided whether or not antibiotic therapy was needed; if needed, antibiotic prophylaxis was withheld while antibiotic therapy was given. The patients were asked to record all events in a diary, including the dose and duration of antibiotic therapy given for infections other than UTI. At the end of 12 months, study subjects underwent a renal ultrasound, MCU and $^{99m}$Tc-DMSA scan.

### Primary and secondary outcomes

The primary outcome was the proportion of patients developing UTI within 12 months. Secondary outcomes included asymptomatic bacteriuria, UTI with bacteria resistant to TMP-SMX, antibiotic administration for concomitant infections and worsening of scarring on renal scintigraphy.

### Sample size and statistical analysis

At the time of designing this study, there were no published trials comparing the effects of antibiotic prophylaxis with no treatment or placebo; only the data on the proportions of patients developing UTI with VUR treated with antibiotic prophylaxis were available. Wheeler et al. [7] in a systematic review reported that 20 % of children on antibiotic prophylaxis would develop UTI over 1 year. Due to this lack of data, we estimated that 40 % children not receiving antibiotic prophylaxis would develop UTI. For a reduction in UTI by 50 % in the patients treated with antibiotic prophylaxis, 91 patients were required in each group with 80 % power and an alpha error of 5 %. To account for a 5 % dropouts rate, our aim was to recruit 190 children with VUR randomized to either the treatment or no treatment group. All analyses were performed on the basis of the intention-to-treat principle. Treatment effects were described in terms of absolute risk difference and hazard ratio (HR) with the 95 % confidence interval (CI). All reported *P* values are two-sided. We also compared the proportions of children with primary outcome in the two groups using time-to-event analysis with log-rank test. 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 UTI were censored at 365 days.

## Results

### Recruitment and follow-up

From December 2006 to January 2012, we screened 121 patients with VUR, subsequently excluding 20: Two had secondary VUR, five were aged <1 year, seven had an eGFR of <30 ml/min/1.73 $m^2$ or a serum creatinine level of >1.5 mg/dl and 11 had grade V VUR (Fig. 1). No child was found to have voiding dysfunction or chronic constipation. Three patients refused to participate in the trial, leaving 93 children who underwent randomization; of these 47 were allocated to receive antibiotic prophylaxis while 46 received placebo. The enrolment was stopped at 93 instead of the proposed 190 patients primarily due to slow enrolment of subjects, who were recruited at a single center. The decision to cease recruitment was made without any knowledge of the outcomes. Eight patients were lost to follow-up (1 in the placebo group, 7 in the antibiotic group). Two patients in each group were withdrawn due to treatment failure (2 UTI in 6 months).

### Baseline characteristics

The baseline characteristics of the patients in the two groups were similar (Table 1). Overall the median age at enrolment

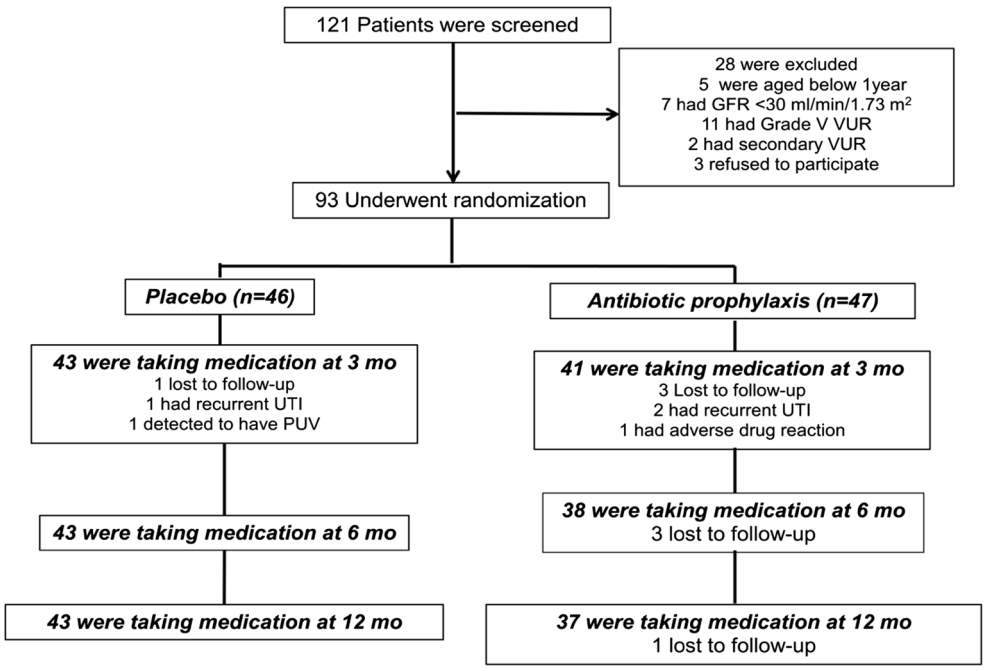


**Fig. 1** Flow of participants in the study. *GFR* Glomerular filtration rate, *VUR* vesicoureteric reflux, *PUV* posterior urethral valve

**Table 1** Baseline characteristics of patients

| Baseline characteristics | Antibiotic group ($n$=47) | Placebo group ($n$=46) | $P$ |
|---|---|---|---|
| Age (years) | 5.7±3.2 | 4.8±3.1 | 0.1 |
| Age group | | | 0.2 |
| 1–5 years | 21 (44.7) | 28 (60.9) | |
| >5 years | 26 (55.3) | 18 (39.1) | |
| Boys | 31 (65.9) | 31 (67.4) | 0.9 |
| History of urinary tract infection | | | 0.4 |
| Index infection only | 23 (48.9) | 19 (41.3) | |
| 2 infections | 9 (19.2) | 14 (30.4) | |
| >2 infections | 15 (31.9) | 13 (28.3) | |
| Family history of VUR | 3 | 0 | |
| Circumcision | 4 (8.5) | 2 (4.3) | |
| Bilateral VUR | 26 (55.3) | 29 (63.0) | 0.6 |
| Maximum grade of VUR | | | 0.2 |
| Grade I–II | 10 (21.3) | 15 (32.6) | |
| Grade III–IV | 37 (78.7) | 31 (67.4) | |
| Renal scarring | | | 0.3 |
| None | 11 (23.4) | 6 (13.0) | |
| Multiple scar | 20 (42.6) | 21 (45.7) | |
| Generalized damage | 20 (42.5) | 21 (47) | |

Data are presented as the mean ± the standard deviation or as the number with the percentage (if relevant) in parenthesis, where appropriate

VUR, vesicoureteric reflux

was 4.6 years; 66.7 % patients were boys. Forty-nine (52.7 %) patients were aged <5 years. Grade III or IV reflux was present in 68 (73.1 %) children. At enrollment, 42 (45.2 %) children had their first UTI, and 74 (79.6 %) patients had a renal scar. All patients were able to provide clean catch samples since the majority of children <3 years of age were boys; transurethral catheter sampling was not required. Two urine samples were found to be contaminated at the monthly visit and repeated.

Compliance to the study medication was not different between the two groups of patients, based on checks on the amount of drug remaining at each monthly visit.

## Primary outcome

During the study, at least one symptomatic UTI occurred in ten of the 47 (21.3 %) patients receiving antibiotic prophylaxis and in three of the 46 (6.5 %) patients receiving placebo (HR in antibiotic group 3.9; 95 % CI 1–14; log rank test $P$=0.02) (Fig. 2). Compared to the placebo group, the antibiotic group had a 14.8 % absolute increase in the risk of UTI (95 % CI 1–28; $P$=0.03) (Table 2). The difference in the risk of UTI persisted after adjustment for age, gender and grade of VUR. Of those patients with grade III–IV VUR, 8/37 (21.6 %) in the antibiotic group and 3/31 (9.7 %) in the placebo group developed symptomatic UTI (risk difference −11.9; 95 % CI −28.8 to 4.9; $P$=0.2). In the subgroup with grade I–II VUR, the frequency of UTI was 20 % in the antibiotic prophylaxis group and zero in the placebo group (no child with UTI). The median time to first UTI was 70 (95 % CI 44.8–155.9) days in patients in the antibiotic prophylaxis group versus 90 (95 % CI 90–105) days in those in the placebo group.

UTIs caused by *Escherichia coli* accounted for nine of 12 and two of five UTI episodes in the antibiotic prophylaxis group and placebo group, respectively. In the antibiotic prophylaxis group, two UTI episodes were due to *Klebsiella pneumonia* and one was due to *Pseudomonas aeruginosa*; in the placebo group, *Proteus mirabilis* and *Klebsiella pneumonia* accounted for two and one episodes, respectively. All patients responded to empirical antibiotic treatment, which was initiated pending the urine culture reports; no patient required a change of antibiotics, and no patient required hospitalization for the treatment of UTI.

## Secondary outcomes

Seven of the 12 isolates causing UTI in the antibiotic group and one of five isolates in the placebo group were resistant to TMP-SMX (risk difference −38.3; 95 % CI −83 to 6.4); $P$=0.3 (Table 2). Two isolates in the antibiotic prophylaxis group were resistant to amoxicillin, third-generation cephalosporins and quinolones; however, both these episodes responded to treatment with co-amoxiclav.

Twenty-one (44.6 %) patients had 67 episodes of asymptomatic bacteriuria in the antibiotic prophylaxis group while 27 (58.6 %) patients on placebo had 68 episodes of asymptomatic bacteriuria ($P$=0.3). Five episodes of asymptomatic

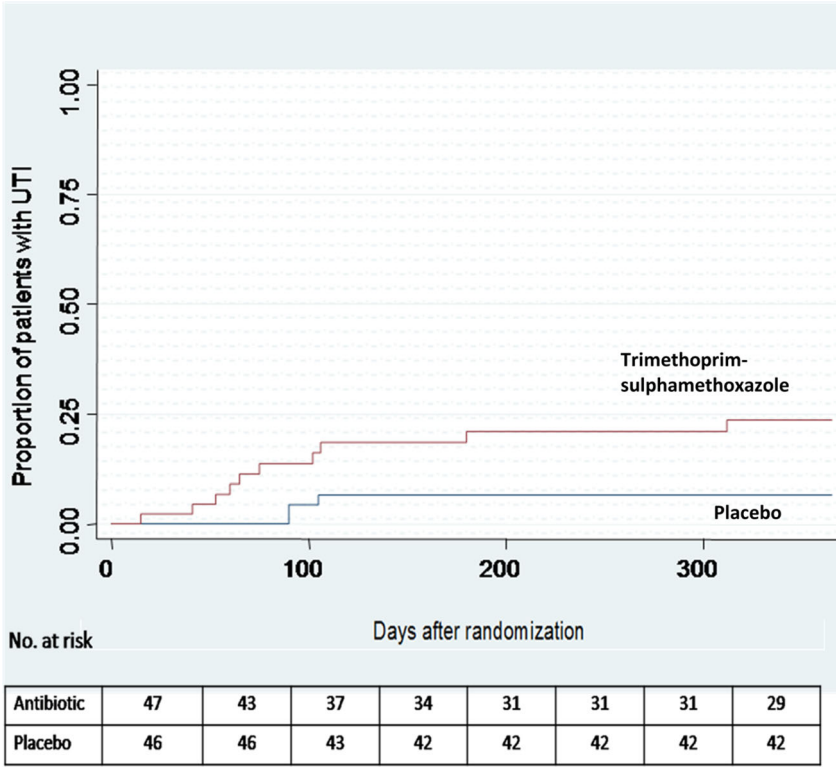


**Fig. 2** Kaplan–Meier graph showing time to first UTI (log rank test $P=0.02$). *UTI* urinary tract infection

bacteriuria in the antibiotic prophylaxis group and two in placebo were associated with leukocyturia. The number of isolates resistant to TMP-SMX was similar in the two groups.

Three children had UTI following asymptomatic bacteriuria, of whom two had grown *E. coli* which were extended spectrum beta-lactamase-positive, and one had grown *K. pneumonia*. All three children were receiving antibiotic prophylaxis. Asymptomatic bacteriuria was diagnosed 10–60 days before the occurrence of symptomatic UTI in these patients. Sixteen patients in the prophylaxis and 11 children in

**Table 2** Outcomes

| Outcome | Antibiotic group ($n=47$) | Placebo group ($n=46$) | Risk difference (95 % CI) | $P$ |
|---|---|---|---|---|
| Primary | | | | |
| Patients with symptomatic UTI | 10 (21.3) | 3 (6.5) | −14.8 (−28 to −1) | 0.03 |
| Febrile UTI | 7 (14.9) | 2 (4.3) | −10.5 (−22.3 to 1.2) | 0.07 |
| Symptomatic UTI in high-grade VUR (grade III–IV) | 8/37 (21.6) | 3/31 (9.7) | −11.9 (−28.8 to 4.9) | 0.2 |
| Median (95 % CI) time to first UTI (days) | 70 (44.8–155.9) | 90 (90–105) | | 0.5 |
| Secondary | | | | |
| UTI isolates resistant to TMP-SMX | 7/12 (58.3) | 1/5 (20) | −38.3 (−83 to 6.4) | 0.3 |
| Patients with asymptomatic bacteriuria | 21 (44.6) | 27 (58.6) | 14 (−6 to 34) | 0.3 |
| Patients with asymptomatic bacteriuria resistant to TMP-SMX | 13 (61.9) | 12 (44.4) | −17.5 (−45.4 to 10.5) | 0.2 |
| No. of episodes of asymptomatic bacteriuria | 67 | 68 | | |
| Asymptomatic bacteriuria isolates resistant to TMP-SMX | 25 (37.3) | 26 (38.2) | 0.9 (−17 to 15) | 0.9 |
| Use of antibiotics for other infections | 16 (34.0) | 11 (23.9) | 10.1 (−28.4 to 8.1) | 0.3 |
| Adverse events | 12 | 11 | | |
| DMSA scan at 12 months | | | | |
| No. of patients | 37 | 43 | | |
| Appearance of new scar | 4 (10.8) | 3 (7.0) | −3.8 (−16.4 to 8.7) | 0.6 |

Data are reported as the number with the percentage in parenthesis, unless indicated otherwise

TMP–SMX, Trimethoprim–sulfamethoxazole; DMSA $^{99m}$ technetium-99 m-labelled dimercaptosuccinic acid; CI, confidence interval; UTI, urinary tract infection

the placebo group required antibiotic therapy for other infections.

Thirty-seven patients in the antibiotic prophylaxis group and 43 in the placebo group underwent DMSA scan at 1 year. New scars appeared in four (10.8 %) patients in the prophylaxis and three (7.0 %) patients in the placebo group ($P$=0.6). Worsening of a pre-existing scar or the appearance of a new scar occurred in six (16.2 %) patients on antibiotic prophylaxis and in seven (16.3 %) patients on placebo ($P$=0.9). A total of 12 and 11 adverse events were recorded in the antibiotic prophylaxis and placebo groups, respectively. The former 12 adverse events included six episodes of upper respiratory tract infection, two episodes of diarrhea, one episode each of skin infection, nail injury and enteric fever; none of these were assessed to be due to the drug. One child in this group had a skin rash which was attributed to the drug. The 11 adverse events in the placebo group consisted of seven episodes of upper respiratory tract infection, two episodes of diarrhea and one episode each of gingivitis and hepatitis A infection. The grade of VUR improved in 16 of 42 patients in placebo group and in 23 of 37 patients in the antibiotic prophylaxis group ($P$=0.2).

## Discussion

Our results show that in our patient cohort long-term low-dose antibiotic prophylaxis with TMP-SMX was associated with an increased risk of UTI as compared to placebo. Most cases of UTI recurrence occurred within 3 months of randomization, resulting in a significant difference in event rates in the two groups at this point in time (Fig. 2). This result is in agreement with that of the PRIVENT trial, which reported that half of the recurrences in the placebo arm occurred in the first 3 months [17]. The rates of infections other than UTI which required antibiotic usage were similar in the antibiotic prophylaxis and placebo groups. The adverse events were uncommon.

In the last decade, several randomized-controlled trials comparing antibiotic prophylaxis with no treatment or placebo for the prevention of UTI in children with and without VUR have been published [10–13, 17, 18]. Initial studies involving children with absent or lesser grades of VUR demonstrated similar rates of recurrent UTI in the treatment versus no treatment groups [10–13]. However these trials were not placebo-controlled and did not report adherence to treatment. The first large randomized, placebo-controlled (PRIVENT) trial [17] involving 576 children with absent or any grade of reflux demonstrated a marginal benefit of 6 % with antibiotic prophylaxis. The Swedish Reflux Study [18] reported on 203 children aged 1–2 years with grade III–IV dilating VUR, who were randomized to antibiotic prophylaxis, surgical correction or observation. A reduced rate of recurrent UTI was found in girls in the treatment groups compared with observation. No treatment benefit was observed in boys. A Cochrane meta-analysis of these trials showed no statistically significant difference in the antibiotic-treated and untreated groups for either symptomatic or febrile UTI during the 1- or 2 year follow-up [19]. There was considerable heterogeneity among the studies for these outcomes. Similar to our findings, there was no significant difference in the urine culture positivity in asymptomatic patients treated with or without antibiotics [19]. Results of the RIVUR trial have been recently published and show that antibiotic prophylaxis reduced recurrences of UTI by 50 % [20]. The benefits of the treatment were greater in children with febrile index UTI and in those with bladder-bowel dysfunction (BBD). Results of subgroup analyses of the RIVUR trial with reasonable numbers of subjects and event rates showed that the effect of prophylaxis was not significant in children with grade III–IV VUR and in the absence of BBD. Thus, it would appear that in this study group prophylaxis was beneficial to a distinct patient population comprised of girls with low-grade reflux and BBD.

The RIVUR trial included 91 % girls, limiting the applicability of its results to boys. Although primary VUR is commonly reported in girls, such a huge gender disparity has not been shown outside the USA [2, 18, 21]. Most patients in the RIVUR trial had grade I–III reflux and scarring was present in less than 5 %. While our patients were mostly boys with severe renal scarring, other studies have also consisted of patient groups comprising 35–40 % boys and an associated 40–57 % scarring at baseline [11, 18, 20]. A majority of renal scarring in severe grades of reflux, as seen in our study, would represent renal dysplasia. While this phenotype of VUR may represent severe disease, it is this population of VUR which is likely to develop ESRD and hypertension, where the benefit of intervention is most needed and requires to be demonstrated. Our results suggest that antibiotic prophylaxis may be particularly harmful in a VUR population consisting predominantly of boys with high-grade VUR and baseline renal scarring. This is somewhat similar to findings of the Swedish trial where boys with grade III–IV VUR and baseline scarring did not benefit from antibiotic prophylaxis, as opposed to girls [18]. In contrast, gender difference in terms of the efficacy of antibiotic prophylaxis was not demonstrated in the PRIVENT trial [17].

Similar to the results of our study, Garin et al. [13] also found that the risk of pyelonephritis was higher in those treated with antibiotic prophylaxis than in untreated children. Although statistically insignificant, Pennesi et al. [11] also found a trend favouring more UTI in children on antibiotic prophylaxis, although the difference was not statistically significant. The increased risk of UTI in children on antibiotic prophylaxis as compared to placebo could possibly be due to eradication of the protective periurethral flora, leading to colonization and later infection with virulent bacteria in

antibiotic-treated patients. Since the compliance to medication was carefully monitored in our trial, it is unlikely that lack of adherence to antibiotic prophylaxis resulted in breakthrough UTI. VUR is increasingly being recognized as a heterogeneous condition with regional and genetic differences [22]. Differences in demographic and clinical characteristics could explain the variability in the effectiveness of antibiotic prophylaxis in various studies.

The proportion of children developing new scars or worsening of pre-existing scars in our study was small and did not differ in the two groups. However, this study was not primarily designed to assess renal scarring in the two groups. Most studies, including the RIVUR trial, but with the exception of the Swedish study, failed to show a significant difference in the occurrence of new renal damage or the progression of existing renal damage [10–13, 17, 18, 20]. The authors of a Cochrane analysis concluded that 33 children would need long-term antibiotic prophylaxis to prevent one more child from developing renal damage over 2–3 years [19].

In our study, more UTI-causing isolates were resistant to TMP-SMX in the antibiotic-treated children than in the placebo group, but the difference was not statistically significant. All studies that have described antimicrobial resistance to the prophylactic drug in subsequent symptomatic UTI have shown that the incidence was increased compared to the no treatment or placebo arm [11, 12, 17, 18, 20]. While resistance to TMP-SMX in children not treated with antibiotic prophylaxis was 20 % in our study, it was 16 % in the PRIVENT trial [17] and 36 % in the Swedish reflux study [18]. Overall estimated risk of prophylactic drug resistance in the repeat UTI was 3-fold fold higher with the use of antibiotic prophylaxis [19].

An important limitation of this study is that the recruitment was stopped before the pre-determined sample size was met due to slow recruitment. While underpowered studies are more likely to be falsely negative, our study showed a statistically significantly increased risk of symptomatic UTI in children receiving antibiotic prophylaxis than in those receiving placebo. There was also a trend of increased febrile UTI in the former group, but the difference was not statistically significant. As the study was well designed with two-tailed sample size calculations and the outcomes measured and analyzed appropriately, the results in the direction opposite to the hypothesis cannot be ignored. Since it is recognized that underpowered studies can overestimate the effect size, the confidence intervals of the results are important. The confidence interval of increased risk of UTI in the prophylaxis group in our study ranged from 1 % (clinically irrelevant) to as high as 28 %. Since we did not anticipate an increased risk of UTI with antibiotic prophylaxis, we did not a priori include an interim analysis in the trial. A pre-planned interim analysis in this study would have very likely have resulted in the trial being stopped at the present sample size.

In conclusion, our study showed a higher risk of symptomatic UTI in children with VUR treated with TMP-SMX as compared to those receiving placebo. This is likely due to increased bacterial resistance in those treated with antibiotic prophylaxis. While the results of this study do not support the use of low-dose prophylaxis with TMP-SMX for prevention of UTI in children with grade I–IV VUR, they do raise a serious safety concern about this intervention. Future trials on antibiotic prophylaxis in VUR should be designed to analyse subgroups, specifically gender, severity of VUR and baseline scarring, and to consider the inclusion of an interim analysis to assess the possible harm of this intervention to the study subjects.

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