Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Williams G, Craig JC

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Long-term antibiotics for preventing recurrent urinary tract infection in children

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ABSTRACT

Background
Urinary tract infection (UTI) is common in children. Symptoms include fever, lethargy, anorexia, and vomiting. UTI is caused by Escherichia coli in over 80% of cases and treatment is a course of antibiotics. Due to acute illness caused by UTI and the risk of pyelonephritis-induced permanent kidney damage, many children are given long-term antibiotics aimed at preventing recurrence.

Objectives
To determine the efficacy and harms of long-term antibiotics to prevent recurrent UTI in children.

Search methods
In November 2010 we searched without language restriction MEDLINE, EMBASE, CENTRAL (in the Cochrane Library), the Cochrane Renal Group’s Specialised Register, reference lists of review articles and contacted content experts.

Selection criteria
Randomised comparisons of antibiotics with other antibiotics, placebo or no treatment to prevent recurrent UTI.

Data collection and analysis
Two authors independently assessed and extracted information. A random-effects model was used to estimate risk ratio (RR) and risk difference (RD) for recurrent UTI with 95% confidence intervals (CI).

Main results
Twelve studies (1557 children) were identified with six (five analysed, 1069 children) comparing antibiotics with placebo/no treatment. Duration of antibiotic prophylaxis varied from 10 weeks to 12 months. Compared to placebo/no treatment, when all studies were included, antibiotics did not appear to reduce the risk of symptomatic UTI (RR 0.75, 95% CI 0.36 to 1.53) however when we evaluated the effects of antibiotics in studies with low risk of bias, there was a statistically significant reduction (RR 0.68, 95% CI 0.48 to 0.95). The effect was similar in children with vesicoureteric reflux (VUR) (RR 0.65, 95% CI 0.39 to 1.07) compared to those without VUR (RR 0.56, 95% CI 0.15 to 2.12). There was no consistency in occurrence of adverse events. Three studies reported antibiotic resistance, showing a non-significant increased risk for resistance to the antibiotic in the active treatment groups (RR 2.4, 95% CI 0.62 to 9.26).
Five studies (4 analysed, 367 children) compared one antibiotic with another but all compared different combinations or different outcomes and studies were not pooled. Two studies reported microbial resistance, nitrofurantoin having a significantly lower risk of resistance than cotrimoxazole (RR 0.54, 95% CI 0.31 to 0.92).

One study compared alternate with every day cefadroxil treatment.

**Authors' conclusions**

Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance.

**PLAIN LANGUAGE SUMMARY**

**Long-term antibiotics for preventing recurrent urinary tract infection in children**

Bladder and kidney infections (urinary tract infection - UTI) are common in children, especially girls. They cause an uncomfortable illness that can include vomiting, fever and tiredness. In some children kidney damage may occur, as can repeat illnesses. With repeated infections the risk of kidney damage increases. Some doctors prescribe long-term antibiotics to try to prevent infections recurring, but this may cause the child to be unwell in other ways, e.g. vomiting. This review of randomised controlled trials (RCTs) found evidence that long-term antibiotics did reduce the risk of more symptomatic infections but the benefit is small and must be weighed against the likelihood that future infections may be with bacteria that are resistant to the antibiotic given.
BACKGROUND

Acute urinary tract infection (UTI) is common in children. By the age of seven years, 8.4% of girls and 1.7% of boys will have suffered at least one episode (Hellstrom 1991). Death is now a rare complication but hospitalisation is frequently required (40%), particularly in infancy (Craig 1998). Transient damage to the kidneys occurs in about 40% of children affected (Craig 1998), and permanent damage occurs in about 5% (Coulthard 1997), sometimes even following a single infection. Symptoms are systemic rather than localised in early childhood and consist of fever, lethargy, anorexia, and vomiting. UTI is caused by *Escherichia coli* in over 80% of cases (Rushton 1997) and treatment consists of a course of antibiotics.

Children who have had one infection are at risk of further infections. Recurrent UTI occurs in up to 30% (Winberg 1975). The risk factors for recurrent infection are vesicoureteric reflux (VUR), bladder instability and previous infections (Hellerstein 1982; Rushton 1997). Recurrence of UTI occurs more commonly in girls than boys (Bergstrom 1972; Winberg 1975).

Due to the unpleasant acute illness caused by UTI and the risk of pyelonephritis-induced permanent kidney damage, many children are given long-term antibiotics aimed at preventing recurrence. Cotrimoxazole, nitrofurantoin and trimethoprim are commonly used for this purpose. These medications may cause side effects and promote the development of resistant bacteria.

OBJECTIVES

The aims of this review were to assess whether long-term antibiotic prophylaxis was more effective than placebo/no treatment in preventing recurrence of UTI in children, and if so which antibiotic in clinical use was the most effective. We also assessed the harms of long-term antibiotic treatment.

METHODS

Criteria for considering studies for this review

Types of studies

- All randomised controlled trials (RCTs) and quasi-RCTs (allocation based on alternation, date of birth, hospital medical record number) of antibiotic treatment versus placebo/no treatment for the prevention of recurrent UTI.
- All RCTs and quasi-RCTs that compared antibiotics with placebo/no treatment or compared two or more antibiotics administered daily for a period of at least two months for the prevention of recurrent UTI, were included.

Types of participants

Children less than 18 years of age who were at risk of recurrence were included. Studies were included if the majority of participants (> 50%) did not have a predisposing cause such as a renal tract abnormality, or a major neurological, urological or muscular disease.

Types of interventions

Long-term antibiotic versus placebo/no treatment, and studies that compared two or more antibiotics with each other. Long-term prophylaxis was defined as antibiotic administered daily for a period of at least two months.

Types of outcome measures

Primary outcomes

The primary outcome was the number of repeat symptomatic UTIs, confirmed by bacterial growth in the urine, in combination with signs or symptoms of a urine infection while on treatment/placebo.

Secondary outcomes

The secondary outcomes were total number of positive urine cultures, adverse reactions to treatment, hospitalisation with UTI and microbial resistance.

Search methods for identification of studies

Review update

For the current update we searched the Cochrane Renal Group's specialised register (November 2010) and MEDLINE/EMBASE (November 2010). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (Renal Group 2011).

Initial search

Relevant studies were obtained from the following sources (see Appendix 1 - Electronic search strategies)

5. Reference lists of relevant articles, reviews and studies.
6. Pharmaceutical industry representatives.
7. Known authors in the field.

There were no language restrictions.

Data collection and analysis

Selection of studies

Review update

This update was undertaken by two authors (GW, JC). The search results were screened and studies included or excluded based on the selection criteria list above.

Initial review and first update

The initial review and first update were undertaken by three (AL, GW, JC) and four authors (GW, AL, JC, LW) respectively. The search strategy described above was used independently by two of three authors to obtain titles of abstracts relevant to the review. The titles were independently screened by two of three authors, who discarded studies that were irrelevant. The selection was overly inclusive to ensure no relevant studies were missed. Two of three authors screened the resulting list of articles independently to assess whether the studies met our inclusion criteria. Disagreements were resolved by discussion with a third author.
Data extraction and management

Full articles of the included studies were examined, under open conditions to extract the necessary information. Methods (definition of initial UTI), participant details (numbers, age, gender), type of antibiotic, frequency and dose regime, duration of treatment, outcomes (recurrent UTI, adverse reactions to treatment) were extracted. Discrepancies in data extraction were resolved by discussion.

Assessment of risk of bias in included studies

Review update

For the current update the risk of bias tables were completed by GW after review of all papers. The following items were assessed by using the risk of bias assessment tool (Higgins 2008) (see Appendix 2).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

Initial review and first update

The quality of eligible studies was assessed independently, under open conditions by two of three authors (AL, GW, LW) with disagreements resolved after consultation with a third. Blinding, losses to follow-up, heterogeneity of study group participants, standardisation of outcome assessment, and whether intention-to-treat analysis was conducted, were assessed.

Measures of treatment effect

The primary outcome was the proportion of patients experiencing a recurrence of symptomatic UTI. The results of each study were calculated as point estimates with their corresponding 95% confidence intervals (CI). The risk ratio (RR) and risk difference (RD) were used as the measures of summary treatment effects. Number needed to treat (NNT) and number needed to harm (NNH) estimates (1/RD) were calculated to compare the benefits and harmful effects of antibiotics. Analysis was conducted for studies;

- comparing antibiotics with placebo/no treatment,
- comparing one type of antibiotic with another type.

Dealing with missing data

Further information was sought from authors where papers did not contain sufficient information to make an appropriate decision about inclusion.

Assessment of heterogeneity

Heterogeneity was analysed using the Q statistic with a threshold for the P value < 0.1 and the I² test (Higgins 2003).

Assessment of reporting biases

Publication bias was to be assessed using a funnel plot, however there were insufficient studies to carry out this assessment.

Data synthesis

Results were pooled using a random effects model.

Subgroup analysis and investigation of heterogeneity

Univariate analyses were used to explore the antibiotic treatment effect on repeat positive urine culture. Subgroup analysis was used to examine how patients VUR status, study quality (risk of bias table fields) and intervention (duration of treatment, type of antibiotic) influenced the summary treatment effect.

RESULTS

Description of studies

Included studies

Twelve studies met our inclusion criteria (see Characteristics of included studies). Two crossover studies did not provide data on the first phase and thus could not be included in the meta-analyses, but findings are described in the text (Carlsten 1985; Lohr 1977). Of the 10 studies with appropriately reported data, five examined antibiotics versus placebo/no treatment (Montini 2008; PRIVENT Study 2009; Savage 1975; Stansfeld 1975; Smellie 1978). The patient populations in the early studies were almost all girls with previous frequent recurrent UTI and normal renal tracts. The most recent studies (Montini 2008; PRIVENT Study 2009) involved a more balanced gender ratio and with the expected proportion having VUR (30% to 40%). The duration of long-term antibiotic treatment (nitrofurantoin, cotrimoxazole, co-amoxiclav or ampicillin) varied from 10 weeks to 12 months. The crossover study comparing nitrofurantoin with placebo (Lohr 1977) included 18 girls with frequent recurrences, 10 of whom commenced the study on nitrofurantoin, crossing to placebo after six months and eight commenced on placebo and crossed over to nitrofurantoin after six months.

Five studies compared the effectiveness of one antibiotic with another. The crossover study (Carlsten 1985) compared nitrofurantoin with pivmecillinam in 35 children and was excluded from the analysis due to incomplete data. Four studies were analysed (Belet 2004; Brendstrup 1990; Falakaflaki 2007; Lettgren 2002) and each was small (80, 130, 132 and 60 children respectively) and in general, poorly reported.

One small study (33 children) compared cefadroxil given every day with cefadroxil given on alternate days (Baculis 2003).

Excluded studies

Twenty studies were excluded. Ten studies were acute treatment studies, three studies were not antibiotic prophylaxis. Five studies included > 50% of participants with neurological/renal tract abnormalities (Garin 2006; Lee 2007; Pennesi 2006; Ray 1970; Roussey-Kesler 2008). Three of these (Garin 2006; Pennesi 2006; Roussey-Kesler 2008) will be included in a Cochrane review of treatment for VUR (Hodson 2007). Two studies were not RCTs; all children received treatment (see Characteristics of excluded studies).
Risk of bias in included studies

Prior to this update analysed studies were poorly reported for methodological detail. Montini 2008 was published initially in abstract form and in this update the primary publication from the study is included with much greater methodological detail. One large, recent study (PRIVENT Study 2009) was well designed, well reported and powered appropriately for the study question (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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<th>Allocation concealment</th>
<th>Blinding?</th>
<th>Incomplete outcome data addressed?</th>
<th>Free of selective reporting?</th>
<th>Free of other bias?</th>
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<td>PRIVENT Study 2009</td>
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<td>Smellie 1978</td>
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Adequate sequence generation

Three studies (Montini 2008; PRIVENT Study 2009; Stansfeld 1975) reported how the randomisation sequence was generated; the remaining studies did not provide any details.

Allocation

Five studies (Brendstrup 1990; Lohr 1977; Montini 2008; PRIVENT Study 2009; Stansfeld 1975) reported that allocation to treatment group was concealed and unable to be influenced by the treating physician. For the remaining studies this was unclear.

Blinding

Four studies stated that they were double blinded or stated who was blind to treatment allocation (Brendstrup 1990; Lohr 1977; PRIVENT Study 2009; Stansfeld 1975). Six studies stated or it was apparent that there was no blinding (Belet 2004; Bacilusi 2003; Carlsen 1985; Montini 2008; Savage 1975; Smellie 1978) and for two studies (Falakafiaki 2007; Lettgen 2002) blinding was unclear.

Incomplete outcome data

Eight studies provided explanations for changes in numbers of children reported at the start and finish of the studies. For four studies (Baciulis 2003; Falakafiaki 2007; Lettgen 2002; Lohr 1977) numbers reported were inconsistent for the start and finish of the study or varied across the reported outcomes without explanation.

Selective reporting

Seven studies reported the most appropriate primary outcome, repeat symptomatic UTI for the question (Brendstrup 1990; Falakafiaki 2007; Lohr 1977; Montini 2008; PRIVENT Study 2009; Savage 1975; Smellie 1978), while the remaining five studies reported a less relevant primary outcome of repeat positive urine culture.

Other potential sources of bias

For many studies it was difficult to determine who the children were and how many were reviewed for possible inclusion in the study and therefore the ability to determine the extent of selection bias was very limited. Only one study, PRIVENT Study 2009, clearly reported the number of patients screened and the reasons for exclusion or non-enrolment.

Definitions and criteria for diagnosis of initial and recurrent UTI differed enormously between the studies and were generally poorly reported. Misclassification was possible in most studies and largely ignored.

Effects of interventions

Antibiotics versus placebo/no treatment

Recurrence of symptomatic UTI

Antibiotics did not appear to reduce the risk of symptomatic UTI (Analysis 1.1 (4 studies, 1034 participants): RR 0.75, 95% CI 0.0.36 to 1.53; RD -8%, 95% CI -21 to 4). Heterogeneity was high (I² = 62%) and this reflects the variability in the early studies. When the two later and largest studies (Montini 2008; PRIVENT Study 2009) were analysed separately, there was a statistically significant reduction with no heterogeneity (Analysis 1.3.1 (2 studies, 914 participants): RR 0.68, 95% CI 0.48 to 0.95; RD -5%, 95% CI -9 to 0; I² = 0%). In the crossover study comparing nitrofurantoin with placebo (Lohr 1977) 14 symptomatic UTIs occurred during the placebo periods and none during nitrofurantoin treatment.

Presence of VUR and recurrence of symptomatic UTI

Three studies reported data on children without VUR (Montini 2008; PRIVENT Study 2009; Smellie 1978) with the summary point estimate suggesting a reduced risk of repeat symptomatic UTI in those on antibiotic prophylaxis compared to those on placebo/no treatment but with considerable imprecision (Analysis 1.2.1: RR 0.56, 95% CI 0.15 to 2.12; RD -12%, 95% CI -29 to 5). The more recent studies (Montini 2008; PRIVENT Study 2009) gave greater consistency and smaller imprecision, with point estimates showing little difference between antibiotic and placebo/no treatment groups.

Two studies reported results for children with VUR (Montini 2008; PRIVENT Study 2009) and showed a small benefit in antibiotic treatment similar to those for all children (Analysis 1.2.2: RR 0.65, 95% CI 0.39 to 1.17; RD -6%, 95% CI -14 to 1).

Study design and risk of bias

Two studies had adequate allocation concealment (Montini 2008; PRIVENT Study 2009) and gave a point estimate with high precision (Analysis 1.3.1: RR 0.68, 95% CI 0.48 to 0.95; RD -5%, 95% CI -9 to 0) while the two studies with unclear allocation concealment (Savage 1975; Smellie 1978) showed considerable imprecision (Analysis 1.3.2: RR 0.35, 95% CI 0.0 to 2.73; RD -16%, 95% CI -73 to 40).

A single study was appropriately blinded (PRIVENT Study 2009) and the point estimate is almost identical to that of the three unblinded studies (Analysis 1.3.3: RR 0.65, 95% CI 0.44 to 0.96; RD -7%, 95% CI -13 to -1 compared to Analysis 1.3.4: RR 0.66, 95% CI 0.15 to 2.90; RD -11%, 95% CI -37 to 15).

Repeat positive urine culture

Compared to placebo/no treatment, antibiotics reduced the risk of repeat positive urine culture (Analysis 1.4.1: RR 0.31, 95% CI 0.08 to 1.18; RD -28% 95% CI -51 to -5) (Montini 2008; Savage 1975; Smellie 1978; Stansfeld 1975). Studies were heterogeneous (I² = 91%) and there was considerable variability in the rates of repeat positive urine cultures in the control groups of the four studies, ranging from 21% to 85%.

Studies with adequate allocation concealment showed a RR of 0.21 (95% CI 0.2 to 2.5; RD -29%, 95% CI -68 to 11) (Analysis 1.5.1) for repeat positive urine culture, while those with inadequate or unclear allocation concealment had the same RR (0.21) but much larger 95% CI, indicating imprecision (95% CI 0.00 to 32.38; RD -28%, 95% CI -71 to 15) (Analysis 1.5.2). One study stated that it was blinded and their results gave a RR of 0.05 (95% CI 0.0 to 0.72; RD -50%, 95% CI -71 to -29) (Analysis 1.5.3). Studies that described an open study or unclear blinding, gave a RR of 0.48 (95% CI 0.15 to 1.54; RD -21%, 95% CI -44 to 3) (Analysis 1.5.4).

Adverse events

Two studies reported adverse events within each treatment arm (Montini 2008; PRIVENT Study 2009), with very different findings. The unblinded study of Montini 2008 showed no events in the no-treatment arm and PRIVENT Study 2009 showed more events in the
placebo arm than the active arm. The RR was 2.31 with very wide 95% CI (95% CI 0.03 to 170.67; RD 2%, 95% CI -7 to 11) (Analysis 1.6.1).

**Microbial resistance**

Three studies reported results for microbial resistance (Montini 2008; PRIVENT Study 2009; Stansfeld 1975). Two of these reported for repeat symptomatic UTI (Montini 2008; PRIVENT Study 2009) and showed bacteria resistance to the active treatment with a RR of 2.40 (95% CI 0.62 to 9.26; RD 25%, 95% CI -9 to 60) (Analysis 1.7) meaning resistance was more than twice as likely in the active treatment arms than the non-treatment or placebo groups. The third showed a single positive culture in the placebo group (Stansfeld 1975)

**Comparison between two antibiotics**

Four studies compared one antibiotic with another antibiotic (Belet 2004; Brendstrup 1990; Falakaflaki 2007; Lettgen 2002), two studies reported their primary outcome as symptomatic UTI and two reported positive urine culture. No data could be combined since studies with the same outcome used different antibiotic comparisons.

**Nitrofurantoin versus other antibiotics**

For the outcome symptomatic UTI, Falakaflaki 2007 showed superiority of nitrofurantoin over cotrimoxazole (Analysis 2.1.1: RR 0.57, 95% CI 0.35 to 0.92; RD -20%, 95% CI -36 to 4). Brendstrup 1990 compared nitrofurantoin with trimethoprim and showed nitrofurantoin was superior for the outcome of repeat positive urine cultures (Analysis 2.2.1: RR 0.32, 95% CI 0.19 to 0.56; RD -42%, 95% CI -58 to -26). However, patients receiving nitrofurantoin were twice as likely to experience side effects (nausea, vomiting or stomach ache) than patients receiving trimethoprim (Analysis 2.4.3: RR 2.18, 95% CI 1.39 to 3.41; RD 33%, 95% CI 17 to 50). This suggests that the side effects of nitrofurantoin (NNH = 3, 95% CI 2 to 6) are similar to the prophylactic benefit (NNT = 5, 95% CI 3 to 33) compared with trimethoprim. Lettgen 2002 compared nitrofurantoin with cefixime. For the outcome repeat positive urine culture there was no significant difference between the two treatments (Analysis 2.2.2: RR 1.35, 95% CI 0.24 to 7.48; RD 3%, 95% CI -12 to 17).

A crossover study (Carlsen 1985) compared nitrofurantoin with pimveccillinam in 32 children. Allocation concealment and blinding were unclear. Ten repeat positive urine cultures occurred during pimveccillinam treatment and six while taking nitrofurantoin.

**Other antibiotic comparisons**

Belet 2004 compared three antibiotics (cotrimoxazole, cephaloxil and cefpazil) with cephalaxil appearing the most effective (Analysis 2.1.3; Analysis 2.1.4; Analysis 2.1.5). No results were statistically significant and the study was underpowered (N = 21, 25 and 34) for the small differences in event rates (8%, 14% and 21%).

**Dose comparisons**

Baculis 2003 compared every night cefadroxil treatment with alternate evening therapy. No difference between the doses was evident (Analysis 3.1: RR 0.9, 95% CI 0.24 to 3.41; RD -2%, 95% CI -30 to 26). The study was small (N = 33) and very poorly reported.

**Crossover studies, excluded from meta-analyses**

In neither of the crossover studies was it possible to determine what outcomes occurred before the crossover, and they were excluded from the analyses.

**DISCUSSION**

Long-term, low dose antibiotics were associated with a modest decrease in the number of repeat symptomatic UTI in children; however the estimate from all studies was not statistically significant.

Earlier versions of this review concluded that the evidence to support the use of antibiotics to prevent recurrent symptomatic UTI was weak. The addition of data from two recent, large and well reported studies has changed this conclusion (PRIVENT Study 2009; Montini 2008). PRIVENT Study 2009 was optimally designed with all features of good designed reported in the article (randomisation process, allocation concealment, blinding, explanations for incomplete data, appropriate outcome reporting and consideration for other bias). Montini 2008, while somewhat smaller, unblinded and with no placebo treatment, gave a RR (0.75) that was reasonably consistent with results from the PRIVENT Study 2009 (RR 0.65); only the PRIVENT Study 2009 reached statistical significance. These estimates are the least biased and therefore likely to reflect the true effect of prophylactic antibiotic treatment.

The estimated absolute risk reduction was 8% and corresponds to the need to treat between 12 and 13 children for 12 months to prevent one symptomatic UTI. The absolute treatment effect appears consistent in children with and without VUR, a known risk factor for further UTI. Although antibiotic prophylaxis prevents UTI overall, the data suggest that prolonged administration results in changes in the susceptibility of pathogenic bacteria with an increased risk of symptomatic UTI caused by bacteria resistant to the prophylactic agent.

The smaller and older studies gave highly variable and inconsistent findings, highlighting the effect of poor design and chance effects on study findings. Earlier studies tended to report repeat positive urine culture as their primary outcome and significant reductions in the risk of repeat positive urine cultures were found in the antibiotic groups of these studies. However, the appropriateness of this as an outcome is questionable given that few doctors would treat asymptomatic bacteruria. Further limitations to these studies are the quality of their design. Only 2/4 studies used adequate allocation concealment and 1/4 reported double blinding. Our analyses show that the poorly designed studies inflate the treatment effect by 49%, and ranging from 100% to 400% (using Analysis 1.3.2) compared to those with better design.

Only the PRIVENT Study 2009 reported sufficient detail to identify the time frame for recurrence of symptomatic UTI, in this study 36% of UTIs in the active arm and 47% in the placebo arm occurred within three months of randomisation. A further 19% and 29% (active and placebo arms respectively) of repeat symptomatic UTIs occurred between three and six months post randomisation. This implies the risk of repeat symptomatic infection is highest during the three months following initial infection and may suggest an initial course of treatment of three months with possible extension to six months.
The side effects of active treatment compared to placebo or no treatment were reported in two studies (Montini 2008; PRIVENT Study 2009). The unblinded study (Montini 2008) reported 15 events in the active treatment arm and none in the no-treatment group, while the blinded study (PRIVENT Study 2009) showed considerably more events in the placebo arm compared to active treatment (10 versus 4). This suggests interpretation of adverse events is influenced by knowledge of treatment group, suggesting the blinded study is a more reliable estimate of rates of adverse events.

Three studies reported the numbers of urine cultures causing symptomatic UTI that grew bacteria resistant to the active treatment in the studies with placebo comparisons. Two studies reported that 8% of the cultures in the no treatment arm were resistant to the active drug but the PRIVENT Study 2009 showed that 18% of urine infections were caused by bacteria resistant to the active treatment. This suggests the baseline risk of resistance in the non-treated group is not zero and is likely to be closer to 18% given the greater reliability of PRIVENT Study 2009. PRIVENT Study 2009 and Montini 2008 reported bacterial resistance in the active treatment arms, with over half (53%) of UTIs in the active arm in Montini 2008 and 28% of UTIs in the active arm of PRIVENT Study 2009 being attributed to bacteria resistant to the active treatment drug. While the RR is imprecise (2.4), as shown by the large 95% CI (0.62 to 9.26), the risk appears increased.

Although nitrofurantoin was more effective than trimethoprim or cotrimoxazole in preventing repeat symptomatic infection or repeat positive urine culture, it was associated with a greater number of side effects. The harmful effects of nitrofurantoin outweigh the prophylactic benefit and suggest that nitrofurantoin may not be an acceptable therapy. Patient compliance would be an important factor to consider in deciding on the use of nitrofurantoin as prophylaxis.

The combined analysis of the studies included in this review show there is a small benefit in long-term antibiotic treatment to prevent repeat symptomatic UTI however this should be weighed up against the increased likelihood of bacterial resistance in subsequent infections, the baseline risk of repeat symptomatic infection and how strongly parents and physicians wish to avoid a possible repeat illness.

AUTHORS’ CONCLUSIONS

Implications for practice
Prior to Montini 2008 and PRIVENT Study 2009, the evidence to support long-term, low dose antibiotics for the prevention of recurrent UTI in children without VUR consisted of a small number of poor quality studies that gave inconsistent and imprecise results. The addition of data from two much larger and better designed studies changes this. The analysis now demonstrates, with considerable consistency, a small benefit of low dose antibiotics to prevent repeat symptomatic UTI in children. The data show little adverse effects from the antibiotic treatment but demonstrate an increased risk of bacterial resistance to the treatment drug in subsequent infections. A single study reported event time periods and showed that the greatest risk of repeat symptomatic infection occurs in the three to six months following initial UTI. Nitrofurantoin appeared the most effective treatment but led to considerable adverse events.

Implications for research
Publication of two larger, better designed studies have provided evidence on which physicians making decisions about low dose antibiotics to prevent repeat symptomatic UTI in children can be guided. Benefits and harms are now much clearer and can be used in decisions about this treatment. Older studies tended to be poorly designed with biases known to overestimate the true treatment effect.

ACKNOWLEDGEMENTS

We are grateful to Dr Anna Lee who contributed to the original iteration and first update of this review (Williams 2001; Williams 2006), contributing to the design, quality assessment, data collection, entry, analysis and interpretation, and writing.

We are grateful to Lei Wei who contributed to the first review update (Williams 2006), contributing to the quality assessment, data collection, entry, analysis and interpretation, and writing.

The authors acknowledge Dr Smellie for her content expertise.
Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

References to studies included in this review

Baciulis 2003 [published data only]

Belet 2004 [published data only]

Brendstrup 1990 [published data only]

Carlsen 1985 [published data only]

Falakaflaki 2007 [published data only]

Lettgen 2002 [published data only]

Lohr 1977 [published data only]

Montini 2008 [published data only]


PRIVENT Study 2009 [published data only]


Savage 1975 [published data only]

Smellie 1978 [published data only]

Stansfeld 1975 [published data only]

References to studies excluded from this review

Bose 1974 [published data only]

Clemente 1994 [published data only]

Feldman 1975 [published data only]

Fennell 1980 [published data only]

Fischbach 1979 [published data only]

Garin 2006 [published data only]

Garin 2000 [published data only]

Goszczyk 2000 [published data only]

Lee 2007 [published data only]

Lee 2000 [published data only]

Lin 2009 [published data only]

Lindberg 1978 [published data only]

Madsen 1973 [published data only]

Montini 2003 [published data only]


Pennis 2006 [published data only]

Pennis 2006 [published data only]


Pisani 1982 [published data only]

Ray 1970 [published data only]
Roussey-Kesler 2008 {published data only}


Smellie 1976 {published data only}

Stranieri 2003 {published data only}

Winberg 1973 {published data only}

Yilmaz 2007 {published data only}

References to ongoing studies

RIVUR Study {published data only}


Additional references

Bergstrom 1972

Coulthard 1997

Craig 1998

Hellerstein 1982

Hellstrom 1991

Higgins 2003

Higgins 2008

Hodson 2007

Renal Group 2011
Rushton 1997

Winberg 1975

References to other published versions of this review
Williams 2001

Williams 2006

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

**Baciulis 2003**

Methods  
- Study design: parallel open-label RCT  
- Follow-up: 6 months

Participants  
- > 2 episodes of acute pyelonephritis/year  
- Number: every night (15); alternate nights (18)  
- Age: birth to 16 years  
- Sex (M/F): 1/32

Interventions

Treatment group 1  
- Cefadroxil  
  * 12.5 to 15 mg/kg every night  
  * Duration: 6 months

Treatment group 2  
- Cefadroxil  
  * 12.5 to 15 mg/kg on alternate nights  
  * Duration: 6 months

Outcomes  
- Repeat positive urine culture

Notes  
- Translated from Lithuanian

Risk of bias

<table>
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<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Baculis 2003 (Continued)

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<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Too few details reported for certainty</td>
</tr>
</tbody>
</table>

### Belet 2004

**Methods**
- Study design: parallel RCT
- Follow-up: 6 months

**Participants**
- No definitions of UTI; urine samples screened at visits; no children with VUR
- Number (TMP-SMX/cephadroxil/cefprozil): 21/25/34

**Interventions**
- **Treatment group 1**
  - TMP/SMX
    - Duration: 3 months
- **Treatment group 2**
  - Cephadroxil
    - Duration: 3 months
- **Treatment group 3**
  - Cefprozil
    - Duration: 3 months

**Outcomes**
- Repeat symptomatic UTI
- Asymptomatic UTI
- Adverse reactions

**Notes**
- 20 excluded after randomisation

### Risk of bias

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<td>No missing data evident, no losses during follow-up reported</td>
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<td>Primary outcome is appropriate</td>
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</table>

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Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Brendstrup 1990

Methods
- Study design: parallel RCT
- Follow-up: 6 months

Participants
- Children with UTI in the previous year were included
- Number: 130
- Sex (M/F): 4/126
- VUR: 30
- Abnormal urography: 30

Exclusion criteria
- Serum creatinine > 120 μmol/L; myelomeningocele; obstruction to flow; immunodeficiency; allergic reactions to nitrofurantoin or TMP; concomitant antibiotic treatment

Interventions

Treatment group 1
- Nitrofurantoin
  * 1 to 1.5 mg/kg
  * Duration: 6 months

Treatment group 2
- TMP
  * 2 to 3 mg/kg
  * Duration: 6 months

Outcomes
- Number of repeat infections/group
- Number of children who discontinued antibiotics due to adverse reactions

Notes
- Urines screened every month and if the child developed symptoms. Discussion states they did not record symptoms so cannot distinguish between asymptomatic UTI and symptomatic UTI
- Separate outcomes for abnormal urography, reflux and normal children presented in paper
- 10 children withdrew from study
- Initial UTI defined a clean-catch midstream urine > 100,000 cfu/mL

Risk of bias

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<th>Bias</th>
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<td>10 children withdrew during follow-up, not included in the analysis</td>
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Brendstrup 1990 (Continued)

<table>
<thead>
<tr>
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<th>Primary outcome is positive culture rather than symptomatic UTI</th>
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<td>Unclear risk</td>
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</table>

Carlsen 1985

Methods
- Study design: crossover RCT

Participants
- Number: 35
- Age: 1 to 13 years
- Sex (M/F): 4/31
- VUR: 17
- Recurrent UTI: 18

Exclusion criteria
- Previous intolerance to nitrofurantoin, VUR > grade 3

Interventions
Treatment group 1
- Pivmecilliam
  * 100 mg/d for children < 6 years
  * 200 mg/d for children > 6 years

Treatment group 2
- Nitrofurantoin
  * 1.5 mg/kg/d

Crossover
- 6-10 months for 1st antibiotic, crossed over to 2nd antibiotic for 6 months

Outcomes
- Number of repeat positive urine cultures
- Tolerance/side effects
- Changes in faecal flora

Notes
- Urine samples screened each visit

Risk of bias

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Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Carlsen 1985 (Continued)

<table>
<thead>
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</tr>
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</table>

### Falakaflaki 2007

**Methods**
- Study design: parallel RCT

**Participants**
- Previous UTI; no previous prophylaxis; normal renal function and at least one of the following: > 3 UTIs/year, VUR grades 1 to 4, obstructive lesions, other anatomical abnormalities, or aged < 1 year
- Setting: outpatient paediatric nephrology clinics
- Age: 3 months to 12 years
- Number: 132
  - VUR: 56

**Exclusion criteria**
- Impaired renal function; contraindication for nitrofurantoin or TMP/SMX (e.g. G6PD deficiency); any side effects of drugs

**Interventions**

<table>
<thead>
<tr>
<th>Treatment group 1</th>
</tr>
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<tbody>
<tr>
<td><strong>TMP/SMX</strong></td>
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<tr>
<td>* 2 mg/kg/d</td>
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<tr>
<td>* Duration: 6 months</td>
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<table>
<thead>
<tr>
<th>Treatment group 2</th>
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</thead>
<tbody>
<tr>
<td><strong>Nitrofurantoin</strong></td>
</tr>
<tr>
<td>* 1 to 2 mg/kg/d</td>
</tr>
<tr>
<td>* Duration: 6 months</td>
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</tbody>
</table>

**Outcomes**
- Repeat symptomatic UTI (culture + fever or other symptoms)

**Notes**
- Included bag samples.
- Patients kept on the trial after a recurrence, and changed prophylaxis type if recurrence was with a bacterial agent resistant to their allocated treatment.

### Risk of bias

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Falakaflaki 2007 (Continued)

Free of selective reporting? Low risk
Primary outcome symptomatic UTI

Free of other bias? Unclear risk
Many details not reported, difficult to determine

Lettgen 2002

Methods
• Study design: open RCT
• Follow-up: 6 to 12 months

Participants
• Number: 60
• Sex (M/F): 0/60
• Age: 1 to 11 years
• VUR: NS

Exclusion criteria
• Existing UTI or < 2 UTIs within the previous year; pyelonephritis urolithiasis neurogenic bladder urinary tract obstruction

Interventions
Treatment group 1
• Cefixime
  * 2 mg/kg
  * Duration: 6 to 12 months

Treatment group 2
• Nitrofurantoin
  * 1 mg/kg
  * Duration: 6 to 12 months

Outcomes
• Number of repeat clinical infections (not all culture verified)
• Number of children who experienced adverse reactions of treatment

Notes
• Initial UTI diagnosed by MSU > 100,000 cfu/mL

Risk of bias

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<td>Primary outcome is clinical diagnosis, not all were culture verified</td>
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</table>
**Lettgen 2002** (Continued)

| Free of other bias? | Unclear risk | Many methodological details missing, uncertain of other biases |

**Lohr 1977**

**Methods**
- Study design: crossover RCT

**Participants**
- Number: 18
- Age: mean 6.4 years (range 3 to 13 years)
- VUR: 1
- Previously undergone urinary tract surgery for urethral dilatation: 4

Exclusion criteria
- G6PD deficiency

**Interventions**

Treatment group
- Nitrofurantoin
  - * 50 mg/d for children > 20 kg
  - * 25 mg/d for children < 20 kg

Control group
- Placebo tablets matched to both tablet sizes

Crossover
- Antibiotic or placebo for 6 months then crossed over to alternate for 6 further months

**Outcomes**
- Number of repeat symptomatic and asymptomatic infections/group

**Notes**

**Risk of bias**

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</table>

**Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)**

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Montini 2008

Methods
- Study design: open label RCT
- Time frame: May 2000 to August 2006

Participants
- Setting: Multicentre (22 paediatric units)
- Country: Italy
- Children with normal renal function and 1st febrile UTI, pyuria ≥ 25 cells/μL on 2 consecutive urine samples and urine culture 1 organism ≥ $10^8$ cfu/L on 2 consecutive bag samples. 2 urinalysis results had to be concordant. Symptoms had to at least 2 of; fever > 38°C, erythrocyte sedimentation rate > 30 mm in 1 standard hour or C reactive protein ≥ 3 times upper limit of normal and neutrophil count above normal
- Number: 338
- Age: 2 months to 7 years

Exclusion criteria
- Complex urologic malformations, and/or severe renal damage (DMSA < 30% relative function).

Interventions
- Treatment group 1
  - Cotrimoxazole
    - 15 mg/kg/d
    - Duration: 12 months
- Treatment group 2
  - Co-amoxiclav
    - 15 mg/kg/d
    - Duration: 12 months
- Control group
  - No prophylaxis (no placebo)

Outcomes
- Repeat febrile UTI
- Repeat positive urine culture

Notes

Risk of bias

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<td>Low risk</td>
<td>Well reported study</td>
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</table>
PRIVENT Study 2009

Methods
- Study design: placebo controlled RCT

Participants
- Setting: Multicentre
- Country: Australia
- One or more symptomatic and microbiologically proven UTI; all grades of reflux included
- Number: 576
- Age: birth to 18 years

Exclusion criteria
- Known neurologic, skeletal, or urologic predisposing cause or known contraindication to TMP-SMX

Interventions

Treatment group
- TMP
  - 2 mg/kg/d
- SMX
  - 10 mg/kg/d

Control group
- Colour and taste matched placebo in the same volume

Outcomes
- Symptomatic UTI within 12 months

Notes

Risk of bias

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<td>Low risk</td>
<td>Well reported study</td>
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Savage 1975

Methods
- Randomised open RCT
- Follow-up: to 6 months
Participants

- Criteria for initial UTI diagnosis was > 100,000 cfu/mL on 3 consecutive occasions
- Number: 63
- VUR: 19
- Age: 5 years to 7 years 10 months
- Sex (M/F): 0/63

Exclusion criteria

- Past history of UTI or "unwell"

Interventions

Treatment group

- Antibiotic treatment according to sensitivities
  * nitrofurantoin
    - 4 mg/kg/d
    - Duration: 10 weeks after 2 weeks acute treatment, or
  * cotrimoxazole
    - 20 to 40 mg TMP; 100 to 200 mg SMX
    - Duration: twice daily for 10 weeks after 2 weeks acute treatment

Control group

- No treatment for 10 weeks after 2 weeks of acute treatment with ampicillin

Outcomes

- Number of symptomatic UTI
- Number of repeat positive cultures

Notes

Risk of bias

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<th>Support for judgement</th>
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<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Many methodology details missing</td>
</tr>
</tbody>
</table>

Smellie 1978

Methods

- Study design: open RCT
- Follow-up: to 1 year

Participants

- Initial UTI defined by urine culture, but no cfu given
Smellie 1978 (Continued)

- Number: 47 reported
- Sex (M/F): 5/40 stated (however 47 reported)
- Age: 2 to 12 years
- VUR: None

Exclusion criteria: NS

### Interventions

#### Treatment group 1
- Low dose cotrimoxazole
  - SMX
    - 10 mg/kg/d
    - Duration: 6 to 12 months
  - TMP
    - 2 mg/kg/d
    - Duration: 6 to 12 months

#### Treatment group 2
- Nitrofurantoin
  - 1 to 2 mg/kg/d
  - Duration: 6 to 12 months

#### Control group
- No treatment

### Outcomes
- Number of repeat infection per group, asymptomatic reported as well as symptomatic

### Notes
- Use events within 10 months since treatment was 6 to 12 months and on average 10 months.
- Follow-up extended after treatment, ignore events in post-treatment period. Assume 1 asymptomatic UTI occurred by 6 months

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>States randomised, no details given</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Treatment allocation know to clinician, possibly manipulatable more children with a history of prior UTIs received prophylaxis</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>High risk</td>
<td>Clinicians aware of treatment group, likely parents also aware</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>Losses to follow-up detailed</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>Reports asymptomatic and symptomatic UTI just can’t tell in what time frame the single asymptomatic UTI occurred</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Many methods details are not detailed</td>
</tr>
</tbody>
</table>

*UTI*
### Stansfeld 1975

**Methods**
- Study design: RCT
- Follow-up: to 6 months

**Participants**
- Initial UTI defined as two or more consecutive, significant and consistent urine cultures accompanied by pyuria
- Number: 45
- Age: 6 months to 14 years
- Sex (M/F): 3/42
- VUR: 10

Exclusion criteria
- Neonates; children with impaired drainage due to obstruction or bladder paralysis

**Interventions**

- **Treatment group**
  - Cotrimoxazole
  - No dosage stated
  - Duration: 6 months

- **Control group**
  - Placebo tablets
  - Duration: 6 months

**Outcomes**
- Number of repeat positive cultures

**Notes**
- Urine samples screened at each visit

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>Sequence generated and held in pharmacy, independent to investigators</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Clinician unable to manipulate allocation</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Reported as double blinded, means treating clinician and parents/patient unaware of which treatment the child was on. Dummy tablets used</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Low risk</td>
<td>Loss to follow up detailed</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>High risk</td>
<td>Primary outcome positive culture, not symptomatic UTI</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Many methods poorly reported</td>
</tr>
</tbody>
</table>

cfu - colony forming units; NS - not stated; SMX - sulfamethoxazole; TMP - trimethoprim; UTI - urinary tract infection; VUR - vesicoureteric reflux

### Characteristics of excluded studies [ordered by study ID]

---
<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bose 1974</td>
<td>Acute treatment of two types of antibiotics followed by nitrofurantoin prophylaxis i.e. no prophylactic control group</td>
</tr>
<tr>
<td>Clemente 1994</td>
<td>RCT pidotimod, an immunostimulant agent, plus antibiotics versus placebo for 60 days</td>
</tr>
<tr>
<td>Feldman 1975</td>
<td>RCT, 4 week &quot;short term&quot; TMP-SMX versus SMX</td>
</tr>
<tr>
<td>Fennell 1980</td>
<td>RCT, 10 day treatment of ampicillin versus cotrimoxazole versus cephalixin</td>
</tr>
<tr>
<td>Fischbach 1979</td>
<td>Acute treatment for 2 weeks</td>
</tr>
<tr>
<td>Garin 2006</td>
<td>52% of participants had VUR, our inclusion criteria is &lt; 50% with VUR</td>
</tr>
<tr>
<td>Goszczyk 2000</td>
<td>Not a trial of antibiotic treatment, Uro-Vaxom</td>
</tr>
<tr>
<td>Lee 2007</td>
<td>All children had VUR, our criteria is &lt; 50% with VUR</td>
</tr>
<tr>
<td>Lin 2009</td>
<td>RCT of probiotics in children, children did not have UTI</td>
</tr>
<tr>
<td>Lindberg 1978</td>
<td>Treatment consisted of nitrofurantoin for 10 days, only received 6 month treatment if they had 2 recurrences</td>
</tr>
<tr>
<td>Madsen 1973</td>
<td>Double blinded study of cotrimoxazole versus methacycline for 14 days in mostly adults</td>
</tr>
<tr>
<td>Montini 2003</td>
<td>Acute treatment trial, not long-term prophylaxis</td>
</tr>
<tr>
<td>Pennesi 2006</td>
<td>All children have VUR, our inclusion is &lt; 50% with VUR</td>
</tr>
<tr>
<td>Pisani 1982</td>
<td>RCT of acute treatment for 10 days</td>
</tr>
<tr>
<td>Ray 1970</td>
<td>&gt; 50% of participants had neurogenic/renal abnormalities</td>
</tr>
<tr>
<td>Roussey-Kesler 2008</td>
<td>All children have VUR, our inclusion is &lt; 50% with VUR</td>
</tr>
<tr>
<td>Smellie 1976</td>
<td>Non-RCT of cotrimoxazole in VUR and non-VUR children</td>
</tr>
<tr>
<td>Stranieri 2003</td>
<td>Not a trial all children received antibiotic treatment</td>
</tr>
<tr>
<td>Winberg 1973</td>
<td>A series of studies (1) RCT short (10 days) versus long (60 days) treatment of sulfonamide; (2) non-RCT with 3 groups: no prophylaxis, sulfafurazole, nitrofurantoin for 60 days</td>
</tr>
<tr>
<td>Yilmaz 2007</td>
<td>Duration of treatment was too short, single dose of Vitamin A</td>
</tr>
</tbody>
</table>

RCT - randomised controlled trial; SMX - sulframethoxazole; TMP - trimethoprim; VUR - vesicoureteric reflux

**Characteristics of ongoing studies** [ordered by study ID]

### RIVUR Study

**Trial name or title**
- randomised intervention for children with vesicoureteral reflux (RIVUR)

**Methods**
- Allocation: randomised
- Control: Placebo Control
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
### Participants

**Inclusion criteria**

- Age at randomisation: at least 2 months, but less than 6 years of age. Note that children as young as 1 month may be screened for the study.
- Diagnosed first or second febrile or symptomatic UTI within 112 days prior to randomisation
- Presence of Grade I-IV VUR based on radiographic VCUG performed within 112 days of diagnosis of index UTI.
- Appropriately treated index febrile or symptomatic UTI

**Exclusion criteria**

- Index UTI diagnosis more than 112 days prior to randomisation; history of more than two UTIs prior to randomisation; for patients less than 6 months of age at randomisation, gestational age less than 34 weeks; co-morbid urologic anomalies; hydronephrosis, SFU Grade 4; ureterocoele; urethral valve; solitary kidney; profoundly decreased renal size unilaterally on ultrasound, (based on 2 standard deviations below the mean for age and length) performed within 112 days after diagnosis of index UTI; multicystic dysplastic kidney; neurogenic bladder; pelvic kidney or fused kidney; known sulfa allergy, inadequate renal or hepatic function, G6PD deficiency or other conditions that are contraindications for use of TMP/SMZ; history of other renal injury/disease; unable to complete the study protocol; congenital or acquired immunodeficiency; underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as chronic gastrointestinal conditions (i.e., malabsorption, inflammatory bowel disease), liver or kidney failure, or malignancy; complex cardiac disease as defined in the Manual of Procedures; any known syndromes associated with VUR or bladder dysfunction; index UTI not successfully treated; unlikely to complete follow-up; family history of anaphylactic reaction to sulfa medications

### Interventions

**TMP/SMZ**

- Cherry-flavored liquid suspension in which each 5 mL contains 200 mg SMZ and 40 mg TMP. Prophylactic dose is based on TMP component: 3 mg/kg body weight taken once daily

**Placebo**

- Cherry flavored liquid suspension matched to active comparator

### Outcomes

**Primary outcome measures**

- Recurrent febrile or symptomatic urinary tract infection during 2-year follow-up

**Secondary outcome measures**

- Renal scarring based on DMSA scan performed 1 and 2 years after enrollment
- Severe renal scarring on outcome scan
- Treatment failure composite based on multiple recurrent UTIs or, in children with baseline scarring of grade 3 or higher, new renal scarring at 12-months or further scarring at any time following recurrent febrile UTI
- Presence of E.coli resistant to TMP/SMZ (based on rectal swab)
- Recurrent febrile or symptomatic UTI caused by TMP/SMZ-resistant organism

### Starting date

May 2007

### Contact information

http://www.cscu.unc.edu/rivur/

### Notes

This multicenter, randomised, double-blind, placebo-controlled trial is designed to determine whether daily antimicrobial prophylaxis is superior to placebo in preventing recurrence of urinary tract infection (UTI) in children with vesicoureteral reflux (VUR). Patients will be randomly assigned to treatment for 2 years with daily antimicrobial prophylaxis (trimethoprim-sulfamethoxazole) or
The study is designed to recruit 600 children (approximately 300 in each treatment group) over a 24 month period. The protocol will encourage prompt evaluation of children with UTI symptoms and early therapy of culture-proven UTIs. It is expected that approximately 10% of children will have to discontinue study medication due to allergic reactions. Assuming a 20% placebo event rate and 10% non-compliance rate, the study has 83% power to detect an absolute 10% event rate in the antimicrobial prophylaxis group. If the placebo event rate is instead 25%, power is 97% to detect an absolute 10% event rate in the treated group, even if non-compliance is as high as 15%.

In addition to collecting follow-up data on urinary tract infections, renal scarring and antimicrobial resistance, quality of life, compliance, safety parameters, utilization of health resources, and change in VUR will be assessed periodically throughout the study.

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**DATA AND ANALYSES**

**Comparison 1. Antibiotic treatment versus placebo/no treatment**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Recurrence of symptomatic UTI</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 All studies</td>
<td>4</td>
<td>1024</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.75 [0.36, 1.53]</td>
</tr>
<tr>
<td>2 Recurrence of symptomatic UTI: VUR status</td>
<td>3</td>
<td>862</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.69 [0.44, 1.08]</td>
</tr>
<tr>
<td>2.1 Children without VUR</td>
<td>3</td>
<td>491</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.56 [0.15, 2.12]</td>
</tr>
<tr>
<td>2.2 Children with VUR</td>
<td>2</td>
<td>371</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.39, 1.07]</td>
</tr>
<tr>
<td>3 Recurrence of symptomatic UTI: risk of bias fields</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Adequate allocation concealment studies</td>
<td>2</td>
<td>914</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.68 [0.48, 0.95]</td>
</tr>
<tr>
<td>3.2 Unclear allocation concealment studies</td>
<td>2</td>
<td>110</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.35 [0.00, 27.93]</td>
</tr>
<tr>
<td>3.3 Double-blinded studies</td>
<td>1</td>
<td>576</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.44, 0.96]</td>
</tr>
<tr>
<td>3.4 Open label, unblinded studies</td>
<td>3</td>
<td>448</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.66 [0.15, 2.90]</td>
</tr>
<tr>
<td>4 Repeat positive urine culture</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 All studies</td>
<td>4</td>
<td>467</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.31 [0.08, 1.18]</td>
</tr>
<tr>
<td>5 Repeat positive urine culture: risk of bias fields</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-----------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>5.1 Adequate allocation concealment studies</td>
<td>2</td>
<td>383</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.21 [0.02, 2.50]</td>
</tr>
<tr>
<td>5.2 Unclear allocation concealment</td>
<td>2</td>
<td>110</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.21 [0.00, 32.38]</td>
</tr>
<tr>
<td>5.3 Double-blinded studies</td>
<td>1</td>
<td>45</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.05 [0.00, 0.72]</td>
</tr>
<tr>
<td>5.4 Open label, unblinded studies</td>
<td>3</td>
<td>448</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.48 [0.15, 1.54]</td>
</tr>
<tr>
<td>6 Adverse events</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1 All adverse events</td>
<td>2</td>
<td>914</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.2 Discontinuation of treatment due to adverse events</td>
<td>1</td>
<td>576</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.4 [0.13, 1.26]</td>
</tr>
<tr>
<td>7 Microbial resistance to prophylactic drug</td>
<td>2</td>
<td>118</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>2.40 [0.62, 9.26]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 1 Recurrence of symptomatic UTI.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>1.1.1 All studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smellie 1978</td>
<td>0/25</td>
<td>10/22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savage 1975</td>
<td>7/29</td>
<td>4/34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montini 2008</td>
<td>15/211</td>
<td>12/127</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIVENT Study 2009</td>
<td>36/288</td>
<td>55/288</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>553</td>
<td>471</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 58 (Antibiotic), 81 (Placebo/no treatment)
Heterogeneity: Tau²=0.29; Chi²=7.87, df=3(P=0.05); I²=61.89%
Test for overall effect: Z=0.79(P=0.43)

Favours antibiotic 0.002 0.1 1 10 500 Favours placebo/no treatment

### Analysis 1.2. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 2 Recurrence of symptomatic UTI: VUR status.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>1.2.1 Children without VUR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montini 2008</td>
<td>5/129</td>
<td>3/81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIVENT Study 2009</td>
<td>15/119</td>
<td>17/115</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours antibiotic 0.002 0.1 1 10 500 Favours placebo/no treatment
### Table 1.3.1 Adequate allocation concealment studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smellie 1978</strong></td>
<td>0/25</td>
<td>10/22</td>
<td></td>
<td>2.57%</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>273</td>
<td>218</td>
<td></td>
<td>44.02%</td>
<td>0.56[0.15,2.12]</td>
</tr>
</tbody>
</table>

Total events: 20 (Antibiotic), 30 (Placebo/no treatment)

Heterogeneity: $\tau^2=0.28; \chi^2=5.14, df=2(P=0.08); I^2=62.35$

Test for overall effect: $Z=0.85(P=0.4)$

### Table 1.3.2 Unclear allocation concealment studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smellie 1978</strong></td>
<td>0/25</td>
<td>10/22</td>
<td></td>
<td>2.57%</td>
<td></td>
</tr>
<tr>
<td><strong>Savage 1975</strong></td>
<td>7/29</td>
<td>4/34</td>
<td></td>
<td>54.16%</td>
<td>2.05[0.67,6.31]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>54</td>
<td>56</td>
<td></td>
<td>100%</td>
<td>0.35[0.27,0.93]</td>
</tr>
</tbody>
</table>

Total events: 14 (Antibiotic), 14 (Placebo/no treatment)

Heterogeneity: $\tau^2=8.84; \chi^2=8.64, df=1(P=0.07); I^2=88.42$

Test for overall effect: $Z=0.47(P=0.64)$

### Table 1.3.3 Double-blinded studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIVENT Study 2009</strong></td>
<td>36/288</td>
<td>55/288</td>
<td></td>
<td>100%</td>
<td>0.65[0.44,0.96]</td>
</tr>
</tbody>
</table>

Total events: 36 (Antibiotic), 55 (Placebo/no treatment)

Heterogeneity: Not applicable

Test for overall effect: $Z=2.15(P=0.03)$
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
</tbody>
</table>

### 1.3.4 Open label, unblinded studies

- Smellie 1978: 0/25 vs. 10/22
  - Risk Ratio: 18.02%
  - Weight: 0.04 [0, 0.68]
- Montini 2008: 15/211 vs. 12/127
  - Risk Ratio: 43.78%
  - Weight: 0.75 [0.36, 1.56]
- Savage 1975: 7/29 vs. 4/34
  - Risk Ratio: 38.2%
  - Weight: 2.05 [0.67, 6.31]
- **Subtotal (95% CI)**: 265 vs. 183
  - Total events: 22 (Antibiotic), 26 (Placebo/no treatment)
  - Heterogeneity: Tau²=1.17; Chi²=7.92, df=2 (P=0.02); I²=74.74%
  - Test for overall effect: Z=0.56 (P=0.58)
  - Favours antibiotic: 500 (P=0.002)
  - Favours placebo/no treatment: 10 (P=0.1)

### Analysis 1.4. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 4 Repeat positive urine culture.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
</tbody>
</table>

1.4.1 All studies

- Montini 2008: 20/195 vs. 24/117
  - Risk Ratio: 34.84%
  - Weight: 0.29 [0.12, 0.86]
- Savage 1975: 23/29 vs. 29/34
  - Risk Ratio: 36.6%
  - Weight: 0.74 [0.47, 1.17]
- Smellie 1978: 0/25 vs. 11/22
  - Risk Ratio: 14.26%
  - Weight: 0.56 [0.29, 1.07]
- Stansfeld 1975: 0/21 vs. 12/24
  - Risk Ratio: 14.3%
  - Weight: 0.05 [0.01, 0.32]
- **Subtotal (95% CI)**: 270 vs. 197
  - Total events: 43 (Antibiotic), 76 (Placebo/no treatment)
  - Heterogeneity: Tau²=1.26; Chi²=32.47, df=3 (P<0.0001); I²=90.76%
  - Test for overall effect: Z=1.72 (P=0.08)
  - Favours antibiotic: 500 (P=0.002)
  - Favours placebo/no treatment: 10 (P=0.1)

### Analysis 1.5. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 5 Repeat positive urine culture: risk of bias fields.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
</tbody>
</table>

1.5.1 Adequate allocation concealment studies

- Montini 2008: 20/211 vs. 24/117
  - Risk Ratio: 63.89%
  - Weight: 0.29 [0.12, 0.87]
- Stansfeld 1975: 0/21 vs. 12/24
  - Risk Ratio: 36.11%
  - Weight: 0.05 [0.01, 0.32]
- **Subtotal (95% CI)**: 232 vs. 151
  - Total events: 20 (Antibiotic), 36 (Placebo/no treatment)
  - Heterogeneity: Tau²=2.41; Chi²=3.32, df=1 (P=0.07); I²=69.92%
  - Test for overall effect: Z=1.23 (P=0.22)
  - Favours antibiotic: 1000 (P=0.001)
  - Favours placebo/no treatment: 10 (P=0.1)

1.5.2 Unclear allocation concealment

- Savage 1975: 23/29 vs. 29/34
  - Risk Ratio: 53.77%
  - Weight: 0.74 [0.47, 1.17]
- Smellie 1978: 0/25 vs. 11/22
  - Risk Ratio: 46.23%
  - Weight: 0.04 [0.01, 0.62]
- **Subtotal (95% CI)**: 54 vs. 56
  - Total events: 36 (Antibiotic), 76 (Placebo/no treatment)
  - Heterogeneity: Tau²=3.21; Chi²=2.58, df=1 (P=0.11); I²=69.92%
  - Test for overall effect: Z=1.23 (P=0.22)
  - Favours antibiotic: 1000 (P=0.001)
  - Favours placebo/no treatment: 10 (P=0.1)
### Study or subgroup

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 23 (Antibiotic), 40 (Placebo/no treatment)

Heterogeneity: $\tau^2=12.2$; $\chi^2=13.08$, df=1 ($p<0.05$); $I^2=92.36$

**Test for overall effect:** $Z=0.6$ ($p=0.55$)

#### 1.5.3 Double-blinded studies

- **Stansfeld 1975**
  - 0/21 (Antibiotic)
  - 12/24 (Placebo/no treatment)
  - Risk Ratio: 100%
  - Weight: 0.05
  - M-H, Random, 95% CI: [0.0, 0.72]

- **Subtotal (95% CI)**
  - 21/24
  - Risk Ratio: 100%
  - Weight: 0.05
  - M-H, Random, 95% CI: [0.0, 0.72]

**Total events:** 0 (Antibiotic), 12 (Placebo/no treatment)

Heterogeneity: $\tau^2=0$; $\chi^2=0$, df=0 ($p<0.0001$); $I^2=100$

**Test for overall effect:** $Z=2.19$ ($p=0.03$)

#### 1.5.4 Open label, unblinded studies

- **Montini 2008**
  - 20/211 (Antibiotic)
  - 24/127 (Placebo/no treatment)
  - Risk Ratio: 41.86%
  - Weight: 0.5
  - M-H, Random, 95% CI: [0.29, 0.87]

- **Savage 1975**
  - 23/29 (Antibiotic)
  - 29/34 (Placebo/no treatment)
  - Risk Ratio: 45.33%
  - Weight: 0.93
  - M-H, Random, 95% CI: [0.74, 1.17]

- **Smellie 1978**
  - 0/25 (Antibiotic)
  - 11/22 (Placebo/no treatment)
  - Risk Ratio: 12.81%
  - Weight: 0.04
  - M-H, Random, 95% CI: [0.0, 0.62]

- **Subtotal (95% CI)**
  - 265/183
  - Risk Ratio: 100%
  - Weight: 0.48
  - M-H, Random, 95% CI: [0.15, 1.54]

**Total events:** 43 (Antibiotic), 64 (Placebo/no treatment)

Heterogeneity: $\tau^2=0.77$; $\chi^2=19.21$, df=2 ($p<0.0001$); $I^2=89.59$

**Test for overall effect:** $Z=1.24$ ($p=0.22$)

### Analysis 1.6. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 6 Adverse events.

#### 1.6.1 All adverse events

- **Montini 2008**
  - 15/211 (Antibiotic)
  - 0/127 (Placebo/no treatment)
  - Risk Ratio: 45.6%
  - Weight: 18.72
  - M-H, Random, 95% CI: [1.13, 310.14]

- **PRIVENT Study 2009**
  - 4/288 (Antibiotic)
  - 10/288 (Placebo/no treatment)
  - Risk Ratio: 54.4%
  - Weight: 0.4
  - M-H, Random, 95% CI: [0.13, 1.26]

- **Subtotal (95% CI)**
  - 499/415
  - Risk Ratio: 100%
  - Weight: 2.31
  - M-H, Random, 95% CI: [0.03, 170.67]

**Total events:** 19 (Antibiotic), 10 (Placebo/no treatment)

Heterogeneity: $\tau^2=8.51$; $\chi^2=8.11$, df=1 ($p=0.08$); $I^2=87.6$

**Test for overall effect:** $Z=0.38$ ($p=0.7$)

#### 1.6.2 Discontinuation of treatment due to adverse events

- **PRIVENT Study 2009**
  - 4/288 (Antibiotic)
  - 10/288 (Placebo/no treatment)
  - Risk Ratio: 100%
  - Weight: 0.4
  - M-H, Random, 95% CI: [0.13, 1.26]

- **Subtotal (95% CI)**
  - 288/288
  - Risk Ratio: 100%
  - Weight: 0.4
  - M-H, Random, 95% CI: [0.13, 1.26]

**Total events:** 4 (Antibiotic), 10 (Placebo/no treatment)

Heterogeneity: Not applicable

**Test for overall effect:** $Z=1.56$ ($p=0.12$)
## Analysis 1.7. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 7 Microbial resistance to prophylactic drug.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Montini 2008</td>
<td>8/15</td>
<td>1/12</td>
<td>31.41% 6.4[0.92,44.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIMENT Study 2009</td>
<td>10/36</td>
<td>10/55</td>
<td>68.59% 1.53[0.71,3.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>51</strong></td>
<td><strong>67</strong></td>
<td><strong>100% 2.4[0.62,9.26]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (Antibiotic), 11 (Placebo/no treatment)
Heterogeneity: $\hat{I}^2=48.88\%$
Test for overall effect: $Z=1.27(\text{P}=0.21)$

Favours antibiotic

### Comparison 2. Comparison between two types of antibiotics

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recurrence of symptomatic UTI</td>
<td>2</td>
<td>177</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.1 Nitrofurantoin versus cotrimoxazole</td>
<td>1</td>
<td>96</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>1.2 Cotrimoxazole versus cephadroxil</td>
<td>1</td>
<td>120</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>1.3 Cotrimoxazole versus cefprozil</td>
<td>1</td>
<td>57</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.03 [-0.12, 0.17]</td>
</tr>
<tr>
<td>2 Repeat positive urine culture</td>
<td>2</td>
<td>177</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.19 [-0.67, 0.28]</td>
</tr>
<tr>
<td>2.1 Nitrofurantoin versus trimethoprim</td>
<td>1</td>
<td>120</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.42 [-0.58, -0.26]</td>
</tr>
<tr>
<td>2.2 Nitrofurantoin versus cefixime</td>
<td>1</td>
<td>57</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>0.03 [-0.12, 0.17]</td>
</tr>
<tr>
<td>3 Microbial resistance to prophylactic drugs</td>
<td>2</td>
<td>96</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Nitrofurantoin versus cotrimoxazole</td>
<td>2</td>
<td>96</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.54 [0.31, 0.92]</td>
</tr>
<tr>
<td>4 Adverse events</td>
<td>3</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4.1 Cotrimoxazole versus cephadroxil</td>
<td>1</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>4.2 Nitrofurantoin versus cefixime</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>4.3 Nitrofurantoin versus trimethoprim</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>4.4 Discontinuation of treatment due to adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

**Analysis 2.1. Comparison 2 Comparison between two types of antibiotics, Outcome 1 Recurrence of symptomatic UTI.**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic 1 n/N</th>
<th>Antibiotic 2 n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Nitrofurantoin versus cotrimoxazole</td>
<td>Falakaflaki 2007</td>
<td>17/66</td>
<td>30/66</td>
<td>0.57 [0.35, 0.92]</td>
</tr>
<tr>
<td>2.1.2 Cotrimoxazole versus cephadroxil</td>
<td>Belet 2004</td>
<td>3/21</td>
<td>2/25</td>
<td>1.79 [0.33, 0.7]</td>
</tr>
<tr>
<td>2.1.3 Cotrimoxazole versus cefprozil</td>
<td>Belet 2004</td>
<td>3/21</td>
<td>7/34</td>
<td>0.69 [0.22, 0.39]</td>
</tr>
<tr>
<td>2.1.4 Cephadroxil versus cefprozil</td>
<td>Belet 2004</td>
<td>2/25</td>
<td>7/34</td>
<td>0.39 [0.09, 1.71]</td>
</tr>
</tbody>
</table>

**Analysis 2.2. Comparison 2 Comparison between two types of antibiotics, Outcome 2 Repeat positive urine culture.**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic 1 n/N</th>
<th>Antibiotic 2 n/N</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.1 Nitrofurantoin versus trimethoprim</td>
<td>Brendstrup 1990</td>
<td>12/60</td>
<td>37/60</td>
<td>49.77%</td>
<td>-0.42 [-0.58, -0.26]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>60</td>
<td>49.77%</td>
<td>-0.42 [-0.58, -0.26]</td>
</tr>
<tr>
<td></td>
<td>Total events: 12 (Antibiotic 1), 37 (Antibiotic 2)</td>
<td></td>
<td>49.77%</td>
<td>-0.42 [-0.58, -0.26]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td>Test for overall effect: Z=5.13 (P&lt;0.0001)</td>
<td>49.77%</td>
<td>-0.42 [-0.58, -0.26]</td>
</tr>
<tr>
<td>2.2.2 Nitrofurantoin versus cefixime</td>
<td>Lettgen 2002</td>
<td>3/30</td>
<td>2/27</td>
<td>50.23%</td>
<td>0.03 [0.12, 0.17]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>27</td>
<td>50.23%</td>
<td>0.03 [0.12, 0.17]</td>
</tr>
<tr>
<td></td>
<td>Total events: 3 (Antibiotic 1), 2 (Antibiotic 2)</td>
<td></td>
<td>50.23%</td>
<td>0.03 [0.12, 0.17]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td>Test for overall effect: Z=0.35 (P=0.73)</td>
<td>50.23%</td>
<td>0.03 [0.12, 0.17]</td>
</tr>
</tbody>
</table>
### Analysis 2.3. Comparison 2 Comparison between two types of antibiotics, Outcome 3 Microbial resistance to prophylactic drugs.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic 1 n/N</th>
<th>Antibiotic 2 n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.1 Nitrofurantoin versus cotrimoxazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brendstrup 1990</td>
<td>4/12</td>
<td>28/37</td>
<td>43.19%</td>
<td>0.44[0.19,1]</td>
<td></td>
</tr>
<tr>
<td>Falakaffaki 2007</td>
<td>6/17</td>
<td>17/30</td>
<td>56.81%</td>
<td>0.62[0.3,1.27]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>29</td>
<td>67</td>
<td>100%</td>
<td>0.54[0.31,0.92]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 10 (Antibiotic 1), 45 (Antibiotic 2)

Heterogeneity: Tau²=0; Chi²=0.39, df=1(P=0.53); I²=0%

Test for overall effect: Z=2.26(P=0.02)

Favours antibiotic 1

Favours antibiotic 2

### Analysis 2.4. Comparison 2 Comparison between two types of antibiotics, Outcome 4 Adverse events.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic 1 n/N</th>
<th>Antibiotic 2 n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.1 Cotrimoxazole versus cefprozil</td>
<td></td>
<td></td>
<td></td>
<td>1.62[0.36,7.29]</td>
</tr>
<tr>
<td>Belet 2004</td>
<td>3/21</td>
<td>3/34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4.2 Nitrofurantoin versus cefixime</td>
<td></td>
<td></td>
<td></td>
<td>0.42[0.21,0.81]</td>
</tr>
<tr>
<td>Lettgen 2002</td>
<td>8/31</td>
<td>18/29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4.3 Nitrofurantoin versus trimethoprim</td>
<td></td>
<td></td>
<td></td>
<td>2.18[1.39,3.41]</td>
</tr>
<tr>
<td>Brendstrup 1990</td>
<td>37/60</td>
<td>17/60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4.4 Discontinuation of treatment due to adverse events</td>
<td></td>
<td></td>
<td></td>
<td>3.17[1.36,7.37]</td>
</tr>
<tr>
<td>Brendstrup 1990</td>
<td>19/60</td>
<td>6/60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours antibiotic 1

Favours antibiotic 2

### Comparison 3. Dose comparison

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Repeat positive urine culture</td>
<td>1</td>
<td></td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 3.1. Comparison 3 Dose comparison, Outcome 1 Repeat positive urine culture.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baculis 2003</td>
<td>3/15</td>
<td>4/18</td>
<td>-0.02 [-0.3, 0.26]</td>
<td></td>
</tr>
</tbody>
</table>

APPENDICES

Appendix 1. Electronic search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL</td>
<td>#1 Urinary Tract Infections explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#2 Schistosomiasis haematobia, this term only in MeSH</td>
</tr>
<tr>
<td></td>
<td>#3 (#1 AND NOT #2)</td>
</tr>
<tr>
<td></td>
<td>#4 (urin* next tract next infect*) or (urin* next infect*) in All Fields</td>
</tr>
<tr>
<td></td>
<td>#5 uti</td>
</tr>
<tr>
<td></td>
<td>#6 bacteriuria</td>
</tr>
<tr>
<td></td>
<td>#7 pyuria</td>
</tr>
<tr>
<td></td>
<td>#8 Urine explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#9 (#8 AND bacter*)</td>
</tr>
<tr>
<td></td>
<td>#10 urin* near bacter* in All Fields</td>
</tr>
<tr>
<td></td>
<td>#11 (#9 OR #10)</td>
</tr>
<tr>
<td></td>
<td>#12 (#3 OR #4 OR #5 OR #6 OR #7 OR #11)</td>
</tr>
<tr>
<td></td>
<td>#13 Child explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#14 child*</td>
</tr>
<tr>
<td></td>
<td>#15 girl*</td>
</tr>
<tr>
<td></td>
<td>#16 boy*</td>
</tr>
<tr>
<td></td>
<td>#17 Pediatrics explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#18 pediatric*</td>
</tr>
<tr>
<td></td>
<td>#19 paediatric*</td>
</tr>
<tr>
<td></td>
<td>#20 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)</td>
</tr>
<tr>
<td></td>
<td>#21 Antibiotic Prophylaxis explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#22 antibio* near prophyla*</td>
</tr>
<tr>
<td></td>
<td>#23 Anti-Bacterial Agents explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#24 Anti-Infective Agents, Urinary explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#25 &quot;long term&quot; and (antibiot* or prophylax*)</td>
</tr>
<tr>
<td></td>
<td>#26 (#21 OR #22 OR #23 OR #24 OR #25)</td>
</tr>
<tr>
<td></td>
<td>#27 (#12 AND #20 AND #26)</td>
</tr>
<tr>
<td></td>
<td>#28 Recurrence explode all trees in MeSH</td>
</tr>
<tr>
<td></td>
<td>#29 recurren*</td>
</tr>
<tr>
<td></td>
<td>#30 prevent*</td>
</tr>
<tr>
<td></td>
<td>#31 (#28 OR #29 OR #30)</td>
</tr>
<tr>
<td></td>
<td>#32 (#12 AND #20 AND #31)</td>
</tr>
<tr>
<td></td>
<td>#33 (#32 OR #27)</td>
</tr>
<tr>
<td>MEDLINE</td>
<td>1. urinary tract infections/ or bacteriuria/ or pyuria/</td>
</tr>
<tr>
<td></td>
<td>2. UTI.tw.</td>
</tr>
<tr>
<td></td>
<td>3. urinary tract infectionS.tw.</td>
</tr>
<tr>
<td></td>
<td>4. bacteriuria.tw.</td>
</tr>
<tr>
<td></td>
<td>5. pyuria.tw.</td>
</tr>
<tr>
<td></td>
<td>6. bacterial infectionS.tw.</td>
</tr>
</tbody>
</table>

Long-term antibiotics for preventing recurrent urinary tract infection in children (Review) 35
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7. or/1-6
8. exp child/
9. child$.tw.
10. girl$.tw.
11. boy$.tw.
12. exp pediatrics/
13. pediatric$.tw.
14. paediatric$.tw.
15. or/8-14
16. and/7,15
17. Antibiotic Prophylaxis/
18. (antibiotic$ adj5 prophyla$).tw.
19. exp ANTIBIOTICS/
20. exp Bacterial Infections/
21. anti-infective agents, urinary/
24. recurrence/
25. recurren$.tw.
26. prevent$.tw.
27. or/17-26
28. and/16,27
29. randomised controlled trial.pt.
30. controlled clinical trial.pt.
31. randomised controlled trials/
32. random allocation/
33. double blind method/
34. single blind method/
35. or/29-34
36. animal/ not (animal/ and humans/)
37. 35 not 36
38. clinical trial.pt.
39. exp clinical trials/
40. (clinic$ adj25 trial$).ti,ab.
41. cross-over studies/
42. (crossover or cross-over or cross over).tw.
43. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
44. placebos/
45. placebo$.ti,ab.
46. random$.ti,ab.
47. research design/
48. or/38-47
49. 48 not 36
50. 37 or 49
51. 28 and 50

EMBASE

1. exp Urinary Tract Infection/
2. asymptomatic bacteriuria/ or bacteriuria/
3. Pyuria/
4. UTI.tw.
5. urinary tract infection$.tw.
6. bacteriuria.tw.
7. pyuria.tw.
8. or/1-7
9. exp child/
10. exp Pediatrics/
11. child$.tw.
12. girl$.tw.
13. boy$.tw.
14. or/9-13
15. and/8,14
Appendix 2. Risk of bias assessment tool

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there adequate sequence generation?</td>
<td><strong>Yes</strong> (<em>low risk of bias</em>): Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</td>
</tr>
<tr>
<td></td>
<td><strong>No</strong> (<em>high risk of bias</em>): Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</td>
</tr>
<tr>
<td></td>
<td><strong>Unclear</strong>: Insufficient information about the sequence generation process to permit judgement.</td>
</tr>
<tr>
<td>Was allocation adequately concealed?</td>
<td><strong>Yes</strong> (<em>low risk of bias</em>): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; se-</td>
</tr>
<tr>
<td>Question</td>
<td>Yes (low risk of bias)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Was knowledge of the allocated interventions adequately prevented during the study?</td>
<td>No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.</td>
</tr>
<tr>
<td>Were incomplete outcome data adequately addressed?</td>
<td>The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).</td>
</tr>
</tbody>
</table>
Was the study apparently free of other problems that could put it at a risk of bias?

**Yes (low risk of bias):** The study appears to be free of other sources of bias.

**No (high risk of bias):** Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

**Unclear:** Insufficient information to permit judgement of ‘Yes’ or ‘No’.

### What's New

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 February 2011</td>
<td>New citation required and conclusions have changed</td>
<td>Four new studies added</td>
</tr>
</tbody>
</table>

### History

Review first published: Issue 4, 2001

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 October 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>22 May 2006</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

### Contributions of Authors

- The search strategy was used independently by AL and GW.
- The titles were independently screened by AL and GW.
- AL and GW screened the resulting list of articles independently to assess whether the studies met the inclusion criteria.
- Disagreements were resolved by consultation with JC.
- The quality of eligible studies was assessed independently, under open conditions by AL and GW.
- Disagreements resolved after consultation with JC.
- Full articles of the included studies were examined, under open conditions by AL and GW to extract the necessary information.
- Discrepancies in data extraction were resolved by discussion with JC.
- Issue 3 2006: Titles and abstracts were reviewed for inclusion by WL. Text and data were updated by GW and JC.
- Issue 3 2011: Titles and abstract review, data extraction and text revisions GW
- Text review JC

### Declarations of Interest

Authors of this review are also authors of the PRIVENT Study 2009.

### Sources of Support

**Internal sources**

- The Children’s Hospital Fund Clinical Research Grant, Australia.
External sources

- National Health and Medical Research Council, Australia.
- Australian Kidney Foundation, Australia.

Differences Between Protocol and Review

2010 - Risk of bias assessment tool replaced the quality assessment of allocation concealment, blinding, losses to follow-up, heterogeneity of study group participants, standardisation of outcome assessment, and intention-to-treat analysis.

Index Terms

Medical Subject Headings (MeSH)

Acute Disease; Anti-Infective Agents, Urinary [adverse effects] [*therapeutic use]; Nitrofurantoin [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Secondary Prevention; Urinary Tract Infections [drug therapy] [*prevention & control]; Vesico-Ureteral Reflux [prevention & control]

MeSH check words

Child; Female; Humans; Male