Interventions for primary vesicoureteric reflux (Review)

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[Intervention Review]

Interventions for primary vesicoureteric reflux

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Editorial group: Cochrane Renal Group.
Publication status and date: Edited (conclusions changed), published in Issue 6, 2011.
Review content assessed as up-to-date: 8 November 2010.

Citation: Nagler EVT, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD001532. DOI: 10.1002/14651858.CD001532.pub4.

ABSTRACT

Background

Vesicoureteric reflux (VUR) results in urine passing retrograde up the ureter. Urinary tract infections (UTI) associated with VUR have been considered a cause of permanent renal parenchymal damage in children with VUR. Management of these children has been directed at preventing UTI by antibiotic prophylaxis and/or surgical correction of VUR. The optimum strategy is not clear.

Objectives

To evaluate the benefits and harms of different treatment options for primary VUR.

Search strategy

In August 2010 we searched CENTRAL, MEDLINE and EMBASE and screened reference lists of papers and abstracts from conference proceedings.

Selection criteria

RCTs in any language comparing any treatment of VUR including surgical or endoscopic correction, antibiotic prophylaxis, non-invasive non-pharmacological techniques and any combination of therapies.

Data collection and analysis

Two authors independently searched the literature, determined study eligibility, assessed quality, extracted and entered data. We expressed dichotomous outcomes as risk ratios (RR) and their 95% confidence intervals (CI) and continuous data as mean differences (MD) and their 95% CI's Data were pooled using the random effects model.

Main results

Twenty RCTs (2324 children) were included. Long-term low-dose antibiotic prophylaxis compared to no treatment/placebo did not significantly reduce repeat symptomatic UTI (846 children: RR 0.68, 95% CI 0.39 to 1.17) or febrile UTI (946 children: RR 0.77, 95% CI 0.47 to 1.24) at two years. There was considerable heterogeneity in the analyses and only one study was adequately blinded. At one to three years, antibiotic prophylaxis reduced the risk of new or progressive renal damage on DMSA scan (446 children: RR 0.35,

95% CI 0.15 to 0.80). Side effects were infrequent when reported, but antibiotics increased the likelihood of bacterial drug resistance threefold (132 UTIs: RR 2.94, 95% CI 1.39 to 6.25).

When long-term antibiotic prophylaxis was compared with surgical or endoscopic correction of VUR plus antibiotics for one to 24 months (10 studies, 1141 children), the risk of symptomatic UTI was not significantly different at any time point. Combined surgical and antibiotic treatment caused a 57% reduction in febrile UTI by five years (2 studies, 449 children: RR 0.43, 95% CI 0.27 to 0.70) but did not decrease the risk of new or progressive renal damage at any time point. Postoperative obstruction was seen in 0% and 7% of children in two surgical studies and 0% in one endoscopic study.

Authors' conclusions

Compared with no treatment, use of long-term, low-dose antibiotics did not significantly reduce the number of repeat symptomatic and febrile UTIs in children with VUR. Considerable heterogeneity in the analyses and inclusion of only one adequately blinded study, made drawing firm conclusions challenging. Antibiotic prophylaxis significantly reduced the risk of developing new or progressive renal damage, but assuming an 8% baseline risk, 33 children would need long-term antibiotic prophylaxis to prevent one more child developing kidney damage over the course of two to three years.

The added benefit of surgical or endoscopic correction of VUR over antibiotic treatment alone remains unclear. Eight children would require combined surgical and antibiotic treatment to prevent one additional child developing febrile UTI by five years, but it would not cause fewer children developing renal damage.

PLAIN LANGUAGE SUMMARY

Interventions for primary vesicoureteric reflux

Vesicoureteric reflux (VUR) is the backflow of urine from the bladder up the ureters to the kidney. People with VUR are thought to be more likely to get urinary tract infections (UTIs) involving the kidney tissue, which may cause permanent kidney damage. Current treatment options include reimplantation of the ureters or endoscopic surgery, long-term antibiotics, endoscopic correction (injection of a substance around the entry of the ureter into the bladder) using different materials, or a combination of interventions. This review found no strong evidence that long-term antibiotic prophylaxis prevented repeat UTIs in children with VUR. Associated side effects were infrequent and minor, but prophylaxis was associated with a threefold increased risk of bacterial resistance to the treatment drug in subsequent infections. Surgery decreased the number of UTIs with fever, but did not change the number of children developing symptomatic UTI or kidney damage.

BACKGROUND

Primary vesicoureteric reflux (VUR) is thought to be a maturational abnormality of the vesicoureteric junction, which results in retrograde passing of urine up the ureter during voiding. Although the exact prevalence in children is unknown, about a third investigated after a urinary tract infection (UTI), shows signs of VUR (Smellie 1994). UTI is common, affecting 5% to 10% of all children (Hellstrom 1991), with 30% to 50% of them likely to suffer a recurrence (Smellie 1994). VUR is thought to predispose for UTI, renal involvement during UTI and hence to potentially cause subsequent permanent renal damage in 15% of patients (Montini 2007). Retrospective analyses of selected individuals with renal scarring, have reported hypertension and chronic kidney disease (CKD) in approximately 20% and 10% respectively (Martinell 1996; Smellie 1998). However recent data from a prospective cohort study have indicated, that possibly due to better treatment of acute infections, these adverse outcomes now occur considerably less frequently (Wennerstrom 2000a; Wennerstrom 2000b).

As a result of the hypothesized causal link between VUR and renal scarring, VUR screening and treatment strategies have largely been directed towards avoidance of UTI induced-damage (Belman 1995). To this end, both antibiotic prophylaxis with or without surgical VUR correction have been used. In addition to the common Politano-Leadbetter, Lich-Gregoir and Cohen surgical techniques, newer, less invasive techniques involving endoscopic periureteric injections of polydimethylsiloxane (Macroplastique), dextranomer/hyaluronic acid copolymer (Deflux) or glutaraldehyde

cross-linked bovine collagen have been assessed (Capozza 2002; Frankenschmidt 1997; Frey 1997; Oswald 2002). Although VUR is a common problem in childhood, there has been no consensus regarding the optimal management strategy and practice varies widely.

OBJECTIVES

The aim of this review was to evaluate the available evidence for both benefits and harms of the currently available treatment options for primary VUR: operative, non-operative or no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which evaluated any treatment for primary VUR were included.

Types of participants

Inclusion criteria

Males and females of any age with primary VUR diagnosed by voiding cystourethrogram (VCUG) with or without UTI.

Exclusion criteria

Patients with VUR associated with posterior urethral valves, spina bifida, other urological abnormalities or kidney transplants.

Types of interventions

Treatments of VUR including surgery (open and endoscopic techniques), antibiotic prophylaxis of any duration, non-invasive techniques such as bladder training and any combination of therapies.

Types of outcome measures

Primary outcomes

- Number of patients with symptomatic UTI, defined as symptoms consistent with a UTI together with a positive urine culture.

Secondary outcomes

- Number of patients with UTI accompanied by fever (temperature > 38°C or > 100.4°F)
- Number of patients with at least one repeat positive urine culture during follow-up.
- Renal parenchymal abnormality, defined as new, progression from pre-existing damage, resolution, end-stage kidney disease (ESKD) and diagnosed by ultrasound, intravenous pyelography (IVP) or ^{99m}Tc-DMSA (dimercaptosuccinic acid) scintigraphy (DMSA scan).
- Number of previously unaffected subjects who developed hypertension, defined as greater than 140 mm Hg systolic, 90 mm Hg diastolic for adults and above the 95th percentiles for systolic and diastolic blood pressures in children.
- Renal function impairment was defined as an estimated glomerular filtration rate (eGFR) (measured either directly or calculated from serum creatinine) less than the 95th percentile for age, or a decrease in renal function over the duration of the study.
- Correction of VUR, defined as the number of children and/or ureters without VUR on follow up VCUG.
- Microbial resistance, obstruction following correction of VUR, death or serious injury resulting from the anaesthetic, wound infection, fever, adverse effects of medication including urticaria and gastro-intestinal reaction.

Search methods for identification of studies

Initial search

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

- The Cochrane Renal Group Specialised Register (November 2003).
- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, Issue 4, 2003.
- MEDLINE (1966 to February 2003).
- EMBASE (1988 to February 2003).
- Reference lists of relevant articles, reviews and studies.
- Pharmaceutical industry representatives.
- Known authors in the field.

There were no language restrictions.

Review update search

For the first and the current update, the Cochrane Renal Group's specialised register (August 2010) and The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library* Issue 8, 2010) were searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2011). 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).

Data collection and analysis

Selection of studies

Titles and abstracts obtained from the above searches were screened for selection independently by at least two authors. In all cases an overly inclusive selection was preferred to avoid losing relevant studies and to ensure additional studies could be identified from the reference lists. Where suitability was uncertain or no abstract available, the full article was obtained and screened by the same authors. Any disagreements were resolved by discussion with a third author. Authors were contacted to obtain raw or missing data where necessary.

Data extraction and management

Data extraction was conducted independently by at least two authors, using a standardised data extraction form. All studies, reported in a non-English journal, were translated prior to assessment. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Any disagreements were resolved by discussion with a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors 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?

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes, the risk ratio (RR) and corresponding 95% confidence interval (CI) were chosen to describe the treatment effects and the precision of their point estimates. Number needed to treat (NNT) estimates were calculated to compare the benefits and harms of each active treatment.

Continuous outcomes

Where continuous scales of measurement were used to assess effects of treatment such as blood pressure and kidney function measured by eGFR, the mean difference (MD) and 95% CI was used. Where summary statistics were missing, they were derived from accompanying P values.

Planned treatment comparisons

- Antibiotics versus surgery or endoscopic treatment
- Antibiotics versus placebo or no treatment
- One antibiotic treatment versus another
- Surgical or endoscopic correction with no other treatment
- Any combinations of any active treatment

Assessment of heterogeneity

Heterogeneity between studies was analysed using the Cochran's Q statistic with the threshold for statistical significance set at alpha = 0.1 (Lau 1997). It was also tested by means of the I^2 test, reflecting the percentage of total variation across studies that could be ascribed to heterogeneity (Higgins 2003). Due to an insufficient number of studies, formal evaluation of the different sources of heterogeneity was not possible.

Assessment of reporting biases

Publication bias was to be assessed using a funnel plot; there were insufficient studies to do so.

Data synthesis

A random effects model was used, with subsequent testing for robustness of the analysis by applying a fixed effects model.

Sensitivity analysis

To determine the effect of study quality on the primary outcome's pooled summary measure, sensitivity and subgroup analysis was performed to examine the influence of allocation concealment and blinding on results.

RESULTS

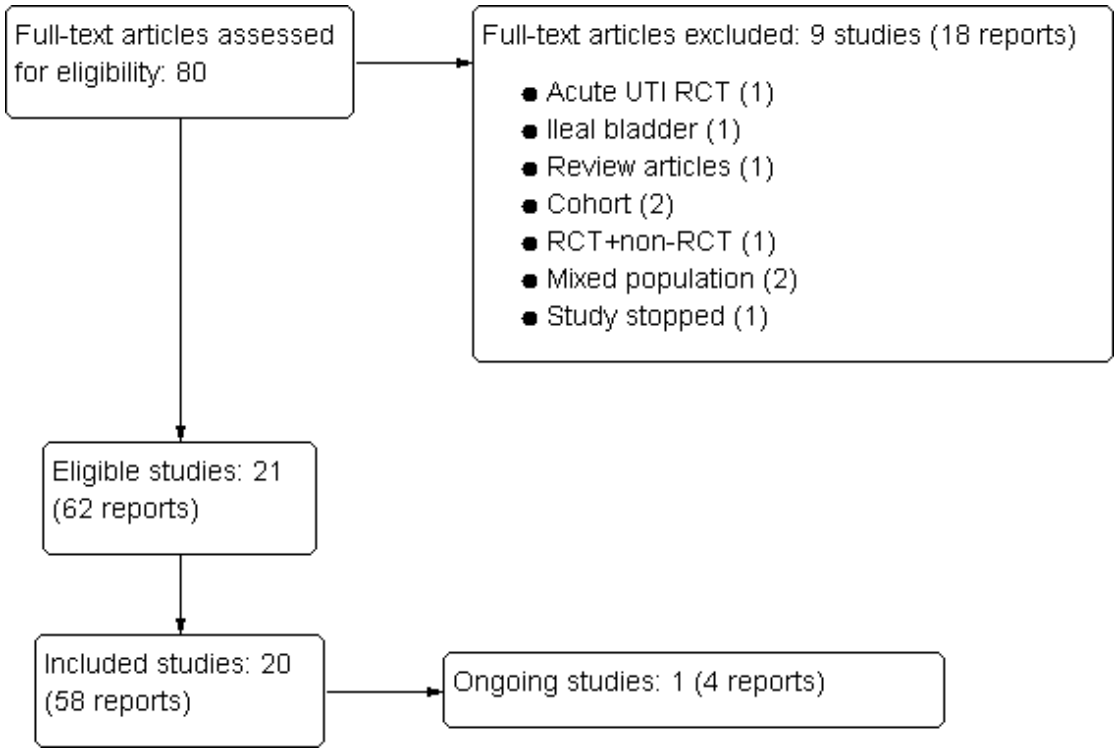
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We originally identified 10 studies after full paper assessment (Wheeler 2004). The International Reflux Study was reported in a European (IRS EUR 1981-2003) and an American arm (IRS USA 1992) and so we treated them as two separate studies. We captured two studies by screening reference lists of the authors. Both studies were published in conference proceedings only (Morris 1991; Reddy 1997). During a second search in June 2006 (Hodson 2007), we found one new study (Garin 2006) and two additional reports of the European arm of the International Reflux Study. Finally, after a search in August 2010, we included an additional nine RCTs (Craig 2002; Dite 2007; Lee 2007; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Scott 1968; Swedish Reflux Trial 2010). Craig 2002 was only published as an abstract and Dite 2007 was originally published in Czech and translated before assessment. We found another three papers that belonged to previously included studies (Garin 2006; IRS EUR 1981-2003; IRS USA 1992). We also identified one ongoing study (RIVUR Study), which is scheduled to finish in October 2011. See Figure 1 for study selection diagram.

Figure 1. Study flow diagram.



Included studies

In eight studies (1039 children) antibiotic treatment was compared with surveillance (Garin 2006; Montini 2008; Pennesi 2006; Reddy 1997; Roussey-Kesler 2008; Swedish Reflux Trial 2010) or with placebo (Craig 2002; PRIVENT Study 2009). In most of these studies, participants were recruited after at least one symptomatic UTI (Garin 2006; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010), with subsequent exclusion of children with severe VUR, defined as grade IV (Garin 2006; Montini 2008; Roussey-Kesler 2008) or grade V (Pennesi 2006). Overall, girls outnumbered boys, with a maximum reported ratio of 4:1 (Garin 2006). In three studies (Garin 2006; Montini 2008; PRIVENT Study 2009), the investigators included both children with and without VUR. For this review, we only included the data from children with VUR. In Reddy 1997 no treatment was compared with two antibiotic prophylaxis regimens (daily or intermittent antibiotic administration). Additionally, Lee 2007 (125 children) compared probiotics with antibiotic prophylaxis. Overall the duration of the antibiotic treatment varied from one to three years.

In 10 studies (1141 children) the effectiveness of low-dose antibiotic prophylaxis, given for one to five years, was compared with ureteric reimplantation by open surgery (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001; Scott 1968) or endoscopic subureteric injection of Deflux (Capozza 2002; Dite 2007; Swedish Reflux Trial 2010). All who underwent a surgical or endoscopic procedure received antibiotic prophylaxis for one to 24 months, with a variety of open surgical techniques being used to correct VUR. Generally, only children with higher (dilating) grades of VUR were included. The gender distribution was usually poorly reported. Outcomes were reported at three months to 10 years post randomisation.

One study had a three-arm design (203 children), and children were randomised to endoscopic VUR correction and antibiotic prophylaxis, antibiotic prophylaxis alone, or surveillance (Swedish Reflux Trial 2010).

In two studies (88 children), researchers compared different materials for subureteric injection to correct VUR (Frey 1997; Oswald 2002). We did not find a single RCT in which an open surgical procedure was compared with endoscopic correction of VUR, nor one in which antibiotic use was compared with surgery alone, or with other treatment strategies such as management for voiding dysfunction.

In total, we have included 20 studies (58 reports) enrolling 2324 children under the age of 18 years from the USA, Europe, Australasia and South Korea. The number of participants varied between 10 and 321. Nine studies included less than 100, eight studies included between 100 and 200, and three studies enrolled more than 200 children. Data for at least one outcome was available from 2219 participants. Trimethoprim-sulphamethoxazole was the predominant chemoprophylactic drug of choice, but trimethoprim, nitrofurantoin, cefadroxil or amoxicillin-clavulanic acid were also used for antibiotic chemoprophylaxis.

Excluded studies

We excluded nine studies (18 reports). There was one acute treatment study (Montini 2003) and one study that was conducted in patients with ileal bladders (Osman 2004). There were two cohort studies (Cheskis 1995; Lindberg 1978) and one review (Becker 2004). One study was terminated before collection of outcome data because of inadequate patient recruitment (Ransley 2004). One study was omitted because it was impossible to separate the outcomes for randomised patients from those of a non-randomly selected group of children reported in the same publication (Scholtmeijer 1993). Finally both COBSG 1978 and NCBRG 1981 had included patients with and without VUR, but provided insufficient data to allow for separate analysis of the children with VUR.

Risk of bias in included studies

Before we conducted the current update, overall reporting of methodology in primary studies was generally not very detailed. In four of the most recently included studies, authors adhered to a higher standard of both design and reporting (Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008). An overview is provided in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

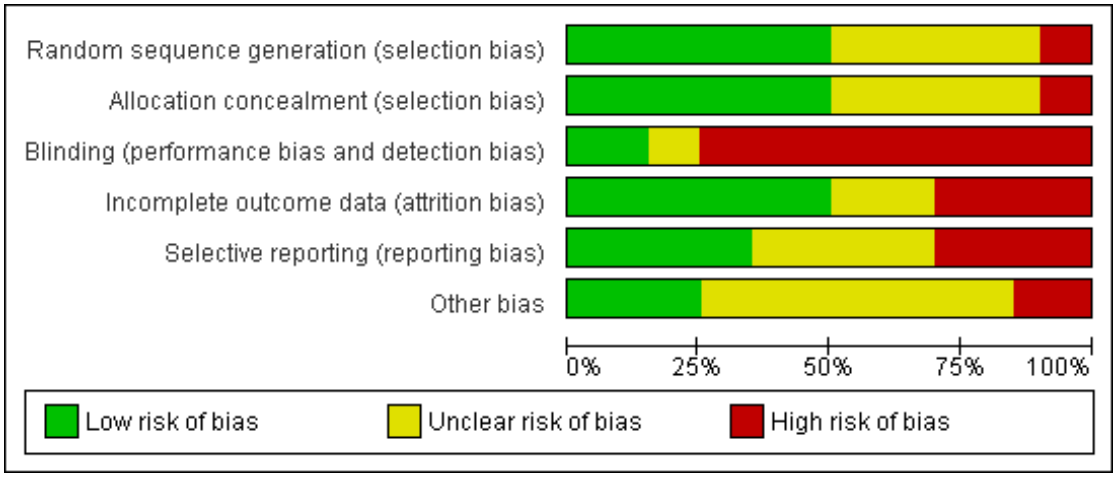
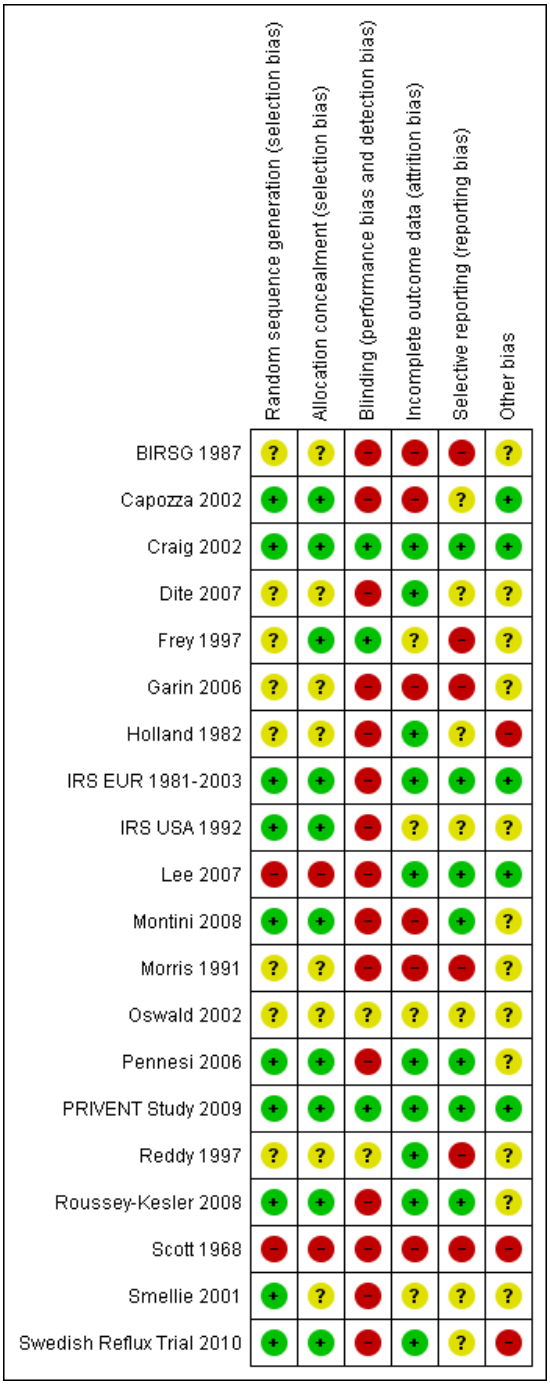


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

The method of sequence generation and treatment allocation was satisfactory in nine studies (Capozza 2002; Craig 2002; IRS EUR 1981-2003; IRS USA 1992; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010). The other eleven used a quasi-random method or did not detail the applied procedure.

Blinding

Given the nature of the intervention, blinding of investigators and participants was not possible in studies comparing the potential benefits and harms of surgical and endoscopic treatments with antibiotic prophylaxis. Yet only four explicitly reported that assessment of radiological outcomes occurred without knowledge of the treatment groups (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Swedish Reflux Trial 2010). Overall, in only three studies all participants, caregivers, outcome assessors and data analysts were adequately blinded (Craig 2002; Frey 1997; PRIVENT Study 2009).

Incomplete outcome data

Only seven studies re-included all cases for analysis that had been withdrawn during the course of follow-up (Craig 2002; Lee 2007; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). In the remainder it was not possible to determine whether the analysis had been done on an intention-to-treat basis. Losses to follow-up over the short-term were however generally low: 0% and 10% at one to two years; 11% at three years; 5% and 42% at five to 10 years.

Selective reporting

Nine studies reported the most appropriate primary outcome, repeat symptomatic UTI (Garin 2006; Dite 2007; IRS EUR 1981-2003; Lee 2007; Montini 2008; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). Frey 1997 only described VUR correction; the other 10 described the less relevant primary outcome of repeat positive urine culture.

Other potential sources of bias

For many studies it was difficult to discern who the children were and how many were reviewed for possible inclusion in the study protocol, thereby largely limiting the ability to evaluate the extent of selection bias. Only IRS EUR 1981-2003 and PRIVENT Study 2009 clearly denoted the number of patients screened and the reasons for their exclusion or non-enrolment.

Definitions and criteria for diagnosis of initial or recurrent UTI and renal abnormalities greatly differed between the various studies and, apart from in the most recent ones, were largely inadequately reported.

Effects of interventions

Antibiotic prophylaxis versus surveillance/no treatment

The data were analysed using a random and fixed effects model, without there being an appreciable difference between the summary estimates. Results are presented using the random effects model.

Symptomatic UTI and febrile UTI

Of the eight studies that compared antibiotic prophylaxis with placebo or no treatment, six had repeat symptomatic UTI as the primary outcome and allowed distinction of febrile UTI as a separate entity. One and two year incidence of symptomatic UTI varied from 12% to 36% in the group treated with antibiotics and 2% to 41% in the surveillance group. The point estimate for overall effect favoured antibiotic prophylaxis, but the result was not statistically significant for either symptomatic UTI (Analysis 1.1.1 (5 studies, 846 children): RR 0.68, 95% CI 0.39 to 1.17) or febrile UTI by one to two years of follow-up (Analysis 1.1.2 (6 studies, 946 children): RR 0.77, 95% CI 0.47 to 1.24). For both outcomes, there was a large amount of unexplained heterogeneity among studies. We could not identify systematic differences in allocation mechanism, blinding or participant characteristics that would have explained the heterogeneity. For allocation concealment, heterogeneity appeared to be related to Garin 2006, however removing this study did not alter the statistical significance of the result (Analysis 1.2.1 (5 studies, 833 children): RR 0.69, 95% CI 0.45 to 1.05). One study was optimally designed with adequate blinding (PRIVENT Study 2009). Its point estimate again favoured antibiotic prophylaxis, but the result was not statistically significant and patient numbers were too small to give sufficient power to the analysis (Analysis 1.3).

Repeat positive urine culture

In six studies the outcome of repeat positive urine culture was reported for urine samples taken in asymptomatic subjects (Craig 2002; Garin 2006; Montini 2008; Pennesi 2006; Reddy 1997; Roussey-Kesler 2008). The analysis did not show a significant reduction in routine positive urine cultures associated with the use of antibiotics (Analysis 1.1.3 (6 studies, 636 children): RR 0.84,

95% CI 0.57 to 1.25). In addition to comparing a daily antibiotic regimen with surveillance, Reddy 1997 introduced an extra treatment arm to compare intermittent treatment three times/week, with no specific therapy. In the group treated with intermittent antibiotics 2/14 participants (14%) had a positive urine culture, in the surveillance group the culture was positive for 5/16 patients (31%) (Analysis 1.1.4 (1 study, 30 children): RR 0.46, 95% CI 0.10 to 2.00).

Renal parenchymal abnormality

In five studies, the acquisition of new renal abnormalities was evaluated by comparing DMSA scans, taken both at study commencement and completion of follow-up (Craig 2002; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010). Two studies had no events in either group and hence did not contribute to any of the analyses (Craig 2002; Pennesi 2006). Overall there was no significant reduction in either the number of children with new renal damage (Analysis 1.4.1 (5 studies, 782 children): RR 0.27, 95% CI 0.06 to 1.23) or progression of existing renal abnormalities (Analysis 1.4.2 (3 studies, 446 children): RR 0.68, 95% CI 0.27 to 1.73), although the point estimates favoured antibiotic prophylaxis in both instances. When the number of children with new or progressive renal damage were considered as a single outcome measure, the reduction was statistically significant, although only two studies contributed to the analysis (Analysis 1.4.3 (3 studies, 446 children): RR 0.35, 95% CI 0.15 to 0.80). All physicians evaluating the DMSA scans had been adequately blinded to the treatment group and there was no substantial heterogeneity.

Two additional studies also reported development of renal abnormality but had done the baseline DMSA scan either at the time of acute pyelonephritis (Garin 2006) or not at all (Reddy 1997). In both these studies it was impossible to distinguish those who had developed the abnormality as a result of the index UTI from those in whom antibiotic prophylaxis had failed to prevent the renal damage. Overall no appreciable difference was seen in either group at one to three years when combined in meta-analysis (Analysis 1.4.4 (2 studies, 142 children): RR 1.70, 95% CI 0.36 to 8.07). Similarly, Reddy 1997 showed no meaningful difference in the risk of renal parenchymal injury between intermittent prophylaxis given three times/week and no prophylaxis (Analysis 1.4.5 (1 study, 30 children): RR 0.38, 95% CI 0.02 to 8.59).

Other outcomes

One small study (46 children), only published in abstract form, reported on estimated GFR, calculated with the MDRD equation, and renal growth at the end of a three year follow-up period (Craig 2002). Results were only reported as means, but standard deviations could be derived from the accompanying P value. Neither the difference in estimated GFR, 119 mL/min/1.73 m² in the group treated with antibiotics versus 108 mL/min/1.73 m² in the placebo group (Analysis 1.5 (1 study, 41 children): MD -11.00 mL/min/1.73 m², 95% CI -31.53 to 9.53), nor the difference in renal growth, 2.42 cm versus 2.38 cm (Analysis 1.6 (1 study, 41 children): MD 0.04 cm, 95% CI -0.04 to 0.12) was statistically significant at three years follow-up. Three studies (Pennesi 2006; Reddy 1997; Swedish Reflux Trial 2010) reported the VUR status after a two year follow-up. Overall there was no significant difference in the number of children with persisting VUR (Analysis 1.7 (3 studies, 262 children): RR 1.46, 95% CI 0.71 to 2.99).

Adherence

Adherence was addressed in 4/7 studies (Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010).

- Pennesi 2006 tested the urine samples of children that developed a febrile UTI for presence of the prophylactic drug. He found all patients were compliant.
- Montini 2008 found 71% of participants were adherent when assessed by measuring antimicrobial activity in a sample of screened urine samples. The reported compliance was 86% according to the visual analogue questionnaire.
- PRIVENT Study 2009 was the only placebo-controlled study and investigators tested adherence by weighing the bottles at each clinic visit as well as by direct questioning of the parents. The authors reported no difference in the frequency of measured non-adherence between the groups. In-depth analysis of the compliance data is currently under assessment and no numeric data were available.
- The Swedish Reflux Trial 2010 report stated that adherence to the antibiotic prophylaxis had been assessed by asking questions during every follow-up visit, but no findings were provided.

Adverse events

Only three studies reported side effects and the findings were very different for each study (Garin 2006; Montini 2008; PRIVENT Study 2009) (Analysis 1.8).

- Garin 2006 explicitly stated to have had 'no reported side effects associated with the use of urinary antibiotic prophylaxis'.
- In PRIVENT Study 2009 two participants developed thrush while on antibiotics and five developed a rash while on placebo.
- Montini 2008 reported 25 minor adverse events (out of 211 participants), mainly vomiting or gastro-intestinal intolerance. These data however included patients without VUR and were not reported per treatment group.

Microbial resistance

Four studies described bacterial resistance to the prophylactic drug in subsequent symptomatic UTIs (Pennesi 2006; PRIVENT

Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). Overall the estimated risk of prophylactic drug resistance in a repeat symptomatic UTI was three times higher for children that received antibiotics (Analysis 1.9.1 (4 studies, 132 urine cultures): RR 2.94, 95% CI 1.39 to 6.25). In Garin 2006, in which both frequencies of symptomatic febrile and afebrile UTIs were collected, all of the seven pyelonephritis cases in children given antibiotics were caused by a resistant micro-organism, as opposed the one case in the no treatment group which was caused by a sensitive strain. This estimate however was based on the pooled data of only three studies, with high levels of heterogeneity and imprecision due to small numbers.

Anatomic VUR correction with surgery or endoscopic injection plus antibiotics (1-24 months) versus antibiotics alone

We had planned to analyse the results of studies comparing antibiotic prophylaxis (for one to five years) with surgical VUR correction together with studies comparing antibiotic prophylaxis with endoscopic VUR correction to obtain summary measures of treatment effects. However, we separated outcomes according to follow-up time (one to two, four to five, five to 10, and more than 10 years) and for none of the time-points did the analyses include both surgical and endoscopic interventions to estimate the treatment effect. There was no appreciable difference between the summary estimates using random and fixed effects models. There were insufficient studies to explore potential effect modification using subgroup analysis or meta-regression.

Symptomatic and febrile UTI

The overall incidence of symptomatic UTI (febrile and non-febrile) was reported in three studies (Dite 2007; IRS EUR 1981-2003; Swedish Reflux Trial 2010). There was no significant difference at any time point up to 10 years between children who had undergone either surgical or endoscopic VUR correction on top of receiving antibiotics for up to 24 months (Analysis 2.1.1 to Analysis 2.1.4). Two studies reported the number of children developing febrile UTI by two years of follow-up (Dite 2007; Swedish Reflux Trial 2010). Both were studies comparing subureteric injection of Deflux and the use of antibiotics with antibiotics alone. When combined, we found no significant difference in frequency of repeat symptomatic UTI (Analysis 2.1.1 (2 studies, 179 children): RR 0.88, 95% CI 0.26 to 3.01) or febrile UTI (Analysis 2.1.5 (2 studies, 179 children): RR 0.73, 95% CI 0.15 to 3.60). Numeric results of the individual studies contradicted each other but both studies were small and CI's wide. Both arms of the International Reflux Study (IRS EUR 1981-2003; IRS USA 1992) reported outcomes by five years of follow-up. In these studies children underwent surgical reimplantation of the ureter. After five years, there were significantly fewer children developing a febrile UTI in the group that had undergone surgery and received prophylactic antibiotics (8% to 10%) than in the group only receiving antibiotics (22%) (Analysis 2.1.6 (2 studies, 429 children): RR 0.43, 95% CI 0.27 to 0.70). The effect persisted for between five and 10 years (Analysis 2.1.7 (1 study, 252 children): RR 0.34, 95% CI 0.14 to 0.82) so that overall in children followed for 10 years there were significantly fewer febrile UTIs among children that had undergone surgical correction plus antibiotic treatment compared with children receiving only antibiotic treatment (Analysis 2.1.8 (1 study, 252 children): RR 0.54, 95% CI 0.32 to 0.92). Conversely, there tended to be fewer children with a repeat symptomatic afebrile UTI in the group treated antibiotics alone, but this result was not significant at any of the time-points.

Repeat positive urine culture

Repeat positive urine culture was examined in eight studies (BIRSG 1987; Capozza 2002; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001; Scott 1968). The number of children with a repeat positive urine culture did not significantly differ between the group treated with antibiotics alone and the group that underwent surgical VUR correction in addition to receiving antibiotic prophylaxis at one to three years (Analysis 2.1.9 (5 studies, 388 patients): RR 0.89, 95% CI 0.55 to 1.44) and four to five years follow-up (Analysis 2.1.10 (3 studies, 479 children): RR 0.99, 95% CI 0.79 to 1.26).

Renal parenchymal abnormality

Renal parenchymal abnormalities were examined in six studies (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Swedish Reflux Trial 2010). The frequency of renal parenchymal abnormality (scars and renal parenchymal thinning) on IVP at study entry was 56% to 100% with no difference between children receiving antibiotic prophylaxis alone and those treated with surgery plus antibiotics. There was no difference in the number of children developing a new renal parenchymal abnormality, either at two years (Analysis 2.2.1 (2 studies, 171 children): RR 1.06, 95% CI 0.33 to 3.42) or at four to five years (Analysis 2.2.2 (4 studies, 572 children): RR 1.09, 95% CI 0.79 to 1.49). Similarly, there was no difference in the risk of progression of an existing abnormality either at two years (Analysis 2.2.3 (1 study, 10 children): RR 7.00, 95% CI 0.45 to 108.26) or at four to five years (Analysis 2.2.4 (3 studies, 468 children): RR 0.99, 95% CI 0.69 to 1.42). When the development of a new or a progressive abnormality were considered as a single outcome at four to five years, there was no difference between the two groups (Analysis 2.2.6 (3 studies, 468 children): RR 1.05, 95% CI 0.85 to 1.29). The European (IRS EUR 1981-2003) and US arms (IRS USA 1992) of the International Reflux Study differentiated renal scarring and renal parenchymal thinning on IVP. There was no significant difference in the number of patients with renal scars on IVP at zero to five years (Analysis 2.3.1 (2 studies, 418 children): RR

1.28, 95% CI 0.84 to 1.94), at five to 10 years (Analysis 2.3.2 (1 study, 223 children): RR 1.03, 95% CI 0.07 to 16.22) or zero to 10 years in children followed for 10 years in the European arm of the International Reflux Study (Analysis 2.3.3 (1 study, 223 children): RR 1.03, 95% CI 0.53 to 2.00). In the IRS EUR 1981-2003, renal scarring on IVP was present at entry in 49% of the 306 children originally treated and in 51% of 223 children studied by IVP at 10 years. During the first five years of follow-up, 40 children (surgery plus antibiotic group (21); antibiotic group (19)) developed new scars. Of these, 28 were among the 223 followed radiologically at 10 years. Only two more children, one from each therapy group, developed new scars between five and 10 years.

When the data were examined according to the total number of kidneys, there were also no significant differences at two years in new (Analysis 2.4.1 (2 studies, 235 children): RR 1.03, 95% CI 0.31 to 3.37), progressive (Analysis 2.4.2 (2 studies, 235 children): RR 1.56, 95% CI 0.24 to 10.08) or total renal parenchymal abnormalities (Analysis 2.4.3 (2 studies, 235 children): RR 1.54, 95% CI 0.24 to 9.95). Similarly, the risks for new abnormality (Analysis 2.4.4 (2 studies, 319 children): RR 0.85, 95% CI 0.24 to 3.09), progression in abnormality (Analysis 2.4.5 (2 studies, 319 children): RR 0.84, 95% CI 0.50 to 1.41) or total abnormality (Analysis 2.4.6 (2 studies, 319 children): RR 0.84, 95% CI 0.53 to 1.34) did not differ at four to five years.

Two studies evaluated renal parenchymal abnormality with DMSA scan (IRS EUR 1981-2003; Swedish Reflux Trial 2010). In the Swedish Reflux Trial 2010, the number of children developing new renal damage or deterioration of already existing damage did not significantly differ between children that underwent endoscopic correction and received antibiotics versus those receiving antibiotic prophylaxis alone (Analysis 2.5.1 (1 study, 133 children): RR 2.09, 95% CI 0.66 to 6.61). In the IRS EUR 1981-2003, 97% of children had a scintigraphy performed at five years and 73% of children at 10 years. Parenchymal abnormalities were present in 83% of children at study entry. Relative to the antibiotics-only group, in the surgical plus antibiotic treatment group there was no significantly increased risk of new or progressive DMSA scan abnormalities (Analysis 2.5.2 (1 study, 287 children): RR 0.97, 95% CI 0.58 to 1.62) or of deterioration in DMSA scan appearance between five to 10 years (Analysis 2.5.3 (1 study, 216 children): RR 0.71, 95% CI 0.31 to 1.58).

Finally in Capozza 2002, renal damage was evaluated with ultrasound. There was no significant difference in the risk of abnormality at one year between medically and surgically treated participants (Analysis 2.6.1 (1 study, 81 children): RR 0.36, 95% CI 0.04 to 3.31) though only four children developed abnormalities.

Renal growth was evaluated in four studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) at two to 10 years by measurements of changes in renal length standard deviation score (SDS) (3 studies, 510 children) or renal area (1 study, 82 children) on IVP. No significant differences between groups were found at any time point or in any age group. Combining data in meta-analysis was not possible because of differences in reporting.

Other outcomes

Five other outcomes were reported in 10 studies. The two outcomes of greatest clinical importance, ESKD and hypertension, were reported in three studies (BIRSG 1987; IRS EUR 1981-2003; Smellie 2001). Six children developed ESKD and 14 developed hypertension during follow-up. There was no significant difference in the risk of ESKD (Analysis 2.7.1 (2 studies, 154 children): RR 1.07, 95% CI 0.23 to 5.04) or hypertension (Analysis 2.7.2 (2 studies, 154 children): RR 0.93, 95% CI 0.25 to 3.42) between treatment groups at five years or for hypertension at 10 years (Analysis 2.7.3 (1 study, 252 children): RR 0.15, 95% CI 0.01 to 2.78).

Five studies (BIRSG 1987; Capozza 2002; IRS EUR 1981-2003; Morris 1991; Smellie 2001) reported on GFR but these were unable to be combined because of insufficiently reported point estimate and variance data. Individually, no study reported any significant difference between groups. Data from IRS EUR 1981-2003 showed no significant differences in GFR measured by the Schwartz formula at study entry (Analysis 2.8.1), at five years (Analysis 2.8.2) and at 10 years (Analysis 2.8.3).

Growth was investigated in IRS EUR 1981-2003. There was no significant difference in height SDS at study entry (Analysis 2.9.1) or at 10 years (Analysis 2.9.2).

Resolution of VUR was an outcome described in eight studies (BIRSG 1987; Capozza 2002; Dite 2007; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Scott 1968; Swedish Reflux Trial 2010). Combining individual study data was only possible for two studies examining endoscopic VUR correction. Unsurprisingly more children in the endoscopic group than in the antibiotics alone group had full VUR resolution after one to two years (Analysis 2.10.1 (2 studies, 164 children): RR 2.69, 95% CI 1.57 to 4.63). But assuming a spontaneous resolution rate of 15% over one to two years when treated with antibiotics alone, two to three patients would have to be treated endoscopically for one additional patient to have a response compared with antibiotic treatment alone. Capozza 2002 included VUR grade I in its definition of resolution. Still the success rate was lower than in the other two studies that evaluated endoscopic VUR correction (69% versus 38%).

We did not combine individual study data for the surgical studies, because of differences in reporting practices (patients and ureters), not all patients having had follow-up VCUGs and missing data. In four studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) the postoperative resolution rate at four to five years for ureters was 93% to 99%. Over a follow-up period of three to five years, 16% to 49% of patients had spontaneous resolution of VUR (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Scott 1968). In IRS EUR 1981-2003, 130/

155 children in the antibiotics-only group had persisting VUR at five years though in 50 other children VUR grade had diminished. Among 102 children undergoing voiding VCUGs at 10 years, VUR was still present in 27 children (22 with grade IV and five with grade III). In Scott 1968, 6/31 had persistent VUR three years postoperatively and 4/31 had successful operations, but developed VUR in the opposite ureter at a later date.

Adverse events

Adverse events for either group were generally not well reported. Postoperative obstruction to the urinary tract occurred in 7% of children (10/151) in the European arm of the International Reflux Study. The Birmingham Reflux Study stated that no cases of postoperative obstruction were found after five years. None of children treated with endoscopic injection in the Swedish Reflux Trial 2010 suffered vesicoureteric obstruction. The authors did report six other adverse events. One boy had transient ureteral and renal pelvic dilatation on ultrasound at one month, one boy developed urine retention after endoscopic injection, and one boy aspirated during anaesthesia and required overnight observation in the intensive care unit. One girl suffered abdominal pain with pelvic dilatation and decreasing split function. The authors stated this resulted from a crossing vessel at the pelviureteral junction and was not related to the intervention. Finally, in one boy a fibrous narrowing of the bulbar urethra without obstruction was detected during the first endoscopic procedure. A weakening urine stream and obstructive flow curve pattern led to repeat endoscopic investigation, which revealed deterioration of bulbar narrowing. Ultimately internal urethrotomy was done. No other study referred to obstruction. No other adverse outcomes of surgery or endoscopy were reported.

Endoscopic VUR correction plus antibiotics (minimum of three months) versus no treatment

Symptomatic and febrile UTI

Being a three-arm study, the Swedish Reflux Trial 2010 allowed comparison of endoscopic correction versus no treatment. All children had received antibiotic prophylaxis for a period of at least three months after the endoscopic procedure when a follow-up VCUG was done. Only if this showed downgrading of the VUR status to grade I, prophylaxis was stopped. At two years follow-up, in the group who had undergone endoscopic intervention, 45% fewer children developed symptomatic UTI (Analysis 3.1.1 (1 study, 134 children): RR 0.55, 95% CI 0.33 to 0.94). Similarly, fewer children developed febrile UTI, although this result did not reach statistical significance (Analysis 3.2 (1 study, 134 children): RR 0.58, 95% CI 0.33 to 1.01).

Renal parenchymal abnormality

Although the point estimate was in favour of the combined treatment, the number of children with renal damage on DMSA scan was not significantly reduced for new damage (Analysis 3.3 (1 study, 133 children): RR 0.70, 95% CI 0.26 to 1.85), progressive damage (Analysis 3.4 (1 study, 133 children): RR 0.52, 95% CI 0.14 to 2.00) or combined new and progressive damage (Analysis 3.5 (1 study, 133 children): RR 0.70, 95% CI 0.30 to 1.60).

Other outcomes

Endoscopic treatment significantly reduced the number of children with persistent VUR at two years of follow-up (Analysis 3.6.1 (1 study, 117 children): RR 2.50, 95% CI 1.28 to 4.86). However 14 children required at least a second subureteric injection and 21% of children in the endoscopic group did not have repeat VCUG performed at the end of the study.

Different materials for subureteric injection to correct VUR

Oswald 2002 compared endoscopic subureteric injections of Macroplastique with Deflux. Although the data seemed to indicate a lower rate of persistent VUR beyond grade I at both three months (Analysis 4.1.1 (1 study, 114 children): RR 0.48, 95% CI 0.22 to 1.04) and one year (Analysis 4.1.2 (1 study, 73 children): RR 0.62, 95% CI 0.28 to 1.40), the results were not statistically significant. Conversely, patients injected with Deflux seemed less at risk for developing afebrile UTI during follow-up, although the difference was not significant and events in both groups were sparse (Analysis 4.1.3 (1 study, 72 children): RR 1.68, 95% CI 0.52 to 5.44). Temporary pelvicaliceal dilatation however was more common following Macroplastique (Analysis 4.1.4 (1 study, 114 children): RR 1.85, 95% CI 1.02 to 3.35). No data on renal parenchymal abnormalities were reported.

One small study (Frey 1997) compared endoscopic subureteric injections of different concentrations of cross-linked collagen (GAX 65, GAX 35). VUR was five times and significantly more likely to persist following GAX 35 than GAX 65 injections (Analysis 4.2.1 (1 study, 28 children): RR 0.21, 95% CI 0.05 to 0.85). Recurrence of VUR was not significantly different between therapies (Analysis 4.2.2 (1 study, 28 children): RR 0.30, 95% CI 0.07 to 1.29). No data on UTIs or renal parenchymal abnormalities were reported.

Probiotic versus antibiotic prophylaxis

Lee 2007 compared the potential benefits and harms of probiotic versus antibiotic prophylaxis in a single centre study including 120 children. There was no appreciable difference between the two interventions in symptomatic (Analysis 5.1.1 (1 study, 24 children): RR 0.85, 95% CI 0.41 to 1.74) and febrile UTI (Analysis 5.1.2 (1 study, 24 children): RR 0.82, 95% CI 0.37 to 1.83) by one year.

By the end of the one year follow-up period, 2/13 patients in the antibiotics group that had experienced a repeat UTI, had developed a new renal scar, versus 1/11 in the probiotics group. In the probiotics group, seven symptomatic UTI recurrences (64%) had *Escherichia coli* identified as the causative organism, versus nine (69%) in the antibiotics group. Whereas three of these were resistant to trimethoprim-sulphamethoxazole in the probiotic group, all of them were resistant in the antibiotic group (Analysis 5.2 (1 study, 16 children): RR 0.46, 95% CI 0.21 to 1.02).

DISCUSSION

Summary of main results

The benefits and harms of interventions for primary VUR were assessed in 20 studies involving 2324 children.

Antibiotic prophylaxis versus surveillance/no treatment

Overall, low-dose long-term antibiotic prophylaxis tended to reduce the number of recurrent symptomatic and febrile UTIs, but the result was not statistically significant. Only one of the included studies was adequately blinded. Its point estimate favoured antibiotic prophylaxis, but the result was not significant and patient numbers too small to adequately power this analysis. Long-term low-dose antibiotic prophylaxis reduced the number of children developing new or progressive renal damage by 60% compared with no treatment. Assuming a baseline risk of 8% (Analysis 1.4.3; baseline risk 17/220), 33 children would need prophylaxis to prevent one extra child developing a new or progressive renal scar over the course of two to three years. Side effects of the preventive treatment were minor and infrequent but poorly reported. Little data were provided as to how side-effects had affected adherence. Reported compliance rates varied between 70% and 100%, but they were inconsistently measured. Since previous studies have shown poor compliance for daily antibiotic regimens for VUR (Cohen 2005; Greenfield 1997), it raises the question whether antibiotics were inherently not very effective or not being used as prescribed. Treating VUR patients with long-term low-dose antibiotics was associated with a threefold increased risk of microbial resistance against the prophylactic drug in breakthrough infection. This estimate however was based on the pooled data of only three studies, with high levels of heterogeneity and imprecision due to small numbers.

VUR correction with surgery plus antibiotics (1-24 months) versus antibiotics alone

Only the European arm of the IRS study evaluated the differential risk of symptomatic UTI between medical and surgical management. Both strategies included prescription of antibiotics, for five years or until VUR resolution in medically treated children as opposed to six months in the surgically treated children. By four to five years there was no difference in symptomatic UTI. Both the European and the American arms of the IRS study however, investigated the risk of febrile UTI and found a significant benefit for those children who underwent surgical VUR correction. Assuming a baseline risk of 22% of developing febrile UTI when on antibiotics alone (Analysis 2.1.6; baseline risk 48/218), the estimated RR of 0.43 would translate into a RD of 13% and eight patients needing surgery to prevent one extra febrile UTI over the course of five years. Further analysis at 10 years confirmed these results. It supports the idea that although surgery might not provide an added benefit over antibiotic prophylaxis in preventing symptomatic lower UTI, it might keep the infection from spreading to the upper tract, and ultimately prevent subsequent renal damage. No evidence was found to corroborate this theory however, since the risk of developing new or progressive areas of renal damage at five and 10 years was no different between the treatment groups. You could argue that if VUR were an important modifiable risk factor for the development of UTI and renal damage, we would expect significant reduction in these outcomes for the group of surgically treated patients. It may be that delayed treatment of acute pyelonephritis is the more important risk factor, hence explaining why adverse outcomes of renal damage are currently seen less frequently than they used to (Wennerstrom 2000a; Wennerstrom 2000b). In addition, no differences between treatment groups were demonstrated for hypertension or CKD, but small numbers resulted in large imprecision and follow-up time was too short.

Potential benefits of surgery need to be weighed against its potential adverse effects. Whereas the Birmingham Reflux Study stated that no cases of postoperative obstruction were found after five years, they occurred in 7% of children (10/151) in the European arm of the International Reflux Study, corresponding to one every 14 to 15 patients undergoing the procedure.

Endoscopic treatment for VUR correction

When compared with long-term low-dose antibiotic prophylaxis alone, endoscopic correction combined with antibiotics did not significantly reduce either symptomatic or febrile UTI by two years. There was also no significant difference in new or progressive renal damage. Results however were derived from only two small studies with contradicting point estimates. When endoscopic correction was compared with no treatment in the Swedish Reflux Trial 2010, 45% fewer children developed symptomatic UTI by two years. A similar risk reduction was seen for febrile UTI, but the result was not significant. Children that underwent endoscopic VUR correction also received antibiotic prophylaxis for a mini-

mum of three months. Given that in the comparison of endoscopic treatment versus antibiotic prophylaxis, the point estimate favoured the prophylactic treatment alone, it seems unlikely that the endoscopic treatment was responsible for the reduced risk of febrile UTI in the comparison with no treatment.

Assuming correction were beneficial, endoscopic subureteric injection of various materials could offer an alternative method of correcting VUR. It is currently widely used in North America and Europe since it is known to be associated with less pain and postoperative recovery time compared with open surgery. Four studies included in this review have demonstrated acceptable rates of VUR correction with three different materials. In a systematic review of 63 studies involving 5527 patients, the success rates for correction of VUR grades I and II, III, IV and V were 78.5%, 72%, 63% and 51% after one treatment; second treatments had an overall success rate of 68% (Elder 2006). Therefore rates of correction appeared to be lower than those reported with surgical reimplantation techniques particularly for high grade VUR.

Overall completeness and applicability of evidence

For the primary outcome of symptomatic UTI and febrile UTI, study participants had mostly lower grades of VUR. Only five participants in the PRIVENT Study 2009 had VUR grade V. These patients are generally viewed as having the highest risk of developing renal scars after pyelonephritis. Hence we should be careful with extrapolating the results from this review to children with VUR grade V. Similarly, the studies that compared surgery and antibiotics with antibiotics alone only included participants with higher degrees of VUR. This reflected the view that chances of spontaneous resolution would be slimmer and risks of renal scarring greater. VUR grade V however was also excluded from the International Reflux Study, since it was regarded to be part of a widespread malformation of the urinary tract instead of an isolated problem of the vesicoureteric junction and thought to experience a greater benefit from surgery.

A randomised comparison between antibiotic treatment and surgery alone has not been performed since in all studies, antibiotics were also given for a variable length of time. Only studies designed to assess the incremental benefit of surgery over antibiotics alone have been conducted.

Quality of the evidence

The quality of conduct and reporting of these studies was variable, with many studies omitting crucial methodological information used to assess the risk of bias.

This review update has mainly added new studies that compared antibiotics to no treatment. Although in general both methodological quality and standard of reporting were good, only the PRIVENT Study 2009 was optimally designed, providing placebo and ensuring blinding of all participants, caregivers, outcome assessors and data analysts.

The effect estimate of incremental benefit of surgery was based on only one study that included 429 patients in the analysis. Given the nature of the intervention, it was not possible to blind participants or health care providers. Since this tends to result in overestimation of the treatment effect (Schulz 1995), bias might have played a part in producing the statistically significant difference in febrile UTI in favour of surgical management.

Agreements and disagreements with other studies or reviews

For over five decades, scientific published work has suggested the existence of a link between recurrent UTI, VUR and renal scarring (Olbing 2003; Smellie 1975; Smellie 1994; Smellie 1998). VUR has been thought to facilitate the involvement of the upper urinary tract during UTI by allowing retrograde passage of infected urine to the ureter. Subsequently all interventions have been targeted at preventing UTI-induced damage to the kidney. Earlier versions of this review (Hodson 2007; Wheeler 2004) were not been able to provide evidence as to whether the common practice of diagnosing and treating children with VUR conferred important health benefits, since no adequately powered studies had included a no treatment arm. Five new studies have since been published that compare the administration of antibiotics with placebo or no treatment. Although the addition of these studies produced a risk estimate in favour of long-term low-dose antibiotics, the result was not statistically significant. Only one of studies was optimally designed with adequate blinding of all participants and personnel involved in the study (PRIVENT Study 2009). When analysed by itself it produced a RR of 0.70. The result was not significant (95% CI 0.35 to 1.24), but patient numbers too small to adequately power the analysis. In the original study, the investigators had included 576 children both with and without VUR. They found a 6% absolute risk reduction (95% CI 1 to 13) for the group treated with antibiotics versus those treated with placebo and the effect of preventive antibiotic treatment did not differ according to the VUR status.

In comparison to the previous review, we have highlighted symptomatic and febrile UTI as more relevant primary end points rather than positive urine cultures.

AUTHORS' CONCLUSIONS

Implications for practice

Compared with no treatment, use of long-term low-dose antibiotics tended to reduce the number of repeat symptomatic and

febrile UTIs in children with VUR, but the result was not statistically significant. A large amount of unexplained heterogeneity in the analysis and inclusion of only one adequately blinded study, makes drawing firm conclusions challenging. Prophylaxis modestly reduced the risk of new or progressive renal damage, produced few side effects but was associated with a threefold increase in prophylactic drug resistance in subsequent UTIs.

The added benefit of surgery over long-term low-dose antibiotic use remains uncertain. Although there was a significant reduction in repeat episodes of febrile UTI, there were no differences in either symptomatic UTI or renal damage. Informed decision making should consider the risk of adverse events associated with surgery. Correcting VUR using endoscopic approaches would theoretically reduce these risks it but was not associated with a reduced number of symptomatic or febrile UTIs or a reduction in new or progressive renal damage.

Implications for research

We still need a well-designed, blinded and adequately powered study in children with VUR to resolve the remaining uncertainty surrounding the benefit of antibiotic prophylaxis in preventing UTI and renal damage. Hence we await with interest the results of the ongoing, placebo-controlled 'randomised Intervention for children with VesicoUreteral Reflux' study (RIVUR Study), which examines the effect of low-dose antibiotic treatment on symptomatic UTI and renal parenchymal injury assessed by DMSA scan. The role of surgery in the management of VUR needs further exploration. Of specific interest would be the impact of VUR correction by endoscopic subureteric injection without antibiotics versus no treatment on the incidence of febrile UTI and renal parenchymal injury assessed by DMSA scan.

ACKNOWLEDGEMENTS

- We are grateful to Danielle Wheeler, Dushyanthi Vimalachandra, L Paul Roy and Grahame Smith who were authors of the original review (Wheeler 2004), contributing to the design, quality assessment, data collection, entry, analysis and interpretation, and writing.
- We would like to thank Professor Les Irwig for his help with methodology and manuscript preparation, and those authors and experts in the field who replied to our requests for study information.
- This study was initially funded in part by a seeding grant from the Australian Kidney Foundation (Grant no. S2/99).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

BIRSG 1987

Methods	• Study design: parallel RCT • Study duration: NS
Participants	Inclusion criteria • Country: UK • Setting: single centre (recruitment from consultant paediatricians, general practitioners and emergency room of investigating centre) • Children with primary VUR grade II with scarring or grade III, IV, V in absence of UTI within last 12 months • Number: 179 (161 analysed) • Age: < 15 years Exclusion criteria • VUR secondary to obstruction, completely duplicated ureter or neurogenic bladder; urinary calculus
Interventions	Treatment group 1 • Trimethoprim or nitrofurantoin • Dose: 1 to 2 mg/kg • Duration: antibiotics given for 2 years if resolution of VUR or 5 years Treatment group 2 • Surgical reimplantation and antibiotics • Antibiotics given for 2 years
Outcomes	• UTI (culture positive) • Renal damage on IVP and DMSA scan • Renal function impairment, measured by GFR • Correction of VUR • Renal length on IVP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Central stratified block randomisation, method not clearly stated.
Allocation concealment (selection bias)	Unclear risk	Allocation by opening next sealed envelope in batch of 8, so that last ones per batch could theoretically be predicted

BIRSG 1987 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Only radiological outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	18/179 (10%) excluded from analysis at 2 years, due to failure to comply with study protocol; lost to follow-up and exclusions not distinguishable
Selective reporting (reporting bias)	High risk	Symptomatic UTI was not primary outcome since assessed by routine screening for bacteriuria or positive culture
Other bias	Unclear risk	Patient flow from recruitment to randomisation not clearly stated in terms of numbers

Capozza 2002

Methods	• Study design: parallel RCT • Study duration: NS
Participants	Inclusion criteria • Setting: University teaching hospital • Country: Italy • Children with primary VUR grade II to IV for at least 6 months • Number: 61 (60 analysed) • Age: > 1 year Exclusion criteria • Recurrent UTI; duplex systems; neurogenic bladder

Interventions	Treatment group 1
	• Antibiotic: NS
	• Dose: NS
	• Duration: 1 year
	Treatment group 2
	• Surgery: Subureteric implantation of Deflux
	• Antibiotics
	  ○ Antibiotic: NS
	  ○ Dose: NS
	  ○ Duration: 1 month

Outcomes	• UTI • Renal damage on ultrasound at start and after 12 months • Kidney function as GFR (change) • Resolution of VUR

Capozza 2002 (*Continued*)

Notes	• For antibiotic therapy, the drug(s) and regimen were determined on a case-by-case basis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	SAS software; 2:1 randomisation
Allocation concealment (selection bias)	Low risk	"blinded allocation"
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	One excluded after randomisation but before treatment start not included in analysis Eight exclusions after 6 months due to persistent VUR after endoscopic treatment - included in analysis
Selective reporting (reporting bias)	Unclear risk	UTI definition and method of collection: NS
Other bias	Low risk	Patient flow from recruitment to randomisation stated

Craig 2002

Methods	• Study design: placebo-controlled RCT • Study duration: 3 year follow-up
Participants	Inclusion criteria • Setting: Multicentre study • Country: Australia • Children < 3 months with isolated VUR • Number: 46 (41 analysed) • Age: < 3 months Exclusion criteria: NS
Interventions	Treatment group 1 • Matched placebo for 3 years Treatment group 2 • Antibiotic: TMP-SMX • Dose: 2/10 mg/kg/d in single daily dose • Duration: 3 years

Craig 2002 (*Continued*)

	Co-interventions: NS	
Outcomes	• First UTI (definition - NS) within 3 years • New renal parenchymal abnormality (interpreted as new damage on DMSA) at 3 years	
Notes	Only published as an abstract. Raw data obtained from authors.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated sequence generation with stratification according to centre, referral source, frequency of previous UTI, VUR status, age, sex, according to method of minimization
Allocation concealment (selection bias)	Low risk	Randomisation centrally by telephone by an independent trials centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of all participants, healthcare providers, outcome collectors and data-analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up accounted for (5/46, 11%) 3 placebo, 2 antibiotic. Bias due to loss-to follow-up unlikely
Selective reporting (reporting bias)	Low risk	Primary outcome appropriate
Other bias	Low risk	Raw data available, no industry funding

Dite 2007

Methods	• Study design: parallel RCT • Study duration: recruitment from 2003-2006
Participants	Inclusion criteria • Setting: Single centre, Urology department of a university hospital • Country: Czech Republic • Children with primary VUR grade III to V • Number: 44 (44 analysed) • Age: 1 to 32 months Exclusion criteria • Posterior urethral valves, decompensated lower UTI, para-urethral diverticulum, or any morphological anomaly of the lower urinary tract

Dite 2007 (*Continued*)

Interventions	Treatment group 1
	• Surgery: Subureteric implantation of Deflux
	• Antibiotics
	  ○ Antibiotic: NS
	  ○ Dose: NS
	  ○ Duration: 1 month
	Treatment group 2
	• Antibiotics
	  ○ Antibiotic: NS
	  ○ Dose: NS
	  ○ Duration: given for entire follow-up period

Outcomes	• UTI (definition - NS) • Acute pyelonephritis (definition - NS) • Correction of VUR
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States randomised but method NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and healthcare providers not blinded due to nature of intervention. No data on outcome assessors and data analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions Loss to follow-up: 0%
Selective reporting (reporting bias)	Unclear risk	Definition of UTI: NS
Other bias	Unclear risk	No information on recruitment, making it impossible to evaluate selection bias. No information on funding.

Frey 1997

Methods	• Study design: parallel RCT • Study duration: Recruitment period 1995 to 1997
Participants	Inclusion criteria • Setting: Single centre university hospital study • Country: Switzerland • Children with primary VUR grades I to III • Number: 18 (total analysed unclear due to switch from children to ureters as unit of analysis) • Age: 1.1 to 10.7 years (average 4.6 years) Exclusion criteria: NS
Interventions	Treatment group 1 • Surgery: Subureteric implantation of GAX 65 Treatment group 2 • Surgery: Subureteric implantation of GAX 35
Outcomes	• Correction of VUR • Recurrence of VUR
Notes	• Data on ureters not patients presented

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, method NS
Allocation concealment (selection bias)	Low risk	Centrally prepared injections, coding disclosed post-analysis
Blinding (performance bias and detection bias) All outcomes	Low risk	The 2 injectable preparations, which have exactly the same consistency and visual appearance, were packed in coded 1 mL syringes. Coding was only disclosed after analysis of results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Switch from randomised patients to number of ureters
Selective reporting (reporting bias)	High risk	Primary outcome not appropriate: > surrogate outcome grade of VUR instead of clinical outcome of UTI
Other bias	Unclear risk	Selection bias: patient flow from recruitment to randomisation not reported

Garin 2006

Methods	• Study design: parallel RCT • Study duration: recruitment period December 1998 to December 2003 • Follow-up: 1 year follow-up
Participants	Inclusion criteria • Setting: Multicentre, international study • Countries: Chile, Spain, USA • Children with acute pyelonephritis (fever 38.5°C, pyuria, > 100,000 colonies/mL) defined as focal/diffuse areas of decreased uptake on DMSA scan performed 2 to 7 days after UTI diagnosis • Number: 218 analysed ○ 113 had VUR; 105 had no VUR • Age: median 2 years (range 3 months to 12 years) • Sex (M/F): 22/91 (VUR only) Exclusion criteria • VUR grade IV or V; neurogenic bladder; posterior urethral valves; urinary diversion; bladder diverticulum; ureterocoele; kidney failure; pregnancy
Interventions	Treatment group 1 • No treatment Treatment group 2 • Antibiotic: TMP-SMX (1 to 2 mg/kg/d trimethoprim) or nitrofurantoin (1.5 mg/kg/d) • Duration: 12 months Co-interventions: NS
Outcomes	• Recurrence of UTI • Type of recurrence: cystitis (definition not provided) or pyelonephritis • Development of renal scars on DMSA scintigraphy
Notes	• Loss to follow-up and exclusions after randomisation excluded from analysis • Study included children with or without VUR. Stratified before randomisation. Only patients with VUR included • Urine screened 3 monthly

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified for VUR through simple randomisation, but method NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) All outcomes	High risk	not blinded for participants or healthcare providers (blinding status of outcome collectors and data-analysts NS) Choice of type antibiotic was left to each centre

Garin 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	No clear distinction between loss to follow-up and exclusion. Loss to follow-up: 9% of 236 children with or without VUR did not complete follow-up and were excluded from analysis
Selective reporting (reporting bias)	High risk	Positive culture is stated as primary outcome instead of symptomatic UTI
Other bias	Unclear risk	Patent flow from recruitment to randomisation not clearly reported.

Holland 1982

Methods	• Study design: Triple-arm RCT with allocation to the third arm when patient was deemed ineligible for surgery by urologist or parent. • Recruitment time-frame: NS. • Loss to follow-up: none, but exclusions after randomisation not analysed. Follow-up 5 months to 3 years with median of 1 year and 5 months.
Participants	Inclusion criteria • Setting: Single-centre study • Country: USA • Children with primary VUR grades II to IV • Number: 10 (10 analysed) • Age: mean 4.75 years (range 2 months to 10 years) Exclusion criteria • Secondary VUR; hypertension; kidney dysfunction
Interventions	Treatment group 1 • Antibiotics • Antibiotic: TMP-SMX or nitrofurantoin • Dose: 1 mg/kg • Duration: mean 17 months (range 5-36 months) Treatment group 2 • Surgery: Surgical reimplantation (technique - NS) • Antibiotics ○ Duration: mean 17 months (range 5-36 months)
Outcomes	• UTI: culture positive • Renal damage on IVP • Adverse effects of antibiotics
Notes	• Monthly screening by urinalysis the first 6 months, bimonthly screening after that
Risk of bias	

Holland 1982 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States random assignment, but method not clearly stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Patients and clinicians not blinded due to nature of intervention Assessors: unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up; exclusions accounted for
Selective reporting (reporting bias)	Unclear risk	Positive urine culture as primary outcome, not clear whether symptoms were required
Other bias	High risk	Concerns about selection bias being introduced by providing alternative non-randomised plan for those after enrolment but excluded by urologist or parents for surgery. Patient flow from recruitment to randomisation not clear

IRS EUR 1981-2003

Methods	• Study design: parallel group RCT • Study duration: NS
Participants	Inclusion criteria • Setting: Multicentre international study, university teaching hospitals • Countries: Belgium, Finland, Germany, Sweden • Children with primary VUR grades III to IV • Number: 321 (297 analysed) • Age: 6 days to 11 years Exclusion criteria • Primary VUR grades I and II; major urinary tract abnormality; previous urinary tract surgery; kidney dysfunction
Interventions	Treatment group 1 • Antibiotic: Nitrofurantoin or trimethoprim • Dose: 1 to 2 mg/kg • Duration: continued till resolution of VUR or 5 years Treatment group 2 • Surgery: PL, Cohen, LG • Antibiotics: continued for 6 months

IRS EUR 1981-2003 (*Continued*)

Outcomes	• UTI: culture positive • Renal damage on IVP and DMSA scan • Obstruction postoperatively • Resolution of VUR • Renal length on IVP
Notes	• No intention to treat with loss to follow-up and exclusions after randomisation not included in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation by a computer program
Allocation concealment (selection bias)	Low risk	At the coordinating centre
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and clinicians not blinded given nature of intervention. Radiologists were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up at 5 years
Selective reporting (reporting bias)	Low risk	Primary outcome appropriate, secondary outcomes detailed
Other bias	Low risk	Patient flow from recruitment to randomisation clearly stated

IRS USA 1992

Methods	• Study design: parallel RCT • Study duration: NS
Participants	Inclusion criteria • Setting: Multicentre; recruitment from university teaching hospitals • Country: USA • Children with primary VUR grade III to IV • Number: 142 (132 analysed) • Age: < 10 years Exclusion criteria • Major urinary tract abnormality; previous urinary tract surgery; kidney dysfunction

IRS USA 1992 (*Continued*)

Interventions	Treatment group 1 • Antibiotics: Nitrofurantoin or trimethoprim • Dose: 1 to 2 mg/kg • Duration: given till resolution of VUR or 5 years Treatment group 2 • Surgery: PL, Cohen, or other reimplantation • Antibiotics given for 6 months
Outcomes	• UTI: culture positive • Renal damage on IVP • Resolution of VUR • Renal area on IVP
Notes	• No intention to treat

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation blocking stratified system, stratified for each centre as to sex, age group, and presence or absence of pre-existing renal scar
Allocation concealment (selection bias)	Low risk	Allocation by sealed envelope
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and clinicians not blinded given nature of intervention. Radiologists were blinded to radiological outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear when participants were excluded from the study, prior or after randomisation and whether they were included in analysis
Selective reporting (reporting bias)	Unclear risk	Positive urine culture as primary outcome, not clear whether symptoms were required
Other bias	Unclear risk	Patent flow from recruitment to randomisation clearly stated but not clear when excluded participants left the study, or how they switched groups, hereby potentially creating selection bias

Lee 2007

Methods	• Study design: parallel RCT • Study duration: recruitment from 2002 to 2006 • Follow-up: 1year follow-up with intention-to-treat analysis
Participants	Inclusion criteria • Setting: Single centre; university teaching hospital • Country: South Korea • Children, VUR status (not clearly stated): persistent primary VUR grade I to IV (method of diagnosis NS) after 1 year of prophylactic antibiotics with TMP-SMX • Number: 125 (120 analysed) • Age: 13-36 months • Sex (M/F): 91/31 Exclusion criteria • Secondary VUR
Interventions	Treatment group 1 • Antibiotic: TMP-SMX • Dose: 2/10 mg/kg/d single daily dose • Duration: presumed for one year Treatment group 2 • Lactobacillus acidophilus (antibio300 Hanwa Co. Korea) • Dose: 1.0 x 10^8 CFU/g ATCC 4356) twice a day • Duration: presumed for one year
Outcomes	• Number of recurrent symptomatic febrile UTI • Number of recurrent symptomatic afebrile UTI • Number of children with new renal scar • Number of recurrent symptomatic UTI caused by *E coli* resistant to TMP-SMX
Notes	• No exclusions after randomisation but before intervention. • UTI defined as 10^5 CFU/L in supra-pubic aspirated urine culture, or >10^8 CFU/L in clean catch urine culture in toilet trained children. • Renal scar defined as 'Positive' DMSA scan taken at 3 to 6 months after recurrent DMSA + UTI • Raw data obtained from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stratified randomisation according to VUR status with subsequent alternate allocation according to the order of enrolment.
Allocation concealment (selection bias)	High risk	Investigators and parents were aware of treatment allocation. The investigator openly communicated there was less evidence for the preventive effect of probiotics versus antibiotics up until the study.

Lee 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Only data analyst was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions, loss to follow-up: 4%
Selective reporting (reporting bias)	Low risk	Primary outcome appropriate
Other bias	Low risk	Patient flow from recruitment to randomisation clear. Study not funded.

Montini 2008

Methods	• Study design: parallel group RCT • Study duration: Recruitment from May 2000 to August 2006 • Follow-up: 1 year
Participants	Inclusion criteria • Setting: Multi-centre study (22 centres) • Country: North-east Italy • Children aged 2 months to 7 years; with or without primary non-severe VUR (I to III); normal kidney function after first febrile UTI • Number: 132 (132 analysed) • Age: 2 to 72 months Exclusion criteria • Complex urologic malformations; severe kidney damage defined as relative function on 1 kidney of < 30% on DMSA
Interventions	Treatment group 1 • No treatment Treatment group 2 • Antibiotic: Co-trimoxazole (15 mg/kg/d) or amoxicillin clavulanic acid (15 mg/kg/d) • Duration: 1 year
Outcomes	• Number of recurrent febrile UTI • Number of repeat positive urine cultures • Number of children with new renal scar • Number of repeat positive urine cultures caused by bacteria resistant to TMP-SMX (all patients) • Adverse events (all patients)
Notes	• Positive urine culture defined as $>10^5$ CFU/mL of 1 microorganism in 2 consecutive samples • Raw data requested from authors • Intention-to-treat analysis.

Montini 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated, stratified block design by centre, gender, and clinical group on the basis of presence or absence of VUR end parenchymal localization of the acute UTI.
Allocation concealment (selection bias)	Low risk	Distribution of codes in opaque envelopes in first part, later centrally
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	Not quite sure of total numbers, and % of VUR with new renal scar that had VUR not clear. Loss-to follow-up: 26/338 (8%) but included in analysis in best and worst case scenario.
Selective reporting (reporting bias)	Low risk	Primary outcomes appropriate
Other bias	Unclear risk	Funding not commercial, patient flow from recruitment to randomisation not clearly stated.

Morris 1991

Methods	• Study design: parallel group RCT • Study duration: Recruitment between November 1983 and December 1987 • Follow-up: 2 years
Participants	Inclusion criteria • Setting: Single centre • Country: New Zealand • Children with primary VUR grade III to IV • Number: 138 (118 analysed) • Age: 6 months to 10 years Exclusion criteria • Major urological abnormality
Interventions	Treatment group 1 • Antibiotic: NS • Dose: NS

Morris 1991 (*Continued*)

	• Duration: 2 years Treatment group 2 • Surgery: Cohen reimplantation • Antibiotics for 3 months
Outcomes	• UTI: culture positive • GFR • Resolution of VUR
Notes	• Both loss to follow-up and exclusions after randomisation excluded from analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that patients were stratified (stratified block randomisation) and then randomly assigned to treatment, but method not clear
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) All outcomes	High risk	Patients and clinicians not blinded due to nature of treatment. Unsure whether assessors were or not.
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention to treat Loss to follow-up: 20/138 (14%)
Selective reporting (reporting bias)	High risk	Only published in conference proceedings. GFR evolution reported, but renal scarring and UTI not whereas stated in methods
Other bias	Unclear risk	Insufficient detail about patient flow from recruitment to randomisation.

Oswald 2002

Methods	• Study design: parallel group RCT • Time frame: recruitment from January 2000 to June 2001 • Follow-up: one year
Participants	Inclusion criteria • Setting: Single centre study, university urological department • Country: Austria • Children with primary VUR grades II to IV • Number: 70 • Age (mean): group 1 (33 months); group 2 (36 months) • Sex (M/F): 16/54

Oswald 2002 (*Continued*)

	Exclusion criteria • Duplex systems; failed surgical reimplantation; neurogenic bladder; voiding dysfunction
Interventions	Treatment group 1 • Subureteric injection of polydimethylsiloxane (Macroplastique) Treatment group 2 • Subureteric injection of Deflux
Outcomes	• Correction of VUR • UTI • Adverse effects
Notes	• Data provided according to ureters for VUR correction. Total analysed unclear due to switch from children to ureters as unit of analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding of the healthcare providers and unclear blinding status of the participants, outcome collectors and data-analysts
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ureters were reported instead of patients, making it difficult to follow. Intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	Primary outcome not appropriate: grade of VUR as surrogate outcome instead of a clinical outcome UTI. VCUG not available (under progress) for all patients at 12 months.
Other bias	Unclear risk	Patent flow from recruitment to randomisation: NS. Representativeness questionable

Pennesi 2006

Methods	• Study design: parallel group RCT • Study duration: recruitment from November 1999 to March 2003 • Follow-up: 2-years
Participants	Inclusion criteria • Setting: Multi-centre study (7 paediatric units) • Country: Northern Italy • Children with first episode of acute pyelonephritis, with VUR grades II to IV • Number: 100 (100 analysed) • Age: 1 day to 30 months • SEX (M/F): 48/52 Exclusion criteria • VUR grade I and V; previous pyelonephritis; recurrence pyelonephritis before first DMSA scan if positive for renal scars
Interventions	Treatment group 1 • No treatment Treatment group 2 • Antibiotic: TMP-SMX • Dose: 1 to 2/5 to 12 mg/kg single daily dose • Duration: 1 year
Outcomes	• Number of patients with repeat acute pyelonephritis by 2 years • Number of patients with worse renal damage on DMSA after 2 years • Number of patients with development of new renal damage on DMSA after 2 • Number of patients with persistent VUR • Number of repeat acute pyelonephritis caused by bacteria resistant to TMP-SMX
Notes	• Urine collected by clean catch unless patient was septic, in which case a bladder tap was performed • Standard outcome assessment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation using computerised minimization.
Allocation concealment (selection bias)	Low risk	Centralised, not possible to manipulate by participating centres
Blinding (performance bias and detection bias) All outcomes	High risk	Only radiologist and microbiologist were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, intention-to-treat analysis.

Pennesi 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	Primary outcome appropriate, Secondary outcome detailed
Other bias	Unclear risk	24 parents refused, not clear why, might introduce selection bias

PRIVENT Study 2009

Methods	• Study design: parallel group RCT • Study duration: recruitment from December 1998 to March 2007 • Follow-up: 12 months
Participants	Inclusion criteria • Setting: Multicentre study • Country: Australia • $\geq$ 1 symptomatic UTI defined as symptoms consistent with UTI with positive urine culture, defined as any growth of a pathogenic organism from a suprapubic bladder tap, 10^7 CFU/L single organism from catheter or, 10^8 CFU/L midstream voided urine sample. All grades of VUR. Recurrent infection. VUR from no VUR separable • Number: 243 • Age: 0 to 18 years • Sex (M/F): 92/151 Exclusion criteria • Known neurologic, skeletal or urologic predisposition; known contra-indication to TMP-SMX therapy
Interventions	Treatment group 1 • Placebo: matched for colour, taste and texture • Dose: single daily dose • Duration: 1 year Treatment group 2 • Antibiotic: TMP-SMX • Dose: 2 mg/10 mg/kg single daily dose • Duration: 1 year
Outcomes	• Recurrent symptomatic UTI (same definition as inclusion criteria) at 1 year • Recurrent febrile UTI (> 38ºC) at 1 year • New renal parenchymal abnormality (interpreted as any change on DMSA) at 1 year • Deterioration renal parenchymal abnormality at 1 year • Adverse events • Recurrent UTI caused by micro-organism resistant to TMP-SMX
Notes	• Secondary outcomes were extracted from raw data

Risk of bias

PRIVENT Study 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence generation with stratification according to centre, referral source, frequency of previous UTI, VUR status, age, sex, according to method of minimization. Randomisation centrally by telephone by an independent trials centre.
Allocation concealment (selection bias)	Low risk	Randomisation centrally by telephone by an independent trials centre.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of all participants, healthcare providers, outcome collectors and data-analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up small and accounted for (3/243; 1%), intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Primary outcome appropriate
Other bias	Low risk	Funding not commercial, patient flow from recruitment to randomisation clearly stated.

Reddy 1997

Methods	• Study design: parallel, triple arm RCT • Study duration: NS • Follow-up: 1 year
Participants	Inclusion criteria • Setting: Single centre study (university teaching hospital) • Country: USA • Children with primary VUR (grade NS), newly diagnosed • Number: 43 (43 analysed) • Age: NS Exclusion criteria: NS
Interventions	Treatment group 1 • Antibiotic prophylaxis • Antibiotic: NS • Dose: NS • Duration: 1 year Treatment group 2 • Intermittent antibiotics: given on Mondays, Wednesdays and Fridays • Daily urine nitrate testing

Reddy 1997 (*Continued*)

	• Duration: 1 year Treatment group 3 • No antibiotics • Surveillance with daily urine nitrate
Outcomes	• UTI • Renal damage on DMSA • Resolution of VUR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method: NS
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	Low risk	Non-compliant patients were withdrawn from the study but included in analysis; intention to treat analysis performed.
Selective reporting (reporting bias)	High risk	Primary outcome not appropriate. Both symptomatic and asymptomatic UTI reported together with no distinction between the two
Other bias	Unclear risk	Patent flow from recruitment to randomisation not at all reported.

Roussey-Kesler 2008

Methods	• Study design: parallel group RCT • Study duration: Recruitment from June 2001 to December 2004 • Follow-up: 1.5 years
Participants	Inclusion criteria • Setting: Multicentre (17 paediatric centres) • Country: France • Children after a first episode of febrile UTI, with VUR grade I to III • Number: 225 (225 analysed) • Age: 1 month to 3 years

Roussey-Kesler 2008 (*Continued*)

	• Sex (M/F): 69/156 Exclusion criteria • Abnormal renal echography, obstructive uropathy, high grade VUR, allergy to sulfamide
Interventions	Treatment group 1 • No treatment Treatment group 2 • Antibiotic: TMP-SMX • Dose: 2 mg/10 mg/kg single daily dose • Duration: 18 months
Outcomes	• Number of patients with repeat febrile UTI • Number of patients with repeat symptomatic or asymptomatic afebrile UTI • Number of repeat UTI caused by *E coli* resistant to TMP-SMX
Notes	• Use of bag-urine in non-toilet trained children • Raw data obtained from authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block design according to centre and gender
Allocation concealment (selection bias)	Low risk	Centrally prepared sealed opaque envelopes in batches of 20 per gender
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo administered
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up: 13/225 (6%) included in analysis; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Primary outcome: Bag-urine was used however for non-toilet trained kids, hereby increasing risk of contamination in screening-samples
Other bias	Unclear risk	Recruitment process not clearly stated.

Scott 1968

Methods	• Study design: parallel group RCT • Study duration: NS • Follow-up: 3 years
Participants	Inclusion criteria • Setting: Single centre (university teaching hospital) • Country: UK • Children with history of ≥1 UTI, with any grade VUR • Number: 58 (47 analysed) • Age: NS • Sex (M/F): 7/40 Exclusion criteria • Mechanical obstruction in the urethra, such as posterior valves, neurogenic bladder
Interventions	Treatment group 1 • Antibiotics: according to microbial sensitivity. • Treatment after 'several' months of disease free survival. In majority it was given at least 6 months, and in those who developed recurrences of infection it was continued for a year or longer. Two were not infected at moment of enrolment and hence were not given antibiotics. Treatment group 2 • Surgery: Bischoff operation (plastic surgery of the ureteral meatus), ureteral reimplantation. NS how many of each, only that in case when Bischoff had failed, subsequent reimplantation was successful and this case was included in analysis. 2 other cases were excluded after reappearance of VUR and 3 after first failed operation.
Outcomes	• Number of repeat symptomatic or asymptomatic UTI • Pyelonephritic scarring -not outcome only at start of study • Correction of VUR
Notes	• Exclusions: 8/58 (14%), all in surgical group due to persistence of VUR. Loss to follow-up: 3/58 (5%) • Some underwent bladder neck plastic operation in both groups: 9 in the antibiotics group, 11 in the operative group for non-obstructive bladder neck obstruction, which was later discarded as an entity altogether. • Authors contacted for additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Children were allotted at random to either the operated or control groups according to whether their birthdays fell on even or odd days.
Allocation concealment (selection bias)	High risk	Inadequate see above

Scott 1968 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, healthcare providers, outcome assessors or data-analysts
Incomplete outcome data (attrition bias) All outcomes	High risk	Three cases were excluded because they could not be traced at the end of the 3 year follow-up period. Eight in the operation group were also excluded because their VUR had persisted
Selective reporting (reporting bias)	High risk	Symptomatic UTI not reported
Other bias	High risk	Differential chance of being in operation versus antibiotic group. Patient flow from enrolment to randomisation not clear.

Smellie 2001

Methods	• Study design: parallel group RCT • Study duration: Recruitment from November 1985 to December 1989 • Follow-up: 10 years follow-up
Participants	Inclusion criteria • Setting: single centre (urology and nephrology clinic of a university teaching hospital) • Country: UK • Children with primary VUR, grade III to V, renal scarring on IVP • Number: 53 (50 analysed) • Age: 1 to 12 years Exclusion criteria • Major urological abnormality
Interventions	Treatment group 1 • Antibiotic: Nitrofurantoin, trimethoprim or TMP-SMX • Dose: 1 to 2 mg/kg • Variable duration of antibiotics Treatment group 2 • Cohen procedure and antibiotics • Antibiotic duration: 6 months
Outcomes	• UTI: culture positive • Renal damage on IVP • GFR (change) • Renal length (change)
Notes	

Smellie 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block randomisation according age and GFR with sealed envelopes containing equal number of cards for each treatment arm, with second investigator picking envelope.
Allocation concealment (selection bias)	Unclear risk	Due to small numbers in each stratum, sequence could be anticipated if recruiter knew the stratification method.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients and clinicians not blinded due to nature of treatment; blinding only for the radiologists
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up. No intention to treat, but only one exclusion.
Selective reporting (reporting bias)	Unclear risk	Definition of UTI: culture positive Method of collection: NS Secondary outcomes reported
Other bias	Unclear risk	Size of recruitment pool NS but flow and decision making noted.

Swedish Reflux Trial 2010

Methods	• Study design: three-arm parallel group RCT • Study duration: Recruitment from 2000 until 2006 • Follow-up: 2 years follow-up
Participants	Inclusion criteria • Setting: Multicentre study (22 paediatric centres from county to university hospital covering 80% of Swedish population and 1 paediatric centre in Oslo) • Country: Sweden • Grade III or IV VUR (graded according to International Reflux Study in children standards) at ages 1 to less than 2 years; dilating VUR diagnosed before age of 1 year were eligible if repeat VCUG between age 1 and 2 showed grade III or IV • Number: 203, (203 analysed) • Age: 1 to 2 years • Sex (M/F): 75/128 Exclusion criteria • Previous urogenital surgery; malformation except duplication; known urological disease; stone disease; GFR < 70 mL/min/1.73 m^2; split renal function below 15 % or

Swedish Reflux Trial 2010 (*Continued*)

	suspected non-compliance (inability to understand Swedish or previous non-compliance)
Interventions	Treatment group 1 • Antibiotic (choice at discretion of physician) ○ Trimethoprim (primary choice): 0.5 to 1 mg/kg once daily ○ Nitrofurantoin: 1 mg/kg once daily ○ Cefadroxil: 5 mg/kg once daily Treatment group 2 • Surgery: Endoscopic injection of Deflux. Each injection was followed by VCUG after three months • Antibiotics: Concomitant prophylaxis until new VCUG showed absent VUR or improvement to grade I to II Treatment group 3 • No specific treatment All groups had run-in period before randomisation • 2 weeks of TMP-SMX (2/10mg/kg) single daily dose
Outcomes	• Febrile UTI during 2 year time period • Progression of DMSA uptake defects on initial examination or new damage reappearing during 2 year follow-up • VUR status after 2 year follow-up period: Correction defined as VUR grade 0 and downgrading as VUR grade I or II • Microbial resistance: rate of UTI caused by resistant bacteria • Symptomatic UTI • Adverse events to endoscopic treatment • Bladder dysfunction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Children were randomly assigned by computer, matching for gender, previous UTI, VUR grade, DMSA uptake defect, bladder size, duplication and centre using minimisation procedures." Judgement: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Patients were randomised immediately after consent form was signed, and allocation status could not be manipulated.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no: open trial Health care providers: no Data analysts: no

Swedish Reflux Trial 2010 (*Continued*)

		Radiologist: yes; quote" all radiological investigations were reevaluated by the same radiologist blinded to the treatment group" Nuclear medicine specialist: yes; quote: "data files from each investigation were reviewed at the coordinating centre by the same nuclear medicine specialist blinded to treatment group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data analysed according to intention to treat with censoring of patients with incomplete follow-up in survival analysis
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes appropriate.
Other bias	High risk	Sponsor bias: One of the authors states a financial interest with the manufacturer of the Deflux used in the endoscopic treatment Selection bias: patient flow from enrolment to randomisation not clear

DMSA scan - 99m-techetium dimercaptosuccinic acid scan; Deflux - Dextranomer/hyaluronic acid copolymer; GAX 65 and 35: Cross-linked collagen with 65 mg/mL and 35 mg/mL of collagen; GFR - glomerular filtration rate; IVP - Intravenous pyelogram; NS: not stated; Reimplantation - PL (Politano-Leadbetter procedure), Cohen (Cohen procedures), LG (Lich-Gregoir procedure); TMP-SMX - trimethoprim-sulphamethoxazole; UTI - urinary tract infection; VUR vesicoureteric reflux

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

Study	Reason for exclusion
Becker 2004	Review article (pros and cons of VUR treatment)
Cheskis 1995	Not a RCT (cohort study of surgically managed VUR patients)
COBSG 1978	Inclusion of children with and without VUR, separate numbers for children with VUR not extractable
Lindberg 1978	Not a RCT (cohort study on asymptomatic bacteriuria in schoolgirls)
Montini 2003	RCT comparing early oral versus intravenous antibiotics for treating UTI in VUR patients
NCBRG 1981	Inclusion of children with and without VUR, separate numbers for children with VUR not extractable

(*Continued*)

Osman 2004	RCTs comparing antireflux procedures in ileal bladders
Ransley 2004	Study discontinued due to insufficient recruitment numbers and excessive refusal to participate
Scholtmeijer 1993	Unable to differentiate randomised from non-randomised patients

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

RIVUR Study

Trial name or title	RIVUR
Methods	Multi-centre study, using centralized permuted block randomisation, with blinding of participants, healthcare providers, outcome assessors and data analysts, placebo-controlled, parallel group design, conducted in the USA. Recruitment from May 2007, study expected to finish in October 2011, from 5 core clinical trial centres and 14 satellite centres. 2 year follow-up and intention to treat analysis.
Participants	Inclusion criteria • Children aged 2-72 months, with appropriately treated first or second UTI within 112 days before randomisation and VUR grade I to IV • Age: 2-72 months Exclusion criteria • History of other renal injury/disease, congenital or acquired immunodeficiency, underlying anomalies or chronic diseases that could interfere with response to therapy, complex cardiac disease, syndromes associated with VUR or bladder dysfunction
Interventions	Treatment group 1 • Placebo: cherry flavoured liquid suspension matched for taste, colour, odour and consistency to the active comparator. Bottled in identical 500 mL amber container high-density polyethylene containers with child-proof caps', administered for period of 2 years Treatment group 2 • TMP-SMX: Cherry-flavoured liquid suspension in which each 5 mL contains 200 mg sulfamethoxazole and 40 mg trimethoprim. Prophylactic dose is based on trimethoprim component: 3 mg/kg body weight taken once daily for 2 years
Outcomes	• Number of recurrent febrile UTI • Number of recurrent non-febrile, symptomatic UTI • Number of patients with development of new renal scar • Number of recurrent febrile or non-febrile symptomatic UTI caused by TMP-SMX resistant bacteria • Number of patients with stool-cultures of E-coli resistant to TMP-SMX • Adherence
Starting date	May 2007
Contact information	

RIVUR Study (*Continued*)

Notes	

DATA AND ANALYSES

Comparison 1. Antibiotic prophylaxis versus surveillance or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary tract infection	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All symptomatic UTI by 1-2 years: antibiotics versus no prophylaxis	5	846	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.17]
1.2 Febrile UTI by 1-2 years: antibiotics versus no prophylaxis	6	946	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.47, 1.24]
1.3 Repeat positive urine cultures by 1-3 years: continuous antibiotics versus no prophylaxis	6	636	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.25]
1.4 Repeat positive urine cultures by 1-3 years: intermittent antibiotics versus no prophylaxis	1	30	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.10, 2.00]
2 All symptomatic UTI by 1-2 years: allocation concealment	6	946	Risk Ratio (IV, Random, 95% CI)	0.77 [0.47, 1.25]
2.1 Adequate allocation concealment	5	833	Risk Ratio (IV, Random, 95% CI)	0.69 [0.45, 1.05]
2.2 Unclear allocation concealment	1	113	Risk Ratio (IV, Random, 95% CI)	7.38 [0.94, 58.07]
3 All symptomatic UTI by 1-2 years: blinding	6	946	Risk Ratio (IV, Random, 95% CI)	0.77 [0.47, 1.25]
3.1 Blinded studies	1	243	Risk Ratio (IV, Random, 95% CI)	0.66 [0.35, 1.24]
3.2 Non-blinded studies	5	703	Risk Ratio (IV, Random, 95% CI)	0.81 [0.43, 1.53]
4 Renal parenchymal abnormality on DMSA scan: unit of analysis (children)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 New renal abnormality by 1-3 years	5	782	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.06, 1.23]
4.2 Deterioration of existing abnormality by 1-2 years	3	446	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.27, 1.73]
4.3 Total new and progressive abnormality by 1-3 years	3	446	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.80]
4.4 All abnormalities detected on DMSA scan by 1-3 years: continuous antibiotics versus surveillance	2	142	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.36, 8.07]
4.5 All abnormalities detected on DMSA scan by 1-3 years: intermittent antibiotics versus surveillance	1	30	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.02, 8.59]

5 GFR at 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Renal growth at 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Resolution of VUR	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Resolution of VUR after 1-2 years: unit of analysis (children)	3	262	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.71, 2.99]
7.2 Resolution of VUR after 2 years: unit of analysis (ureters)	1	266	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.09]
8 Adverse events	2	356	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 2.01]
9 Microbial resistance to prophylactic drug	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Microbial resistance to prophylactic drug: unit of analysis (UTI)	4	132	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.39, 6.25]
10 All symptomatic UTI by 1-2 years: addressing of incomplete outcome data	6	946	Risk Ratio (IV, Random, 95% CI)	0.77 [0.47, 1.25]
10.1 Adequate addressing of incomplete outcome data	5	833	Risk Ratio (IV, Random, 95% CI)	0.69 [0.45, 1.05]
10.2 Inadequate addressing of incomplete outcome data	1	113	Risk Ratio (IV, Random, 95% CI)	7.38 [0.94, 58.07]
11 Febrile UTI by 1-2 years: allocation concealment	6	946	Risk Ratio (IV, Random, 95% CI)	0.77 [0.47, 1.24]
11.1 Adequate allocation concealment	5	833	Risk Ratio (IV, Random, 95% CI)	0.69 [0.46, 1.04]
11.2 Unclear allocation concealment	1	113	Risk Ratio (IV, Random, 95% CI)	7.38 [0.94, 58.07]
12 Febrile UTI by 1-2 years: blinding	5	964	Risk Ratio (IV, Random, 95% CI)	0.72 [0.44, 1.19]
12.1 Blinded studies	1	243	Risk Ratio (IV, Random, 95% CI)	0.58 [0.28, 1.22]
12.2 Non-blinded studies	5	721	Risk Ratio (IV, Random, 95% CI)	0.78 [0.42, 1.44]
13 Febrile UTI by 1-2 years: addressing of incomplete outcome data	6	946	Risk Ratio (IV, Random, 95% CI)	0.77 [0.47, 1.24]
13.1 Adequate addressing of incomplete outcome data	5	833	Risk Ratio (IV, Random, 95% CI)	0.69 [0.46, 1.04]
13.2 Inadequate addressing of incomplete outcome data	1	113	Risk Ratio (IV, Random, 95% CI)	7.38 [0.94, 58.07]

Comparison 2. Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary tract infection	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

1.1 All symptomatic UTI by 1-2 year: endoscopic correction + antibiotics versus antibiotics alone	2	179	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.26, 3.01]
1.2 All symptomatic UTI by 4-5 years: surgical correction + antibiotics versus antibiotics alone	1	297	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.67, 1.35]
1.3 All symptomatic UTI between 5-10 years: surgical correction + antibiotics versus antibiotics alone	1	252	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.26]
1.4 All symptomatic UTI in children followed for 10 years: surgical correction + antibiotics versus antibiotic alone	1	252	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.44]
1.5 Febrile UTI by 1-2 year: endoscopic correction +antibiotics versus antibiotics alone	2	179	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.15, 3.60]
1.6 Febrile UTI by 5 years: surgical correction + antibiotics versus antibiotics alone	2	429	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.70]
1.7 Febrile UTI between 5-10 years: surgical correction + antibiotics versus antibiotics alone	1	252	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.14, 0.82]
1.8 Febrile UTI in children followed for 10 years: surgical correction + antibiotics versus antibiotics alone	1	252	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.92]
1.9 Repeat positive urine culture by 1-3 years: surgical or endoscopic correction + antibiotics versus antibiotics alone	5	388	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.44]
1.10 Repeat positive urine cultures by 4-5 years: surgical correction + antibiotics versus antibiotics alone	3	479	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.79, 1.26]
2 Renal parenchymal defects (scars and thinning) on IVP: unit of analysis (children)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 New defects at 2 years: surgical correction + antibiotics versus antibiotics alone	2	171	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.33, 3.42]
2.2 New defects (scars and thinning of parenchyma) at 4-5 years: surgical correction + antibiotics versus antibiotics alone	4	572	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.79, 1.49]

2.3 Progression of existing defects at 2 years: surgical correction + antibiotics versus antibiotics alone	1	10	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.45, 108.26]
2.4 Progression of existing defects (scars and parenchymal thinning) at 4-5 years: surgical correction + antibiotics versus antibiotics alone	3	468	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]
2.5 Total new and progressive renal parenchymal defects at 2 years: surgical correction + antibiotics versus antibiotics alone	1	10	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.61, 133.08]
2.6 Total new and progressive renal parenchymal defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone	3	468	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.85, 1.29]
3 Renal scars on IVP: unit of analysis (children)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 New scars at 4-5 years: surgical correction + antibiotics versus antibiotics alone	2	418	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.84, 1.94]
3.2 New scars developing by 5-10 years in children followed for 10 years: surgical correction + antibiotics versus antibiotics alone	1	223	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.07, 16.22]
3.3 New scars at 10 years in children followed for 10 years: surgical correction + antibiotics versus antibiotics alone	1	223	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.53, 2.00]
4 Renal parenchymal defects on IVP: unit of analysis (kidneys)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 New defects at 2 years: surgical correction + antibiotics versus antibiotics alone	2	235	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.31, 3.37]
4.2 Progression of existing defects at 2 years: surgical correction + antibiotics versus antibiotics alone	2	235	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.24, 10.08]
4.3 Total new and progressive defects at 2 years: surgical correction + antibiotics versus antibiotics alone	2	235	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.24, 9.95]
4.4 New defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone	2	319	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.24, 3.09]

4.5 Progression of existing defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone	2	319	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.50, 1.41]
4.6 Total new and progressive defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone	2	319	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.34]
5 Renal parenchymal abnormalities on DMSA scan: unit of analysis (children)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Total new and progressive abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 All abnormalities detected on DMSA at 5 years: surgical correction + antibiotics versus antibiotics alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Deterioration of existing abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 New abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.5 Deterioration of existing abnormalities between 5-10 years: surgical correction + antibiotics versus antibiotics alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Renal damage on ultrasound	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 New renal parenchymal defect at 1 year for endoscopic correction + antibiotics versus antibiotics alone: unit of analysis (children)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 New renal scar at 1 year for endoscopic correction + antibiotics versus antibiotics alone: unit of analysis (kidneys)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Outcomes of hypertension and ESKD	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 ESKD	2	154	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.23, 5.04]
7.2 Hypertension	2	154	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.25, 3.42]
7.3 Hypertension at 10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.78]
8 GFR measured by Schwartz formula	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

8.1 GFR at entry: surgical correction + antibiotics versus antibiotics alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 GFR at 5 years: surgical correction + antibiotics versus antibiotics alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 GFR at 10 years: surgical correction + antibiotics versus antibiotics alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Height Standard Deviation Score (SDS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 Height SDS at entry for surgical correction + antibiotics versus antibiotics alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Height SDS at 10 year follow-up for surgical correction + antibiotics versus antibiotics alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Correction of VUR: unit of analysis (children)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Correction of VUR after 1-2 year for endoscopic correction + antibiotics versus antibiotics alone	2	164	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.57, 4.63]
10.2 Correction of VUR after 3 years: surgical correction + antibiotics versus antibiotics alone	1	55	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.55, 3.05]
11 Correction of VUR: unit of analysis (ureters)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Correction of VUR after 2 years: surgical correction + antibiotics versus antibiotics alone	1	134	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.13, 1.53]
11.2 Correction of VUR after 2 years: endoscopic correction + antibiotics versus antibiotics alone	1	240	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.47, 2.54]
11.3 Correction of VUR at 5 years: surgical correction + antibiotics versus antibiotics alone	1	612	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.00]
12 Microbial resistance to the prophylactic drug	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 Unit of analysis (febrile UTI)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All symptomatic UTI by 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Febrile UTI by 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 New parenchymal defects on DMSA scan at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Deterioration of existing parenchymal defects on DMSA scan at 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Total new and progressive damage on DMSA scan	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Correction of VUR	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Correction of VUR after 2 years: unit of analysis (children)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Correction of VUR after 2 years: unit of analysis (ureters)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Microbial resistance to prophylactic drug	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Unit of analysis (children)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 unit of analysis (febrile UTIs)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Different materials for subureteric injection to correct VUR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Macroplastique versus Deflux	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Number of ureters with persistent VUR > grade 1 at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Number of ureters with persistent VUR > grade 1 at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Number of children with afebrile UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Number of kidneys with temporary renal dilatation after injection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Collagen GAX 65 versus Collagen GAX 35	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Number of ureters with persistent VUR at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

2.2 Number of ureters with recurrence of VUR	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Probiotics versus antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 All symptomatic UTI by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Febrile UTI by 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 *E coli* resistance to prophylactic drug	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Renal parenchymal defects on DMSA scan	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Patient data at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

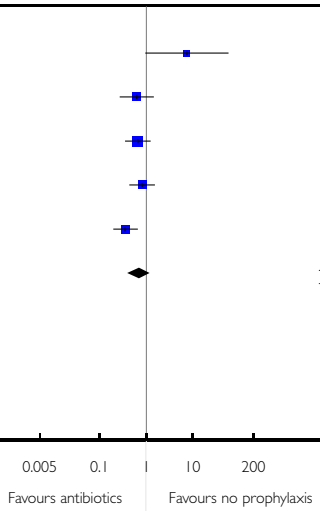
Analysis 1.1. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 1 Urinary tract infection.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 1 Urinary tract infection

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All symptomatic UTI by 1-2 years: antibiotics versus no prophylaxis					
Garin 2006	7/55	1/58		5.9 %	7.38 [0.94, 58.07]
Montini 2008	10/82	9/46		20.1 %	0.62 [0.27, 1.42]
PRIVENT Study 2009	14/122	21/121		25.0 %	0.66 [0.35, 1.24]
Roussey-Kesler 2008	13/103	19/122		24.3 %	0.81 [0.42, 1.56]
Swedish Reflux Trial 2010	10/69	28/68		24.7 %	0.35 [0.19, 0.67]
Subtotal (95% CI)	**431**	**415**		**100.0 %**	**0.68 [0.39, 1.17]**
Total events: 54 (Prophylaxis), 78 (No prophylaxis)					
Heterogeneity: Tau² = 0.21; Chi² = 9.38, df = 4 (P = 0.05); I² =57%					
Test for overall effect: Z = 1.40 (P = 0.16)					
2 Febrile UTI by 1-2 years: antibiotics versus no prophylaxis					



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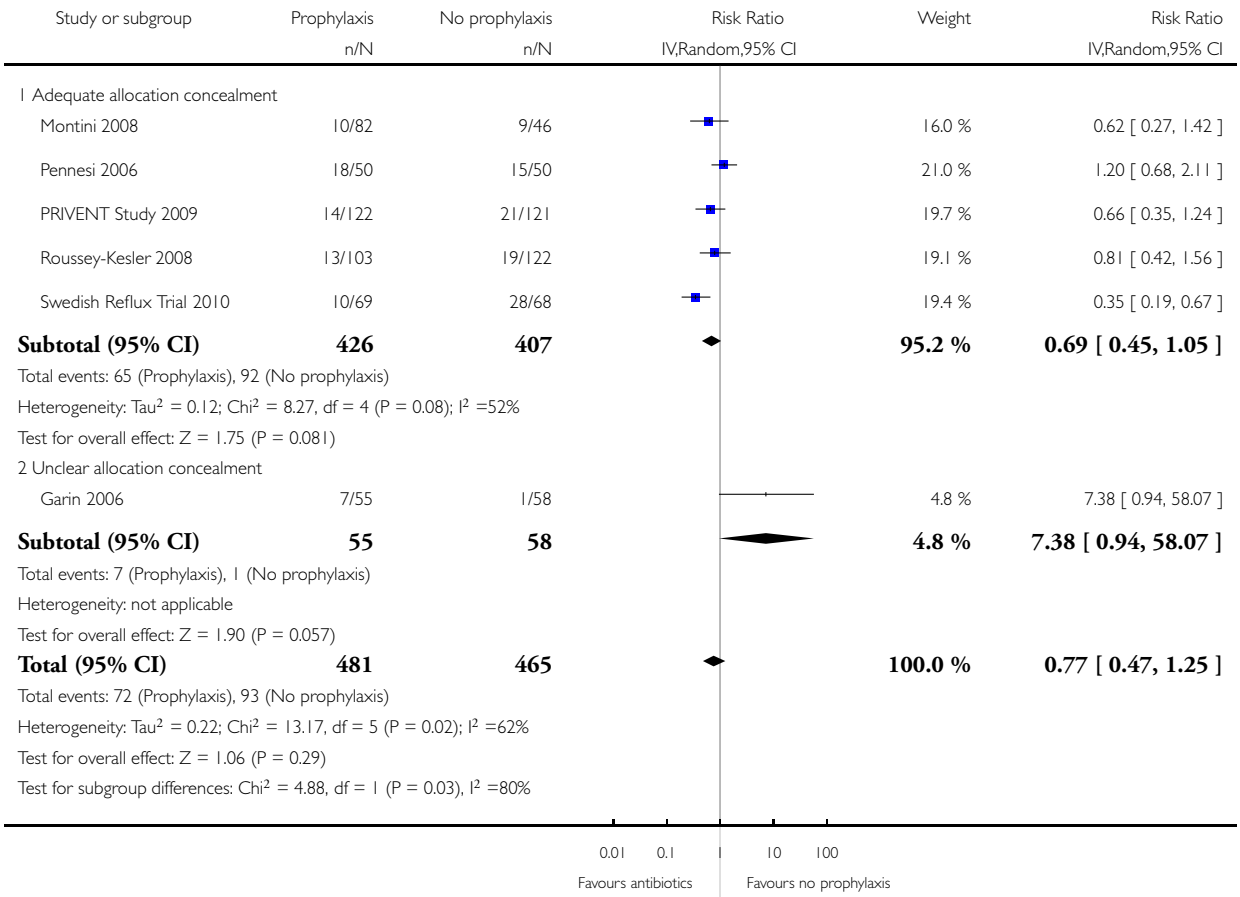
Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Garin 2006	7/55	1/58		4.7 %	7.38 [0.94, 58.07]
Montini 2008	10/82	9/46		16.2 %	0.62 [0.27, 1.42]
Pennesi 2006	18/50	15/50		21.8 %	1.20 [0.68, 2.11]
PRIVENT Study 2009	10/122	17/121		17.9 %	0.58 [0.28, 1.22]
Roussey-Kesler 2008	13/103	19/122		19.7 %	0.81 [0.42, 1.56]
Swedish Reflux Trial 2010	10/69	25/68		19.7 %	0.39 [0.21, 0.76]
Subtotal (95% CI)	**481**	**465**		**100.0 %**	**0.77 [0.47, 1.24]**
Total events: 68 (Prophylaxis), 86 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 11.85$, df = 5 (P = 0.04); $I^2 = 58\%$					
Test for overall effect: Z = 1.08 (P = 0.28)					
3 Repeat positive urine cultures by 1-3 years: continuous antibiotics versus no prophylaxis					
Craig 2002	0/21	2/20		1.7 %	0.19 [0.01, 3.75]
Garin 2006	13/55	10/58		19.7 %	1.37 [0.66, 2.87]
Montini 2008	10/82	9/46		16.8 %	0.62 [0.27, 1.42]
Pennesi 2006	18/50	15/50		27.7 %	1.20 [0.68, 2.11]
Reddy 1997	1/13	5/16		3.6 %	0.25 [0.03, 1.85]
Roussey-Kesler 2008	18/103	32/122		30.4 %	0.67 [0.40, 1.11]
Subtotal (95% CI)	**324**	**312**		**100.0 %**	**0.84 [0.57, 1.25]**
Total events: 60 (Prophylaxis), 73 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.96$, df = 5 (P = 0.22); $I^2 = 28\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
4 Repeat positive urine cultures by 1-3 years: intermittent antibiotics versus no prophylaxis					
Reddy 1997	2/14	5/16		100.0 %	0.46 [0.10, 2.00]
Subtotal (95% CI)	**14**	**16**		**100.0 %**	**0.46 [0.10, 2.00]**
Total events: 2 (Prophylaxis), 5 (No prophylaxis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					

Analysis 1.2. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 2 All symptomatic UTI by 1-2 years: allocation concealment.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 2 All symptomatic UTI by 1-2 years: allocation concealment

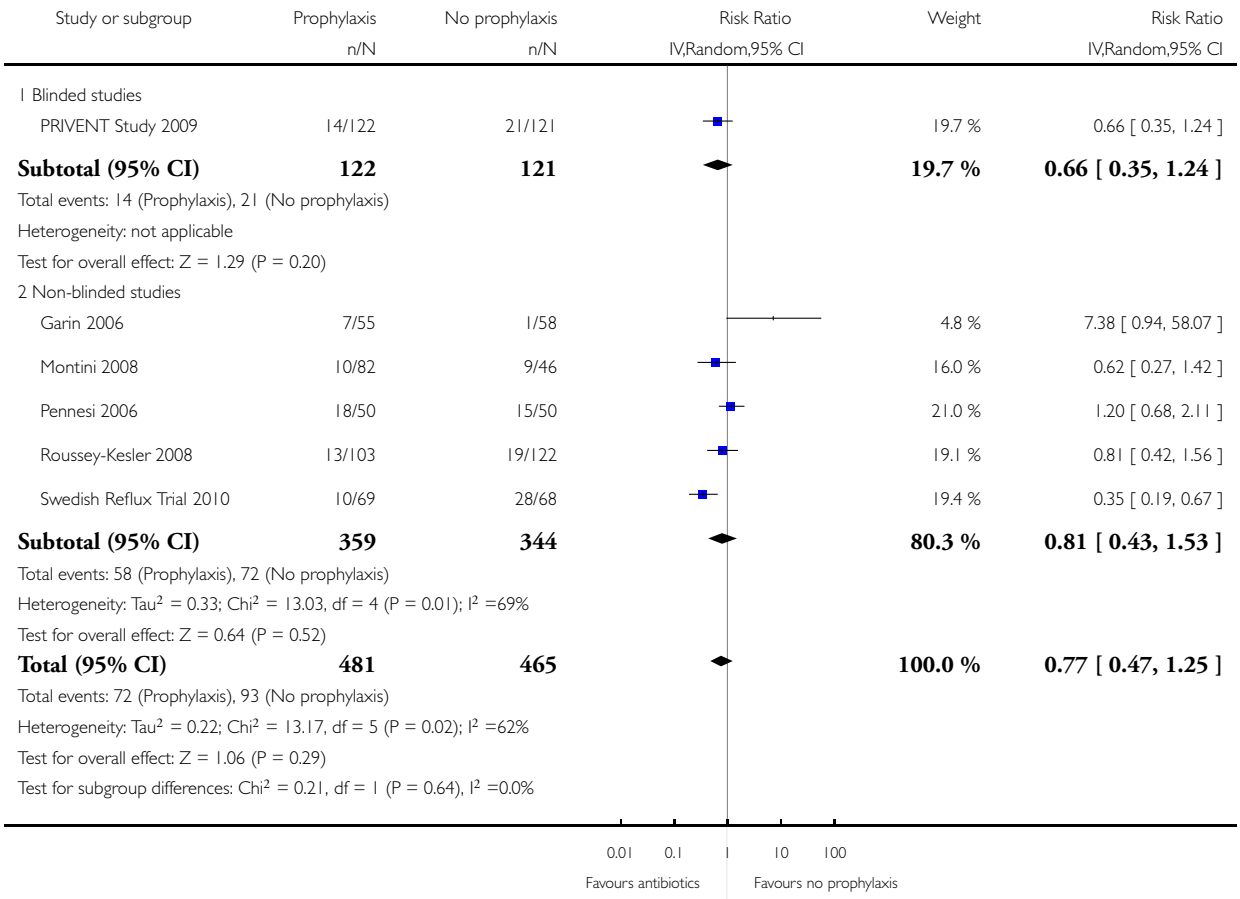


Analysis 1.3. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 3 All symptomatic UTI by 1-2 years: blinding.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 3 All symptomatic UTI by 1-2 years: blinding



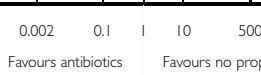
Analysis 1.4. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 4 Renal parenchymal abnormality on DMSA scan: unit of analysis (children).

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 4 Renal parenchymal abnormality on DMSA scan: unit of analysis (children)

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 New renal abnormality by 1-3 years				
Craig 2002	0/21	0/20		0.0 [0.0, 0.0]
Montini 2008	2/187	2/108		0.58 [0.08, 4.04]
Pennesi 2006	0/50	0/50		0.0 [0.0, 0.0]
PRIVENT Study 2009	0/109	1/101		0.31 [0.01, 7.50]
Swedish Reflux Trial 2010	0/68	9/68		0.05 [0.00, 0.89]
Subtotal (95% CI)	**435**	**347**		**0.27 [0.06, 1.23]**
Total events: 2 (Prophylaxis), 12 (No prophylaxis)				
Heterogeneity: Tau² = 0.19; Chi² = 2.22, df = 2 (P = 0.33); I² =10%				
Test for overall effect: Z = 1.70 (P = 0.089)				
2 Deterioration of existing abnormality by 1-2 years				
Pennesi 2006	0/50	0/50		0.0 [0.0, 0.0]
PRIVENT Study 2009	3/109	4/101		0.69 [0.16, 3.03]
Swedish Reflux Trial 2010	4/68	6/68		0.67 [0.20, 2.26]
Subtotal (95% CI)	**227**	**219**		**0.68 [0.27, 1.73]**
Total events: 7 (Prophylaxis), 10 (No prophylaxis)				
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.97); I² =0.0%				
Test for overall effect: Z = 0.81 (P = 0.42)				
3 Total new and progressive abnormality by 1-3 years				
Pennesi 2006	0/50	0/50		0.0 [0.0, 0.0]
PRIVENT Study 2009	3/109	5/101		0.56 [0.14, 2.27]
Swedish Reflux Trial 2010	4/68	15/68		0.27 [0.09, 0.76]
Subtotal (95% CI)	**227**	**219**		**0.35 [0.15, 0.80]**
Total events: 7 (Prophylaxis), 20 (No prophylaxis)				
Heterogeneity: Tau² = 0.0; Chi² = 0.68, df = 1 (P = 0.41); I² =0.0%				
Test for overall effect: Z = 2.47 (P = 0.014)				
4 All abnormalities detected on DMSA scan by 1-3 years: continuous antibiotics versus surveillance				
Garin 2006	5/55	2/58		2.64 [0.53, 13.03]
Reddy 1997	0/13	1/16		0.40 [0.02, 9.18]
Subtotal (95% CI)	**68**	**74**		**1.70 [0.36, 8.07]**



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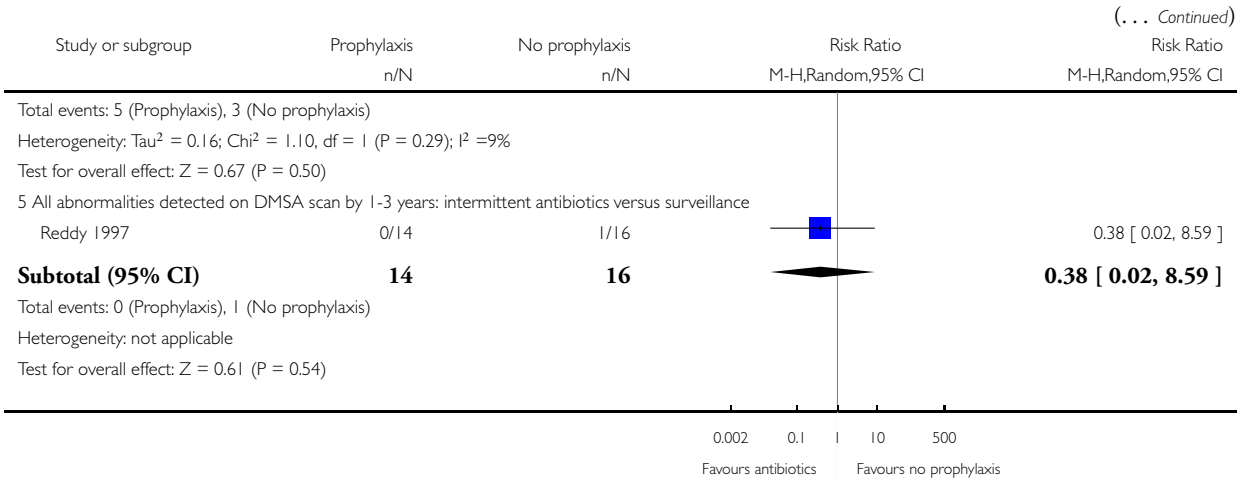
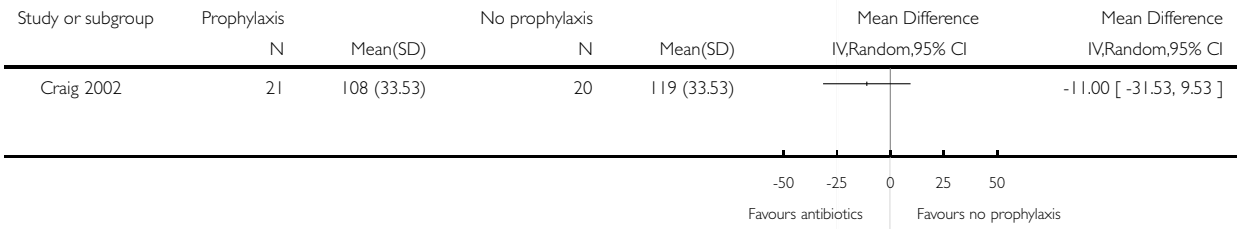


Analysis 1.5. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 5 GFR at 3 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 5 GFR at 3 years



Analysis 1.6. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 6 Renal growth at 3 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 6 Renal growth at 3 years

Study or subgroup	Prophylaxis N	Mean(SD)	No prophylaxis N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Craig 2002	21	2.42 (0.128)	20	2.38 (0.128)		0.04 [-0.04, 0.12]

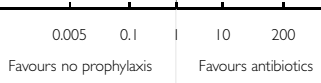
Analysis 1.7. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 7 Resolution of VUR.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 7 Resolution of VUR

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Resolution of VUR after 1-2 years: unit of analysis (children)					
Pennesi 2006	19/50	10/50		52.8 %	1.90 [0.98, 3.67]
Reddy 1997	2/13	0/16		5.6 %	6.07 [0.32, 116.33]
Swedish Reflux Trial 2010	9/68	10/65		41.6 %	0.86 [0.37, 1.98]
Subtotal (95% CI)	**131**	**131**		**100.0 %**	**1.46 [0.71, 2.99]**
Total events: 30 (Prophylaxis), 20 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 3.06$, df = 2 (P = 0.22); $I^2 = 35\%$					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Resolution of VUR after 2 years: unit of analysis (ureters)					
Swedish Reflux Trial 2010	46/136	55/130		100.0 %	0.80 [0.59, 1.09]
Subtotal (95% CI)	**136**	**130**		**100.0 %**	**0.80 [0.59, 1.09]**
Total events: 46 (Prophylaxis), 55 (No prophylaxis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
Test for subgroup differences: $Chi^2 = 2.27$, df = 1 (P = 0.13), $I^2 = 56\%$					



Analysis 1.8. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 8 Adverse events.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 8 Adverse events

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Garin 2006	0/55	0/58		0.0 [0.0, 0.0]
PRIVENT Study 2009	2/122	5/121		0.40 [0.08, 2.01]
Total (95% CI)	**177**	**179**		**0.40 [0.08, 2.01]**

Total events: 2 (Prophylaxis), 5 (No prophylaxis)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Analysis 1.9. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 9 Microbial resistance to prophylactic drug.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 9 Microbial resistance to prophylactic drug

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Microbial resistance to prophylactic drug: unit of analysis (UTI)					
Pennesi 2006	18/18	0/15		6.6 %	31.16 [2.03, 477.34]
PRIVENT Study 2009	8/13	3/19		23.0 %	3.90 [1.27, 11.99]
Roussey-Kesler 2008	10/13	7/19		34.5 %	2.09 [1.08, 4.04]
Swedish Reflux Trial 2010	8/10	9/25		36.0 %	2.22 [1.21, 4.08]

Analysis 1.10. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 10 All symptomatic UTI by 1-2 years: addressing of incomplete outcome data.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 10 All symptomatic UTI by 1-2 years: addressing of incomplete outcome data

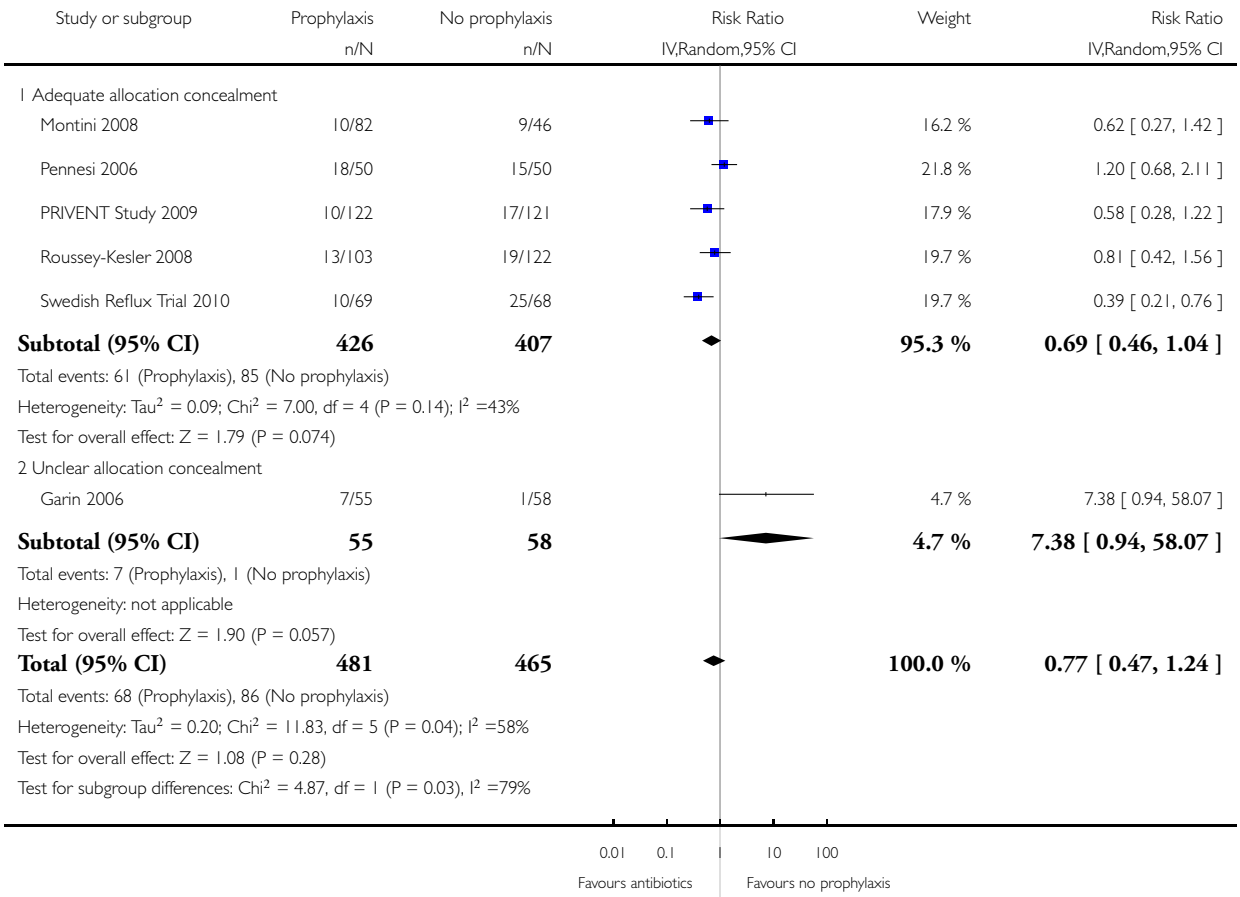
Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Adequate addressing of incomplete outcome data					
Montini 2008	10/82	9/46		16.0 %	0.62 [0.27, 1.42]
Pennesi 2006	18/50	15/50		21.0 %	1.20 [0.68, 2.11]
PRIVENT Study 2009	14/122	21/121		19.7 %	0.66 [0.35, 1.24]
Roussey-Kesler 2008	13/103	19/122		19.1 %	0.81 [0.42, 1.56]
Swedish Reflux Trial 2010	10/69	28/68		19.4 %	0.35 [0.19, 0.67]
Subtotal (95% CI)	**426**	**407**		**95.2 %**	**0.69 [0.45, 1.05]**
Total events: 65 (Prophylaxis), 92 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.27$, df = 4 (P = 0.08); $I^2 = 52\%$					
Test for overall effect: Z = 1.75 (P = 0.081)					
2 Inadequate addressing of incomplete outcome data					
Garin 2006	7/55	1/58		4.8 %	7.38 [0.94, 58.07]
Subtotal (95% CI)	**55**	**58**		**4.8 %**	**7.38 [0.94, 58.07]**
Total events: 7 (Prophylaxis), 1 (No prophylaxis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.057)					
Total (95% CI)	**481**	**465**		**100.0 %**	**0.77 [0.47, 1.25]**
Total events: 72 (Prophylaxis), 93 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 13.17$, df = 5 (P = 0.02); $I^2 = 62\%$					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: $Chi^2 = 4.88$, df = 1 (P = 0.03), $I^2 = 80\%$					

Analysis 1.11. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 11 Febrile UTI by 1-2 years: allocation concealment.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 11 Febrile UTI by 1-2 years: allocation concealment

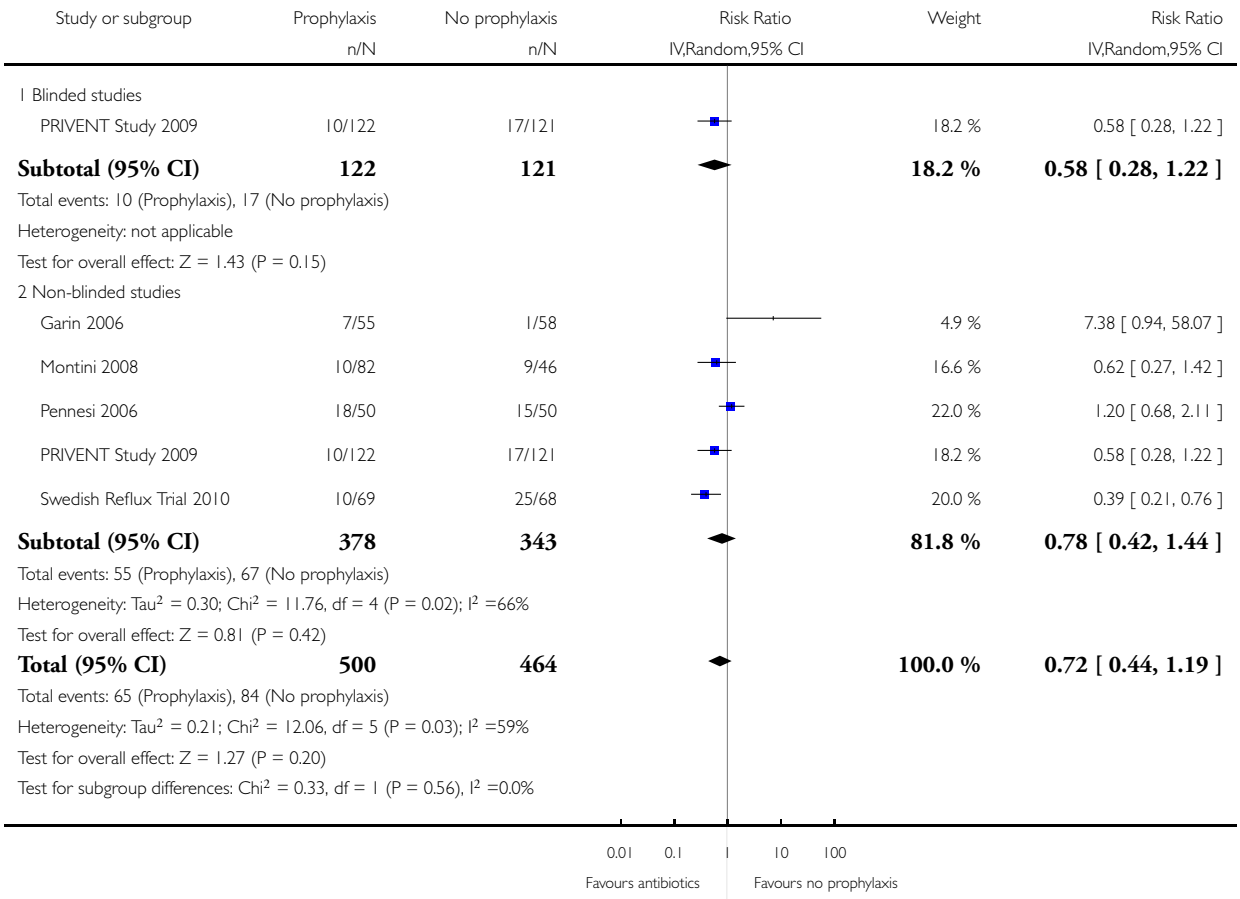


Analysis 1.12. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 12 Febrile UTI by 1-2 years: blinding.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 12 Febrile UTI by 1-2 years: blinding



Analysis 1.13. Comparison 1 Antibiotic prophylaxis versus surveillance or no treatment, Outcome 13 Febrile UTI by 1-2 years: addressing of incomplete outcome data.

Review: Interventions for primary vesicoureteric reflux

Comparison: 1 Antibiotic prophylaxis versus surveillance or no treatment

Outcome: 13 Febrile UTI by 1-2 years: addressing of incomplete outcome data

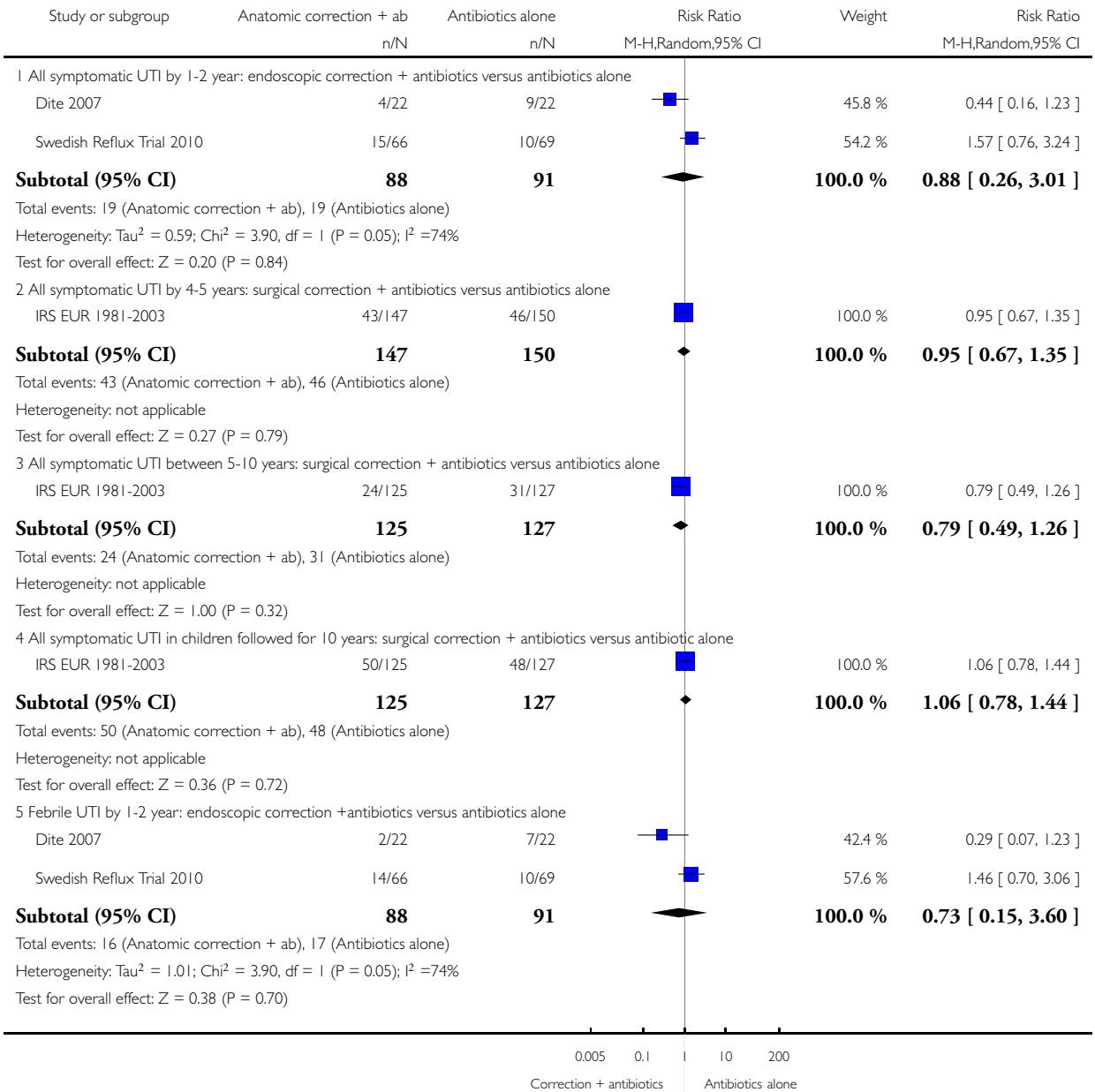
Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Adequate addressing of incomplete outcome data					
Montini 2008	10/82	9/46		16.2 %	0.62 [0.27, 1.42]
Pennesi 2006	18/50	15/50		21.8 %	1.20 [0.68, 2.11]
PRIVENT Study 2009	10/122	17/121		17.9 %	0.58 [0.28, 1.22]
Roussey-Kesler 2008	13/103	19/122		19.7 %	0.81 [0.42, 1.56]
Swedish Reflux Trial 2010	10/69	25/68		19.7 %	0.39 [0.21, 0.76]
Subtotal (95% CI)	**426**	**407**		**95.3 %**	**0.69 [0.46, 1.04]**
Total events: 61 (Prophylaxis), 85 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 7.00$, df = 4 (P = 0.14); $I^2 = 43\%$					
Test for overall effect: Z = 1.79 (P = 0.074)					
2 Inadequate addressing of incomplete outcome data					
Garin 2006	7/55	1/58		4.7 %	7.38 [0.94, 58.07]
Subtotal (95% CI)	**55**	**58**		**4.7 %**	**7.38 [0.94, 58.07]**
Total events: 7 (Prophylaxis), 1 (No prophylaxis)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.057)					
Total (95% CI)	**481**	**465**		**100.0 %**	**0.77 [0.47, 1.24]**
Total events: 68 (Prophylaxis), 86 (No prophylaxis)					
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 11.83$, df = 5 (P = 0.04); $I^2 = 58\%$					
Test for overall effect: Z = 1.08 (P = 0.28)					
Test for subgroup differences: $Chi^2 = 4.87$, df = 1 (P = 0.03), $I^2 = 79\%$					

Analysis 2.1. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 1 Urinary tract infection.

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 1 Urinary tract infection



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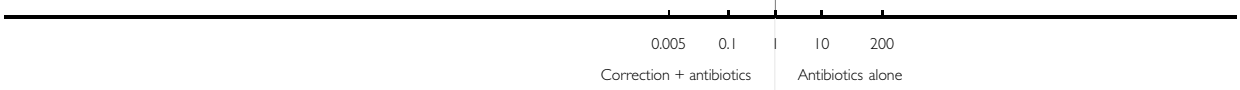
Study or subgroup	Anatomic correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
6 Febrile UTI by 5 years: surgical correction + antibiotics versus antibiotics alone					
IRS EUR 1981-2003	15/147	33/150		73.9 %	0.46 [0.26, 0.82]
IRS USA 1992	5/64	15/68		26.1 %	0.35 [0.14, 0.92]
Subtotal (95% CI)	**211**	**218**		**100.0 %**	**0.43 [0.27, 0.70]**
Total events: 20 (Anatomic correction + ab), 48 (Antibiotics alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 3.38 (P = 0.00073)					
7 Febrile UTI between 5-10 years: surgical correction + antibiotics versus antibiotics alone					
IRS EUR 1981-2003	6/125	18/127		100.0 %	0.34 [0.14, 0.82]
Subtotal (95% CI)	**125**	**127**		**100.0 %**	**0.34 [0.14, 0.82]**
Total events: 6 (Anatomic correction + ab), 18 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.017)					
8 Febrile UTI in children followed for 10 years: surgical correction + antibiotics versus antibiotics alone					
IRS EUR 1981-2003	17/125	32/127		100.0 %	0.54 [0.32, 0.92]
Subtotal (95% CI)	**125**	**127**		**100.0 %**	**0.54 [0.32, 0.92]**
Total events: 17 (Anatomic correction + ab), 32 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.26 (P = 0.024)					
9 Repeat positive urine culture by 1-3 years: surgical or endoscopic correction + antibiotics versus antibiotics alone					
BIRSG 1987	16/73	23/80		34.3 %	0.76 [0.44, 1.33]
Capozza 2002	6/39	0/21		2.8 %	7.15 [0.42, 121.04]
Holland 1982	1/5	2/5		5.1 %	0.50 [0.06, 3.91]
Morris 1991	13/60	8/58		23.0 %	1.57 [0.70, 3.51]
Scott 1968	10/23	16/24		34.8 %	0.65 [0.38, 1.12]
Subtotal (95% CI)	**200**	**188**		**100.0 %**	**0.89 [0.55, 1.44]**
Total events: 46 (Anatomic correction + ab), 49 (Antibiotics alone)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 6.16, df = 4 (P = 0.19); I^2 =35%					
Test for overall effect: Z = 0.48 (P = 0.63)					
10 Repeat positive urine cultures by 4-5 years: surgical correction + antibiotics versus antibiotics alone					
IRS EUR 1981-2003	59/147	59/150		70.5 %	1.02 [0.77, 1.35]
IRS USA 1992	21/64	20/68		21.4 %	1.12 [0.67, 1.85]
Smellie 2001	6/24	11/26		8.1 %	0.59 [0.26, 1.35]
Subtotal (95% CI)	**235**	**244**		**100.0 %**	**0.99 [0.79, 1.26]**
Total events: 86 (Anatomic correction + ab), 90 (Antibiotics alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.76, df = 2 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.04 (P = 0.97)					

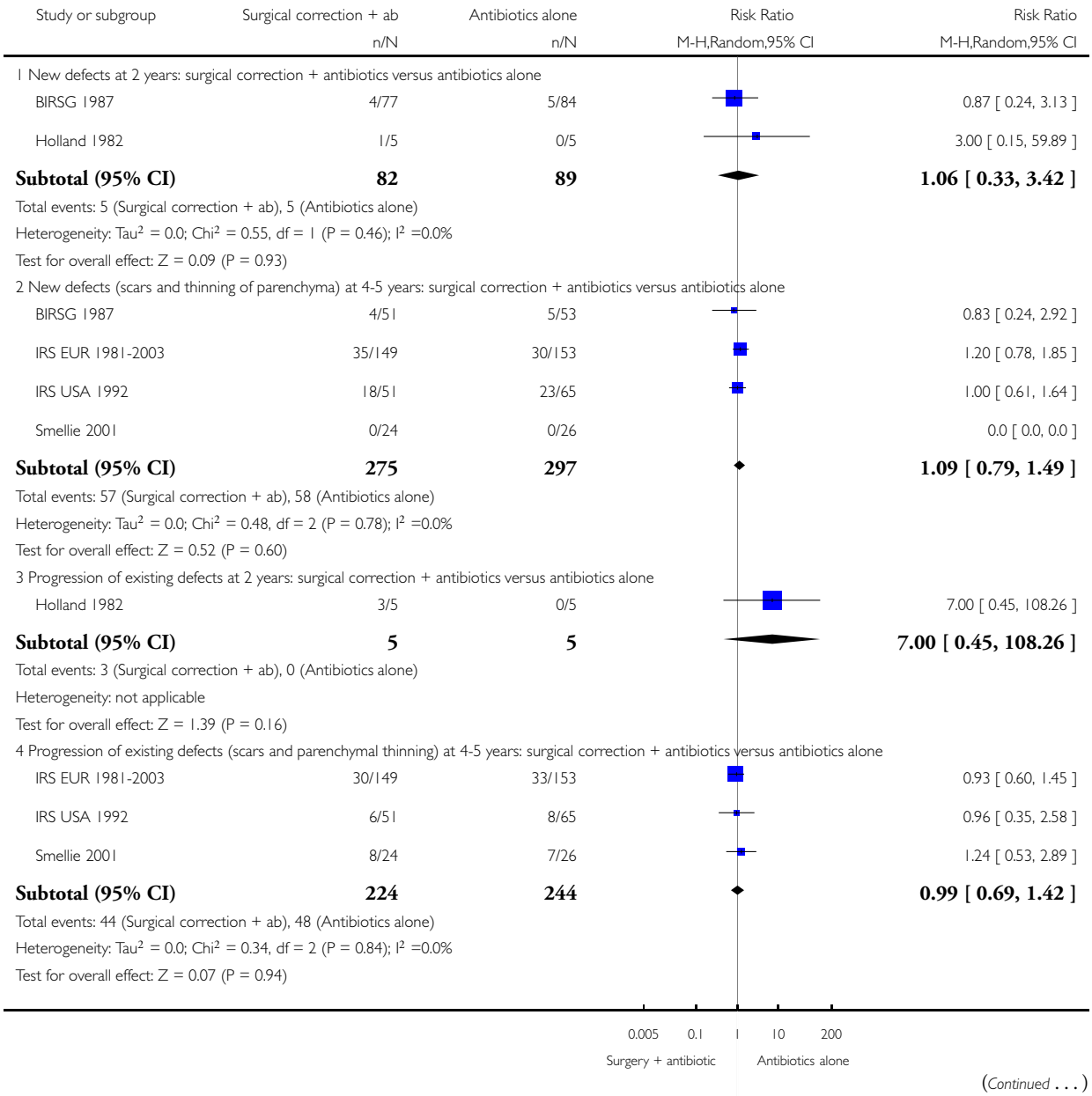


Analysis 2.2. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 2 Renal parenchymal defects (scars and thinning) on IVP: unit of analysis (children).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 2 Renal parenchymal defects (scars and thinning) on IVP: unit of analysis (children)



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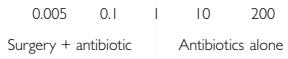
Study or subgroup	Surgical correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
5 Total new and progressive renal parenchymal defects at 2 years: surgical correction + antibiotics versus antibiotics alone				
Holland 1982	4/5	0/5		9.00 [0.61, 133.08]
Subtotal (95% CI)	**5**	**5**		**9.00 [0.61, 133.08]**
Total events: 4 (Surgical correction + ab), 0 (Antibiotics alone)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.60 (P = 0.11)				
6 Total new and progressive renal parenchymal defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone				
IRS EUR 1981-2003	65/149	63/153		1.06 [0.81, 1.38]
IRS USA 1992	24/51	31/65		0.99 [0.67, 1.45]
Smellie 2001	8/24	7/26		1.24 [0.53, 2.89]
Subtotal (95% CI)	**224**	**244**		**1.05 [0.85, 1.29]**
Total events: 97 (Surgical correction + ab), 101 (Antibiotics alone)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 2 (P = 0.88); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.43 (P = 0.67)				

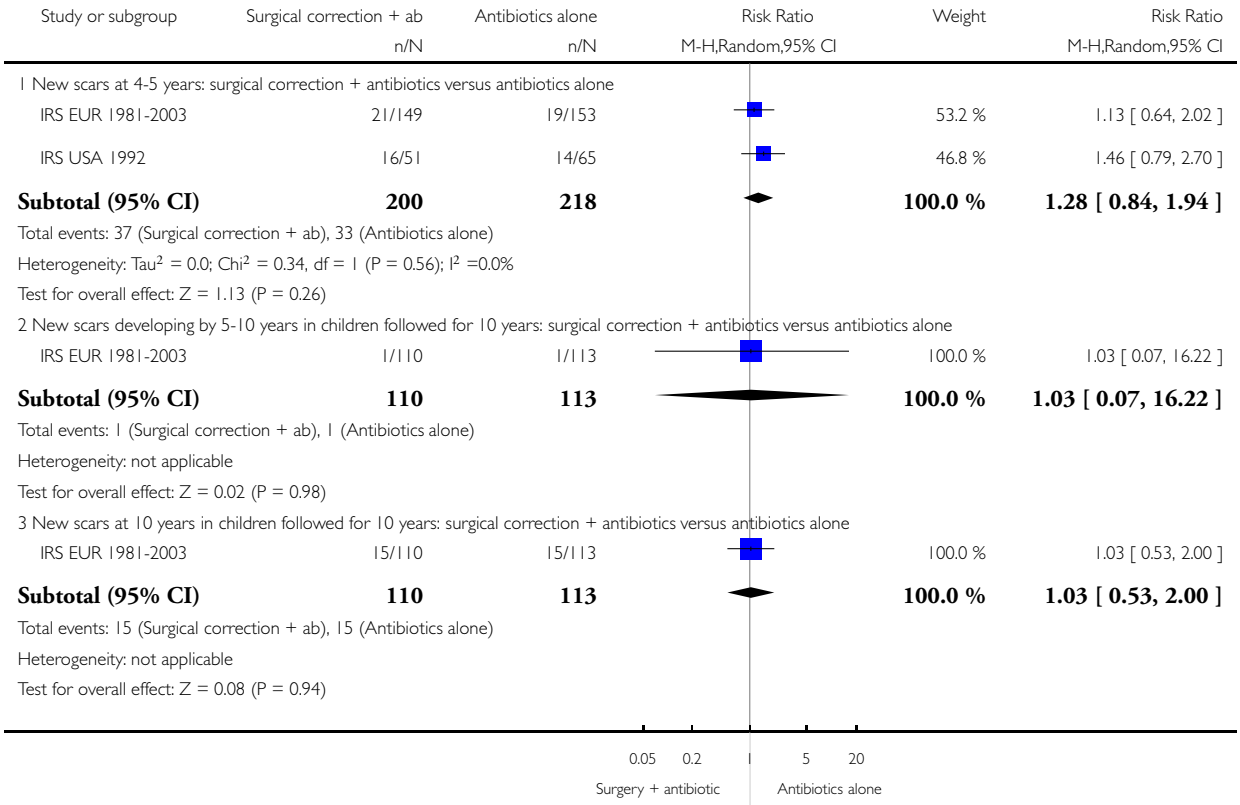


Analysis 2.3. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 3 Renal scars on IVP: unit of analysis (children).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 3 Renal scars on IVP: unit of analysis (children)



Analysis 2.4. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 4 Renal parenchymal defects on IVP: unit of analysis (kidneys).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 4 Renal parenchymal defects on IVP: unit of analysis (kidneys)

Study or subgroup	Surgical correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 New defects at 2 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	4/104	5/111		0.85 [0.24, 3.09]
Holland 1982	1/10	0/10		3.00 [0.14, 65.90]
Subtotal (95% CI)	**114**	**121**		**1.03 [0.31, 3.37]**
Total events: 5 (Surgical correction + ab), 5 (Antibiotics alone)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.54$, df = 1 (P = 0.46); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.05 (P = 0.96)				
2 Progression of existing defects at 2 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	13/104	16/111		0.87 [0.44, 1.71]
Holland 1982	3/10	0/10		7.00 [0.41, 120.16]
Subtotal (95% CI)	**114**	**121**		**1.56 [0.24, 10.08]**
Total events: 16 (Surgical correction + ab), 16 (Antibiotics alone)				
Heterogeneity: $Tau^2 = 1.14$; $Chi^2 = 2.03$, df = 1 (P = 0.15); $I^2 = 51\%$				
Test for overall effect: Z = 0.46 (P = 0.64)				
3 Total new and progressive defects at 2 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	17/104	21/111		0.86 [0.48, 1.54]
Holland 1982	3/10	0/10		7.00 [0.41, 120.16]
Subtotal (95% CI)	**114**	**121**		**1.54 [0.24, 9.95]**
Total events: 20 (Surgical correction + ab), 21 (Antibiotics alone)				
Heterogeneity: $Tau^2 = 1.16$; $Chi^2 = 2.06$, df = 1 (P = 0.15); $I^2 = 51\%$				
Test for overall effect: Z = 0.46 (P = 0.65)				
4 New defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	4/104	5/111		0.85 [0.24, 3.09]
Smellie 2001	0/50	0/54		0.0 [0.0, 0.0]
Subtotal (95% CI)	**154**	**165**		**0.85 [0.24, 3.09]**
Total events: 4 (Surgical correction + ab), 5 (Antibiotics alone)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 0 (P<0.00001); $I^2 = 100\%$				
Test for overall effect: Z = 0.24 (P = 0.81)				
5 Progression of existing defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	14/104	21/111		0.71 [0.38, 1.32]
Smellie 2001	8/50	7/54		1.23 [0.48, 3.16]

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Study or subgroup	Surgical correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**154**	**165**		**0.84 [0.50, 1.41]**
Total events: 22 (Surgical correction + ab), 28 (Antibiotics alone)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.92, df = 1 (P = 0.34); I^2 =0.0%				
Test for overall effect: Z = 0.65 (P = 0.51)				
6 Total new and progressive defects at 4-5 years: surgical correction + antibiotics versus antibiotics alone				
BIRSG 1987	18/104	26/111		0.74 [0.43, 1.27]
Smellie 2001	8/50	7/54		1.23 [0.48, 3.16]
Subtotal (95% CI)	**154**	**165**		**0.84 [0.53, 1.34]**
Total events: 26 (Surgical correction + ab), 33 (Antibiotics alone)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.86, df = 1 (P = 0.35); I^2 =0.0%				
Test for overall effect: Z = 0.74 (P = 0.46)				

Analysis 2.5. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 5 Renal parenchymal abnormalities on DMSA scan: unit of analysis (children).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 5 Renal parenchymal abnormalities on DMSA scan: unit of analysis (children)

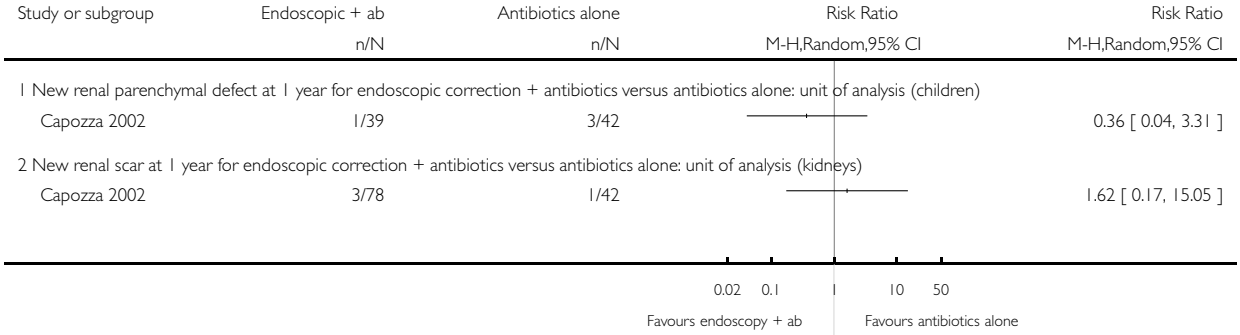
Study or subgroup	Correction + antibiotics n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Total new and progressive abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone				
Swedish Reflux Trial 2010	8/65	4/68		2.09 [0.66, 6.61]
2 All abnormalities detected on DMSA at 5 years: surgical correction + antibiotics versus antibiotics alone				
IRS EUR 1981-2003	23/140	25/147		0.97 [0.58, 1.62]
3 Deterioration of existing abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone				
Swedish Reflux Trial 2010	3/65	4/68		0.78 [0.18, 3.37]
4 New abnormalities at 2 years: endoscopic correction + antibiotics versus antibiotics alone				
Swedish Reflux Trial 2010	6/65	0/68		13.59 [0.78, 236.51]
5 Deterioration of existing abnormalities between 5-10 years: surgical correction + antibiotics versus antibiotics alone				
IRS EUR 1981-2003	9/107	13/109		0.71 [0.31, 1.58]

Analysis 2.6. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 6 Renal damage on ultrasound.

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 6 Renal damage on ultrasound



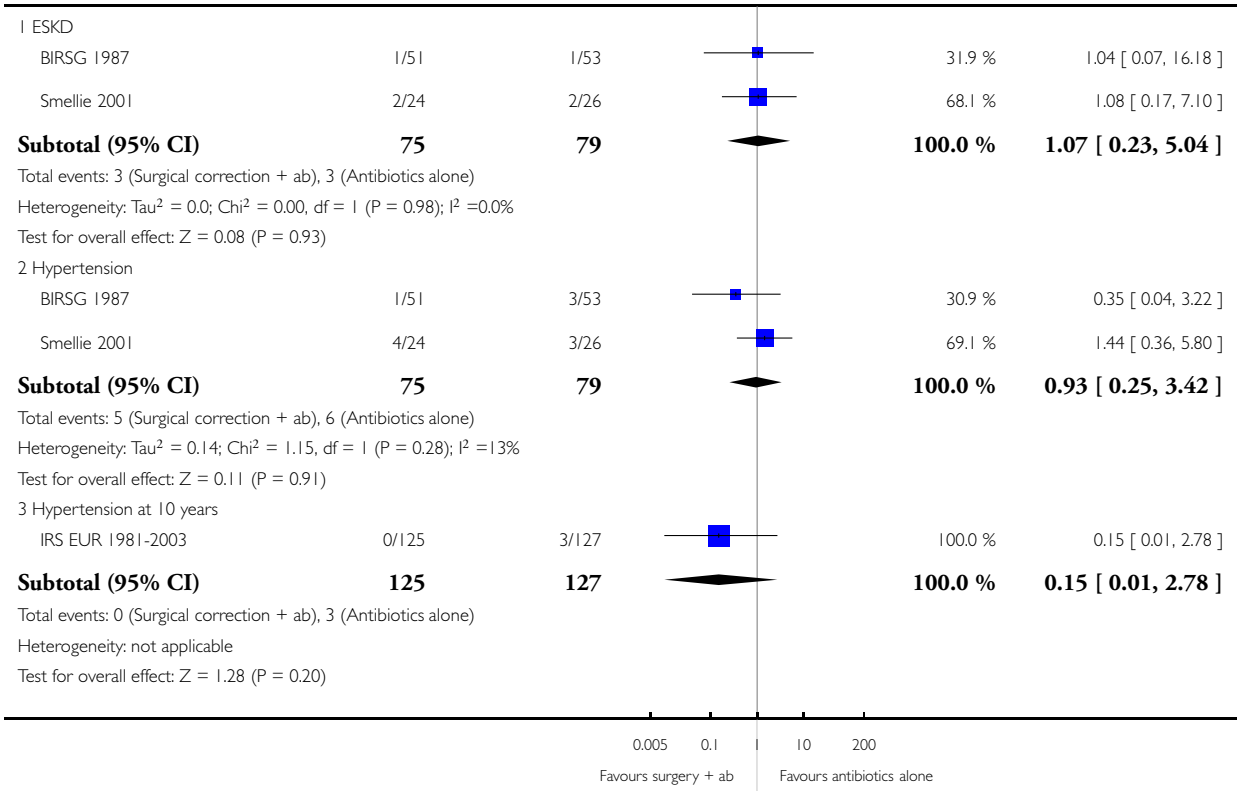
Analysis 2.7. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 7 Outcomes of hypertension and ESKD.

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 7 Outcomes of hypertension and ESKD

Study or subgroup	Surgical correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 ESKD					
BIRSG 1987	1/51	1/53		31.9 %	1.04 [0.07, 16.18]
Smellie 2001	2/24	2/26		68.1 %	1.08 [0.17, 7.10]
Subtotal (95% CI)	**75**	**79**		**100.0 %**	**1.07 [0.23, 5.04]**
Total events: 3 (Surgical correction + ab), 3 (Antibiotics alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.08 (P = 0.93)					
2 Hypertension					
BIRSG 1987	1/51	3/53		30.9 %	0.35 [0.04, 3.22]
Smellie 2001	4/24	3/26		69.1 %	1.44 [0.36, 5.80]
Subtotal (95% CI)	**75**	**79**		**100.0 %**	**0.93 [0.25, 3.42]**
Total events: 5 (Surgical correction + ab), 6 (Antibiotics alone)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 1.15$, df = 1 (P = 0.28); $I^2 = 13\%$					
Test for overall effect: Z = 0.11 (P = 0.91)					
3 Hypertension at 10 years					
IRS EUR 1981-2003	0/125	3/127		100.0 %	0.15 [0.01, 2.78]
Subtotal (95% CI)	**125**	**127**		**100.0 %**	**0.15 [0.01, 2.78]**
Total events: 0 (Surgical correction + ab), 3 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					



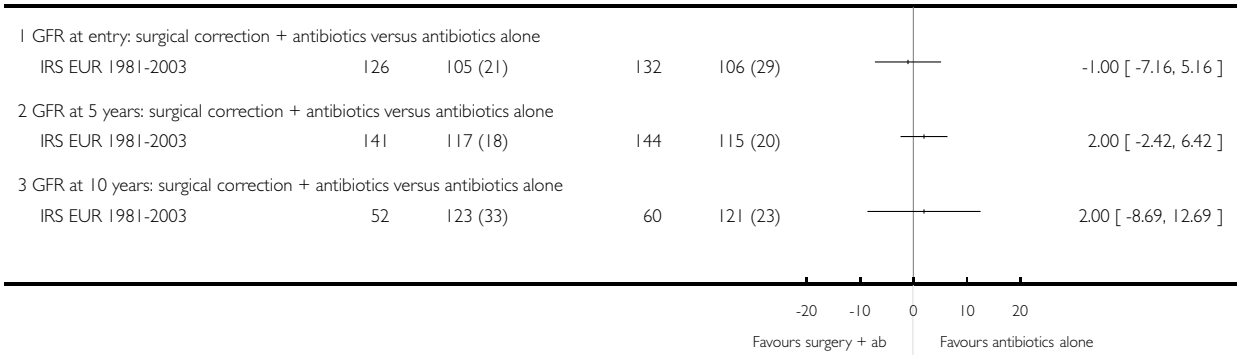
Analysis 2.8. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 8 GFR measured by Schwartz formula.

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 8 GFR measured by Schwartz formula

Study or subgroup	Surgical correction + ab N	Mean(SD)	Antibiotics alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 GFR at entry: surgical correction + antibiotics versus antibiotics alone						
IRS EUR 1981-2003	126	105 (21)	132	106 (29)		-1.00 [-7.16, 5.16]
2 GFR at 5 years: surgical correction + antibiotics versus antibiotics alone						
IRS EUR 1981-2003	141	117 (18)	144	115 (20)		2.00 [-2.42, 6.42]
3 GFR at 10 years: surgical correction + antibiotics versus antibiotics alone						
IRS EUR 1981-2003	52	123 (33)	60	121 (23)		2.00 [-8.69, 12.69]



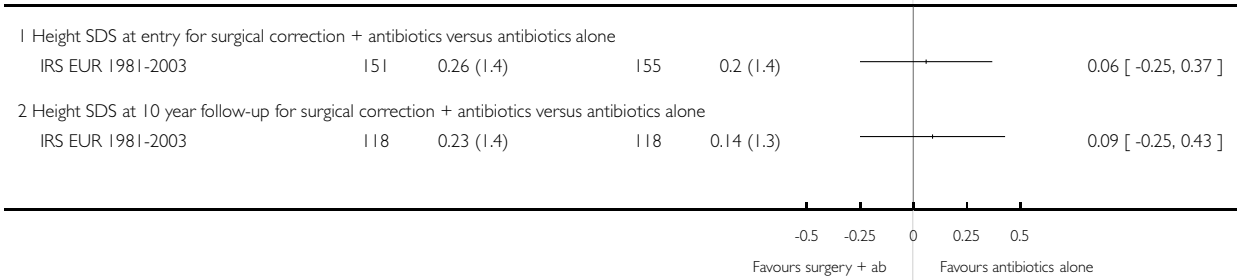
Analysis 2.9. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 9 Height Standard Deviation Score (SDS).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 9 Height Standard Deviation Score (SDS)

Study or subgroup	Surgical correction + ab N	Mean(SD)	Antibiotics alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Height SDS at entry for surgical correction + antibiotics versus antibiotics alone						
IRS EUR 1981-2003	151	0.26 (1.4)	155	0.2 (1.4)		0.06 [-0.25, 0.37]
2 Height SDS at 10 year follow-up for surgical correction + antibiotics versus antibiotics alone						
IRS EUR 1981-2003	118	0.23 (1.4)	118	0.14 (1.3)		0.09 [-0.25, 0.43]



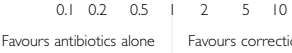
Analysis 2.10. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 10 Correction of VUR: unit of analysis (children).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 10 Correction of VUR: unit of analysis (children)

Study or subgroup	Anatomic correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Correction of VUR after 1-2 year for endoscopic correction + antibiotics versus antibiotics alone					
Dite 2007	12/22	5/22		39.8 %	2.40 [1.02, 5.67]
Swedish Reflux Trial 2010	20/52	9/68		60.2 %	2.91 [1.44, 5.85]
Subtotal (95% CI)	**74**	**90**		**100.0 %**	**2.69 [1.57, 4.63]**
Total events: 32 (Anatomic correction + ab), 14 (Antibiotics alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 1 (P = 0.73); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.58 (P = 0.00034)					
2 Correction of VUR after 3 years: surgical correction + antibiotics versus antibiotics alone					
Scott 1968	10/31	6/24		100.0 %	1.29 [0.55, 3.05]
Subtotal (95% CI)	**31**	**24**		**100.0 %**	**1.29 [0.55, 3.05]**
Total events: 10 (Anatomic correction + ab), 6 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					



Analysis 2.11. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 11 Correction of VUR: unit of analysis (ureters).

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 11 Correction of VUR: unit of analysis (ureters)

Study or subgroup	Anatomic correction + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Correction of VUR after 2 years: surgical correction + antibiotics versus antibiotics alone					
BIRSG 1987	67/69	48/65		100.0 %	1.31 [1.13, 1.53]
Subtotal (95% CI)	**69**	**65**		**100.0 %**	**1.31 [1.13, 1.53]**
Total events: 67 (Anatomic correction + ab), 48 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.57 (P = 0.00036)					
2 Correction of VUR after 2 years: endoscopic correction + antibiotics versus antibiotics alone					
Swedish Reflux Trial 2010	68/104	46/136		100.0 %	1.93 [1.47, 2.54]
Subtotal (95% CI)	**104**	**136**		**100.0 %**	**1.93 [1.47, 2.54]**
Total events: 68 (Anatomic correction + ab), 46 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.72 (P < 0.00001)					
3 Correction of VUR at 5 years: surgical correction + antibiotics versus antibiotics alone					
IRS EUR 1981-2003	282/302	299/310		100.0 %	0.97 [0.93, 1.00]
Subtotal (95% CI)	**302**	**310**		**100.0 %**	**0.97 [0.93, 1.00]**
Total events: 282 (Anatomic correction + ab), 299 (Antibiotics alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.72 (P = 0.085)					
Test for subgroup differences: Chi^2 = 37.98, df = 2 (P = 0.00), I^2 =95%					

Analysis 2.12. Comparison 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone, Outcome 12 Microbial resistance to the prophylactic drug.

Review: Interventions for primary vesicoureteric reflux

Comparison: 2 Anatomic reflux correction with surgery or endoscopy plus antibiotics (1-24 months) versus antibiotics alone

Outcome: 12 Microbial resistance to the prophylactic drug

Study or subgroup	Endoscopy + ab n/N	Antibiotics alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Unit of analysis (febrile UTI)				
Swedish Reflux Trial 2010	7/14	8/10		0.63 [0.34, 1.15]

Analysis 3.1. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 1 All symptomatic UTI by 2 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 1 All symptomatic UTI by 2 years

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Swedish Reflux Trial 2010	15/66	28/68		0.55 [0.33, 0.94]

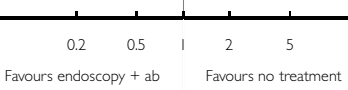
Analysis 3.2. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 2 Febrile UTI by 2 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 2 Febrile UTI by 2 years

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Swedish Reflux Trial 2010	14/66	25/68		0.58 [0.33, 1.01]



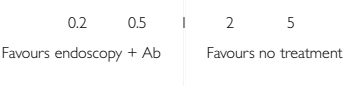
Analysis 3.3. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 3 New parenchymal defects on DMSA scan at 2 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 3 New parenchymal defects on DMSA scan at 2 years

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Swedish Reflux Trial 2010	6/65	9/68		0.70 [0.26, 1.85]



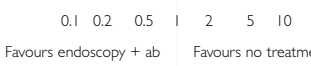
Analysis 3.4. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 4 Deterioration of existing parenchymal defects on DMSA scan at 2 years.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 4 Deterioration of existing parenchymal defects on DMSA scan at 2 years

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Swedish Reflux Trial 2010	3/65	6/68		0.52 [0.14, 2.00]



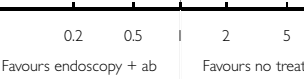
Analysis 3.5. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 5 Total new and progressive damage on DMSA scan.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 5 Total new and progressive damage on DMSA scan

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Swedish Reflux Trial 2010	8/65	12/68		0.70 [0.30, 1.60]



Analysis 3.6. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 6 Correction of VUR.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 6 Correction of VUR

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Correction of VUR after 2 years: unit of analysis (children)				
Swedish Reflux Trial 2010	20/52	10/65		2.50 [1.28, 4.86]
2 Correction of VUR after 2 years: unit of analysis (ureters)				
Swedish Reflux Trial 2010	68/104	55/130		1.55 [1.21, 1.97]

Analysis 3.7. Comparison 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment, Outcome 7 Microbial resistance to prophylactic drug.

Review: Interventions for primary vesicoureteric reflux

Comparison: 3 Endoscopic correction plus antibiotic prophylaxis versus no treatment

Outcome: 7 Microbial resistance to prophylactic drug

Study or subgroup	Endoscopy + antibiotics n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Unit of analysis (children)				
Swedish Reflux Trial 2010	7/66	9/68		0.80 [0.32, 2.03]
2 unit of analysis (febrile UTIs)				
Swedish Reflux Trial 2010	7/14	9/25		1.39 [0.66, 2.91]

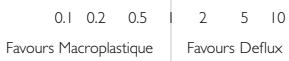
Analysis 4.1. Comparison 4 Different materials for subureteric injection to correct VUR, Outcome 1 Macroplastique versus Deflux.

Review: Interventions for primary vesicoureteric reflux

Comparison: 4 Different materials for subureteric injection to correct VUR

Outcome: 1 Macroplastique versus Deflux

Study or subgroup	Macroplastique n/N	Deflux n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Number of ureters with persistent VUR > grade 1 at 3 months				
Oswald 2002	8/58	16/56		0.48 [0.22, 1.04]
2 Number of ureters with persistent VUR > grade 1 at 1 year				
Oswald 2002	8/41	10/32		0.62 [0.28, 1.40]
3 Number of children with afebrile UTI				
Oswald 2002	6/34	4/38		1.68 [0.52, 5.44]
4 Number of kidneys with temporary renal dilatation after injection				
Oswald 2002	23/58	12/56		1.85 [1.02, 3.35]



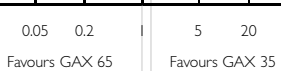
Analysis 4.2. Comparison 4 Different materials for subureteric injection to correct VUR, Outcome 2 Collagen GAX 65 versus Collagen GAX 35.

Review: Interventions for primary vesicoureteric reflux

Comparison: 4 Different materials for subureteric injection to correct VUR

Outcome: 2 Collagen GAX 65 versus Collagen GAX 35

Study or subgroup	GAX 65 n/N	GAX 35 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Number of ureters with persistent VUR at 3 months				
Frey 1997	2/16	7/12		0.21 [0.05, 0.85]
2 Number of ureters with recurrence of VUR				
Frey 1997	2/16	5/12		0.30 [0.07, 1.29]



Analysis 5.1. Comparison 5 Probiotics versus antibiotic prophylaxis, Outcome 1 Urinary tract infection.

Review: Interventions for primary vesicoureteric reflux

Comparison: 5 Probiotics versus antibiotic prophylaxis

Outcome: 1 Urinary tract infection

Study or subgroup	Probiotics n/N	Antibiotics n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 All symptomatic UTI by 1 year				
Lee 2007	11/60	13/60		0.85 [0.41, 1.74]
2 Febrile UTI by 1 year				
Lee 2007	9/60	11/60		0.82 [0.37, 1.83]

Analysis 5.2. Comparison 5 Probiotics versus antibiotic prophylaxis, Outcome 2 *E coli* resistance to prophylactic drug.

Review: Interventions for primary vesicoureteric reflux

Comparison: 5 Probiotics versus antibiotic prophylaxis

Outcome: 2 *E coli* resistance to prophylactic drug

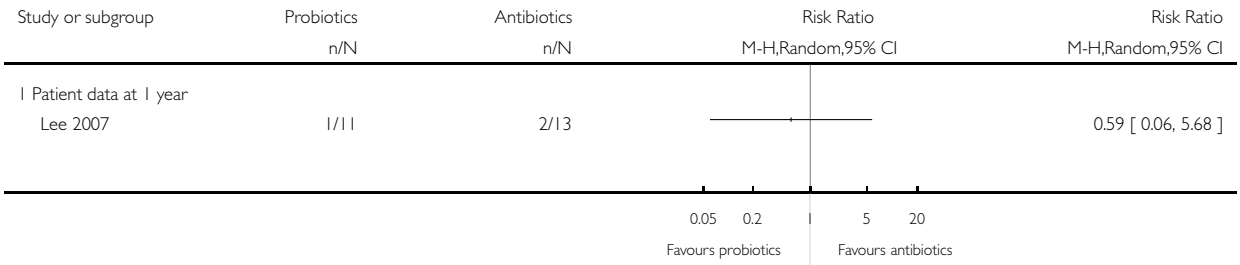
Study or subgroup	Probiotics n/N	Antibiotics n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Lee 2007	3/7	9/9		0.46 [0.21, 1.02]

Analysis 5.3. Comparison 5 Probiotics versus antibiotic prophylaxis, Outcome 3 Renal parenchymal defects on DMSA scan.

Review: Interventions for primary vesicoureteric reflux

Comparison: 5 Probiotics versus antibiotic prophylaxis

Outcome: 3 Renal parenchymal defects on DMSA scan



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (Vesico-Ureter* Reflux):ti,ab,kw or (Vesico* Reflux):ti,ab,kw or (ureter* reflux):kw in Clinical Trials 2. (vesic* or ureter*) and (backflow* or reflux):ti,ab,kw in Clinical Trials 3. (vur):ti,ab,kw or (VUR):ti,ab,kw in Clinical Trials 4. MeSH descriptor Vesico-Ureteral Reflux explode all trees 5. (#1 OR #2 OR #3 OR #4)
MEDLINE	1. Vesico-Ureteral Reflux/ 2. (Vesico-Ureter$ Reflux or Vesico$ Reflux or ureter$ reflux).tw. 3. ((vesic$ or ureter$) and (backflow$ or reflux)).tw. 4. vur.tw. 5. or/1-4
EMBASE	1. Vesicoureteral Reflux/ 2. (vesico-ureter$ reflux or vesico$ reflux or ureter$ reflux).tw. 3. ((vesico$ or ureter$) and (backflow$ or reflux)).tw. 4. vur.tw. 5. or/1-4

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*Yes (low risk of bias):* 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).
	No (high risk of bias): 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.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Was allocation adequately concealed?	*Yes (low risk of bias):* 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; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	No (high risk of bias): Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Was knowledge of the allocated interventions adequately prevented during the study?	*Yes (low risk of bias):* No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
	No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded,

(*Continued*)

	and the non-blinding of others likely to introduce bias.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
Were incomplete outcome data adequately addressed?	*Yes (low risk of bias):* 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.
	No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Are reports of the study free of suggestion of selective outcome reporting?	*Yes (low risk of bias):* 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).
	No (high risk of bias): Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-

(*Continued*)

	analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
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'.

Appendix 3. Quality checklist

Sequence generation

- Truly random sequence: generation using a random numbers table, a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing "lots" or the equivalent such as minimisation.
- Quasi-randomisation: allocation obtained by alternation, use of alternate medical records, date of birth or other predictable methods).

Allocation concealment

- Adequate: A randomisation method described that would not allow investigator/participant to know or influence intervention group.
- Unclear: Randomisation stated but no information on method used.
- Inadequate: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding

- Blinding of participants: Yes/no/not stated
- Blinding of health carers: Yes/no/not stated
- Blinding of outcome assessors: Yes/no/not stated
- Blinding of data analysts: Yes/no/not stated

The above are considered not blinded if the treatment group can be identified in >20% of participants because of side effects of treatments.

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis (ITT) was undertaken and this was confirmed from study assessment

- Unclear: Reported but unable to confirm by study assessment.
- No: Lack of ITT confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive study intervention, because they withdrew from the study or were not included because of protocol violation

Completeness of follow-up

- Percentage of participants with complete data at a defined study endpoint and reasons of loss-to-follow up.

FEEDBACK

Grade of Reflux

Summary

It is difficult to accept the fact that Surgery does not help. There are specific indications for surgery especially in the realm of paediatric VUR. A more appropriate study would have been to compare the two groups (surgery vs conservative)in a similar grade of reflux and as such the controversy exists only in Gr3 reflux.
Regarding the assessment of children with UTI it is clear cut that the first investigation will be Ultrasound examination Followed by MCU.

Reply

Response to Dr Philipraj
This systematic review of randomised controlled trials has summarised the results of published and unpublished trials identified by a comprehensive search of literature sources. The majority of published trials have compared surgery and antibiotic prophylaxis with antibiotic prophylaxis. The large trials (Birmingham Reflux Study, International Reflux Study) only enrolled children with dilating reflux - equivalent to grade 3 or more on the International Classification. The International Reflux Study only enrolled children with grade 3 and 4 reflux; children with grade 5 reflux were excluded. There were no trials identified that compared surgery and antibiotic prophylaxis only and only enrolled children with grade 3 reflux. When data from these trials are combined in meta-analysis, there were no significant differences in the risk for further urinary tract infection or for renal scarring. In the International Reflux Study, the incidence of febrile urinary tract infections over 5 years of follow up was significantly reduced in children undergoing surgery compared with antibiotic prophylaxis. This was the only benefit of surgery over antibiotic prophylaxis that could be demonstrated. Otherwise the available trials have not demonstrated an additional benefit of surgery over antibiotic prophylaxis.
This systematic review of treatment cannot provide any information on the most appropriate investigations for children following urinary tract infection.

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Date Received: 27/08/2004

WHAT'S NEW

Last assessed as up-to-date: 8 November 2010.

Date	Event	Description
30 March 2011	New citation required and conclusions have changed	New studies included, new author team

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2004

Date	Event	Description
13 May 2009	Amended	Contact details updated.
9 October 2008	Amended	Converted to new review format.
15 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- DW: Protocol development, study eligibility, data extraction, data analysis, writing review
- DV: Protocol development, study eligibility, data extraction
- EH: Data extraction, data analysis, writing review
- GS: Protocol development, data extraction, writing review
- GW: Data extraction
- EN: Data extraction, data analysis, writing review
- JC: Protocol development, writing review

DECLARATIONS OF INTEREST

- JC Craig and GJ Williams are authors of the PRIVENT Study 2009
- JC Craig is an author of Craig 2002.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Kidney Foundation, Seeding Grant number S2/99, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The risk of bias assessment tool (Appendix 2) has replaced the quality checklist (Appendix 3)

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotic Prophylaxis; Kidney [abnormalities]; Randomized Controlled Trials as Topic; Urinary Tract Infections [complications; drug therapy]; Vesico-Ureteral Reflux [complications; *therapy]

MeSH check words

Child; Female; Humans; Male