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# Antibiotics for preventing recurrent urinary tract infection in non-pregnant women (Review)

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Antibiotics for preventing recurrent urinary tract infection in non-pregnant women.
*Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD001209.
DOI: 10.1002/14651858.CD001209.pub2.

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[Intervention Review]

# Antibiotics for preventing recurrent urinary tract infection in non-pregnant women

Xavier Albert[1], Isabel Huertas[2], Inmaculado Pereiro[3], José Sanfélix[4], Victoria Gosalbes[5], Carla Perrotta[6]

[1]Health Center of Montcada. Department 6, Valencian Agency of Health, Valencia, Spain. [2]Surveillance and epidemiologic control unit, Conselleria de Sanidad, Valencia, Spain. [3]Direccion de Atencion primaria Area 4, Unidad de Investigacion Trinitat, Valencia, Spain. [4]Health Center of Nazaret, Conselleria de Sanidad, Valencia, Spain. [5]Teaching Unit of Family Practice, EVES-Escuela Valenciana de Estudios para la Salud, Valencia, Spain. [6]Woodview House, UCD School of Public Health and Population Sciences, Dublin, Ireland

**Contact address:** Xavier Albert, Health Center of Montcada. Department 6, Valencian Agency of Health, Av. Mediterraneo s/n, Montcada, Valencia, 46113, Spain. albert_xav@gva.es.

**Editorial group:** Cochrane Kidney and Transplant Group
**Publication status and date:** Edited (no change to conclusions), published in Issue 4, 2008.

**Citation:** Albert X, Huertas I, Pereiro I, Sanfélix J, Gosalbes V, Perrotta C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD001209. DOI: 10.1002/14651858.CD001209.pub2.



## ABSTRACT

### Background

Urinary tract infection (UTI) is a common health care problem. Recurrent UTI (RUTI) in healthy non-pregnant women is defined as three or more episodes of UTI during a twelve month period. Long-term antibiotics have been proposed as a prevention strategy for RUTI.

### Objectives

To determine the efficacy (during and after) and safety of prophylactic antibiotics used to prevent uncomplicated RUTI in adult non-pregnant women.

### Search methods

We searched MEDLINE (from 1966), EMBASE (from 1980), Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*) and reference lists of retrieved articles.

### Selection criteria

Any published randomised controlled trial where antibiotics were used as prophylactic therapy in RUTI.

### Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as relative risk (RR) with 95% confidence intervals (CI).

### Main results

Nineteen studies involving 1120 women were eligible for inclusion.
*Antibiotic versus antibiotic (10 trials, 430 women):* During active prophylaxis the rate range of microbiological recurrence patient-year (MRPY) was 0 to 0.9 person-year in the antibiotic group against 0.8 to 3.6 with placebo. The RR of having one microbiological recurrence (MR) was 0.21 (95% CI 0.13 to 0.34), favouring antibiotic and the NNT was 1.85. For clinical recurrences (CRPY) the RR was 0.15 (95% CI 0.08 to 0.28). The NNT was 1.85. The RR of having one MR after prophylaxis was 0.82 (95% CI 0.44 to 1.53). The RR for severe side effects was 1.58 (95% CI 0.47 to 5.28) and for other side effects the RR was 1.78 (CI 1.06 to 3.00) favouring placebo. Side effects included vaginal and oral candidiasis and gastrointestinal symptoms.

*Antibiotic versus antibiotic (eight trials, 513 women):* These trials were not pooled. Weekly perfloxacin was more effective than monthly. The RR for MR was 0.31(95% CI 0.19 to 0.52). There was no significant difference in MR between continuous daily and postcoital ciprofloxacin.

**Authors' conclusions**

Continuous antibiotic prophylaxis for 6-12 months reduced the rate of UTI during prophylaxis when compared to placebo. After prophylaxis two studies showed no difference between groups. There were more adverse events in the antibiotic group. One RCT compared postcoital versus continuous daily ciprofloxacin and found no significant difference in rates of UTIs, suggesting that postcoital treatment could be offered to woman who have UTI associated with sexual intercourse.

## PLAIN LANGUAGE SUMMARY

**Non-pregnant women who have had several urinary tract infections are less likely to have another infection if they take antibiotics for six to 12 months**

Urinary tract infections (UTI) are infections of the bladder and kidneys. They can cause vomiting, fever and tiredness, and occasionally kidney damage. The review found that non-pregnant women who had two or more UTIs in the past year had less chance of having a further UTI if given a six to 12 month treatment with antibiotics. The most commonly reported side effects are digestive problems, skin rash and vaginal irritation. More research is needed determine the optimal duration for antibiotic treatment.

## BACKGROUND

Urinary tract infection (UTI) is a common health care problem. In a sample of women from US 10.8% of them aged 18 and older reported at least one presumed UTI the past year (Foxman 2000).

Recurrent urinary tract infections (RUTI) is defined in the literature by three episodes of UTI in the last twelve months or two episodes in the last six months. Some studies estimate that 20-30% of women who have a UTI would have an RUTI. According to cohort and case control studies (Hooton 1996; Scholes 2000) risk factors associated with RUTI in sexually active premenopausal women are the frequency of sexual intercourse, the use of spermicides, the age of first UTI (less than 15 years of age indicates a greater risk of RUTI) and history of UTI in the mother; suggesting that genetic factors/long-term environmental exposures might predispose to this condition. Following menopause, risk factors strongly associated to the condition are vesical prolapse, incontinence and post-voiding residual urine. Other risk factors like non-secretor status and history of UTI before menopause need to be confirmed by further research (Raz 2000).

RUTIs cause a significant discomfort to women and a high impact in ambulatory health care costs as a result of outpatients visits, diagnostic tests and prescriptions. Different approaches have been proposed for the prevention of RUTI and include; non-pharmacological therapies such as voiding after sexual intercourse or the ingestion of cranberry juice (Jepson 2004), and the use of antibiotics as preventive therapy antibiotic given in regular basis or postcoital prophylaxis in sexually active women.

With respect to antibiotic prophylaxis, it is not known which antibiotic schedule is best, or what is the optimal duration of prophylaxis, the incidence of adverse events, the recurrence of infections after stopped prophylaxis or the treatment adherence.

## OBJECTIVES

The objective of this systematic review was to assess the efficacy (reduction in number of microbiological and clinical recurrences) and safety (side effects) of antibiotic prophylactic for prevention of RUTI in adult, non-pregnant women.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Any published randomised control trial (RCT) where antibiotics were used as prophylactic therapy in women with recurrent urinary tract infections.

#### Types of participants

Non-pregnant women over 14 years of age with a history of at least two episodes of uncomplicated UTI in the last year. We excluded trials including women with a history of urological surgery, stones or renal function impairment.

#### Types of interventions

- Any antibiotic regimen administered for at least six months as a preventive strategy for RUTI. We included any type of schedule strategy (daily basis, weekly, monthly or postcoital).
- The control group should have received placebo, antibiotic (same antibiotic different schedule, or two different antibiotics), or another pharmacological non-antibiotic treatment.

#### Types of outcome measures

***Recurrences occurring during active prophylaxis period***

- Number of recurrences/patient-year, using microbiological criteria (Microbiological criteria could be: confirmation of diagnosis of recurrence by a positive urine culture of > 100,000 bacteria/ml with isolation or identification of the agent responsible or if there is pyuria plus symptoms > 10,000 bacteria/ml) (MRPY).
- Proportion of patients who experienced at least one recurrence during prophylaxis, using microbiological criteria (%MR).
- Number of recurrences/patient-year during prophylaxis, identified using clinical criteria (dysuria and/or pollakiuria) (CRPY).
- Proportion of patients who experienced at least one recurrence during prophylaxis, identified using clinical criteria (dysuria and/or pollakiuria) (%CR).

***Recurrences occurring after active prophylaxis period***

- Number of recurrences per patient/year after prophylaxis, using microbiological criteria.
- Proportion of patients who experienced at least one recurrence after prophylaxis, using microbiological criteria.
- Number of recurrences per patient/year after prophylaxis, identified using clinical criteria.
- Proportion of patients with at least one recurrence after prophylaxis, identified using clinical criteria.

***Side effects***

- Proportion of patients who had severe side effects (defined as those requiring withdrawal of treatment)
- Proportion of patients with mild side effects (i.e. not requiring withdrawal of treatment).

***Withdrawals***

- Proportion of patients who withdrawal treatment in both groups.

The same numeration is used for the results in the tables of comparisons. Trials which had data of at least one of the first four outcomes were included.

### Search methods for identification of studies

#### Initial search

We attempted to identify as many as relevant published clinical trials as possible in which antibiotics to prevent RUTIs were assessed. We used electronic searching of bibliographic databases and hand-searching, according to the methods described in the Cochrane Collaboration Handbook.

1. MEDLINE from 1966 to April 2004 using the search terms "recurrent urinary tract infection"[in all fields] AND wom* [in all fields] AND prophy* [in all fields] OR preven* [in all fields], combined with the MEDLINE search strategies for randomised

controlled trials suggested by the Cochrane Centre, without language restrictions.
2. EMBASE from 1988 to January 2003 using similar search strategy
3. The Cochrane Central Register of Controlled Trials(CENTRAL in *The Cochrane Library*, Issue 1 2004).
4. The reference list of articles.

### Review updates

The Cochrane Renal Group's specialised register and The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*) and MEDLINE was 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 2007). Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete lis of nephrology conference proceedings searched.

#### *November 2005*

No new studies identified.

#### *March 2007*

Two new ongoing studies were identified and shall be included once they have been completed and published (Beerepoot 2006; McMurdo 2006). Five studies (six reports) were excluded (Donabedian 1995; Ejrnaes 2006; Ferry 2004; Hoivik 1984; Kasanen 1983).

## Data collection and analysis

### Selection of trials

Two reviewers independently selected the trials using the defined inclusion criteria. In case of disagreement a third reviewer was involved. We performed a pilot test to the reproducibility of the decisions between the two reviewers.

### Evaluation of quality

The quality of the trials included was assessed in terms of the randomisation process and internal and external validity, based on the criteria described by Guyatt 1993. The criteria used were:

#### *Was the randomisation list concealed?*

- Allocation adequately concealed (A) (Used central randomisation, allocation through pharmacy, sealed envelopes).
- Method of allocation inadequate (B).
- Method of allocation not specified (C).

#### *Were patients and clinicians "blind" to treatment?*

- Single or double-blind.
- Not blinded.
- Method not reported.

#### *Was the follow-up complete?*

- Loss of less than 20%.
- Loss of 20% or more.
- Not reported.

#### *Were patients analysed in the groups to which they were randomised?*

- Yes.
- No.
- Unclear.

#### *Were groups similar at the start of the trial?*

- No difference in prognostic factors between treatment groups.
- Difference in prognostic factors between treatment groups.
- Not reported.

#### *Aside from the experimental intervention, were the groups treated equally?*

- Yes (Information on confounding treatments is provided).
- No.
- Not reported.

Two reviewers independently estimate the quality of included trials. An overall 'quality score' was not obtained. If heterogeneity was detected in the trials, the quality assessments were used to explain it. Quality was also measured though the Validated Quality Scale (Jadad 1996) which provides a score ranging from 0 to 5; studies not reaching 3 points were considered to be of poor quality.

### Data collection

Two reviewers independently extracted the data using the "extraction data form" specifically designed for this review. The following information was collected from each study:

1. Study setting,
2. Study population (age, co-morbidity, prior treatments);
3. Type of clinical trial;
4. Inclusion criteria;
5. Description of the intervention(s);
6. Duration of the intervention(s);
7. Length of follow-up;
8. Methods used to assess outcomes (urine culture, clinical evaluation);
9. Number of "drop-outs" and how the data were analysed;
10. Results.

### Data analysis

The number of microbiological and clinical recurrences/patient/year during prophylaxis period) were analysed using density incidence. Relative risk (RR) and their confidence interval were calculated using Epi Info version 6.04 (Bernard 1987; Hennekens 1987). Dichotomous outcomes (proportion of patients who experienced at least one recurrence during and after prophylaxis period and proportion of patients with adverse events) where analysed through RR. Absolute risk reduction (ARR) was evaluated using number needed-to-treat ( NNT), 95% confidence intervals (95% CI) where calculated from CI limits of ARR (Altman 1998). We performed pooled analysis for the group antibiotics versus placebo. Heterogeneity was tested by a standard chi-square test and considered to be significant if $P < 0.1$. Sensitivity analysis was done excluding those trials that have different inclusion criteria or tested different schedules.

In the group antibiotic versus antibiotic, pooled analysis of the data was done in five trials that compared nitrofurantoin against another antibiotic. The pooled risk of microbiological recurrences and the pooled risk of adverse events were analysed. The three other trials in this group and the last group (antibiotic versus other pharmacological intervention) did not have any particular feature in common that justified pooled analysis. We described the P value as stated in the original article for MRPY and CRPY. For categorical outcomes we expressed the RR and the 95% CI for each trial.

## RESULTS

### Description of studies

We retrieved 108 studies from the search strategy. Eighty-nine studies were excluded. Reasons for exclusion where:

- Thirty-four were not prophylaxis studies.
- Nineteen were not antibiotic interventions.

Of the remaining 34 (see Characteristics of excluded studies), twenty-five were excluded because they did not meet the inclusion criteria:

- Fourteen studies were before-after studies (Battilana 1988; Brumfitt 1987; Fairley 1974; Harding 1979; Jodal 1989; Light 1981; Masu 1984; Pfau 1983; Pfau 1988; Pfau 1989; Pfau 1994; Privette 1988; Svensson 1982; Westenfelder 1987),
- Four were crossover trials (Biering 1994; Meyhoff 1981; Toba 1991; Wong 1985), and
- Seven were non-randomised or not controlled trials (Harding 1974; Kasanen 1974; Landes 1970; Martens 1995b; Ronald 1975; Sakurai 1994a; Stamey 1977).

The remaining nine trials were not included for other reasons:

- duration of intervention less than six months (MacDonald 1983; Mavromanolakis 1997),
- including children (Fujii 1981), including men (Hardy 1980; Vahlensieck 1992),
- complicated UTIs (Kalowski 1975; Kasanen 1982; Landes 1980; Raz 1991).

Finally, nineteen studies met the inclusion criteria (see Characteristics of included studies and Table 1 and Table 2).

We classified the trials into three groups according to the types of interventions evaluated:

1. Antibiotics versus placebo
2. Antibiotic versus antibiotic, different antibiotic or same antibiotic using different schedule.
3. Antibiotic versus another pharmacologic intervention (non-antibiotic)

#### Antibiotic versus placebo

(Table 1- *Antibiotic versus placebo. Description of studies*).

- Ten trials with a total number of 430 women were studied (Bailey 1971; Gower 1975; Martens 1995; Martorana 1984; Nicolle 1989; Rugendorff 1987; Schaeffer 1982; Scheckler 1982; Stamm 1980; Stappleton 1990). In the study by Stamm 1980, two comparisons were made.
- The recruitment was made from outpatient clinics (urologic, general practice or infection clinics) and one study recruited university students (Stappleton 1990). Women were premenopausal in three trials (Bailey 1971; Martens 1995; Stappleton 1990) and both pre-and postmenopausal in the rest.
- Two trials (Nuñez 1990; Stamm 1980) used two documented urinary infections in the last twelve month instead of three as inclusion criteria. There were two studies where the number of past urinary tract infections were not clarified, the authors stated "history of recurrent urinary tract infections" as inclusion criteria (Bailey 1971, Gower 1975). We did a sensitivity analysis excluding them.
- The antibiotics used were: norfloxacin 200 mg/24 h (Nicolle 1989; Rugendorff 1987), cinoxacin (or ciprofloxacin) 500 mg/24 h (Martorana 1984; Schaeffer 1982; Scheckler 1982) cinoxacin 250 mg/24 h ( Martens 1995), nitrofurantoin 100 mg/24 h ( Stamm 1980), nitrofurantoin 50 mg/24 h (Bailey 1971), cotrimoxazole 40-200/24 h (Stamm 1980), cephalexin 125 mg/24 h ( Gower 1975) and cotrimoxazole 40-200 mg postcoital (Stappleton 1990).
- Active prophylaxis treatment was six months in eight studies and twelve months in two (Nicolle 1989; Gower 1975). In the case of the post coital study, women were instructed to take Cotrimoxazole one dose after sexual intercourse.
- In all studies, prophylaxis was interrupted in cases of recurrence. The definition of clinical recurrence was the presence of bacteriuria plus clinical symptoms of UTI in six studies, or clinical symptoms of UTI (Scheckler 1982).
- In relation to post-intervention follow-up, only two studies performed follow-up six months after the finished prophylaxis period (Schaeffer 1982; Stamm 1980).

#### Antibiotic versus another antibiotic

(Table 2 - *Antibiotic verus antibiotic or other strategy. Description of studies*)

- Six studies with a total of 458 women were included. None of the trials compared the same antibiotic. In five, nitrofurantoin was compared against another antibiotic: cefaclor 250 mg/24 h, norfloxacin 200 mg/24 h, norfloxacin 400 mg/24 h, trimethoprim 100 mg/24 h, trimethoprim 40 mg/24 h and Sulphamethoxazole 200 mg/24 h (Brumfitt 1985; Brumfitt 1991; Brumfitt 1995; Nuñez 1990; Stamm 1980). The other trial compared trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h (Seppanen 1988).
- Women where pre- and postmenopausal and recruitment was made from outpatients clinics (urologic or UTI clinics).
- In the three Brumfitt trials (Brumfitt 1985; Brumfitt 1991; Brumfitt 1985) the duration of prophylaxis was twelve months, the definition of clinical recurrence was the presence of clinical symptoms of urinary infection and patients were told not to interrupt prophylaxis in the case of recurrence (the episode was treated and then prophylaxis was restarted). In the other three trials (Nuñez 1990; Seppanen 1988; Stamm 1980) the prophylaxis period was six months and it was suspended in cases of recurrence. Clinical recurrence was defined by bacteriuria plus clinical symptoms of UTI.
- In two studies there was some data in relation to follow-up. In Seppanen 1988 follow-up was for a period of 4-6 weeks and in Stamm 1980 for six months after the active intervention period.

### Antibiotic versus same antibiotic with different regimen

A total number of 513 women were evaluated in two studies, one comparing pefloxacin 400 mg/wk versus 400 mg/mo (Guibert 1995) and the other Ciprofloxacin 125 mg/24 h versus postcoital (Melekos 1997). In both, the duration of prophylaxis was one year and the follow-up after the active treatment period was three and twelve months. In Guibert 1995 women were pre- and postmenopausal and recruited in family practices. In Melekos 1997 women were premenopausal and sexually active and were screened in urologic outpatient clinics. Patients were told not to interrupt treatment in case of recurrence. The definition of clinical recurrence was the presence of clinical symptoms of UTI in Melekos 1997.

### Antibiotic versus other pharmacological strategy (non-antibiotic)

(Table 2 - *Antibiotic verus placebo or other strategy. Description of studies)*)
A total number of 177 women were evaluated in two studies (Brumfitt 1981; Brumfitt 1983). One comparing trimethoprim 100 mg/24 h versus povidone iodine solution and methenamine hippurate 1 g/12 h (Brumfitt 1983), and the other compared nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h (Brumfitt 1981). In both the duration of the interventions was twelve months, patients were told not to interrupt treatment in case of recurrence and the definition of clinical recurrence was the presence of clinical symptoms of UTI. Women were pre- and postmenopausal and recruitment was made from outpatient UTI clinics.

## Risk of bias in included studies

Overall the quality of the included studies was poor. As it can be seen from Table 3 - *Antibiotic versus placebo. Methodological quality* and Table 4 - *Antibiotic versus antibiotic or other strategy. Methodological quality,* most studies did not provide any information regarding randomisation and allocation concealment. The loss-to-follow-up and adverse events in some studies were unclear, barely described or not described at all. However using the JADAD Quality Scale (Jadad 1996), the 11 double-blind studies obtained 3 points or more.

### Antibiotic versus placebo

(Table 3 - *Antibiotic versus placebo. Methodological quality*).
Only Scheckler 1982 and Martens 1995 provided some description of the methods of randomisation. In the rest of the trials this was unclear. Nine out of ten trials were double-blind while allocation concealment was unclear in all the studies. The withdrawal rate was equal or more than 20% in three. In Nicolle 1989 it was 20% (norfloxacin 200 mg/24 h), in Martens 1995 25% (cinoxacin 250 mg/24 h) and 30% in Scheckler 1982 (cinoxacin 500 mg/24 h).

### Antibiotic versus antibiotic

(Table 4 - *Antibiotic versus antibiotic or other strategy. Methodological quality*)

#### *Antibiotic versus another antibiotic*

Method of randomisation was not stated in most of the studies. In Brumfitt 1985 was made by random chart . Allocation concealment was unclear or inadequate in all of them.
Three studies were not blinded (Brumfitt 1985; Brumfitt 1991; Brumfitt 1995), one study was single blind (Nuñez 1990), and two were double blinded (Seppanen 1988; Stamm 1980).The withdrawals and drop-outs were over 20% in three studies (Brumfitt 1985; Brumfitt 1991; Brumfitt 1995).

#### *Antibiotic versus same antibiotic with different doses*

Melekos 1997 had randomisation inadequate (date of birth), unclear allocation concealment and a rate of drop outs of 11%.Guibert 1995 did not report the randomisation methods, was double blinded and the drop out rate was 7%.

### Studies comparing antibiotic versus non antibiotic

(Table 4 - *Antibiotic versus antibiotic or other strategy. Methodological quality*)
The two studies were unblinded. Withdrawals and drop-outs were over 20% in Brumfitt 1983. Brumfitt 1981 was a crossover design.

## Effects of interventions

### Antibiotics versus placebo (comparison 01)

In 10/11 comparisons, antibiotics showed higher efficacy than placebo to reduce clinical and microbiological recurrences (see additional Table 5 - *Antibiotics versus placebo. MRPY and CRPY)*.

#### *Recurrences occurring during active prophylaxis period*

##### Number of recurrences/patient-year, using microbiological criteria (MRPY)

This outcome was assessed in eight comparisons (Table 5 - *Antibiotics versus placebo. MRPY and CRPY)*. The rate range of MRPY was 0 to 0.9 person-years in the antibiotic group and between 0.8 to 3.6 infections/person-years in the placebo group.

In a subgroup analysis done by Stappleton 1990 patients were stratified according to their intercourse frequency (three groups: less than twice a week, two to three times per week and more than three) and infection rates for each subgroup were calculated. In the subgroup less than twice/wk the MRPY was 0 (n = 10) in the active treatment arm versus 1.8 in the antibiotic arm, 0.6 versus 4.3 for 2-3 times/wk (n = 7), and 0.6 versus 15 for greater than 3 times/wk (n = 7). For patients who were on placebo, increases in intercourse frequency were significantly correlated with increases in infection rate ( r = 0.8, P = 0.004).

##### Proportion of patients who experienced at least one recurrence using microbiological criteria (% MR)

All the trials, which included 372 patients, analysed this outcome *(analyses 01.01 to 01.08)*. The pooled data showed that the RR of having at least one recurrence was 0.21 (95% CI 0.13 to 0.33) favouring antibiotic arm. The heterogeneity test was not significant (P = 0.18) and the NNT was 1.85 (CI 1.60 to 2.20)

We performed two sensitivity analyses. First we excluded the postcoital study (Stappleton 1990) and then we excluded those studies that included patients who had only two infections in the 12 months prior to enrolment instead of three, and those that had as inclusion criteria "history of RUTI". The overall effect remained unchanged.

##### Number of recurrences/patient-year using clinical criteria (CRPY)

Four trials including 136 patients were analysed and showed a statistically significant difference. (Table 5 - *Antibiotics versus placebo. MRPY and CRPY*). The range of having one clinical

recurrence was between 0 to 0.27/person-years in the antibiotic group and 1.12 to 3.6 person-years in the placebo group ( P < 0.01 for both).

#### Proportion of patients who experienced at least one recurrence using clinical criteria (%CR)

In eight comparisons (seven trials), which included 257 patients, RR of having a clinical UTI was 0.15 (95% CI 0.08 to 0.28) favouring antibiotic against placebo. The heterogeneity test was not significant (P = 0.98) and the NNT to prevent one recurrence was 2.2 (CI 1.80 to 2.80). The exclusion of the two studies that includes women with at least two UTI in the last 12 months, those that had as inclusion criteria "history of RUTI", and excluding the postcoital study did not change the effect.

### *Recurrence after prophylaxis*

In relation to post-intervention follow-up two trials had a follow up assessment six months after finished the prophylaxis period (Schaeffer 1982; Stamm 1980). The outcomes used to evaluate patients were MRPY (Stamm 1980) and the proportion of patients with MR in both. In one trial follow up was conducted only in the arm receiving norfloxacin during 12 months (Nicolle 1989 ).

#### Number of recurrences/patient-year after prophylaxis using microbiological criteria (MRPY)

The MRPY was 1.2 (nitrofurantoin) and 1.3 (cotrimoxazole) versus 3 in placebo. However, it was not possible to analyse the statistical significance as the authors did not report the data necessary to construct the coefficient.

#### Proportion of patients who experienced at least one recurrence after prophylaxis using microbiological criteria.( %MR)

Two studies, including 70 patients (Schaeffer 1982; Stamm 1980), were analysed *(analysis 01.05)*.
The RR of having at least one recurrence after prophylaxis was 1.53 (CI 0.69 to 3.38) for cinoxacin versus placebo ( Schaeffer 1982), 0.51 (95% CI 0.25 to 1.04) for nitrofurantoin and 0.75 (CI 0.38 to 1.50) for cotrimoxazole 40-200 mg/24 h (Stamm 1980). The pooled analysis was 0.82 (95% CI 0.44 to 1.53).

#### Number of recurrences/patient-year after prophylaxis using clinical criteria (CRPY)

There were not studies that assessed clinical recurrences after prophylaxis.

### *Side effects*

#### Proportion of patients who had severe side effects

(Table 6 - *Side effects (SE)* "severe side effects" defined as those requiring withdrawal of treatment)
All trials reported severe side effects. In 225 patients, 9 were withdrawn from treatment in the antibiotic groups and 208 patients were withdrawn in the placebo groups. Four left the study because of adverse events. Five trials had no severe side effects.
The pooled RR of severe side effects (*analysis 01.03)* was 1.58 (95% CI ).47 to 5.28) favouring placebo group. The most common described severe side effects were skin rash and nausea. The absolute numbers of severe side effects were: cephalexin = 2 , cinoxacin 500 mg = 3, cinoxacin 250 mg = 3, norfloxacin = 1 and placebo = 4. Nitrofurantoin ( Bailey 1971; Stamm 1980) and trimethoprim-sulfamethoxazole daily and postcoital (Stappleton 1990) studies did not reported any severe side effects.

#### Proportion of patients with other side effects

(Table 6 - *Side effects (SE)* (not needing to withdrawal of treatment)

The ten studies reported side effects. In a total number of 225 patients that received antibiotic 34 side effects were reported and in the placebo arm 15/195 patients had non-severe side effects. The RR of having one side effect was 1.78 (95% CI 1.06 to 3.00) favouring the placebo group. The side effects described were vaginal itching and nausea. Vaginal candidiasis was less frequent (see additional table " Description of side effects" Table 6 ). For non-severe side effects, absolute numbers were: cinoxacin 500 mg = 11, cinoxacin 250 mg = 15, trimethoprim-sulfamethoxazole postcoital = 4, nitrofurantoin = 2, norfloxacin 200 mg = 2, cephalexin = 0 and placebo = 15.

### *Withdrawals and dropouts*

Three studies have 20% or more of dropouts during the prophylaxis period. Martens 1995 had 25%, Scheckler 1982 30% and Nicolle 1989 20%. When we excluded this three studies, there were no differences in the main outcomes.
There were no differences between placebo and intervention groups in relation to withdrawals.

## Antibiotic versus antibiotic (comparison 02)

(Table 7 - *Antibiotic versus antibiotic. MRPY and CRPY)*
Eight trials compared antibiotics - either two different antibiotics or different dosing regimens (Brumfitt 1985; Brumfitt 1991; Brumfitt 1995; Guibert 1995; Melekos 1997; Nuñez 1990; Seppanen 1988; Stamm 1980)

### *Comparison between two different antibiotics*

The studies identified did not compare the same antibiotics. In four studies nitrofurantoin 100 mg/24 h was compared against: norfloxacin 200 mg/24 h, norfloxacin 400 mg/24 h, trimethoprim 100 mg/24 h and trimethoprim 40 mg and sulphamethoxazole 200 mg /24 h (Brumfitt 1985; Brumfitt 1991; Nuñez 1990; Stamm 1980). In another study nitrofurantoin 50 mg/24 h was compared with cefaclor 250 mg/24 h (Brumfitt 1991). The individual results of this studies did not showed a clear benefit of one antibiotic over another. The only trial that showed an effect ( Brumfitt 1985), compared nitrofurantoin 100 mg/24 h versus trimethoprim 100 mg/24 h and had a RR of having microbiological recurrences of 3.58 favouring nitrofurantoin. However the CIs were very wide (95% CI 1.33 to 9.66). The RR for clinical recurrences was 1.72 (95% CI 1.06 to 2.79)

One trial compared trimethoprim 100 mg/24 h with cinoxacin 500 mg/24 h (Seppanen 1988) and showed no significant differences between the two antibiotics.

We tried to pooled the data from the four studies that compared nitrofurantoin 100 mg/24 h against another antibiotic. There was significant heterogeneity between the trials and differences in the way clinical outcomes were assessed. Therefore we decided not to present the pooled data.

In relation to severe adverse events, the pooled data showed more severe adverse events with nitrofurantoin versus the rest

of the antibiotics. Looking at the data, the study that had the most differences compared trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h (Brumfitt 1985), the same study that showed higher efficacy for nitrofurantoin. Excluding this study there were no differences between nitrofurantoin and the rest of antibiotics RR 0.54 (95% CI 0.23 to 1.24) using the random effects model.

With other side effects there were no difference between nitrofurantoin and the rest, but there was heterogeneity among the trials. The most frequent adverse events in all trials were nausea, vaginal candidiasis and oral candidiasis. Nuñez 1990 included in the assessment of adverse events the period while patients were receiving antibiotic as treatment for UTI. This trial had the highest rate of adverse events and most women reported events during the treatment period or during prophylaxis.

***Comparison between same antibiotic but different schedule***

Guibert 1995 compared pefloxacin 400 mg/wk versus pefloxacin 400 mg/mo. In this individual trial weekly pefloxacin was more effective than monthly treatment. The RR of having one microbiological recurrence was 0.31(95% CI 0.19 to 0.52) favouring the weekly schedule. There was no significant difference in the risk in the adverse events rate. The RR for severe adverse events was 2.14 (95% CI 0.76 to 6.02) and 1.32 (95% CI 0.85 to 2.05) for other side effects. The post-intervention follow-up did not showed any differences between the groups in relation to the risk of having a microbiological recurrence.

In Melekos 1997, sexual active women with UTI associated with sexual intercourse received ciprofloxacin 125 mg postcoital versus ciprofloxacin 125 mg/24 h for 12 months and microbiological and clinical outcomes were assessed. The difference in the rate of urinary infections and the rate of side effects between postcoital or daily intake was not significantly difference(MRPY = 0.46 versus 0.42, P = 0.8) after the active prophylaxis period.

***Antibiotic versus other pharmacological intervention (comparison 03)***

(Table 8 - *Antibiotic versus other strategy. MRPY and CRPY)*
Brumfitt 1983 compared trimethoprim 100 mg/24 h versus povidone iodine and trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h. There were 20-25 patients in each arm. There were few differences between groups both in terms of clinical and microbiological recurrence.

Brumfitt 1981 tested nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h. The study was not blinded. The MRPY was 0.19 person-year for nitrofurantoin and 0.57 for the methenamine hippurate group. The severe adverse events were 12/43 patients in the nitrofurantoin arm and 2/56 patients in the hippurate group. In this trial there were crossovers.

## DISCUSSION

Antibiotic intake (cotrimoxazole, nitrofurantoin, cephalexin, or norfloxacin/cinoxacin) reduced the number of clinical and microbiological recurrences when compared to placebo in pre- and postmenopausal women with RUTI. The results of the trials were consistent both in the direction and magnitude of the effect. Only Schaeffer 1982 showed no benefit, however this trial had few events (two in the antibiotic group and four in the placebo arm) and this could explain the lack of significance. Once the antibiotics were suspended, UTIs recurred and equalled those of the placebo arm in the two studies that have look at this outcome. This data confirms clinical suspicions that the effect on UTI is only short acting.

The consequences of taking antibiotics are the adverse events. The rate of adverse events was higher in the antibiotic group than placebo. It is important to highlight here that all the trials have different ways in reporting adverse events. As a result we have analysed studies with a broad range of reported adverse events. For example, in some trials the reported averse event rate in the antibiotic arm was zero, something that is rarely reproduced in real life.

The adverse events were classified in most trials as severe or mild. Severe adverse events were those that forced the suspension of treatment. As a result In some trials adverse events (e.g. oral or vaginal candidiasis) were classified as mild and in others severe. If we put the intervention into the perspective of dally practice where an otherwise healthy women is starting on antibiotics to prevents UTI it seems that an episode of vaginal or oral candidiasis could been perceived as extremely bothersome.

Other factors to take into account are withdrawals and dropouts .Three studies reported more than 20%. This data suggests that outside of clinical trials these figures could be large. It is already difficult to enhance adherence with chronic medications. Patient compliance is an important factor and must to be consider in future studies. Women's preferences are very important in deciding if prophylaxis should be given, and under special circumstances (e.g. travel or student exam periods) the benefits outweigh the risks.

The overall quality of the clinical trials evaluated comparing antibiotic versus placebo was acceptable remembering that some were done in the seventies and others in the eighties, and this may simply reflect a lack of reporting rather than low quality. All but one had 3 or more points in the JADAD scale, however they did not explain randomisation or allocation procedures. The trial with lowest methodological quality was the study that showed no difference. The study was not blinded and had a low rate of recurrence in both groups (Schaeffer 1982).

The different decades of the trials affected the definition of RUTI. The earliest studies considered two UTIs in the past 12 months, while the later studies accepted as a definition for RUTI three or more UTIs. A criticism of the clinical trials reviewed here is the variability among them in relation to outcomes and adverse events assessment and the lack, in most part, of follow-up after finishing the antibiotic prophylaxis intake period.

If deciding to start a patient on antibiotics is a difficult task, deciding which one should be the first selection is even more complicated. We had planned to answer this question analysing the second group of studies (antibiotic versus antibiotic) but the identified trials did not allow us to determine this. Most trials could not be compared with respect to the efficacy outcomes and especially the adverse events data. It would be inappropriate to compare adverse event rates, since most trials assessed this outcomes differently. We were able to perform a pooled data analysis of the five studies comparing nitrofurantoin with other antibiotics. There were no significant differences in effectiveness between nitrofurantoin and the other groups. Nitrofurantoin appears to be more effective than

trimethoprim, but had more side effects in a non-blind study. With respect to adverse events it is difficult to assess wether nitrofurantoin had more episodes than the rest. It seems that had the same risk of adverse events but more withdrawals, the decision of which antibiotic to use should rely on local resistance patterns, cost and adverse events. Consumers must to be informed in relation of the events that they might experience while taking the medication.

Which schedule use is even less clear than the antibiotic selection. Daily intake was the most tested schedule. Two trials tested postcoital schedule in sexually active women. One trial included 27 patients and compared postcoital versus placebo and the other included 135 women and compared postcoital versus daily intake. Postcoital was more effective than placebo in reducing recurrences and daily was as effective as postcoital. These two studies suggest that in sexual active women with UTI related to sexual intercourse, the postcoital approach could be a better option than daily intake.

Another trial compared pefloxacin 400 mg weekly versus monthly. The microbiological recurrences were less in the weekly approach than the monthly.

The other decision that physician needs to make is how long the prophylaxis should be given. Unfortunately the studies identified did not look at prophylaxis longer than 12 months. The threshold for starting prophylactic treatment is also controversial. Some experts advocate as few as two UTIs/year and others as many as six UTI episodes/year (PRODIGY 2003). Again women's preferences should be taking into consideration while deciding the best approach.

Another difficult to answer question is which patients would benefit most from these strategies. We we unable to perform any subgroup analyses. The only data that we have is that most of the studies involved healthy women pre- and postmenopausal. The subgroup analysis done by Stappleton 1990 showed that women with higher frequencies of sexual intercourse/week had higher infections rates, something that is consistent with previous findings.

The definition of recurrences also deserves discussion. Most of the trials used microbiological recurrences as the main outcome. The arguments against this outcome would be that microbiological recurrences are not relevant at all and that the only important outcomes are clinical ones. However, the cohort study done by Hooton 1996 showed that asymptomatic bacteriuria was a strong predictor of UTI. Considering clinical recurrence, the definition was different among studies. Some trials used symptomatic bacteriuria, which seems the most relevant outcome, and others just symptoms. For example, in the three antibiotic versus antibiotic studies by Brumfitt studies (Brumfitt 1985; Brumfitt 1991; Brumfitt 1995) clinical recurrence was defined as the presence of clinical symptoms. It was impressive that clinical recurrences were five times higher than microbiological ones in these three studies suggesting that most patients did not have UTI.

The ecological impact of preventive long-term antibiotics on bacterial resistance needs to be considered in future trials. It is possible that bacterial resistance patterns changes from time to time and between communities. The actual local bacterial resistance should also be considered (Baerheim 2001) when deciding the best strategy.

For future research it would be important to compare antibiotic prophylaxis against other interventions such a self-diagnosis / self-treatment, the ingestion of cranberry juice or oestrogens in postmenopausal women as there are no trials that compared these alternatives. Finally, is crucial that researchers improve the quality of clinical trials in RUTI. The first step should be for a uniform definition of RUTI, the outcomes, assessment of adverse events and the follow-up period.

## AUTHORS' CONCLUSIONS

### Implications for practice

- Continuous antibiotic prophylaxis using, cotrimoxazole, nitrofurantoin, cephalexin, or a quinolone (norfloxacin, cinoxacin) reduces rates of RUTI in non-pregnant women with uncomplicated RUTIs when compared with placebo. The effect lasts during the active antibiotic intake period.
- The duration of the intervention is not clear. The maximal duration tested was one year.
- Side effects are frequent. Described side effects are: vaginal and oral candidiasis, skin rash, nausea. Dropouts and withdrawal were frequent. Three studies (versus placebo) reported rates more than 20%. Nitrofurantoin displayed the highest number of withdrawals, followed by cephalexin and weekly pefloxacin.
- The decision of the best antibiotic choice must relay on community patterns of resistance, adverse events and local costs.
- In women with UTI associated with sexual intercourse, post coital prophylaxis seems to be as effective as daily intake.
- No conclusions can be drawn about the optimal duration of prophylaxis, schedule or doses.
- Women preferences should be taking into account to balance adverse events and the discomfort caused by UTIs.

### Implications for research

- The first goal should be to achieve a standardized the way in which RCTs in this area are performed.
- To allow comparisons, researchers need to established the same definition for RUTI, assess outcomes in similar fashion and to retrieve adverse events in the same way. By doing so, different trials could be easily compared and conclusion more easily reached.
- Research should focus on comparing other strategies (e.g. self-treatment, the ingestion of cranberry juice against antibiotic prophylaxis or vaginal estriol for postmenopausal women).
- Further investigations are needed in relation to predisposing risk factors in both sexually active women and postmenopausal women and to explore other strategies to prevent UTI.
- Regarding long term prophylaxis with antibiotics, there is no clear evidence on the optimal duration of prophylaxis, how often should it be repeated, post-prophylaxis benefits nor the optimal doses of the different antibiotics. The last clinical trial was done in 1997, a surprising fact given the many issues that need to be assessed.
- For future trials it would be desirable to evaluate quality of life, women's preferences and long-term outcomes with each alternative. It would also be helpful cost effectiveness studies of the different alternatives.

## ACKNOWLEDGEMENTS

The authors wish to thank the Iberoamerican Cochrane Centre and the Cochrane Renal Group for their technical support and patience.

To Gerard Urrutia , Marta Roqué and Santiago Pérez.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Bailey 1971

| | |
|---|---|
| Methods | Double blind.<br>Duration of intervention: unclear. If bacteriuria recurred, the patient ended the study. (Outcomes at 26 weeks).<br>Follow-up: not assessed<br>Withdrawals and dropouts: 0.<br>Bacteriological evaluation of urine: every 4 weeks for the first 3 months and thereafter every 6-8 weeks. |
| Participants | 50 women (25 in each group). Assessed efficacy in all.<br>Setting: Urinary infection clinic (Hospital).<br>Inclusion: history of recurrent urinary-tract symptoms with bacteriuria. Premenopausal women.<br>Inclusion after infection and treatment. |
| Interventions | Nitrofurantoin 50 mg each night, versus placebo.<br>Mean time on treatment: 33 weeks (range 5-53) in nitrofurantoin group, and 15.1 weeks (range 1-39) in placebo group. |
| Outcomes | 1. No. of bacteriuria episodes (2, 12 and 26 weeks).<br>2. Episode symptomatic or asymptomatic at 26 weeks |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

#### Brumfitt 1981

| | |
|---|---|
| Methods | Not blinding.<br>Duration intervention: 12 months.<br>Post-intervention follow-up: performed in 28 patients for an average of 143 days.<br>Withdrawals and drop-outs: 11.<br>Bacteriological evaluation of urine: 8 in 12 months (monthly intervals for 6 months, then at 9 and 12 months after entry).<br>Eleven patients originally allocated to nitrofurantoin were changed to methenamine hippurate, and three were changed of methenamine hippurate to nitrofurantoin. |
| Participants | 110 women. Assessed efficacy in 99: 43 in group nitrofurantoin (mean age 31.3 years, SD 13.2), and 56 in group methenamine hippurate (mean age 35.9 years, SD 16.7).<br>Setting: Hospital (UTI Clinic).<br>Inclusion: In the preceding year at least 3 episodes of symptoms of UTI, at least one of these documented microbiologically (not all). |
| Interventions | Nitrofurantoin 50 mg/12 h oral, versus methenamine hippurate 1 g/12 h oral.<br>Mean treatment days: 225.1 in Nitrofurantoin group, 286.3 in methenamine hippurate group.<br>A marked difference was observed on time during which the patients received their respective prophylactic treatment: follow-up period were < 100 days in 44% nitrofurantoin group and 16% in |

**Brumfitt 1981** *(Continued)*

| | |
|---|---|
| | methenamine hippurate group. Also, this were > 400 days in 11.5% nitrofurantoin group and 16% in methenamine hippurate group. |
| Outcomes | 1. Microbiological recurrences patient-days;<br>2. % patients remaining abacteriuric;<br>3. Clinical recurrences patient/days;<br>4. % patients remaining asymptomatic;<br>5. Mean days between bacteriuric and symptomatic episodes;<br>6. Incidence of symptomatic attacks post-intervention.<br>7. Organisms isolated in bacteriuric episodes and sensitivity patterns. |
| Notes | Radiological abnormalities: 29% versus 12%. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Brumfitt 1983**

| | |
|---|---|
| Methods | Not blinding.<br>Duration intervention: 12 months.<br>Post-intervention follow-up: patients were asked to return 3 and 6 months after completion of prophylaxis (but the results were not presented).<br>Withdrawals and drop-outs: 3 not assessed. 15 stopped treatment prematurely.<br>Bacteriological evaluation of urine: 8 in 12 months (monthly intervals for 6 months, then at 9 and 12 months after entry). |
| Participants | 67 women. Assessed efficacy in 64: 20 in trimethoprim group (mean age 39.9 years, SD 20.5), 25 in methenamine hippurate group (mean age 38.2 years, SD 18), and 19 in povidone iodine group (mean age 31.7 years, SD 14.3).<br>Setting: UTI Clinic (Hospital).<br>Inclusion: In the preceding year at least 4 episodes of symptoms of UTI, at least one of these documented microbiologically (not all). |
| Interventions | 1) Trimethoprim 100 mg at night, oral.<br>2) Methenamine hippurate 1 g/12 h oral.<br>3) Povidone iodine solution: frequent application in perineal region (at least twice very day).<br>Mean days treatment: 237 (SD 154) in trimethoprim group, 254 (SD 140) in methenamine hippurate group, and 193 (SD 141) in povidone iodine group. |
| Outcomes | 1. Microbiological recurrences patient-days;<br>2. % patients remaining abacteriuric;<br>3. Clinical recurrences patient-days;<br>4. % patients remaining asymptomatic;<br>5. Mean days between bacteriuric and symptomatic episodes;<br>6. Reduction of symptomatic attacks compared to the interval before prophylaxis started;<br>7. Organisms isolated in bacteriuric episodes and sensitivity pattern;<br>8. Periurethral flora. |
| Notes | Radiological abnormalities: 15%, 12%, 6%. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Brumfitt 1983** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Brumfitt 1985**

| | |
|---|---|
| Methods | Not blinding.<br>Allocated by means of a randomisation chart.<br>Duration intervention: 12 months.<br>No post-intervention follow-up.<br>Withdrawals and drop-outs: 28.<br>Bacteriological evaluation of urine: 8 in 12 months (monthly intervals for 6 months, then at 9 an 12 months after entry). |
| Participants | 100 women. assessed efficacy in 72: 38 in trimethoprim group (mean age 37.6 years, SD 18.2) and 34 in nitrofurantoin group (mean age 40.9 years, SD 18.5).<br>Setting: Hospital (UTI Clinic).<br>Inclusion:. In the preceding year at least 3 episodes of symptoms of UTI, at least one of these documented microbiologically. |
| Interventions | Trimethoprim 100 mg at night, oral, versus nitrofurantoin 100 mg at night, oral.<br>Mean days treatment: 267.1 in trimethoprim group and 322.5 in nitrofurantoin group. |
| Outcomes | 1. Microbiological recurrences patient-days;<br>2. % patients remaining abacteriuric;<br>3. Clinical recurrences patient-days;<br>4. %patients remaining asymptomatic;<br>5. Mean days between bacteriuric and symptomatic episodes;<br>6. % patients remaining asymptomatic and abacteriuric;<br>7. Organisms isolated in bacteriuric episodes and sensitivity patterns;<br>8. Periurethral flora;<br>9. Faecal flora. |
| Notes | 36,4% radiological abnormalities, with differences between groups (46% versus 25%). There were no differences in efficacy between sub-groups with and without radiological abnormalities. |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Brumfitt 1991**

| | |
|---|---|
| Methods | Not blinding.<br>Duration intervention: 12 months.<br>Post-intervention follow-up: patients were asked to return 3 and 6 months after completion of prophylaxis (but only appears improvement versus period pre-prophylaxis).<br>Withdrawals and drop-outs: 23.<br>Bacteriological evaluation of urine: 8 in 12 months (monthly intervals for 6 months, then at 9 and 12 months after entry). |
| Participants | 111 women. Assessed efficacy in 88: 45 in Norfloxacin group (mean age 38.9 years, range 17-83), and 43 in Nitrofurantoin group (mean age 37.2 years, range 20-76).<br>Setting: UTI Clinic (Hospital). |

**Brumfitt 1991** *(Continued)*

| | |
|---|---|
| | Inclusion: In the preceding year at least 4 episodes of symptoms of UTI, at least one of these documented microbiologically. |
| Interventions | Norfloxacin 200 mg at night, oral, versus nitrofurantoin 100 mg at night, oral.<br>Mean days treatment: 323.8 in norfloxacin group and 304.5 in nitrofurantoin group. |
| Outcomes | 1. Microbiological recurrences patient-days;<br>2. % patients remaining free from symptomatic and bacteriuric attacks;<br>3. Clinical recurrences patient-days;<br>4. Mean days between bacteriuric and symptomatic episodes;<br>5. Improved while taking prophylaxis;<br>6. Improved in 6 months after end of prophylaxis;<br>7. Organisms isolated in bacteriuric episodes and sensitivity pattern;<br>8. Faecal flora. |
| Notes | Radiological abnormalities: 22% versus 20%.<br>On a cumulative basis, responded as well as those with no abnormality. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Brumfitt 1995**

| | |
|---|---|
| Methods | Not blinding.<br>Duration intervention: 12 months<br>Post-intervention follow-up: patients were asked to return 3 and 6 months after they had stopped taking the antibiotic (but results not presented).<br>Withdrawals and drop-outs: 37 (in 23 of these assessed side effects and symptomatic improvement compared with before intervention).<br>Bacteriological evaluation of urine: 8 in 12 months (monthly intervals for 6 months, then at 9 and 12 months after entry). |
| Participants | 135 women over 15 years old. Assessed efficacy in 97: 49 in cefaclor group (mean age 45 years, range 20-90), and 48 in nitrofurantoin group (mean age 40 years, range 18-89).<br>Setting:UTI Clinic (Hospital).<br>Inclusion:. In the preceding year at least 4 episodes of symptoms of UTI, at least one of these documented microbiologically. |
| Interventions | Cefaclor 250 mg at bedtime oral versus nitrofurantoin 50 mg at bedtime oral.<br>Mean days treatment: 324.9 in cefaclor group, and 316.8 in nitrofurantoin group. |
| Outcomes | 1. Microbiological recurrences patient-days;<br>2. % patients remaining abacteriuric;<br>3. Clinical recurrences patient-days;<br>4. % patients symptomatically improved compared with before start the intervention;<br>5. Mean days between symptomatic episodes and increase in this interval compared with prior to starting;<br>6. % patients who after prophylaxis had maintained the improvement that had been found during the period of prophylaxis;<br>7. Organisms isolated in bacteriuric episodes and sensitivity patterns;<br>8. Faecal flora. |
| Notes | Radiological abnormalities: 21% versus 34%. |

**Brumfitt 1995** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Gower 1975**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 12 months or until UTI confirmed microbiologically by suprapubic aspiration.<br>No Post-intervention follow-up (see notes).<br>Withdrawals and drop-outs: 7.<br>Bacteriological evaluation of urine: initially monthly, increasing to 3 monthly for a total of 1 year. |
| Participants | 50 women (mean age 31 years, range 20-60 years). Assessed efficacy in 43 (20 in cephalexin group and 23 in placebo group).<br>Setting: Outpatient clinic renal infection clinic (Hospital).<br>Inclusion: History of recurrent urinary infections for 6 months to 10 years.<br>Inclusion after acute urinary tract symptoms confirmed microbiologically and treated. |
| Interventions | Cephalexin 125 mg each night, versus placebo. |
| Outcomes | 1. No. developing bacteriuria (cumulative, 4, 12 , 26 weeks and 1 year) symptomatic or asymptomatic.<br>Completed 1 year follow-up |
| Notes | At the end of 12 months the 20 patients who had remained free of infection while receiving cephalexin were randomly assigned either to continue taking cephalexin or to take the placebo (outcomes not presented). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Guibert 1995**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: for 48 weeks.<br>Post-intervention follow-up: for 3 months (not all).<br>Analysis: intention-to-treat.<br>Withdrawals and drop-outs: 25 (12 in weekly group and 13 in monthly group).<br>Bacteriological evaluation of urine: every 3 months. |
| Participants | 361 women of 18 to 51 years of age: 185 in perfloxacin weekly group (mean age: 37.7 years, SD 9.7), and 176 in perfloxacin monthly group (mean age 36.9 years, SD 9.6).<br>Setting: Family practice.<br>Inclusion: In the preceding year at least 4 episodes of acute cystitis.<br>Inclusion after acute cystitis treated with one dosis of perfloxacin 800 mg oral. |
| Interventions | Perfloxacin 400 mg oral once-a-week, versus perfloxacin 400 mg oral once-a-month and placebo 3 weeks of each 4. ( NO SE ENTIENDE)<br>Mean days treatment: 287.6 (SD 121.6) in weekly group and 268.3 (SD 121.3) in monthly group. |

**Guibert 1995** *(Continued)*

| | |
|---|---|
| Outcomes | 1. Microbiological recurrences patient-years;<br>2. % patients with at least one microbiological recurrence;<br>3. Probability of not having a bacteriologically proven recurrence when taking prophylaxis (Kaplan-Meier method);<br>4. % patients with at least one microbiological recurrence in subsequently 3 months;<br>5. Organisms isolated in bacteriuric episodes. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Martens 1995**

| | |
|---|---|
| Methods | Double blind.<br>Random distribution table.<br>Duration of intervention: 6 months or until UTI.<br>Post-intervention follow-up: urine culture was performed after 2 week and then 1 month after discontinuation of prophylaxis.<br>Withdrawals and dropouts: 15.<br>Bacteriological evaluation: 1 to 2 weeks, 3 to 4 weeks and monthly for up to 6 month. |
| Participants | 60 women 18 years older (88% < 25 years, range 18-35): 32 cinoxacin and 28 placebo.<br>Assessed efficacy in 45 ( 23 cinoxacin group/ 22 placebo group)<br>Setting: outpatient status or discharge for the hospital (Medical Centre).<br>Inclusion: In the preceding year at least 3 episodes including the most recent infection. |
| Interventions | Cinoxacin 250 mg/daily versus placebo 1/daily<br>Median days treatment: 196 cinoxacin group, 50 placebo |
| Outcomes | 1. Clinical response and bacteriologic evaluation:<br>2. % patients with satisfactory response ( no bacteriologic or symptomatic recurrences); median days without bacteriuric or symptomatic episodes. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Martorana 1984**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 6 months or until UTI (bacteriological).<br>No post-intervention follow-up.<br>Withdrawals and drop-outs: 0.<br>Bacteriological evaluation of urine: At 14 days and then monthly. |

**Martorana 1984** *(Continued)*

| | |
|---|---|
| Participants | 40 women (20-65 years old): : 21 in cinoxacin group with mean age of 43 years and 19 in placebo group with mean age of 42.5 years.<br>Setting: Outpatient Urologic clinic (Hospital).<br>Inclusion: at least 3 episodes of UTI in the last year. |
| Interventions | Cinoxacin 500 mg at night oral versus placebo.<br>Mean days treatment: 141 in cinoxacin group and 90 in placebo group. |
| Outcomes | 1. % patients with at least one microbiological recurrence,<br>2. monthly and cumulated %;<br>3. Duration (months) of intervention for every patient;<br>4. Organisms issolated in bacteriuric episodes. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Melekos 1997**

| | |
|---|---|
| Methods | Evaluator blind.<br>Allocation according to date of birth.<br>Duration Intervention: 12 months.<br>Post-intervention follow-up: another 12 months.<br>Withdrawals and drop-outs: 17.<br>Bacteriological evaluation of urine: every 3 months during and after prophylaxis.<br>Cointerventions: All patients were advised to increase oral fluid intake and frequency of micturition, as well as to empty the bladder as soon as possible after intercourse. |
| Participants | 152 sexually active, premenopausal women older than 17 years. Assessed efficacy in 135: 70 in post-coital prophylaxis group (median age 28 years, range 18-45), and 65 in daily prophylaxis ( median age 31 years, range 18-46).<br>Setting: Hospital-Outpatient urologic clinic<br>Inclusion: History of 3 or more documented lower urinary tract infections in the preceding 12 months |
| Interventions | Ciprofloxacin 125 mg, oral, immediately after sexual intercourse, versus ciprofloxacin 125 mg oral daily at bedtime.<br>Mean days treatment: group under postcoital prophylaxis ingested a mean of 120 tablets and had inter-course a mean of 2.44 times/wk. Group under daily prophylaxis ingested a mean of 353 tablets and had intercourse a mean of 2.52 times/wk. |
| Outcomes | 1. Microbiological recurrences patient-year, during and after intervention;<br>2. % patients with at least one microbiological recurrence during and after intervention;<br>3. % patients with at least one clinical recurrence;<br>4. Incidence of UTI per patient during, compared with before intervention;<br>5. Rate of gram-negative pathogens and the emergence of ciprofloxacin resistant organisms in urine and introital cultures during and after intervention. |
| Notes | Underlying abnormalities were excluded in all, but 10 women with mild abnormalities were included. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Melekos 1997** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment? | High risk | C - Inadequate |

**Nicolle 1989**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 12 months or until UTI documented.<br>Post-intervention followup: subjects who have not yet become reinfected have been followed for 12 months or until UTI.<br>Withdrawals and drop-outs: 6.<br>Bacteriological evaluation of urine: monthly intervals. |
| Participants | 30 women of 12 to 75 years: 15 in norfloxacin group ( mean age 53 years, SD 15), and 15 in placebo group ( mean age: 45 years, SD 19).<br>Assessed efficacy in 24: 11 in norfloxacin group and 13 in placebo group.<br>Setting: Infection diseases clinic.<br>Inclusion: at least 3 episodes of acute symptomatic UTI inthe preceding year. |
| Interventions | Norfloxacin 200 mg at bedtime oral versus placebo at bedtime oral.<br>Mean days treatment: 278 in NF group and 155 in placebo group. |
| Outcomes | 1. Microbiological recurrences patient-year;<br>2. % patients with at least one microbiological recurrence;<br>3. Bacteriuria symptomatic or asymptomatic.<br>4. % patients with at least one microbiological recurrence after intervention (outcome only in norfloxacin group);<br>5. Life table analysis of infection-free period during intervention using Kaplan-Meier method;<br>6. Organisms issolated in bacteriuric episodes;<br>7. Periurethral and rectal flora. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Nuñez 1990**

| | |
|---|---|
| Methods | Single blind.<br>Random assignment for full-dose treatment (see interventions).<br>Duration intervention: 24 weeks or until UTI.<br>No post-intervention follow-up.<br>Intention- to-treat analysis for maintained clinical and bacteriological cure through the end of follow-up.<br>Withdrawals and dropouts: 5 (3 versus 2).<br>Bacteriological evaluation of urine: monthly. |
| Participants | 57 women. Assessed efficacy in 52: 26 in norfloxacin group (mean age 45.6 years, SD 11.2) and 26 in nitrofurantoin group (mean age 44.7 years, SD 12.1).<br>Setting: urological service of the Hospital (outpatients).<br>Inclusion: aged 18-65 years with symptomatic episode of UTI and who had a history of at least two UTIs during the previous 12 months (verified by medical records), at least one of them within the most re- |

**Nuñez 1990** *(Continued)*

| | |
|---|---|
| | cent six months. Definitive inclusion was made when a pathogen susceptible to nitrofurantoin and norfloxacin was isolated from the culture. |
| Interventions | Included patients (with infection) were treated orally after random assignment to norfloxacin 400 mg twice a day for ten days (full-dose treatment) followed by 400 mg at bedtime for 24 weeks (follow-up prophylaxis), versus nitrofurantoin 100 mg four times a day for ten days (full-dose treatment) followed by 100 mg bedtime for 24 weeks (follow-up prophylaxis).<br>Clinical failure at day 4 or 11 or bacteriologic failure at day 11 (after full-dose treatment) required withdrawal for follow-up prophylaxis. |
| Outcomes | 1. Reinfection;<br>2. Maintained clinical and bacteriologic cure through the end of follow-up.<br>3. Urine culture included colony counts and susceptibility testing.<br>4. Blood samples for hematologic and biochemical assessments. |
| Notes | Description of adverse effects include period of full-dose treatment. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Rugendorff 1987**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 12 months or until UTI, but outcomes for intermediate assessment after 24 weeks.<br>No post-intervention follow-up.<br>Withdrawals and dropouts: 4 (2 in each group).<br>Bacteriological evaluation of urine: monthly. |
| Participants | 39 women. Assessed efficacy in 35: 18 in norfloxacin group (range age 21-74 years) and 17 in placebo group (rage age 17-77 years).<br>Setting: Hospital-Outpatient urologic clinic<br>Inclusion: 3 or more episodes of uncomplicated UTI during the last year caused by facultative bacteria. |
| Interventions | Norfloxacin 200 mg once a day versus Placebo.<br>Mean weeks treatment: 21.3 in norfloxacin group and 11.9 in Placebo group. |
| Outcomes | 1. Reinfection (clinical and bacteriological);<br>2. Asymptomatic with positive urine culture (unclear);<br>3. Norfloxacin susceptibility. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

### Schaeffer 1982

| | |
|---|---|
| Methods | Not blinding.<br>Duration intervention: 6 months or until UTI (bacteriological).<br>Post-intervention follow-up: 6 months.<br>Withdrawals and drop-outs: 2 stopped treatment prematurely.<br>Bacteriological evaluation of urine: At 2 and 4 weeks, and then monthly during therapy and after therapy. |
| Participants | 30 women : 17 in cinoxacin group (mean age 35.6 years, range 22-63) and 13 in placebo group (mean age 32.5 years, range 20-69).<br>Assessed efficacy in 28.<br>Setting: Urology clinic.<br>Inclusion: In last year at least 3 documented UTI. |
| Interventions | Cinoxacin 500 mg at night oral versus placebo.<br>Mean days treatment: 150.3 in cinoxacin group and 140.4 in placebo group. |
| Outcomes | 1. Microbiological recurrences patient-year during intervention;<br>2. % patients with at least one microbiological recurrence, during and after intervention;<br>3. Mean elapse time to infection after intervention;<br>4. Organisms issolated in bacteriuric episodes and sensitivity patterns;<br>5. Vaginal vestibule flora,<br>6. Fecal flora and sensitivity patterns. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

### Scheckler 1982

| | |
|---|---|
| Methods | Double blind.<br>Randomisation: random code.<br>Duration intervention: 6 months or until UTI (bacteriological).<br>Post-intervention follow-up: at two weeks and one month after stopping therapy, further cultures were obtained (but no results).<br>Withdrawals and drop-outs: 18.<br>Bacteriological evaluation of urine: between the first and second week, between the third and fourth week, and each month thereafter. |
| Participants | 59 women (18-65 years old, 83% < 35 years).<br>Assessed efficacy in 41: 20 in cinoxacin group and 21 in placebo group.<br>Setting: three family practice outpatient clinics and a general urology clinic.<br>Inclusion: 3 or more UTIs in the preceding year. Most them bacteriological. |
| Interventions | Cinoxacin 500 mg once daily oral versus placebo.<br>Range days treatment: 159-220 in cinoxacin group and 54-213 in placebo group. |
| Outcomes | 1. % patients with at least one microbiological recurrence;<br>2. % patients with at least one clinical recurrence;<br>3. individual time elapse to infection after intervention;<br>4. Organisms issolated in bacteriuric episodes |
| Notes | |

**Scheckler 1982** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Seppanen 1988**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 24 weeks or until UTI.<br>Post-intervention follow-up: Additional mid-stream urine analysis was performed 4-6 weeks after discontinuation of treatment.<br>Withdrawals and drop-outs: 0.<br>Bacteriological evaluation of urine: 4-6 times (3-5 times in first treatment period of 12 weeks and 1 at 24 weeks). |
| Participants | 26 women: 12 in trimethoprim group (mean age 27, range 17-63), and 14 in cinoxacin group (mean age 33.4 years, range 18-58).<br>Setting: Urological outpatient department.<br>Inclusion: At least 3 recurrences in last year. |
| Interventions | Trimethoprim 100 mg at bedtime oral versus cinoxacin 500 mg at bedtime oral.<br>Mean days treatment: 168 in both groups |
| Outcomes | 1. Number of microbiological recurrences patient/day during prophylaxis; .<br>2. % patients with at least one microbiological recurrence;<br>3. Number of microbiological recurrences during a follow-up period of 4-6 weeks after the discontinuation of prophylaxis;<br>4. Comparison with recurrences in last year before start the prophylaxis. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Stamm 1980**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 6 months or until UTI.<br>Post-intervention follow-up: 6 months.<br>Withdrawals and drop-outs: 6 (2 in each group).<br>Bacteriological evaluation of urine: monthly. |
| Participants | 45 women (15 in each group). Assessed efficacy in 39 (13 in each group).<br>1)Trimethoprim-sulphamethoxazole (median age 54 years, range 19-73).<br>2) Nitrofurantoin (median age 56 years, range 25-62)<br>3) Placebo (median age 52 years, range 18-60).<br>Setting: Hospital-outpatient infection clinic.<br>Inclusion: History of recurrent bacteriuria and at least 2 culture-documented urinary infections in the preceding 12 months.<br>Patients were seen initially at the time of active UTI. |

**Stamm 1980** *(Continued)*

| | |
|---|---|
| | Mean infections in previous year: 3 (range 2-5), 2 (range 2-5) and 3 (range 2-5) respectively. |
| Interventions | (See notes)<br>1) Trimethoprim 40 mg-sulphamethoxazole 200 mg at bedtime oral,<br>2) Nitrofurantoin 100 mg at bedtime oral, or<br>3) Placebo at bedtime. |
| Outcomes | 1. No. Patients infected during prophylaxis and infections/ patient-year.<br>2. The same for post prophylactic observation. Episodes symptomatics.<br>3. Cumulative % infected during and after prophylaxis.<br>4. Cultures of the rectum, vagina and urethra. |
| Notes | Patients allergic to sulphonamide or to nitrofurantoin were assigned non randomly to receive trimethoprim (Outcomes not presented).<br>9 patients (20%) with minor abnormalities on intravenous pyelogram (3 in each group). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Stappleton 1990**

| | |
|---|---|
| Methods | Double blind.<br>Duration intervention: 6 months or until UTI.<br>Post-intervention follow-up: No.<br>Withdrawals and drop-outs: 2, both in trimethoprim-sulphasoxazole group because of pregnancy<br>Bacteriological evaluation of urine: 2 weeks after study entry and then at monthly intervals. |
| Participants | 27 women. Assessed efficacy in 25: 14 in trimethoprim-sulphamethoxazole group (median age 23 years), and 11 in placebo group (median age 23 years).<br>Setting: University.<br>Inclusion: female university students with a history of at least two culture-documented UTIs in the preceding 12 months (see notes). Their infections could be historically related to intercourse. Estimated intercourse frequency of less than 12 episodes/month.<br>Inclusion 2 to 6 weeks later of their most recent symptomatic UTI. |
| Interventions | Postcoital trimethoprim 40 mg-sulphamethoxazole 200 mg tablets within 2 hours of intercourse, versus postcoital placebo.<br>In both groups: daily placebo in the morning.<br>Intercourse frequency was comparable in both groups: 2.6 episodes per week in trimethoprim-sulphamethoxazole group, versus 2.7 in the placebo group.<br>Compliance rates for postcoital tablets were 92% for trimethoprim-sulphamethoxazole group and 86% for placebo group. |
| Outcomes | 1. No. patients infected during prophylaxis and infections per patient year using microbiological criteria;<br>2. Episodes symptomatics.<br>3. Organisms isolated in bacteriuric episodes and sensitivity patterns.<br>4. Cultures of the rectum, urethra and vagina.<br>5. Cumulative proportion of women remaining free of UTI (Kaplan-Meier and the Mantel-Cox tests).<br>6. Infection rates for each subgroup stratified according to intercourse frequency;<br>7. Linear regression analysis was used to assess the relation-ship between intercourse frequency and infection rate for patients taking the placebo. |

**Stappleton 1990** *(Continued)*

| | |
|---|---|
| Notes | Median No. of culture-documented UTIs in past year: 3 (range 2-30) in trimethoprim-sulphamethoxazole group and 4 (range 2-5) in placebo group.<br>% Diaphragm users: 69 versus 91. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

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

| Study | Reason for exclusion |
|---|---|
| Battilana 1988 | Before-after study |
| Biering 1994 | Patients with spinal cord lesion. Crossover |
| Brumfitt 1987 | Before-after study |
| Donabedian 1995 | Treatment non-prophylaxis |
| Ejrnaes 2006 | Treatment non-prophylaxis |
| Fairley 1974 | Before-after study. Included men and women. |
| Ferry 2004 | Treatment non-prophylaxis |
| Fujii 1981 | Include children. Two before-after comparisons, and two comparisons of two groups. The first one with unclear randomisation. Both comparisons include children |
| Harding 1974 | Not RCT, Included children. |
| Harding 1979 | Before-after study. |
| Hardy 1980 | Include men |
| Hoivik 1984 | Non antibiotic intervention (methenamine hippurate) |
| Jodal 1989 | Before-after study. Patients: girls. |
| Kalowski 1975 | Include men. Include impaired renal function. |
| Kasanen 1974 | No randomised trial. Inclusion: chronic pyelonephritis or recurrent UTI. Women and men. |
| Kasanen 1982 | Include chronic pyelonephritis, renal function impairment. Women and men |
| Kasanen 1983 | Not RCT |
| Landes 1970 | Not RCT |
| Landes 1980 | Include complicated UTI (impaired renal function). Women and men |

| Study | Reason for exclusion |
|---|---|
| Light 1981 | Before-after study with prophylaxis. |
| MacDonald 1983 | Duration intervention: 3 months. Most of participants had radiological abnormalities. Men and women |
| Martens 1995b | Not randomised trial. No controlled trial. Compares intervention on premenopausal and post-menopausal women |
| Masu 1984 | Before-after study, followed by comparison of two groups non randomised (intervention versus nothing) |
| Mavromanolakis 1997 | Duration intervention: one month |
| Meyhoff 1981 | Crossover |
| Pfau 1983 | Before-after study. Several non randomised groups. |
| Pfau 1988 | Before-after study. |
| Pfau 1989 | Before-after study. |
| Pfau 1994 | Before-after study. Randomised groups are pooled for analysis, comparing with pre-intervention period. |
| Privette 1988 | Before-after study. |
| Raz 1991 | Includes calculus and bladder prolapse. High proportion of diabetic women, groups are not comparable. |
| Ronald 1975 | No randomised trial |
| Sakurai 1994a | No controlled trial. Patients with complicated UTI. Intervention less than 6 months. |
| Stamey 1977 | No randomised trial |
| Svensson 1982 | Before-after study. |
| Toba 1991 | Crossover |
| Vahlensieck 1992 | Men and women. Urologic diseases. |
| Westenfelder 1987 | Before-after study. Several non randomised groups. Include corrective surgery and men. |
| Wong 1985 | Crossover |

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

### Beerepoot 2006

| | |
|---|---|
| Trial name or title | A study of non-antibiotic versus antibiotic prophylaxis for recurrent urinary-tract infections in women (the NAPRUTI study) |
| Methods | |

**Beerepoot 2006** *(Continued)*

| | |
|---|---|
| Participants | two interlinked, randomised, clinical non-inferiority trials. In one trial, 280 premenopausal women with recurrent UTI |
| Interventions | Cranberry capsules (twice daily 500 mg) versus standardised antibiotic therapy (once daily 480 mg trimethoprim-sulfamethoxazole). In the second trial, 280 postmenopausal women will receive either oral lactobacilli (twice daily a capsule with > $10^9$ colony-forming units of *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14*) or standardised antibiotic therapy. |
| Outcomes | Recurrent UTI |
| Starting date | September 2005 |
| Contact information | |
| Notes | |

**McMurdo 2006**

| | |
|---|---|
| Trial name or title | Cranberry product versus low dose trimethoprim in the prevention of recurrent urinary infections in older women: a double blind randomised trial of effectiveness and acceptability |
| Methods | |
| Participants | Community dwelling women aged 45 years or over with at least two antibiotic-treated urinary tract infections or episodes of cystitis in the previous 12 months |
| Interventions | Trimethoprim 100 mg daily versus 500 mg cranberry product daily |
| Outcomes | First recurrence of symptomatic urinary tract infection. Acceptability and adherence |
| Starting date | 01/09/2006 |
| Contact information | Prof Marion McMurdo<br>Ageing and Health<br>Division of Medicine and Therapeutics<br>Ninewells Hospital and Medical School<br>Dundee<br>United Kingdom<br>DD1 9SY |
| Notes | |

## DATA AND ANALYSES

**Comparison 1. Antibiotic versus placebo**

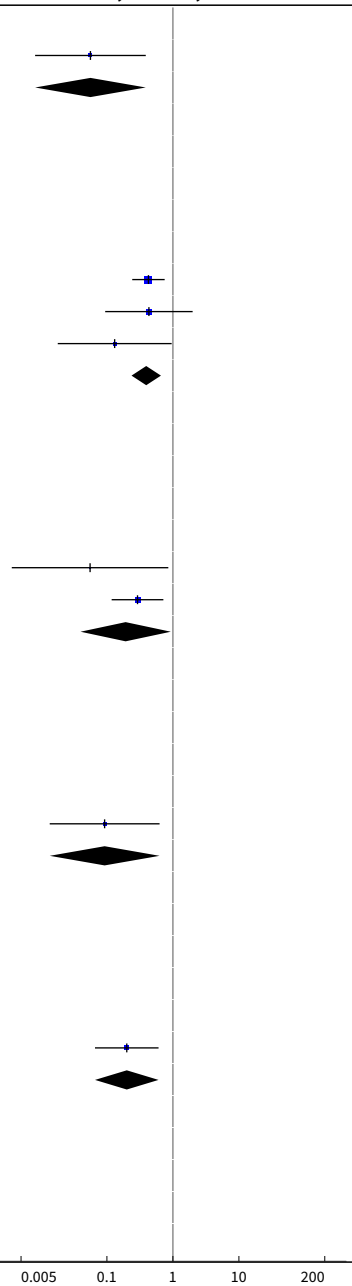
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Patients with at least one microbiological recurrence during prophylaxis | 10 | 372 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.13, 0.34] |
| 1.1 Cinoxacin 250 mg/24 h | 1 | 45 | Risk Ratio (M-H, Random, 95% CI) | 0.06 [0.01, 0.39] |
| 1.2 Cinoxacin 500 mg/24 h | 3 | 109 | Risk Ratio (M-H, Random, 95% CI) | 0.39 [0.24, 0.66] |
| 1.3 Norfloxacin 200 mg/24 h | 2 | 59 | Risk Ratio (M-H, Random, 95% CI) | 0.19 [0.04, 0.93] |
| 1.4 Nitrofurantoin 100 mg/24 h | 1 | 19 | Risk Ratio (M-H, Random, 95% CI) | 0.09 [0.01, 0.63] |
| 1.5 Nitrofurantoin 50 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.07, 0.61] |
| 1.6 Cephalexin 125 mg/24 h | 1 | 43 | Risk Ratio (M-H, Random, 95% CI) | 0.09 [0.01, 0.62] |
| 1.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.11 [0.02, 0.75] |
| 1.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg postcoital | 1 | 27 | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.04, 0.58] |
| 2 Patients with at least one clinical recurrence during prophylaxis | 7 | 257 | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.08, 0.28] |
| 2.1 Cinoxacin 250 mg/24 h | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Cinoxacin 500 mg/24 h | 1 | 39 | Risk Ratio (M-H, Random, 95% CI) | 0.24 [0.06, 0.98] |
| 2.3 Norfloxacin 200 mg/24 h | 2 | 59 | Risk Ratio (M-H, Random, 95% CI) | 0.19 [0.05, 0.66] |
| 2.4 Nitrofurantoin 100 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.11 [0.02, 0.75] |
| 2.5 Nitrofurantoin 50 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.10 [0.01, 0.72] |
| 2.6 Cephalexin 125 mg/24 h | 1 | 43 | Risk Ratio (M-H, Random, 95% CI) | 0.10 [0.01, 0.74] |
| 2.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h | 1 | 19 | Risk Ratio (M-H, Random, 95% CI) | 0.12 [0.02, 0.82] |
| 2.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg postcoital | 1 | 27 | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.04, 0.58] |
| 3 Severe side effects | 10 | 420 | Risk Ratio (M-H, Random, 95% CI) | 1.58 [0.47, 5.28] |
| 3.1 Cinoxacin 250 mg/24 h | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 6.15 [0.33, 114.16] |
| 3.2 Cinoxacin 500 mg/24 h | 3 | 129 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.08, 10.29] |

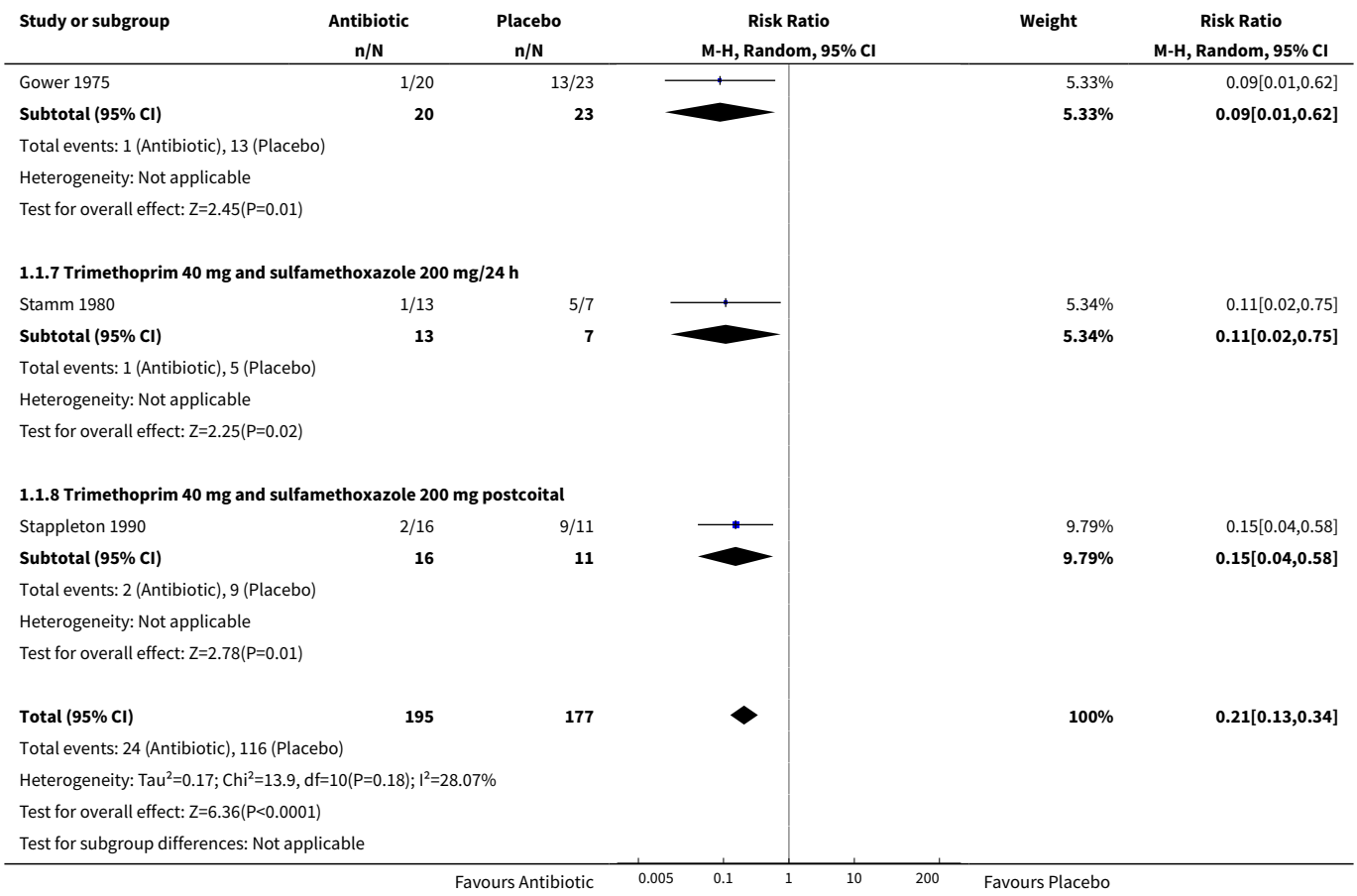
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.3 Norfloxacin 200 mg/24 h | 2 | 65 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.07, 14.55] |
| 3.4 Nitrofurantoin 100 mg/24 h | 1 | 19 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.5 Nitrofurantoin 50 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.6 Cephalexin 125 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 99.16] |
| 3.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg post-coital | 1 | 27 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Other side effects | 10 | 420 | Risk Ratio (M-H, Random, 95% CI) | 1.78 [1.06, 3.00] |
| 4.1 Cinoxacin 250 mg/24 h | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 1.64 [0.82, 3.28] |
| 4.2 Cinoxacin 500 mg/24 h | 3 | 129 | Risk Ratio (M-H, Random, 95% CI) | 2.05 [0.78, 5.40] |
| 4.3 Norfloxacin 200 mg/24 h | 2 | 65 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.16, 6.20] |
| 4.4 Nitrofurantoin 100 mg/24 h | 1 | 19 | Risk Ratio (M-H, Random, 95% CI) | 2.5 [0.14, 45.33] |
| 4.5 Nitrofurantoin 50 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.6 Cephalexin 125 mg/24 h | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg post-coital | 1 | 27 | Risk Ratio (M-H, Random, 95% CI) | 6.35 [0.38, 107.30] |
| 5 Patients with at least one microbiological recurrence after prophylaxis | 2 | 70 | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.44, 1.53] |
| 5.1 Cinoxacin 250 mg/24 h | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Cinoxacin 500 mg/24 h | 1 | 30 | Risk Ratio (M-H, Random, 95% CI) | 1.53 [0.69, 3.38] |
| 5.3 Norfloxacin 200 mg/24 h | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Nitrofurantoin 100 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.51 [0.25, 1.04] |
| 5.5 Nitrofurantoin 50 mg/24 h | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 Cephalexin 125 mg/24 h | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.38, 1.50] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg post-coital | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

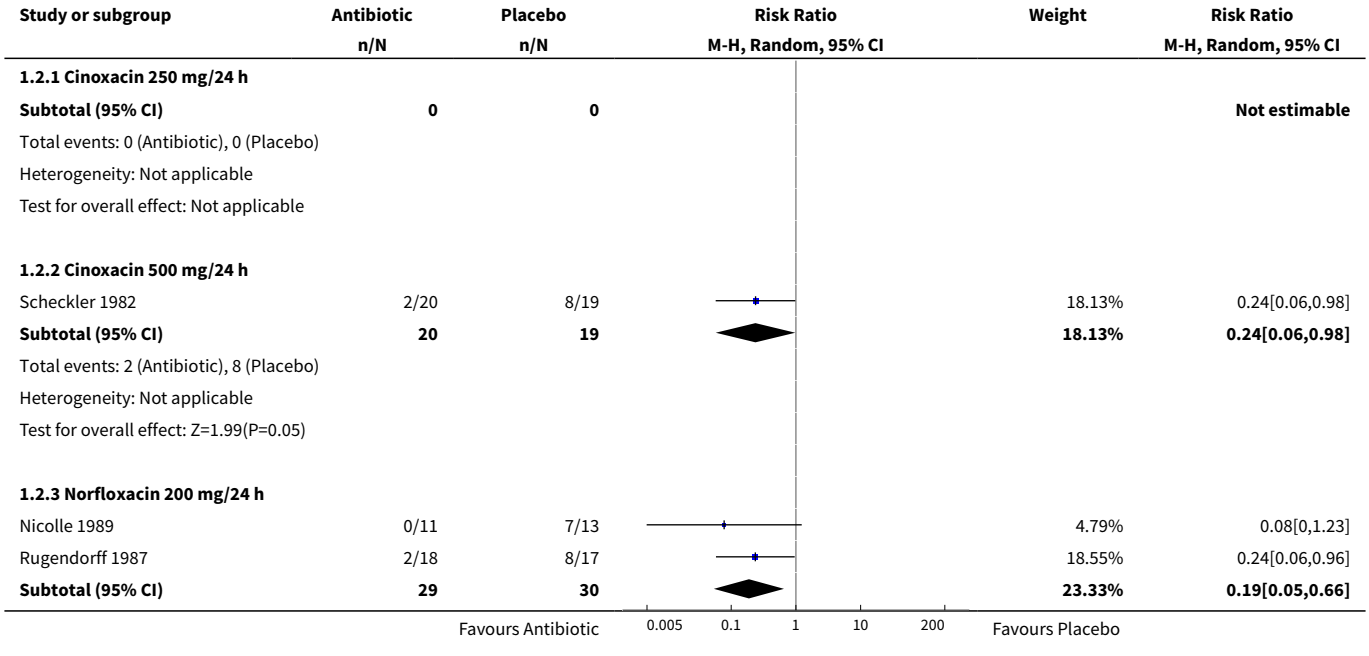
## Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Patients with at least one microbiological recurrence during prophylaxis.

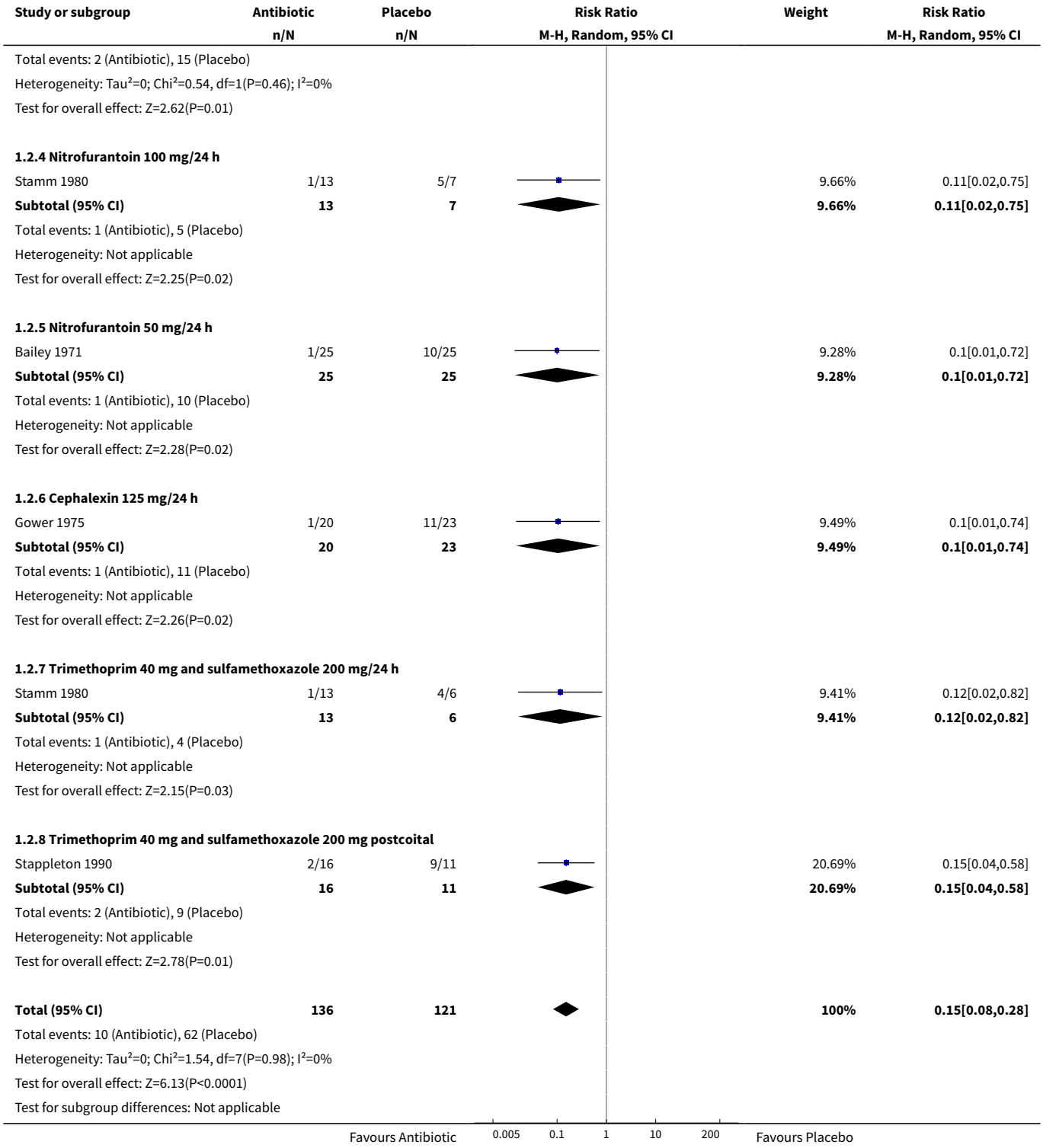
| Study or subgroup | Antibiotic n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Cinoxacin 250 mg/24 h** | | | | | |
| Martens 1995 | 1/23 | 17/22 | | 5.39% | 0.06[0.01,0.39] |
| **Subtotal (95% CI)** | **23** | **22** | | **5.39%** | **0.06[0.01,0.39]** |
| Total events: 1 (Antibiotic), 17 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.92(P=0) | | | | | |
| **1.1.2 Cinoxacin 500 mg/24 h** | | | | | |
| Martorana 1984 | 8/21 | 17/19 | | 24.16% | 0.43[0.24,0.75] |
| Schaeffer 1982 | 2/15 | 4/13 | | 7.91% | 0.43[0.09,1.99] |
| Scheckler 1982 | 1/20 | 8/21 | | 5.13% | 0.13[0.02,0.96] |
| **Subtotal (95% CI)** | **56** | **53** | | **37.21%** | **0.39[0.24,0.66]** |
| Total events: 11 (Antibiotic), 29 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.47, df=2(P=0.48); $I^2$=0% | | | | | |
| Test for overall effect: Z=3.55(P=0) | | | | | |
| **1.1.3 Norfloxacin 200 mg/24 h** | | | | | |
| Nicolle 1989 | 0/11 | 10/13 | | 2.91% | 0.06[0,0.85] |
| Rugendorff 1987 | 4/18 | 13/17 | | 16.04% | 0.29[0.12,0.72] |
| **Subtotal (95% CI)** | **29** | **30** | | **18.95%** | **0.19[0.04,0.93]** |
| Total events: 4 (Antibiotic), 23 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0.65; $Chi^2$=1.6, df=1(P=0.21); $I^2$=37.62% | | | | | |
| Test for overall effect: Z=2.05(P=0.04) | | | | | |
| **1.1.4 Nitrofurantoin 100 mg/24 h** | | | | | |
| Stamm 1980 | 1/13 | 5/6 | | 5.46% | 0.09[0.01,0.63] |
| **Subtotal (95% CI)** | **13** | **6** | | **5.46%** | **0.09[0.01,0.63]** |
| Total events: 1 (Antibiotic), 5 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.44(P=0.01) | | | | | |
| **1.1.5 Nitrofurantoin 50 mg/24 h** | | | | | |
| Bailey 1971 | 3/25 | 15/25 | | 12.53% | 0.2[0.07,0.61] |
| **Subtotal (95% CI)** | **25** | **25** | | **12.53%** | **0.2[0.07,0.61]** |
| Total events: 3 (Antibiotic), 15 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.85(P=0) | | | | | |
| **1.1.6 Cephalexin 125 mg/24 h** | | | | | |





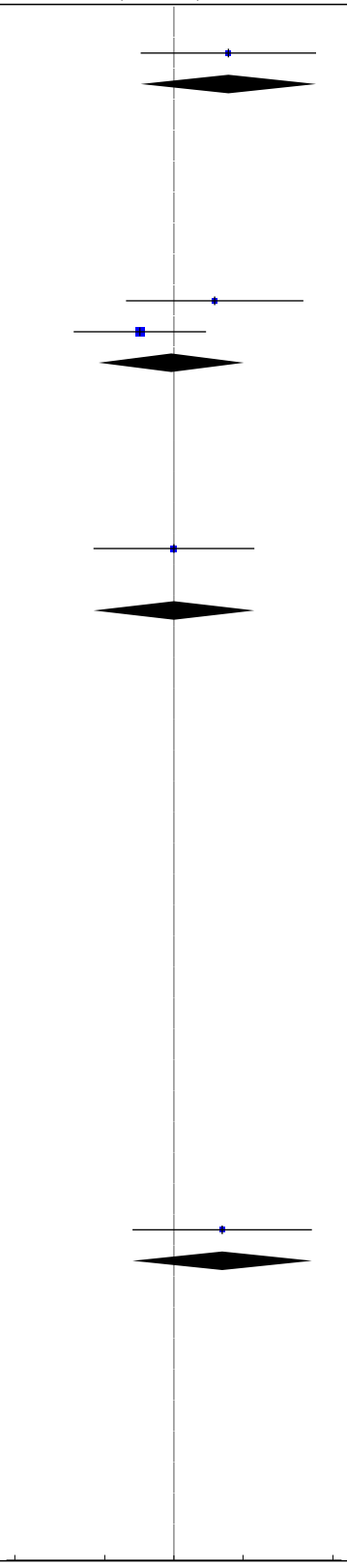

## Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Patients with at least one clinical recurrence during prophylaxis.

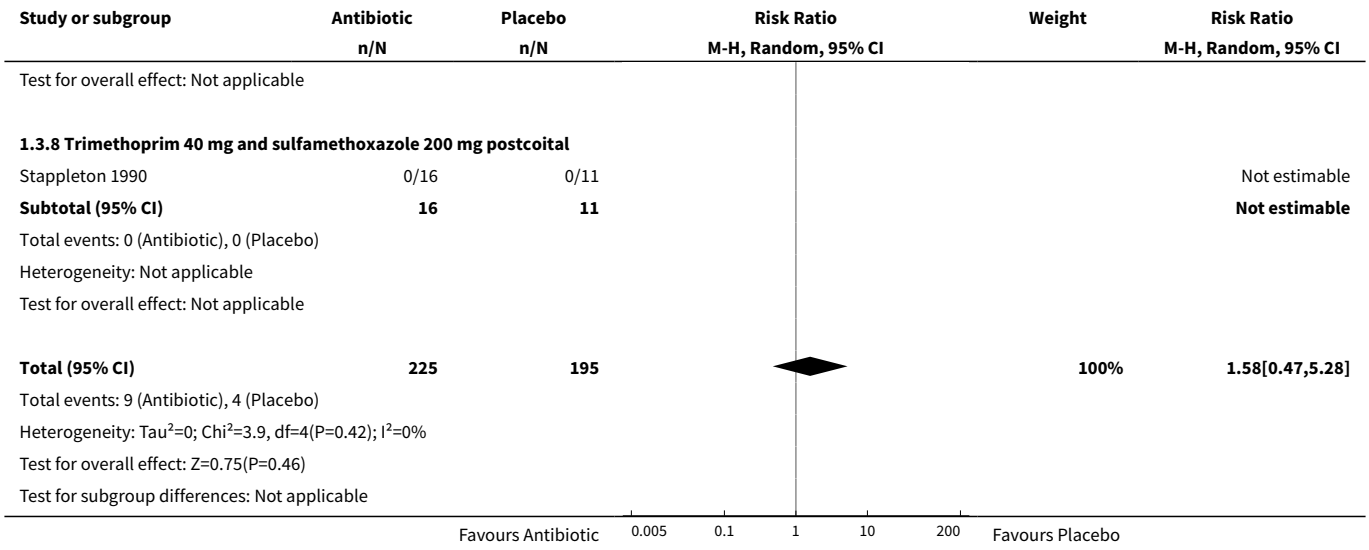




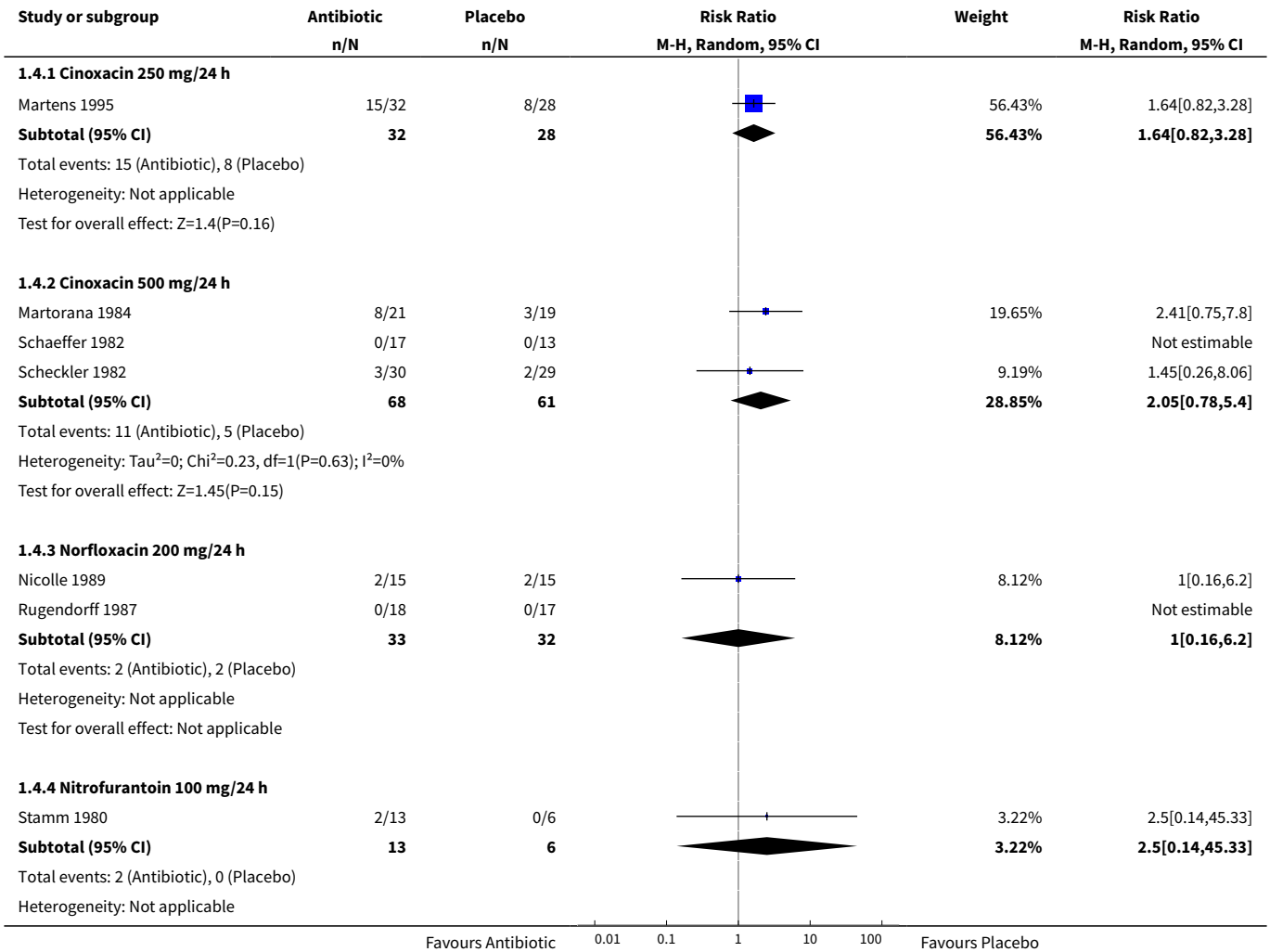
## Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Severe side effects.

| Study or subgroup | Antibiotic n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.3.1 Cinoxacin 250 mg/24 h** | | | | | |
| Martens 1995 | 3/32 | 0/28 | | 17.01% | 6.15[0.33,114.16] |
| **Subtotal (95% CI)** | **32** | **28** | | **17.01%** | **6.15[0.33,114.16]** |
| Total events: 3 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.22(P=0.22) | | | | | |
| **1.3.2 Cinoxacin 500 mg/24 h** | | | | | |
| Martorana 1984 | 0/21 | 0/19 | | | Not estimable |
| Schaeffer 1982 | 2/17 | 0/13 | | 16.62% | 3.89[0.2,74.67] |
| Scheckler 1982 | 1/30 | 3/29 | | 29.86% | 0.32[0.04,2.92] |
| **Subtotal (95% CI)** | **68** | **61** | | **46.48%** | **0.92[0.08,10.29]** |
| Total events: 3 (Antibiotic), 3 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=1.36; $Chi^2$=1.77, df=1(P=0.18); $I^2$=43.45% | | | | | |
| Test for overall effect: Z=0.07(P=0.94) | | | | | |
| **1.3.3 Norfloxacin 200 mg/24 h** | | | | | |
| Nicolle 1989 | 1/15 | 1/15 | | 20.24% | 1[0.07,14.55] |
| Rugendorff 1987 | 0/18 | 0/17 | | | Not estimable |
| **Subtotal (95% CI)** | **33** | **32** | | **20.24%** | **1[0.07,14.55]** |
| Total events: 1 (Antibiotic), 1 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.3.4 Nitrofurantoin 100 mg/24 h** | | | | | |
| Stamm 1980 | 0/13 | 0/6 | | | Not estimable |
| **Subtotal (95% CI)** | **13** | **6** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.3.5 Nitrofurantoin 50 mg/24 h** | | | | | |
| Bailey 1971 | 0/25 | 0/25 | | | Not estimable |
| **Subtotal (95% CI)** | **25** | **25** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.3.6 Cephalexin 125 mg/24 h** | | | | | |
| Gower 1975 | 2/25 | 0/25 | | 16.26% | 5[0.25,99.16] |
| **Subtotal (95% CI)** | **25** | **25** | | **16.26%** | **5[0.25,99.16]** |
| Total events: 2 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.06(P=0.29) | | | | | |
| **1.3.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h** | | | | | |
| Stamm 1980 | 0/13 | 0/7 | | | Not estimable |
| **Subtotal (95% CI)** | **13** | **7** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |

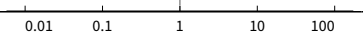





## Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Other side effects.



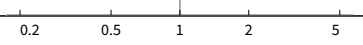
| Study or subgroup | Antibiotic n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z=0.62(P=0.54) | | | | | |
| **1.4.5 Nitrofurantoin 50 mg/24 h** | | | | | |
| Bailey 1971 | 0/25 | 0/25 | | | Not estimable |
| **Subtotal (95% CI)** | **25** | **25** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.4.6 Cephalexin 125 mg/24 h** | | | | | |
| Gower 1975 | 0/25 | 0/25 | | | Not estimable |
| **Subtotal (95% CI)** | **25** | **25** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.4.7 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h** | | | | | |
| Stamm 1980 | 0/13 | 0/7 | | | Not estimable |
| **Subtotal (95% CI)** | **13** | **7** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.4.8 Trimethoprim 40 mg and sulfamethoxazole 200 mg postcoital** | | | | | |
| Stappleton 1990 | 4/16 | 0/11 | | 3.38% | 6.35[0.38,107.3] |
| **Subtotal (95% CI)** | **16** | **11** | | **3.38%** | **6.35[0.38,107.3]** |
| Total events: 4 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.28(P=0.2) | | | | | |
| **Total (95% CI)** | **225** | **195** | | **100%** | **1.78[1.06,3]** |
| Total events: 34 (Antibiotic), 15 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.62, df=5(P=0.9); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.18(P=0.03) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |



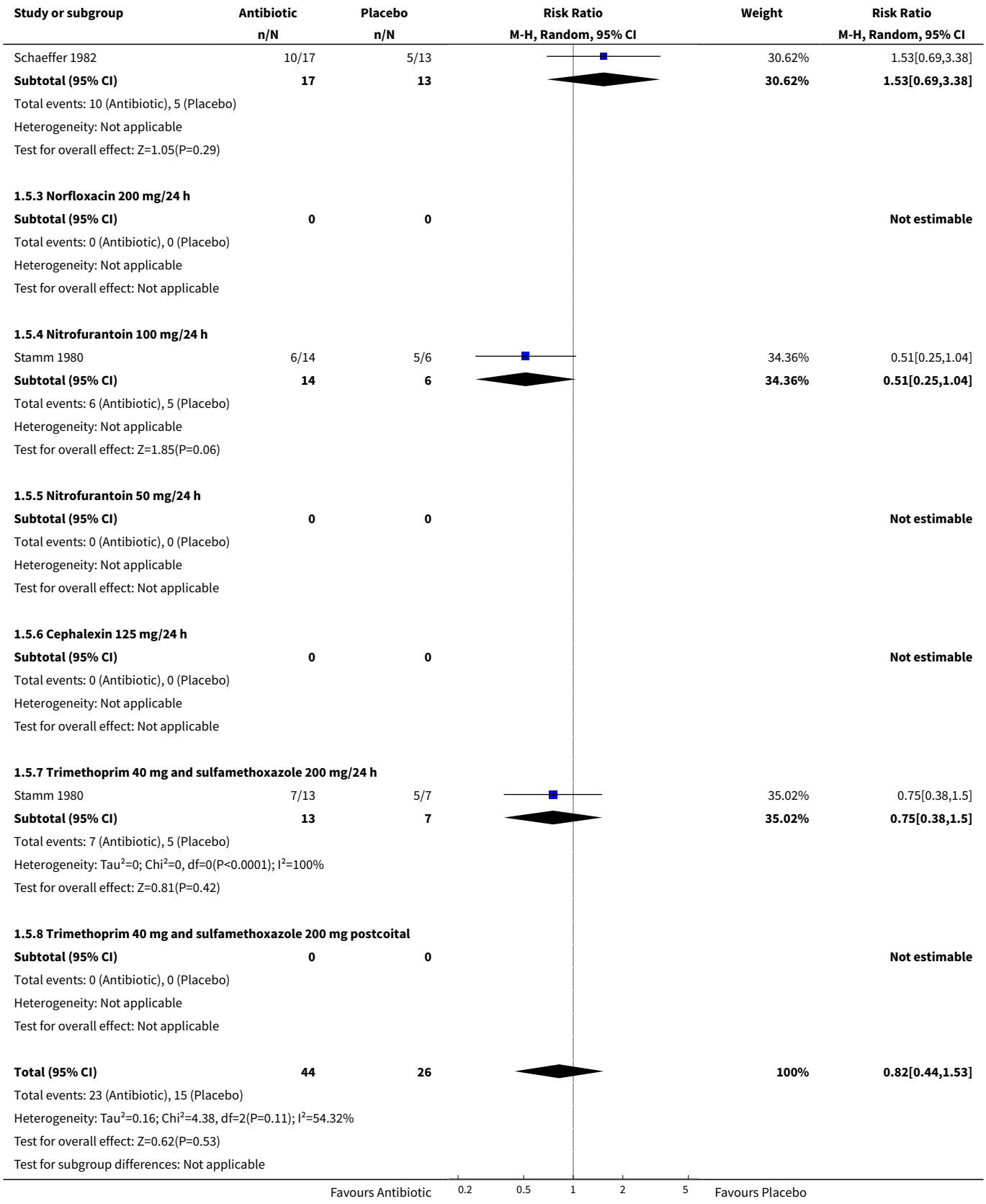

Favours Antibiotic — Favours Placebo

## Analysis 1.5. Comparison 1 Antibiotic versus placebo, Outcome 5 Patients with at least one microbiological recurrence after prophylaxis.

| Study or subgroup | Antibiotic n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.5.1 Cinoxacin 250 mg/24 h** | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | | **Not estimable** |
| Total events: 0 (Antibiotic), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.5.2 Cinoxacin 500 mg/24 h** | | | | | |




Favours Antibiotic — Favours Placebo



**Comparison 2. Comparison between antibiotics**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Patients with at least one microbiological recurrence during prophylaxis | 7 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.7 Pefloxacin 400 mg/wk versus 400 mg/mo | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.8 Ciprofloxacin 125 mg postcoital versus daily | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Patients with at least one clinical recurrence during prophylaxis | 4 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg /24 h versus nitrofurantoin 100 mg/24h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.7 Pefloxacin 400 mg/wk versus 400 mg/mo | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.8 Ciprofloxacin 125 mg postcoital versus daily | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3 Severe side effects | 7 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.7 Pefloxacin 400 mg/wk versus 400 mg/mo | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.8 Ciprofloxacin 125 mg postcoital versus daily | 0 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Other side effects | 8 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.7 Pefloxacin 400 mg/wk versus 400 mg/mo | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.8 Ciprofloxacin 125 mg postocital versus daily | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5 Patients with at least one microbiological recurrence after prophylaxis | 4 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5.1 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Pefloxacin 400 mg/wk versus 400 mg/mo | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Ciprofloxacin 125 mg postcoital versus daily | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

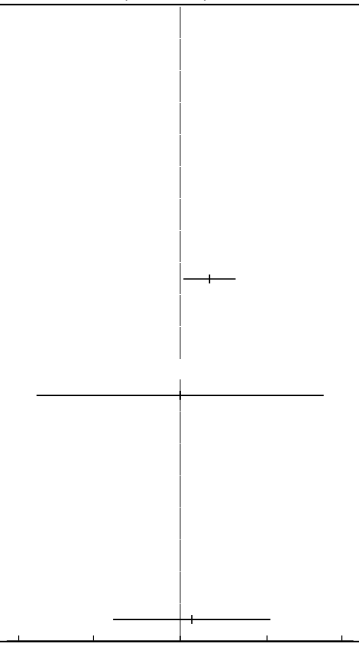
**Analysis 2.1. Comparison 2 Comparison between antibiotics, Outcome 1 Patients with at least one microbiological recurrence during prophylaxis.**

| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.1.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h** | | | | |
| Brumfitt 1995 | 8/49 | 8/48 | | 0.98[0.4,2.4] |
| **2.1.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| **2.1.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Nuñez 1990 | 2/26 | 0/26 | | 5[0.25,99.34] |
| **2.1.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1985 | 16/38 | 4/34 | | 3.58[1.33,9.66] |
| **2.1.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Stamm 1980 | 1/13 | 1/13 | | 1[0.07,14.34] |
| **2.1.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h** | | | | |
| Seppanen 1988 | 1/12 | 2/14 | | 0.58[0.06,5.66] |
| **2.1.7 Pefloxacin 400 mg/wk versus 400 mg/mo** | | | | |
| Guibert 1995 | 17/185 | 52/176 | | 0.31[0.19,0.52] |
| **2.1.8 Ciprofloxacin 125 mg postcoital versus daily** | | | | |
| Melekos 1997 | 2/70 | 2/65 | | 0.93[0.13,6.4] |


Fav. Antibiotic 1 — Fav. Antibiotic 2

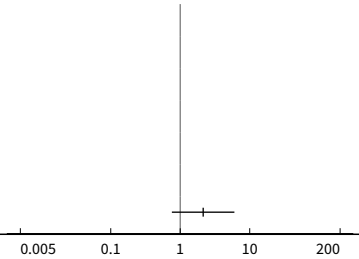
## Analysis 2.2. Comparison 2 Comparison between antibiotics, Outcome 2 Patients with at least one clinical recurrence during prophylaxis.

| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.2.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h** | | | | |
| **2.2.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1991 | 0/1 | 0/1 | | Not estimable |
| **2.2.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| **2.2.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1985 | 25/38 | 13/34 | | 1.72[1.06,2.79] |
| **2.2.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg /24 h versus nitrofurantoin 100 mg/24h** | | | | |
| Stamm 1980 | 1/13 | 1/13 | | 1[0.07,14.34] |
| **2.2.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h** | | | | |
| **2.2.7 Pefloxacin 400 mg/wk versus 400 mg/mo** | | | | |
| **2.2.8 Ciprofloxacin 125 mg postcoital versus daily** | | | | |
| Melekos 1997 | 4/70 | 3/65 | | 1.24[0.29,5.32] |

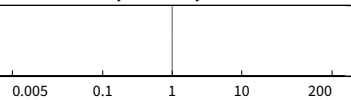



## Analysis 2.3. Comparison 2 Comparison between antibiotics, Outcome 3 Severe side effects.

| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.3.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h** | | | | |
| Brumfitt 1995 | 3/61 | 8/59 | | 0.36[0.1,1.3] |
| **2.3.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1991 | 4/48 | 7/50 | | 0.6[0.19,1.9] |
| **2.3.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Nuñez 1990 | 1/29 | 0/28 | | 2.9[0.12,68.33] |
| **2.3.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1985 | 0/38 | 6/40 | | 0.08[0,1.39] |
| **2.3.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Stamm 1980 | 0/13 | 0/13 | | Not estimable |
| **2.3.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h** | | | | |
| Seppanen 1988 | 0/12 | 0/14 | | Not estimable |
| **2.3.7 Pefloxacin 400 mg/wk versus 400 mg/mo** | | | | |
| Guibert 1995 | 11/174 | 5/169 | | 2.14[0.76,6.02] |

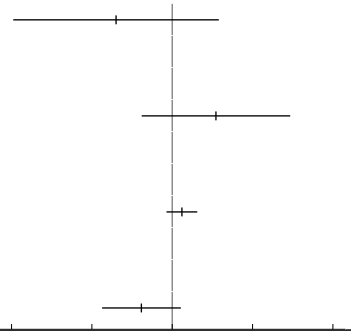


| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.3.8 Ciprofloxacin 125 mg postcoital versus daily** | | | | |



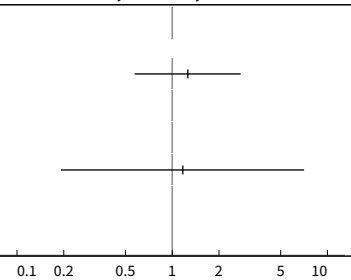

## Analysis 2.4. Comparison 2 Comparison between antibiotics, Outcome 4 Other side effects.

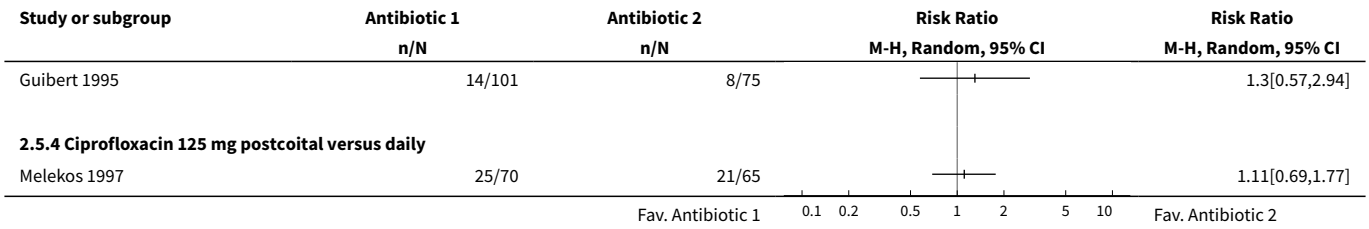
| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.4.1 Cefaclor 250 mg/24 h versus nitrofurantoin 50 mg/24 h** | | | | |
| Brumfitt 1995 | 3/61 | 4/59 | | 0.73[0.17,3.1] |
| **2.4.2 Norfloxacin 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1991 | 6/48 | 8/50 | | 0.78[0.29,2.08] |
| **2.4.3 Norfloxacin 400 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Nuñez 1990 | 28/29 | 21/28 | | 1.29[1.03,1.61] |
| **2.4.4 Trimethoprim 100 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Brumfitt 1985 | 7/38 | 10/34 | | 0.63[0.27,1.46] |
| **2.4.5 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24h** | | | | |
| Stamm 1980 | 0/13 | 2/13 | | 0.2[0.01,3.8] |
| **2.4.6 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h** | | | | |
| Seppanen 1988 | 3/12 | 1/14 | | 3.5[0.42,29.39] |
| **2.4.7 Pefloxacin 400 mg/wk versus 400 mg/mo** | | | | |
| Guibert 1995 | 38/174 | 28/169 | | 1.32[0.85,2.05] |
| **2.4.8 Ciprofloxacin 125 mg postcoital versus daily** | | | | |
| Melekos 1997 | 4/70 | 9/65 | | 0.41[0.13,1.28] |




## Analysis 2.5. Comparison 2 Comparison between antibiotics, Outcome 5 Patients with at least one microbiological recurrence after prophylaxis.

| Study or subgroup | Antibiotic 1 n/N | Antibiotic 2 n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.5.1 Trimethoprim 40 mg and sulfamethoxazole 200 mg/24 h versus nitrofurantoin 100 mg/24 h** | | | | |
| Stamm 1980 | 7/13 | 6/14 | | 1.26[0.57,2.76] |
| **2.5.2 Trimethoprim 100 mg/24 h versus cinoxacin 500 mg/24 h** | | | | |
| Seppanen 1988 | 2/12 | 2/14 | | 1.17[0.19,7.07] |
| **2.5.3 Pefloxacin 400 mg/wk versus 400 mg/mo** | | | | |





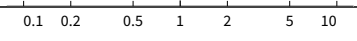

## Comparison 3. Antibiotics versus non-antibiotics

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Patients with at least one microbiological recurrence during prophylaxis | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 1.1 Trimethoprim 100 mg/24 h versus povidone iodine | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Patients with at least one clinical recurrence during prophylaxis | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1 Trimethoprim 100 mg/24 h versus povidone iodine | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Patients who experience severe side effects | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1 Trimethoprim 100 mg/24 h versus povidone iodine | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Patients who experience other side effects | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1 Trimethoprim 100 mg/24 h versus povidone iodine | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 3.1. Comparison 3 Antibiotics versus non-antibiotics, Outcome 1 Patients with at least one microbiological recurrence during prophylaxis.**

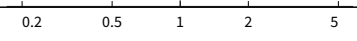
| Study or subgroup | Antibiotic n/N | Non-antibiotic n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **3.1.1 Trimethoprim 100 mg/24 h versus povidone iodine** | | | | |
| Brumfitt 1983 | 8/20 | 10/19 | | 0.76[0.38,1.51] |
| **3.1.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h** | | | | |
| Brumfitt 1981 | 4/43 | 19/56 | | 0.27[0.1,0.75] |
| **3.1.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h** | | | | |
| Brumfitt 1983 | 8/20 | 10/25 | | 1[0.49,2.05] |




Fav. Antibiotic — Fav. Non-Antibiotic

**Analysis 3.2. Comparison 3 Antibiotics versus non-antibiotics, Outcome 2 Patients with at least one clinical recurrence during prophylaxis.**

| Study or subgroup | Antibiotic n/N | Non Antibiotic n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **3.2.1 Trimethoprim 100 mg/24 h versus povidone iodine** | | | | |
| Brumfitt 1983 | 11/20 | 9/19 | | 1.16[0.63,2.15] |
| **3.2.2 Nitrofurantoin 50 mg/12 h versus methenamine hippurate 1 g/12 h** | | | | |
| Brumfitt 1981 | 18/43 | 41/56 | | 0.57[0.39,0.84] |
| **3.2.3 Trimethoprim 100 mg/24 h versus methenamine hippurate 1 g/12 h** | | | | |
| Brumfitt 1983 | 11/20 | 18/25 | | 0.76[0.48,1.22] |



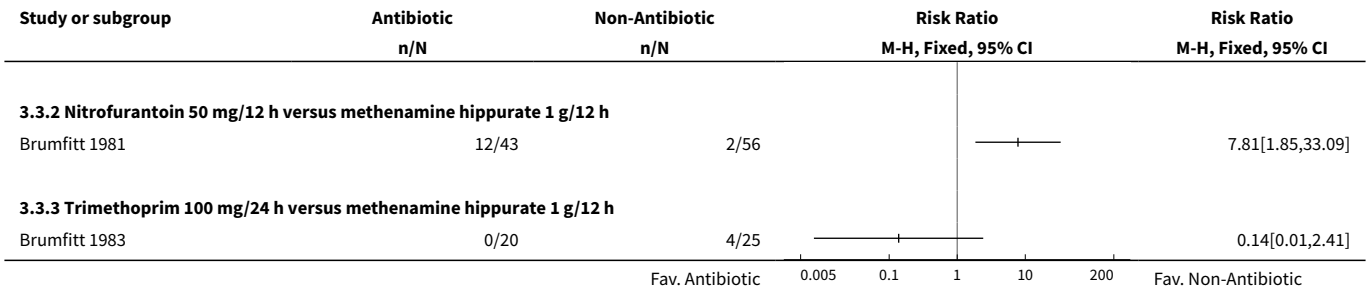

Fav. Antibiotic — Fav. Non-Antibiotic

**Analysis 3.3. Comparison 3 Antibiotics versus non-antibiotics, Outcome 3 Patients who experience severe side effects.**

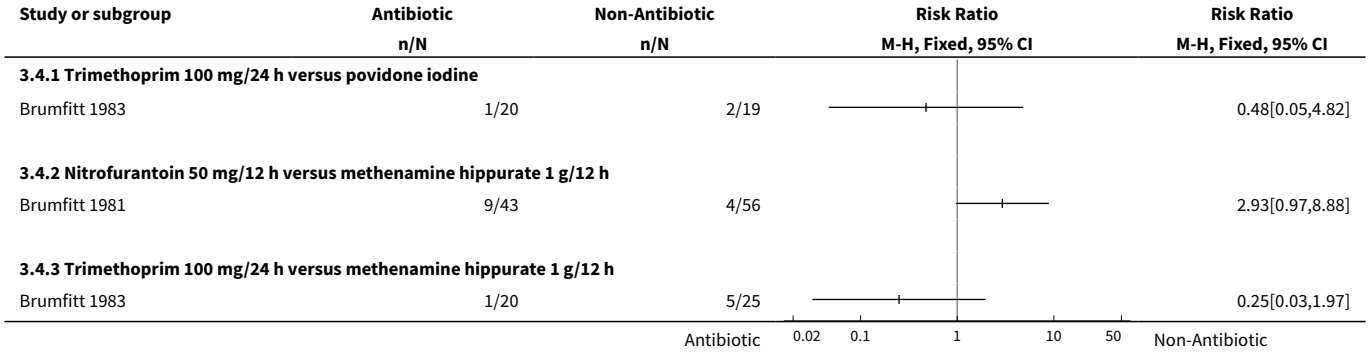
| Study or subgroup | Antibiotic n/N | Non-Antibiotic n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **3.3.1 Trimethoprim 100 mg/24 h versus povidone iodine** | | | | |
| Brumfitt 1983 | 0/20 | 3/19 | | 0.14[0.01,2.47] |




Fav. Antibiotic — Fav. Non-Antibiotic




## Analysis 3.4. Comparison 3 Antibiotics versus non-antibiotics, Outcome 4 Patients who experience other side effects.




## ADDITIONAL TABLES

**Table 1. Antibiotic versus placebo. Description of studies**

| Study (antibiotic) | N | Treatment period | Follow-up | Dose regimen | Fertile cycle, age | Setting | Definition of RUTI | Diagnosis: anatomical abnormality | Definition of clinical RUTI |
|---|---|---|---|---|---|---|---|---|---|
| Martens 1995 (cinoxacin 250) | 60 | 6 months or until UTI | No | Daily | Pre-menopausal range 18 to 35 years (88% < 25 years) | Outpatient clinic (medical centre) | Three episodes | Unclear | ---- |
| Martorana 1984 (cinoxacin 500) | 40 | 6 months or until UTI | No | Daily | Both - pre and post-menopausal range 20 to 65 years | Outpatient urologic clinic | 3 episodes | Unclear | ---- |
| Schaeffer 1982 (cinoxacin 500) | 30 | 6 months or until UTI | 6 months | Daily | Both - range 20 to 69 years | Outpatient urologic clinic | Three documented episodes | Unclear | ---- |
| Scheckler 1982 (cinoxacin 500) | 59 | 6 months or until UTI | No | Daily | Both - range 18 to 65 (83% < 35 years) | 3 family practices 1 general urology clinic | Three episodes, most bacteria | Unclear | Symptoms |
| Nicolle 1989 (norfloxacin 200) | 30 | 12 months or until UTI | Only antibiotic arm | Daily | Both - range 12 to 75 years | Outpatient infection clinic | Three symptomatic episodes | Unclear | Symptomatic bacteriuria |
| Rugendorff 1987 (norfloxacin 200) | 39 | 6 months or until UTI | No | Daily | Both - range 17 to 77 years | Outpatient urologic clinic | Three episodes (facultative bacteria) | Unclear | Symptomatic bacteriuria |
| Stamm 1980 (nitrofurantoin 100; cotrimoxazole 40-200) | 45 | 6 months or until UTI | 6 months | Daily | Both - range 19 to 73 years. Mean 54 years. | Outpatient infection clinic | Two culture documented episodes | Yes, included | Symptomatic bacteriuria |
| Bailey 1971 | 50 | 6 months or until UTI. Unclear | No | Daily | Pre-menopausal | Urinary infection clinic | History of RUTI | Yes, excluded | Symptomatic bacteriuria |

**Table 1. Antibiotic versus placebo. Description of studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (nitrofurantoin 50) | | | | | | | | | |
| Gower 1975 (cephalexin 125) | 50 | 12 months or until UTI | No | Daily | Both - range 20 to 60 years. mean 31 years. | Outpatient renal infection clinic | History of RUTI | Unclear | Symptomatic bacteriuria |
| Stappleton 1990 (cotrimoxazole 40-200) | 27 | 6 months or until UTI | No | Post-coital | Pre-menopausal Median 23 years. | University students (department) | Two documented episodes related to intercourse | Unclear | Symptomatic bacteriuria |
| Total | 430 | | | | | | | | |

**Table 2. Antibiotic versus antibiotic or other strategy. Description of studies**

| Study (antibiotic) | N | Treatment period | Follow-up | Dose regimen | Fertile cycle, age | Setting | Definition RUTI | Diagnosis: anatomical abnormality | Definition of clinical RUTI |
|---|---|---|---|---|---|---|---|---|---|
| Brumfitt 1995 (cefaclor 250; nitrofurantoin 50) | 135 | 12 months | 3-6 months. Not available | Daily | Both Range: 18-90 years. Mean: 45-40 years | Outpatient urinary infection clinic | 4 symptomatic (1 bact.) | Yes, included | Symptoms |
| Brumfitt 1991 (norfloxacin 200; nitrofurantoin 100) | 111 | 12 months | 3-6 months. Not available | Daily | Both Range: 17-83 years. Mean: 39-37 years. | Outpatient urinary infection clinic | 4 symptomatic (1 bact.) | Yes, included | Symptoms |
| Nuñez 1990 (norfloxacin 400; nitrofurantoin 100) | 56 | 6 months or until UTI | No | Daily | Both Mean: 46-45 years. | Outpatient urologic clinic | 2 verified by medical records | Unclear | --- |
| Brumfitt 1985 (trimethoprim 100; nitrofurantoin 100) | 100 | 12 months | No | Daily | Both Mean: 38-41 years | Outpatient urinary infection clinic | 3 symptomatic (1 bact.) | Yes, included | Symptoms |

**Table 2. Antibiotic versus antibiotic or other strategy. Description of studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Stamm 1980 (*Also in Table 1 cotrimoxazole 40-200; nitrofurantoin 100) | 30 | 6 months or until UTI | 6 months | Daily | Both Range 19-73 years. Mean: 54 years. | Outpatient urinary infection clinic | 2 cultures documented | Yes, included (minor) | Symptomatic bacteriuria |
| Seppanen 1988 (trimethoprim 100; cinoxacin 500) | 26 | 6 months or until UTI | 4-6 weeks | Daily | Both Range: 17-63 years. Mean: 27-33 years. | Outpatient urologic clinic | 3 episodes | Yes, excluded | --- |
| Guibert 1995 (pefloxacin 400) | 361 | 11 months (48 weeks) | 3 months (not all women) | Weekly versus monthly | Both Range: 18-51 years. Mean: 38-37 years. | Family Practice | 4 acute cystitis | Yes, excluded | --- |
| Melekos 1997 (ciprofloxazole 125) | 152 | 12 months | 12 months | Postcoital versus daily | Premenopausal Range: 18-46 years. Mean: 28-31 years. | Outpatient urologic clinic | 3 documented | Yes, excluded (included 6% minor) | Symptoms |
| Brumfitt 1983 (trimethoprim 100; povidone iodine; methenamine hippurate 1 g) | 67 | 12 months | 3-6 months. Not available | Trimethoprim: Daily Poividone iodine: Solution Methenamine hippurate: Every 12 h. | Both Mean: 32-38 years. | Outpatient urinary infection clinic | 4 symptomatic (1 bact.) | Yes, included | Symptoms |
| Brumfitt 1981 (nitrofurantoin 50; methenamine hippurate 1 g) | 110 | 12 months | Yes, unclear | Every12 h | Both Mean: 31-36 years. | Outpatient urinary infection clinic | 3 symptomatic (1 bact.) | Yes, included | Symptoms |

Both = pre and post

**Table 3. Antibiotic versus placebo. Methodological quality**

| Study (antibiotic) | Blinding | Randomisation | Allocation concealment | Number/group | Withdrawn (dropouts) | Withdrawn | Withdrawn (other reasons) | Differences between groups |
|---|---|---|---|---|---|---|---|---|

**Table 3. Antibiotic versus placebo. Methodological quality** *(Continued)*

| | | | | | | (side effects) | | |
|---|---|---|---|---|---|---|---|---|
| Martens 1995<br>(cinoxacin 250) | Double | Distribution table | Unclear | 60<br>32-28 | 15 (25%)<br>9-6 | 3-0 | 6-6<br>Missed appointment: 3-6<br>Missed laboratory visits: 2-0<br>Pregnant 1-0 | No |
| Martorana 1984<br>(cinoxacin 500) | Double | -- | Unclear | 40<br>21-19 | 0 (0%) | 0-0 | No | Not reported |
| Schaeffer 1982<br>(cinoxacin 500) | No | -- | Unclear | 30<br>17-13 | 2 (6.6%)<br>2-0 | 2-0 | No | No |
| Scheckler 1982<br>(cinoxacin 500) | Double | Random code | Unclear | 59<br>30-29 | 18 (30%)<br>10-8 | 1-3 | All: 9 treated < 50 days,<br>3 poor compliance<br>4 bacterial culture not protocol<br>4 other protocol violations | Not reported |
| Nicolle 1989<br>(norfloxacin 200) | Double | -- | Unclear | 30<br>15-15 | 6 (20%)<br>4-2 | 1-1 | 3-1: Lost to follow-up 2-0<br>Pregnancy 1-0<br>infected at enrolment 0-1 | Not reported |
| Rugendorff 1987<br>(norfloxacin 200) | Double | -- | Unclear | 39<br>20-19 | 4 (10%)<br>2-2 | No | 2-2<br>Poor compliance | Not reported |
| Stamm 1980<br>(nitrofurantoin 100; cotrimoxazole 40-200) | Double | -- | Unclear | 45<br>15-15-15 | 6 (13.2%)<br>2-2-2 | No | 2-2-2<br>lost to follow up | No |
| Bailey 1971<br>(nitrofurantoin 50) | Double | -- | Unclear | 50<br>25-25 | 0 (0%) | No | | Not reported |
| Gower 1975<br>(cephalexin 125) | Double | -- | Unclear | 50<br>25-25 | 7 (14%)<br>5-2 | 2-0 | 3-2<br>lost to follow up | Not reported |

**Table 3. Antibiotic versus placebo. Methodological quality** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stappleton 1990<br>(cotrimoxazole 40-200) | Double | -- | Unclear | 27<br>16-11 | 2 (7.4%)<br>2-0 | No | 2-0<br>Suspected pregnancy 2-0 | Yes (Diaphragm users)<br>69% vs 91% |

**Table 4. Antibiotic versus antibiotic or other strategy. Methodological quality**

| Study (antibiotic) | Blinding | Randomisation | Allocation concealment | Number/group | Withdrawn (dropouts) | Withdrawn (side effects) | Withdrawn (other reasons) | Differences between groups |
|---|---|---|---|---|---|---|---|---|
| Brumfitt 1995<br>(cefaclor 250; nitrofurantoin 50) | No | -- | Unclear | 135 | 38 (28%)<br>12-11<br>+15? | 3-8 | 12-11:<br>Non compliant or failed to return<br>for three follow-up visits, side effects<br>15 (two groups) 9 violation of protocol,<br>6 failed to return to the clinic. | None |
| Brumfitt 1991<br>(norfloxacin 200; nitrofurantoin 100) | No | -- | Unclear | 111<br>55-56 | 23<br>(20.7%)<br>10-13 | 4-7<br>(of 98) | *Not clear if included side effects<br>13 (7-6) no assessable: 2 left the country, 2 stopped taking their medication after a few days and 9 failed to attend their scheduled appointments.<br>10 (?) Not clinically assessable. | None |
| Nuñez 1990<br>(norfloxacin 400; nitrofurantoin 100) | Single | -- | Unclear | 56<br>29-27 | 5 (9%)<br>3-2 | 1-0 | 2-2<br>Lost to follow-up | None |
| Brumfitt 1985<br>(trimethoprim 100; nitrofurantoin 100) | No | Random chart | Unclear | 100<br>50-50 | 28 (28%)<br>12-16 | 0-6 | 12-10<br>Non compliant or failed to return<br>for three follow-up visits | Yes (Radiological abnormality |

**Table 4. Antibiotic versus antibiotic or other strategy. Methodological quality** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 46% versus 25%) |
| Stamm 1980<br>*Also in Table 3<br>(cotrimoxazole 40-200; nitrofurantoin 100) | Double | -- | Unclear | 45<br>15-15-(15) | 6 (13.3%)<br>2-2-(2) | 0 | 2-2-(2)<br>Lost of follow-up | None |
| Seppanen 1988<br>(trimethoprim 100; cinoxacin 500) | Double | -- | Unclear | 26<br>12-14 | 0 (0%) | 0 | | Not reported |
| Guibert 1995<br>(pefloxacin 400; weekly versus monthly) | Double | --- | Unclear | 361<br>185-176 | 25 (7%)<br>13-12 | 11-5 | Lost | None |
| Melekos 1997<br>(ciprofloxacin 125; postcoital versus daily). | Single | Date of birth | Inadequate | 152<br>?-? | 17 (11.1%) | 5 | 12 (two groups): protocol violation,<br>poor compliance, lost of follow-up,<br>pregnancy or desire to become pregnant | None |
| Brumfitt 1983<br>(trimethoprim 100; povidone iodine; methenamine hippurate 1 g) | No | -- | Unclear | 67 | 3 + 15 (27%) | 0-3-4 | 3- failed to return to the clinic regularly<br>15 (were assessed) stopped treatment prematurely: pain on voiding in 3 in MH group, 1 became pregnant in TMP, 1 lost to follow-up and the remaining 10 failed to attend clinic appointments. | None |
| Brumfitt 1981<br>(nitrofurantoin 50; methenamine hippurate 1 g) | No | -- | Unclear | 110*<br>56-54 | 11 (10%)<br>5-6 | 12-2 | Failed to return for follow-up 3-4,<br>attend only spasmodically 2-2.<br>*11 patients taking NF were changed to MH. 3 taking MH to NF. | Yes (Radiological abnormality, 29% versus 12%) |

**Table 5. Antibiotic versus placebo. MRPY and CRPY**

| Study (antibiotic) | MRPY Antibiotic | MRPY Placebo | RR (95% CI) | P value | CRPY Antibiotic | CRPY Placebo | RR (95% CI) | P value | Duratation Interval |
|---|---|---|---|---|---|---|---|---|---|
| Martens 1995 (cinoxacin 250) | | | | | | | | | 6 months or until UTI |
| Martorana 1984 (cinoxacin 500) | 0.97 (8/8.25) | 3.58 (17/4.75) | 0.27 (0.12, 0.63) | < 0.001 | | | | | 6 months or until UTI |
| Schaeffer 1982 (cinoxacin 50) | 0.4 (3/7) | 0.8 (4/5) | 0.54 (0.12, 2.4) | 0.46 | | | | | 6 months or until UTI |
| Scheckler 1982 (cinoxacin 500) | | | | | | | | | 6 months or until UTI |
| Nicolle 1989 (norfloxacin 200) | 0 (0/11.6) | 1.6 (10/6.3) | 0 (not defined) | < 0.001 | 0 (0/11.6) | 1.12 (7/6.3) | 0 (Nnt defined) | < 0.001 | 12 months or until UTI |
| Rugendorff 1987 (norfloxacin 200) | 0.54 (4/7.4) | 3.3 (13/3.9) | 0.16 (0.05, 0.5) | < 0.001 | 0.27 (2/7.4) | 2.05 (8/3.9) | 0.13 (0.03, 0.6) | 0.004 | 6 months or until UTI |
| Stamm 1980 (nitrofurantoin 100) | 0.14 (1/7.1) | 2.8 (10/3.6) | 0.05 (0.01, 0.4) | < 0.001 | | | | | 6 months or until UTI |
| Bailey 1971 (nitrofurantoin 50) | 0.19 (3/15.9) | 2.06 (15/7.3) | 0.09 (0.03, 0.32) | < 0.001 | 0.06 (1/15.9) | 1.37(10/7.3) | 0.05 (0.01, 0.36) | < 0.001 | 6 months or until UTI |
| Gower 1975 (cephalexin 125) | | | | | | | | | 12 months or until UTI |
| Stamm 1980 (cotrimoxazole - oral) | 0.15 (1/6.7) | 2.8 (10/3.6) | 0.05 (0.01, 0.42) | < 0.001 | | | | | 6 months or until UTI |
| Stappleton 1990 (cotrimoxazole - postcoital) | 0.3 | 3.6 | | 0.001 | 0.3 | 3.6 | | 0.001 | 6 months or until UTI |

**Table 6. Side effects**

| Study | Severe side effects (n/N) | Non-severe side effects (n/N) |
|---|---|---|
| Martens 1995 | **Cinoxacin 250: 3/32**<br>• Nausea and vomiting (1)<br>• Pruritus and urticaria (1)<br>• Dizziness, abdominal pain, anorexia, fever and vomiting (1)<br>**Placebo: 0/28** | **Cinoxacin 250: 15/32***<br>**Placebo: 8/28***<br>*Description of both groups: Vaginitis, genital monilia, vaginal itch and anorexia |
| Martorana 1984 | **Cinoxacin 500: 0/21**<br>**Placebo: 0/19** | **Cinoxacin 500: 8/21**<br>• Pruritus (2)<br>• Insomnia (4)<br>• Urticaria (1)<br>• Nausea (2)<br>• Leukocyturia (2)<br>• Lipothymia (1)<br>**Placebo: 3/19**<br>• Leukocyturia (2)<br>• Nausea (1)<br>• Augment glycaemia (1) |
| Schaeffer 1982 | **Cinoxacin 500: 2/17**<br>• Skin eruptions (rash) (2)<br>**Placebo: 0/13** | Zero in both groups |
| Scheckler 1982 | **Cinoxacin 500: 1/30**<br>• Not described<br>**Placebo: 3/29**<br>• Not described | **Cinoxacin 500: 3/30**<br>• Not described<br>**Placebo: 2/29**<br>• Not described |
| Nicolle 1989 | **Norfloxacin 200: 1/15**<br>• AST elevation (1)<br>**Placebo: 1/15**<br>• Skin rash (1) | **Norfloxacin 200: 2/15**<br>• Vaginitis (2)<br>**Placebo: 2/15**<br>• Vaginitis (1)<br>• Intermittent gastrointestinal upset (1) |
| Rugendorff 1987 | **Norfloxacin 200: 0/18**<br>**Placebo: 0/17** | Zero in both groups |
| Stamm 1980 | **Norfloxacin 100: 0/13**<br>**TMP-SMX: 0/13**<br>**Placebo: 0/13** | **Norfloxacin 100: 2/13**<br>• Minor gastrointestinal side effects (2)<br>**TMP-SMX: 0/13** |

**Table 6. Side effects** *(Continued)*

| | | |
|---|---|---|
| | | **Placebo: 0/13** |
| Bailey 1971 | **Norfloxacin 50: 0/25**<br>**Placebo: 0/25** | Zero in both groups |
| Gower 1975 | **Cephalexin 125: 2/25**<br>• Persistent diarrhoea (1)<br>• Irritating skin rash (1)<br>**Placebo: 0/25** | Zero in both groups |
| Stappleton 1990 | **TMP-SMX: 0/16**<br>**Placebo: 0/16** | **TMP-SMX: 4/16**<br>• Nausea (1)<br>• Confirmed vaginal candidiasis (2)<br>• Vaginal symptoms (1)<br>**Placebo: 0/16** |
| Brumfitt 1995 | **Cefaclor 250: 3/61**<br>**Nitrofurantoin 50: 8/59**<br>*Description include severe and non severe side effects and both groups: "Vaginal irritation and nausea were the most commonly reported events in each group". | **Cefaclor 250: 3/61**<br>**Nitrofurantoin 50: 4/59**<br>(see severe side effects) |
| Brumfitt 1991 | **Norfloxacin 200: 4/48**<br>• Oral/vaginal candidiasis (1)<br>• Abdominal discomfort (2)<br>• Allergic reaction (1)<br>**Nitrofurantoin 100: 7/50**<br>• Nausea (3)<br>• Abdominal discomfort (1)<br>• Allergic reaction (2)<br>• Other (3) | **Norfloxacin 200: 6/48**<br>• Nausea (3)<br>• Oral/vaginal candidiasis (5)<br>**Nitrofurantoin 100: 8/50**<br>• Nausea (3)<br>• Oral/vaginal candidiasis (3)<br>• Other (2) |
| Nuñez 1990 | **Norfloxacin 400: 1/29**<br>• Severe acute gastritis (1)<br>**Nitrofurantoin 100: 0/28** | Includes period of full dose treatment<br>**Norfloxacin** 400: 28/29.<br>**Nitrofurantoin** 100: 21/28<br>Both groups: Nausea, headache, epigastralgia, and arthralgia/myalgia |
| Brumfitt 1985 | **Trimethoprim-sulphamethoxazole 100: 0/38**<br>**Nitrofurantoin 100: 6/48**<br>• Rash (2)<br>• Nausea (2)<br>• Headache (1)<br>• Fever (1) | **Trimethoprim-sulphamethoxazole 100: 7/38**<br>• Candidiasis (4)<br>• Nausea (2)<br>• Rash (1)<br>• Diarrhoea (1)<br>**Nitrofurantoin 100: 10/34** |

**Table 6. Side effects** *(Continued)*

| | | |
|---|---|---|
| | | • Nausea (5)<br>• Diarrhoea (1)<br>• Candidiasis (1)<br>• Others (3) (one report each of macrocytosis, tingling fingers, and mild reaction to alcohol on a single occasion) |
| Seppanen 1988 | **Trimethoprim-sulphamethoxazole 100: 0/12**<br><br>**Cinoxacin 500: 0/14** | **Trimethoprim-sulphamethoxazole 100: 3/12**<br><br>• Vaginal candidiasis (1)<br>• Slightly elevated S-ALT value ("probably due to oral contraceptives") (1)<br>• Transient rise in the eosinophil count (1)<br><br>**Cinoxacin 500: 1/14**<br><br>• Leukocyte count fell transiently to 2.9 (1) |
| Guibert 1995 | **Weekly perfloxacin 400: 11/174**<br><br>**Monthly perfloxacin 400: 5/169**<br><br>*Description include severe and non-severe side effects. The most commonly side effects were digestives (nausea) and insomnia. Some tendinopathy was reported. | **Weekly perfloxacin 400: 38/174**<br><br>**Monthly perfloxacin 400: 28/169**<br><br>(see sever side effects) |
| Melekos 1997 | **Postcoital and daily ciproflocaxin 125: 5/135 (both groups)**<br><br>*Description include severe and non severe side effects. Gastrointestinal distress, headaches, rash and vaginal candidiasis occurred in 13 (4-9) of the initial 152 patients. Five of these women discontinued preventive treatment and were excluded | **Postcoital ciproflocaxin 125: 4/70**<br><br>**Daily ciproflocaxin 125: 9/65**<br><br>(see severe side effects) |
| Brumfitt 1983 | **Trimethoprim 100: 0/20**<br><br>**Povidone iodine: 3/19**<br><br>• Vulval soreness (2)<br>• Vulval rash (1)<br><br>**Methenamine hippurate: 4/25**<br><br>• Nausea and vomiting (2)<br>• Indigestion (1)<br>• Vulval rash (1) | **Trimethoprim 100: 1/20**<br><br>• irritation/rash of vulva or vagina (1)<br><br>**Povidone iodine: 2/19**<br><br>• Indigestion or nausea (1)<br>• Irritation/rash of vulva or vagina (1)<br><br>**Methenamine hippurate: 5/25**<br><br>• Indigestion or nausea (4)<br>• Irritation/rash of vulva or vagina (1) |
| Brumfitt 1981 | **Nitrofurantoin 50: 12/43**<br><br>• Nausea (8 mild, 6 moderate, 7 severe)<br>• Vomiting (3)<br>• Headache (1)<br>• Indigestion (1)<br><br>**Methenamine hippurate: 2/56**<br><br>• Dysuria (4)<br>• Frequency (1) | **Nitrofurantoin 50: 9/43**<br><br>**Methenamine hippurate: 4/56**<br>(see severe side effects) |

**Table 6. Side effects** *(Continued)*

- Abdominal pain (1)
- Nausea (1)
- Dizziness (1)

*Description include severe and non-severe side effects.

**Table 7. Antibiotic versus antibiotic. MRPY and CRPY**

| Study (antibiotics) | MRPY 1 versus 2 | P | CRPY 1 versus 2 | P | Duration of treatment |
|---|---|---|---|---|---|
| Brumfitt 1995 (cefaclor 250, nitrofurantoin 50) | 0.3 (13/43.6) versus 0.29 (12/41.7) | NS | 1.38 (60/43.6) versus 1.51 (63/41.7) | NS | 12 months |
| Brumfitt 1991 (norfloxacin 200; nitrofurantoin 100) | 0.1 (4/39.9) versus 0.14 (5/35.9) | NS | 0.75 (30/39.9) versus 0.86 (31/35.9) | NS | 12 months |
| Nuñez 1990 (norfloxacin 400; nitrofurantoin 100) | 0.16 (2/12.6) versus 0 (0/13) | NS (0.2) | | | 6 months or until UTI |
| Brumfitt 1985 (trimethoprim 100; nitrofurantoin 100) | 1 (28/27.8) versus 0.17 (5/30) | < 0.001 | 1.69 (47/27.8) versus 1.23 (37/30) | NS | 12 months |
| Stamm 1980 (Cotrimoxazole 40-200; nitrofurantoin 100) | 0.15 (1/6.7) versus 0.14 (1/7.1) | NS | | | 6 months or until UTI |
| Seppanen 1988 (trimethoprim 100; cinoxacin 500) | 0.18 (1/5.5) versus 0.31 (2/6.4) | NS (0.6) | | | 6 months or until UTI |
| Guibert 1995 (pefloxacin 400; weekly versus monthly) | 0.16 (23/145.8) versus 0.6 (78/129.4) | < 0.001 | | | 11 months |
| Melekos 1997 (ciprofloxazole 125; postcoital versus daily) | 0.043 (3/70) versus 0.031 (2/65) | NS (0.7) | | | 12 months |

NS = not significant

**Table 8. Antibiotic versus other strategy. MRPY and CRPY**

| Study (interventions) | MRPY: antibotic versus other strategy | P | CRPY: antibiotic versus other strategy | P | Duration of intervention |
|---|---|---|---|---|---|

**Table 8. Antibiotic versus other strategy. MRPY and CRPY** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| Brumfitt 1983 (trimethoprim 100 mg/24 h; povidone iodine) | 1.53 (15/9.8) versus 1.79 (17/9.5) | NS | 2.24 (22/9.8) versus 2.42 (23/9.5) | NS | 12 months |
| Brumfitt 1981 (nitrofurantoin 50 mg/12 h; methenamine hippurate 1 g/12 h) | 0.19 (5/26.5) versus 0.57 (25/43.9) | 0.02 | 1.02 (27/26.5) versus 2.32 (102/43.9) | < 0.001 | 12 months |
| Brumfitt 1983 (trimethoprim 100 mg/24 h; methenamine hippurate 1 g/12 h) | 1.53 (15/9.8) versus 1.38 (24/17.4) | NS | 2.24 (22/9.8) versus 2.01 (35/17.4) | NS | 12 months |

NS = not significant

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 7 July 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 2004

| Date | Event | Description |
|---|---|---|
| 22 March 2007 | Amended | Two new ongoing studies identified which will be included upon their completion. |

## CONTRIBUTIONS OF AUTHORS

- Dr Albert, Dr Huertas, Dr Pereiró, Dr Sanfélix and Dr Gosalbes contributed to the protocol development, selectioned and evaluated the quality of the clinical trials, performed the duplicated data extraction, and writted the first version of the review.
- Dr Huertas and Dr Gosalbes were responsible for the bibliographic search
- Dr Perrotta and Dr Albert were responsible for the statistical and methodological aspects of the review and final report.
- Dr Albert was responsible for the day-to-day work of the review.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- FIS (Fondo de Investigación Sanitaria) 99/117, Spain.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis [adverse effects]; Randomized Controlled Trials as Topic; Secondary Prevention; Urinary Tract Infections [*prevention & control]

### MeSH check words

Female; Humans