Duration of treatment for asymptomatic bacteriuria during pregnancy (Review)

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[Intervention Review]

Duration of treatment for asymptomatic bacteriuria during pregnancy

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ABSTRACT

Background

A Cochrane systematic review has shown that drug treatment of asymptomatic bacteriuria in pregnant women substantially decreases the risk of pyelonephritis and reduces the risk of preterm delivery. However, it is not clear whether single-dose therapy is as effective as longer conventional antibiotic treatment.

Objectives

To assess the effects of different durations of treatment for asymptomatic bacteriuria in pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2011) and reference lists of identified articles.

Selection criteria

Randomized and quasi-randomized trials comparing antimicrobial therapeutic regimens that differed in duration (particularly comparing single dose with longer duration regimens) in pregnant women diagnosed with asymptomatic bacteriuria.

Data collection and analysis

We assessed trial quality and extracted data independently.

Main results

We included 13 studies, involving 1622 women. All were comparisons of single-dose treatment with four- to seven-day treatments. The trials were generally of limited quality. The 'no cure rate' for asymptomatic bacteriuria in pregnant women was slightly higher for the single-dose than for the short-course treatment; however, these results were not statistically significant and showed heterogeneity. When comparing the trials that used the same antibiotic in both treatment and control groups with the trials that used different antibiotics in both groups, the 'no cure rate' risk ratio was similar. There was no statistically significant difference in the recurrence of asymptomatic bacteriuria rate between treatment and control groups. Slight differences were detected for preterm births and pyelonephritis although, apart from one trial, the sample size of the trials was inadequate. Single-dose treatment was associated with a decrease in reports of 'any side-effects' .

Authors' conclusions

Single-dose regimen of antibiotics may be less effective than the seven-day regimen. Women with asymptomatic bacteriuria in pregnancy should be treated by the standard regimen of antibiotics until more data become available testing seven-day compared with three- or five-day regimens.

PLAIN LANGUAGE SUMMARY

Duration of treatment for asymptomatic bacteriuria during pregnancy

Asymptomatic bacteriuria is a urinary tract infection (without symptoms) common in pregnancy. If untreated, it can lead to pyelonephritis (kidney infection). Antibiotic treatment is recommended. This review aimed to identify whether single-dose antibiotic treatments are as effective as longer ones for maternal and newborn outcomes. The review of 13 studies, involving over 1622 women, found that a one-day regimen is significantly less effective than a seven-day regimen.

BACKGROUND

Asymptomatic bacteriuria is a common and potentially serious medical complication when it occurs during pregnancy. The incidence of asymptomatic bacteriuria during pregnancy has been reported to be between 2% and 10% (Andrews 1992; Sweet 1977). *Escherichia coli* is the most common causative organism followed by organisms such as *Staphylococcus saprophyticus*, *Klebsiella spp*, *Enterobacter spp*, *Proteus spp*, *Enterococcus spp*, and others. Between 15% and 45% of pregnant women with asymptomatic bacteriuria, if left untreated, will develop pyelonephritis (Wang 1989). Pyelonephritis is associated with an increase in maternal and fetal morbidity.

There is evidence to show that screening (and treatment) of all pregnant women for asymptomatic bacteriuria is both effective and cost-beneficial when compared to no treatment in reducing the risk of pyelonephritis. A meta-analysis of 14 randomized controlled trials (RCTs) found that treatment of asymptomatic bacteriuria reduced the risk of the development of pyelonephritis when compared to no treatment (Smaill 2007). Using decision analysis modelling to compare no screening to screening for asymptomatic bacteriuria, pyelonephritis was shown to decrease from 23.2 cases per 1000 among unscreened pregnant women to 16.20 cases per 1000 in those screened with leukocyte esterase-nitrite dipstick, to 11.2 cases per 1000 among those screened with the more sensitive test of urine culture (Rouse 1995). In addition, both dipstick and culture screening were shown to be more cost-beneficial when compared to no screening, and had a high level of agreement in the diagnosis of asymptomatic bacteriuria (Rouse 1995).

The association between asymptomatic bacteriuria and preterm delivery has also been studied. Findings from the Cardiff Birth Survey, which prospectively studied 25,844 births, reported that asymptomatic bacteriuria, adjusted for demographic and social factors, was not associated with preterm delivery (odds ratio (OR) 1.20, 95% confidence intervals (CI) 0.90 to 1.50) (Meis 1995a). However, when preterm births were categorized into 'indicated' or 'spontaneous' preterm births (Meis 1995b), a significant association between bacteriuria and indicated preterm birth was found (OR 2.03, 95% CI 1.50 to 2.80). In an overview of antimicrobial interventions to prevent preterm birth (Villar 1997), risk of preterm delivery/low birthweight was found to be significantly decreased for pregnant women who had received antibiotic treatment for asymptomatic bacteriuria when compared to women who did not receive treatment (risk ratio (RR) 0.67, 95% CI 0.52 to 0.85). There was an even greater decrease in risk when the only three trials which had categorized preterm delivery separately from low birthweight were considered (RR 0.53, 95% CI 0.33 to 0.86). An earlier meta-analysis of eight RCTs showed that antibiotic treatment significantly reduced the risk of low birthweight (RR 0.56, 95% CI 0.43 to 0.73); however, preterm delivery was not reported independently (Romero 1989). Another meta-analysis of 14 RCTs found that antibiotic treatment was associated with a reduction in the incidence of low birth weight babies (RR 0.66, 95% CI 0.49 to 0.89) but not with a difference in preterm delivery (Smaill 2007). These findings have the limitations that the antibiotic regimens varied, and that many of the antimicrobials may no longer be prescribed in routine clinical practice. Nonetheless, we think that the evidence supports the view that all pregnant women with asymptomatic bacteriuria should be treated to prevent the development of acute pyelonephritis and reduce the risk of preterm delivery.

The question remains, what is the most effective treatment at the

lowest cost, with the fewest side effects? These answers will depend on the pathogen, the choice and duration of antimicrobial, and the available healthcare services. An earlier meta-analysis of seven RCTs reported that a single dose compared to a four to seven-day antibiotic treatment for bacteriuria showed no statistically significant difference in effectiveness when measuring outcomes of 'cure' and 'recurrence' (Smaill 1992a). However, these studies lacked a uniform definition for 'cure' and 'recurrence', and lacked consistent protocols for follow-up of treatment, making comparisons difficult. Nonetheless, the available data do suggest that single-dose therapy may be as effective as longer, conventional antibiotic treatment. Evidence regarding duration of therapy is especially important because single-dose therapy offers the benefits of greater compliance of women during pregnancy at lower cost. In under-resourced settings, the screening and treatment can be done during the same antenatal care visit.

OBJECTIVES

The objective of the review is to determine the clinical effectiveness of different durations of treatment for asymptomatic bacteriuria in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs comparing treatment regimens for bacteriuria during pregnancy that differ in duration including those that compared different duration of different antimicrobial agents as well as different duration of the same agent. We expected that the majority of trials would attempt to show equivalence between treatments. We have not included trials comparing different therapeutic agents with the same duration of administration in this review, nor those presented only as abstracts.

Types of participants

Women identified during pregnancy as having asymptomatic bacteriuria.

Types of interventions

Antimicrobials of varying duration. Antimicrobial therapy regimens tend to show large variations in duration. For the purposes of this review, we have considered the following interventions distinct and compared to each other:

1. single dose (including one-day treatment with divided doses);
2. short course (four to seven days);
3. long course (14 days);
4. continuous (treatment continued until delivery).

We will group interventions that we identify in future that do not fall into one of the categories listed above in the category that is closest in duration. We will make this allocation without any consideration of the trial results.

Types of outcome measures

The primary outcome will be maternal cure rate defined as the woman having negative culture (test of cure) following initial treatment for asymptomatic bacteriuria. Secondary outcomes will be as follows.

(1) Maternal

(a) Recurrent asymptomatic bacteriuria (in this review, recurrence includes relapse (the recurrence of bacteriuria caused by the same organism, usually within six weeks of the initial infection); and re-infection (the recurrence of bacteriuria involving a different strain of bacteria after successful eradication of the initial infection, limited to the bladder, and occurring at least six weeks after therapy (Davison 1992)).
(b) Pyelonephritis.

(2) Newborn

(a) Preterm delivery (gestational age less than 37 weeks).
(b) Low birthweight (birthweight less than 2500 g).
(c) Preterm delivery or low birthweight (if reported together).
(d) Other birth outcomes.

(3) Side effects

Any side effect related to the antibiotic treatment.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2011).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);

2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of identified articles.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1.

For this update we used the following methods when assessing the trials identified by the updated search (Bayrak 2007; Estebanez 2009; Lumbiganon 2009).

Selection of studies

Two review authors (M Gulmezoglu (MG), M Widmer (MW)) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

For eligible studies, two review authors (MG, MW) extracted the data. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2011) and checked them for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (MG, MW) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator),
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We have assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at

each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomized to each group in the analyses, and analyzed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Because there were more than 10 studies included in the meta-analysis we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes we used the test proposed by Egger 1997, and for dichotomous outcomes we used the test proposed by Harbord 2006.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used the random-effects model as we consider that the effects of using the same antibiotic in the treatment and in the control groups would be different than the effects of using different antibiotics in each of the groups.

Subgroup analysis and investigation of heterogeneity

For the analysis we divided the trials into two groups: (1) trials that compared different duration of the same antimicrobial agent; and (2) trials that compared different duration of different antimicrobial agents. We assessed differences between groups by inspection

of the groups' confidence intervals; non-overlapping confidence intervals indicated a statistically significant difference in treatment effect between the groups.

RESULTS

Description of studies

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

We included 13 studies, involving 1622 women. For a detailed description of studies, *see* Characteristics of included studies.

Eleven trials included in the review were conducted in developed countries (Austria, Denmark, Germany, Italy, New Zealand, Spain, the United Kingdom, or the United States) and two in developing ones (Argentina, Philippines, Thailand, Turkey, and Viet Nam). The laboratory measurements of selected outcomes required facilities in which urine culture and antibiotic sensitivity testing were possible. Three trials were published recently (Bayrak 2007; Estebanez 2009; Lumbiganon 2009). One of the trials was published in 1990 (Thoumsin 1990); eight of the trials were published in the 1980s; the remaining trial was published in 1975 (Reeves 1975). The antimicrobial drugs used in the trials included: ampicillin, nitrofurantoin, cephalexin, fosfomycin trometamol, fosfomycin, amoxicillin-clavulanate, amoxicillin, co-trimoxazole, trimethoprim, and other sulphonamides. Bayrak 2007 compared single dose fosfomycin trometamol with five-day treatment of cefuroxime axetyl. Thoumsin 1990 compared single dose of fosfomycin trometamol single dose with seven-day treatment of nitrofurantoin; Estebanez 2009 compared single dose of fosfomycin with seven-day treatment of amoxicillin-clavulanate; the remaining 10 trials compared different durations of the same antimicrobial family. The duration of antimicrobial used in the experimental group was either single dose or one-day treatment with divided dose, and in the control groups, varied between four and seven days' duration. We included Brumfitt 1982 in spite of inclusion of 24% of symptomatic women in both groups, and Thoumsin 1990 in spite of the publication as preliminary results.

For details of the excluded studies, *see* table of Characteristics of excluded studies.

Risk of bias in included studies

For detailed information on methods *see* table of Characteristics of included studies.

Generation methods for randomization in the 13 trials included: computerized process for simple randomization (Masterton 1985); every other woman (Anderton 1983; Reeves 1975); and blocked randomization (Bayrak 2007; Gerstner 87-89; Lumbiganon 2009). Six trials provided no description of the generation method. Six trials did not describe the mechanism used in allocation concealment; randomized tables were used to allocate women (Brumfitt 1982); the remaining three described concealment as 'envelopes' only (Bailey 1983; Bailey 1986; Masterton 1985).

In all 13 trials, there was inadequate description to determine whether 'contamination' in the short-course treatment group, co-interventions, or protocol deviation occurred. In addition, the degree of blinding for outcome assessment could only be assessed in two trials (Lumbiganon 2009; Masterton 1985). No women were blinded to treatment in any of the trials except for those in the Lumbiganon 2009 trial. Only two trials (Lumbiganon 2009; Masterton 1985) described using blind outcome assessments; the remaining 11 did not provide adequate information to make a determination. Informed consent was mentioned in the majority of trials.

An explanation of the sample size calculation and power calculation were provided in the Bayrak 2007, Lumbiganon 2009 and Masterton 1985 trials.

The only trial that reported on the demographics or number of women who met the study eligibility criteria, but were not included in the study and also on compliance with the treatment regimen, was Lumbiganon 2009.

Loss to follow-up was described in all trials except in Pregazzi 1987. The rates of loss to follow-up were, as expected given the longer duration, generally higher in the comparison group as compared to the experimental (single dose) group (Anderton 1983; Bailey 1983; Bailey 1986; Gerstner 87-89). Although the numbers are small, when two treatments produce a different pattern of withdrawal, then this offers evidence that the groups are not entirely comparable (Jones 1996).

Randomization is less effective in achieving comparable groups in studies with small sample size. For example, in one trial, women in the experimental group were more likely to have a history of urinary tract infection as compared to the control group (50% versus 35%) (Bailey 1983). Disparity in baseline characteristics between treatment groups suggests selection bias due to inadequate randomization or too small a sample size, or both (Villar 1996). Regardless, there is an increased likelihood of selection bias in most of the trials. The total number of women enrolled in these studies ranged from 41 to 778.

In general, the trials lacked evidence of sufficient rigor in the design, conduct and analysis of results.

Effects of interventions

We included 13 trials, involving 1622 women. We divided these trials into two groups: (1) trials that compared different durations of the same agent; and (2) trials that compared different durations of different antimicrobial agents. We analyzed outcomes for each of the two groups separately.

(1) Ten trials involving 1378 women and comparing different duration of the same antimicrobial agent

(a) Maternal outcomes

All trials reported bacteriological success of treatment by repeat cultures (Anderton 1983; Bailey 1983; Bailey 1986; Brumfitt 1982; Gerstner 87-89; Lumbiganon 2009; Masterton 1985; Olsen 1989; Pregazzi 1987; Reeves 1975) The 'no cure' rate for the one-day versus the seven-day treatment had a risk ratio (RR) 1.43, 95% confidence interval (CI) 0.87 to 2.34 (Analysis 1.1)). This pooled result is of limited value because the difference is statistically non-significant and there is heterogeneity in the results. There are three trials (Bailey 1986; Gerstner 87-89; Reeves 1975) that show a protective effect of the single dose although not statistically significant. Conversely, in the trial with the highest methodological quality (Lumbiganon 2009), there were 90 out of 371 failed treatments in the one-day arm compared to 51 out of 370 in the longer treatment group (RR 1.76, 95% CI 1.29 to 2.40).
The risk of recurrent bacteriuria in one-day treatment was similar to that with longer treatment (RR 1.08, 95% CI 0.74 to 1.60) and we found no heterogeneity among trials' results.
Pyelonephritis was reported only by Bailey 1983 and Bailey 1986, with 102 women included in the two trials together. There were four more women with pyelonephritis following single-dose treatment (5/54 versus 1/48, RR 2.97, 95% CI 0.51 to 17.28). Because of the few cases, the confidence intervals are very wide.

(b) Newborn outcomes

Only three of the 10 trials included in this review reported preterm birth rates (Bailey 1983; Bailey 1986; Lumbiganon 2009). In total, 804 women were studied in these three trials and the differential effect of single-dose antibiotic when compared to a four- to seven-day course in preventing preterm birth is slightly in favor of the longer course treatment but statistically non-significant (RR 1.09, 95% CI 0.52 to 2.26).

(c) Side effects

The meta-analysis regarding any side effects (nausea, vomiting, diarrhoea) shows a statistically significant lower incidence of side effects with single-dose treatment (RR 0.77, 95% CI 0.61 to 0.97). The Reeves 1975 study was stopped prematurely due to the side effects (mainly nausea, vomiting, diarrhoea) of sulphadimidine in seven-day treatment. A sensitivity analysis including all trials comparing the same antimicrobial but excluding Reeves 1975 also showed higher, yet statistically non-significant, rates of similar side effects with longer treatment (RR 0.81, 95% CI 0.64 to 1.04).

(2) Three trials involving 244 women and comparing different durations of different antimicrobial agents

(a) Maternal outcomes

Three trials reported bacteriological success of treatment by repeat cultures (Bayrak 2007; Estebanez 2009; Thoumsin 1990). There was almost no difference in the 'no cure' rate for the single-dose treatment versus the short-course treatment, but this is statistically non-significant (RR 0.98, 95% CI 0.49 to 1.95). In Estebanez 2009 the cure rate was slightly higher in the one-day than in the seven-day treatment.
The incidence of recurrent bacteriuria was reported in two of the three included trials (Estebanez 2009; Thoumsin 1990) and there was no difference between the two groups (RR 1.32, 95% CI 0.23 to 7.55).

(b) Newborn outcomes

Rates of preterm births were not reported in the included trials.

(c) Side effects

The three trials (Bayrak 2007; Estebanez 2009; Thoumsin 1990) showed fewer side effects in the single-dose treatment group than in the short-course treatment group (RR 0.16, 95%CI 0.04 to 0.58).

DISCUSSION

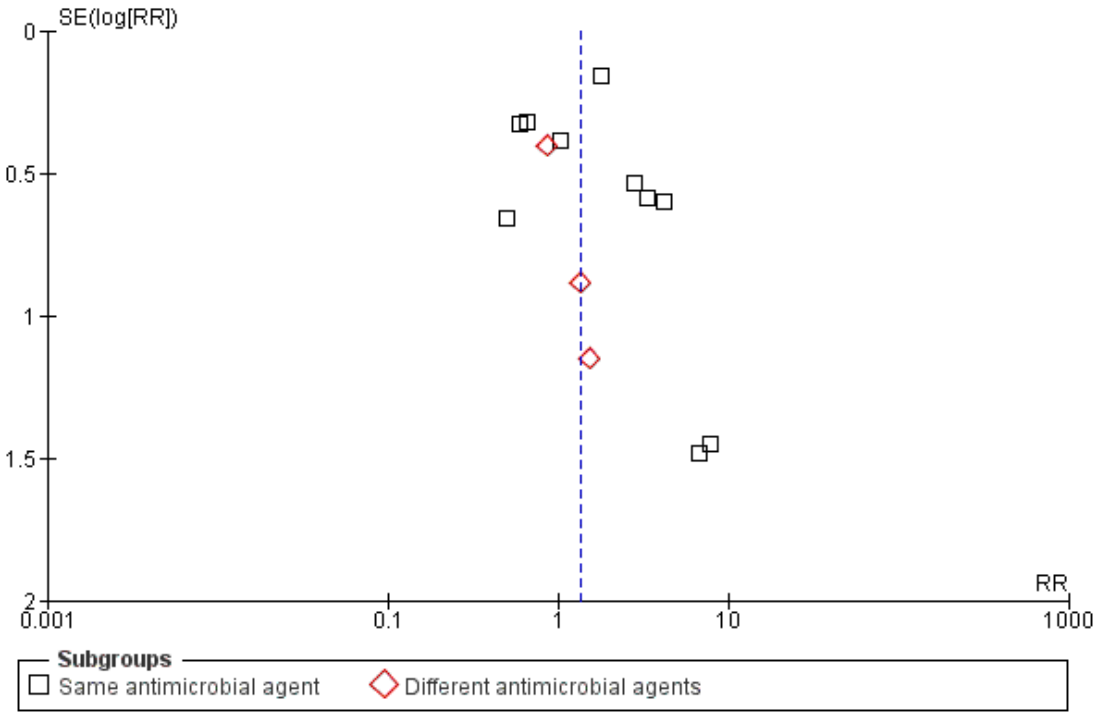
Asymptomatic bacteriuria during pregnancy has serious consequences if it is not treated. Routine screening and antibiotic treatment of positive cases is generally recommended. The optimal duration of the treatment has both cost and practical implications. The routine treatment is for four to seven days. However, single-dose treatment, if effective, could increase compliance (as the treatment can be administered at the healthcare site) and it is likely to be cheaper. These advantages are important in under-resourced countries where women attend antenatal clinics irregularly and where approximately 90% of all preterm deliveries around the world take place (Villar 1994). The objective of this review was to determine the clinical effectiveness of different durations of treatment for asymptomatic bacteriuria in pregnancy. The results show that the cure rate is higher for the four- to seven-day treatment than for the one-day treatment.

In this most recent update, we have added three trials (Bayrak 2007; Estebanez 2009; Lumbiganon 2009). Bayrak 2007 compared single dose of fosfomycin trometamol with five-day regimen of cefuroxime axetyl in 90 pregnant women in their second trimester of gestation. The trial's results show only cure rates and

side effects. Estebanez 2009 compared single dose of fosfomycin with seven-day amoxicillin-clavulanate treatment in 131 pregnant women. There were no differences between the two treatments regarding cure, recurrences, and persistences. Lumbiganon 2009 compared one-day with seven-day nitrofurantoin treatment in 778 pregnant women at gestational ages of 12 to 32 weeks. The cure rate was significantly higher in the short-course regimen than in the single-dose one. Incidence of preterm delivery was higher in the single-dose treatment but non-statistically significant. Side effects were fewer in the single-dose regimen than in the short-course regimen, but this difference was not statistically significant. The neonatal outcomes, low birthweight, and congenital malformations were higher in the single-dose regimen but not statistically significant.

In general, the trials in this review have several methodological limitations which make interpretation of the heterogeneous results difficult. Heterogeneity was mostly due to three trials that demonstrated a protective effect of one-day treatment, however, the three of them had small sample sizes. Small trials tend to be conducted and analyzed with less methodological rigour than larger trials and tend to overestimate the effect of one group. This is of greater concern in equivalence trials where larger sample sizes are required than comparative trials (Jones 1996). The funnel plot (Figure 1) and its relation with publication bias could not be ruled out because of the small number of included trials. The poor methodological quality of these trials may obscure any important clinical and laboratory differences between duration of treatment regimens. The Lumbiganon 2009 trial provides about half of the data to the meta-analysis and is methodologically sound. We therefore think that overall, longer duration of treatment is likely to be more effective. However, there is a drawback that non-adherence may be higher with treatments of longer duration.

Figure 1. Funnel plot of comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, outcome: 1.6 No cure.



AUTHORS' CONCLUSIONS

Implications for practice

It is recommended that until evidence from new trials is available,

practitioners should follow the four- to seven-day treatment regimen for treating asymptomatic bacteriuria in pregnant women.

Implications for research

There is a need for a RCT designed to test whether three-day antimicrobial therapy of first-line of choice drug is as effective as longer treatment regimens in prevention of preterm birth, pyelonephritis, and recurrent infection during the index pregnancy. Future trials should, therefore, be designed taking the following factors into account.

(1) Trial size

The trials should be appropriately sized taking into account the 'equivalence' nature of the comparison.

(2) Trial design

Ideally, these trials should be placebo-controlled to prevent bias.

(3) Outcomes

Immediate bacteriological cure (in one to two weeks) is the relevant outcome as related to the treatments under study.

(4) Interventions

Antibiotics should be researched with regard to the following principles:
(a) the antibiotic of choice should be safe in pregnancy;
(b) in circumstances where culture and sensitivity are not feasible, empiric, broad-spectrum treatment would be appropriate;
(c) where susceptibility is known, narrow-spectrum, specific antibiotic treatment would be appropriate.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anderton 1983

Methods	Alternate allocation. It was unclear whether the following criteria were met: blinding of outcome assessment, measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Providers and pregnant women were not blinded. Informed consent was obtained. No description of sample size or power calculation was provided
Participants	64 women enrolled in study. Setting: out-patient clinic in United Kingdom. Inclusion criteria: pregnant women > 16 years; confirmed asymptomatic bacteriuria with 2 consecutive positive bacteriologic count of identical organisms; urine culture sensitive to amoxicillin. Exclusion criteria: allergic to penicillin or cephalosporins; inability to take oral medications; requires parenteral antibiotics
Interventions	Experimental group: amoxicillin 3 g x 2 doses. Control group: amoxicillin 250 mg 3 times daily x 7 days.
Outcomes	Clinical outcomes: medication side effects. Laboratory outcomes: rate of 'no cure'.
Notes	Type of healthcare provider: unknown. Attrition bias: no loss to follow-up from experimental group 0/33; loss of follow-up for control group 2/34 (6%). Authors state that the 'majority' of study participants had asymptomatic bacteriuria; no description of distribution or breakdown by outcomes is provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The author used alternate allocation which is not a good practice
Allocation concealment (selection bias)	High risk	C - Inadequate.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.

Bailey 1983

Methods	Randomized controlled trial. Envelopes containing group assignment were used (no information re: sealed/opaque). No further description was provided regarding allocation. Method of randomization not described. It was unclear whether the following criteria were met: blinding of outcome assessment, measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Providers and pregnant women were not blinded. Consent process not described. No description of sample size or power calculation
Participants	44 women enrolled in study. Setting: out-patient clinic in New Zealand. Inclusion criteria: pregnant women < 30 weeks estimated gestational age; confirmed asymptomatic bacteriuria with mid-stream urine culture of bacterial count > 100,000, and second urine specimen by suprapubic bladder aspiration showing infection regardless of bacterial count; urine culture was sensitive to co-trimoxazole. Exclusion criteria: allergic to sulphonamides or co-trimoxazole
Interventions	Experimental group: co-trimoxazole 1.92 g x 1 dose. Control group: co-trimoxazole 0.96 g twice daily x 5 days.
Outcomes	Clinical outcomes: preterm delivery, pyelonephritis, medication side effects. Laboratory outcomes: no cure, recurrent asymptomatic bacteriuria
Notes	Type of healthcare provider: unknown. Attrition bias: no loss to follow-up from experimental group 0/24; 2/20 (10%) women lost to follow-up from control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	B-Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 of the women treated with a 5-day course of cotrimoxazole dropped out of the study

Bailey 1986

Methods	Randomized controlled trial. Envelopes containing group assignment were used (no information re: sealed/opaque). No further description was provided regarding allocation. Method of randomization not described. It was unclear whether the following criteria were met: blinding of outcome assessment, measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Providers and pregnant women were not blinded. Consent process not described. No description of sample size or power calculation
Participants	60 women enrolled in study. Population race/ethnicity 28% 'Polynesian'. Setting: out-patient clinic in New Zealand. Inclusion criteria: pregnant women 16-30 weeks' estimated gestational age; confirmed asymptomatic bacteriuria with mid-stream urine culture of bacterial count > 100,000, and second urine specimen by suprapubic bladder aspiration showing infection regardless of bacterial count. Exclusion criteria: not described
Interventions	Experimental group: trimethoprim 600 mg x 1 dose. Control group: trimethoprim 300 mg once daily x 5 days.
Outcomes	Clinical outcomes: preterm delivery, pyelonephritis, medication side effects. Laboratory outcomes: no cure, recurrent asymptomatic bacteriuria
Notes	Type of healthcare provider: unknown. Minimal attrition bias: no loss to follow-up from experimental group 0/30; 2/30 (7%) women lost to follow-up from control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	B - Unclear. Envelopes were used but the allocation was not defined
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 of the women treated with a 5-day course of trimethoprim moved to another city after initial bacteriological follow-up

Bayrak 2007

Methods	Randomized controlled trial. 90 pregnant women were randomized to receive either a single dose fosfomycin trometamol or a 5-day course of cefuroxime axetyl. Pregnant women were not blinded to treatment assignment. It was unclear whether the following criteria were met: measurement of contamination of control group, assessments of co-interventions. Power calculation described, sample size calculation conducted
Participants	90 women were enrolled in the trial. 1 patient in the fosfomycin trometamol group and 5 patients in the cefuroxime axetyl group were lost to follow-up and excluded from the trial. Inclusion criteria: pregnant women in the second trimester of gestation, confirmed asymptomatic bacteriuria with 2 consecutive clean-catch urine specimens yielding positive cultures of the same uropathogen. Exclusion criteria: gravidas presenting leukocytosis, fever, urolithiasis, lower back pain, previous urologic surgery, anomalies of the urinary tract
Interventions	Experimental group: single dose of 3 g fosfomycin trometamol Control group: cefuroxime axetyil 250 mg twice a day for 5 days
Outcomes	Clinical outcome: side effects. Laboratory outcome: bacteriological eradication of uropathogens
Notes	Cure rates are informed only as percentages. No ratios are informed Side effects are informed in percentages. No risk ratios nor confidence intervals are informed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A block randomization method was used to ensure an equal number of patients in each group
Allocation concealment (selection bias)	Low risk	The blocks were numbered, placed into a bag, and a staff member blinded to the research protocol selected the patients into the treatment groups
Blinding (performance bias and detection bias) All outcomes	Low risk	The staff member was blinded but the patient not.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient in the fosfomycin trometamol group and 5 patients in the cefuroxime axetyl group did not come to the follow-up visit; therefore, they were excluded from the study
Selective reporting (reporting bias)	Low risk	

Bayrak 2007 (*Continued*)

Other bias	Low risk	

Brumfitt 1982

Methods	Randomized controlled trial. Randomization tables were used to allocate participants. Unclear measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Providers and pregnant women were not blinded. No description of sample size or power calculation
Participants	54 women enrolled in a out-patient antenatal clinic. Inclusion criteria: pregnant women with culture confirmed asymptomatic bacteriuria during routine screening. Exclusion criteria: allergic to penicillin, infecting organisms were not sensitive to ampicillin
Interventions	Experimental group: oral amoxicillin 3 g x 2 doses during 1 day. Control group: oral amoxicillin 250 mg 3 times daily x 7 days
Outcomes	Clinical outcomes: birthweight, medication side effects. Laboratory outcome: cultures cure rates at 2 and 6 weeks.
Notes	24% were symptomatic in both groups, 65% were in the second trimester

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	B - Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.

Estebanez 2009

Methods	Randomized, prospective, longitudinal, unblinded trial. Allocation concealment done using random number tables. Method of randomization not described
Participants	131 pregnant women enrolled in the study. Setting: out-patient clinic in Spain. Inclusion criteria: pregnant women with asymptomatic bacteriuria ($\geq$ 100,000 CFU/ml of the same microorganism in two consecutive cultures) without fever or symptoms of UTI.

Estebanez 2009 (*Continued*)

	Exclusion criteria: having taken antibiotics 14 days prior to taking the culture for any reason other than having UTI; allergy to penicillins; high-risk pregnancy; admitted to hospital; impossibility of performing follow-up; anomalies in the urinary tract; infection due to microorganisms resistant to either of the two antibiotics and symptomatic UTI
Interventions	Experimental group: fosfomycin 3g x 1 dose Control group: amoxicillin-clavulanate 500mg/125mg tablets every 8 hours for 7 days
Outcomes	Clinical outcomes: microbiological cure, recurrences, reinfection, persistences, secondary effects, and therapeutic compliance
Notes	There were no losses to follow-up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Random number tables
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	

Gerstner 87-89

Methods	Randomized controlled trial. Allocation concealment not described. Allocation to treatment done in blocks of 10-5 per treatment group. It was unclear whether the following criteria were met: blinding of outcome assessment, measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Providers and pregnant women were not blinded. Informed consent was obtained. No description of sample size or power calculation was provided
Participants	91 women (53 single dose, 38 longer course) enrolled in study. Setting: multicenter outpatient clinic in Austria. Inclusion criteria: pregnant women; confirmed asymptomatic bacteriuria with mid-stream urine culture of bacterial count > 100,000 and bladder catheterization with bacterial count > 10,000 diagnosed with the dip-slide method; urine culture sensitive to amoxicillin
Interventions	Experimental group: amoxicillin 3 g x single dose. Control group: amoxicillin 750 mg 3 times daily x 4 days.

Gerstner 87-89 (*Continued*)

Outcomes	Clinical outcomes: medication side effects. Laboratory outcomes: 'no cure', recurrence of asymptomatic bacteriuria after 1 and 4 weeks following therapy
Notes	Healthcare providers: physicians and nurses. Attrition bias: loss to follow-up from experimental group was 7/53 (13%); loss to follow-up from control group was 10/38 (26%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization in groups of 10; 5 patients per regiment.
Allocation concealment (selection bias)	Unclear risk	B - Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.

Lumbiganon 2009

Methods	Randomized, double blind, placebo controlled non-inferiority trial. Pregnant women were randomly allocated to receive either a 1-day or a 7-day course of nitrofurantoin. Compliance was of 98% in both groups. Power calculation described, sample size calculation conducted. Assessment of co-interventions was done. Deviations from protocol were described
Participants	778 were enrolled in the trial. 9 women in the 1-day regimen and 10 women in the 7-day regimen were lost to follow-up. Sociodemographic characteristics of each group were similar at entry. Inclusion criteria: pregnant women at gestational age 12-32 weeks with no symptoms of urinary tract infection. Exclusion criteria: history of urinary tract infection during current pregnancy, under steroids and/or antibiotic treatment, presence of any hematologic disease including glucose-6-phosphate dehydrogenase deficiency
Interventions	Experimental group: one-day nitrofurantoin 100 mg twice a day Control group: seven-day nitrofurantoin 100 mg twice a day.
Outcomes	Clinical outcomes: incidence of symptomatic urinary tract infection, pyelonephritis, preterm delivery, low birthweight, adverse effects Laboratory outcomes: bacteriologic cure after antibiotic treatment assessed by a urine culture 14 days after the initiation of the treatment
Notes	

Lumbiganon 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	it was generated using computer-generated random numbers with randomly varying blocks of 6-8 (SAS software, SAS Institute, Inc., Cary, NC)
Allocation concealment (selection bias)	Low risk	The random allocation was concealed by using sealed, opaque treatment boxes numbering sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the women and the health providers were blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Delivery outcomes were available in 91.7% and 89.0% of the women in the 1-day and 7-day regimen respectively
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Masterton 1985

Methods	Randomized controlled trial. Allocation by computer-generated randomization. There was blinding of outcome assessment and providers (treatment allocation by clinic secretary). Pregnant women were not blinded. It was unclear whether the following criteria were met: measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Informed consent was obtained. Power calculation described; sample size calculation conducted, however, sample size achieved inadequate due to limited trial period
Participants	102 women were enrolled in study, 90 completed the protocol, and 62 women were analyzed as the subgroup 'antenatal asymptomatic bacteriuria'. Wives (British nationality) of servicemen from United Kingdom stationed in Germany. Setting: out-patient clinic. Inclusion criteria: pregnant women 28-36 weeks' estimated gestational age; confirmed asymptomatic bacteriuria with 2 consecutive urine cultures of bacterial count $\geq$ 100,000 colonies/ml urine; urine culture was ampicillin sensitive. Exclusion criteria: pyelonephritis; history of drug sensitivity to beta-lactam agents; or use of antibiotics within last 2 weeks
Interventions	Experimental group: amoxicillin 3 g single dose. Control group: ampicillin 500 mg 4 times daily x 7 days.

Masterton 1985 (*Continued*)

Outcomes	Laboratory outcomes: 'no cure', recurrent asymptomatic bacteriuria. Re-infection assessed at 1 week and 6 weeks after treatment
Notes	Type of healthcare provider: general practitioners and obstetricians. No attrition bias: no women lost from experimental group 0/39, or from control group 0/23. Ampicillin rather than amoxicillin was chosen because it is standard in this hospital

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate. Computer randomization.
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment allocation done by secretary. Obstetrician and microbiologist were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 out of 102 patients enrolled completed the protocol.

Olsen 1989

Methods	Randomized controlled trial. No description of method for generation and concealment of treatment. Providers and pregnant women were not blinded. It was unclear whether the following criteria were met: blinding of outcome assessment, measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Informed consent was obtained. No description of sample size or power calculation
Participants	41 women enrolled in study. Setting: out-patient clinic in Denmark. Inclusion criteria: pregnant women < 36 weeks estimated gestational age; confirmed asymptomatic bacteriuria with 2 consecutive urine cultures of bacterial count $\geqq$ 100,000 colonies/ml urine; urine culture was sensitive to sulfamethizole. Exclusion criteria: signs of urinary tract infection; chronic disease of the genitourinary tract; history of more than two urinary tract infections in previous 12 months; threatening preterm labour > 26 weeks estimated gestational age; allergy to sulphonamides; antibiotic therapy for any reason within 3 weeks prior to study
Interventions	Experimental group: sulfamethizole 2 g x single dose. Control group: sulfamethizole 1 g twice daily x 6 days.
Outcomes	Clinical outcomes: medication side effects. Laboratory outcomes: 'no cure', recurrence of asymptomatic bacteriuria
Notes	Type of healthcare provider: not described. Attrition bias: no women lost from experimental group 0/15; 2/26 (8%) women lost to follow-up from control group

Olsen 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	B - Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts in the longer treatment arm.

Pregazzi 1987

Methods	Randomized controlled trial. 44 pregnant women were divided into 2 groups: 1 treated traditionally and the other with single dose. Allocation to treatment is not described. Pregnant women were not blinded. Consent process is not described. It was unclear whether the following criteria were met: measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. The traditional protocol produced an immediate response in 86.4% of the cases demonstrating its superiority over the single-dose treatment that brought success in 54.5% of the cases
Participants	44 women enrolled in the study. Setting: out-patient clinic in Trieste University. October 1980 to December 1985. Inclusion criteria: pregnant women aged 17-35 years old, confirmed asymptomatic bacteriuria with positive bacteriologic count of > 100,000 CFU/ml. Exclusion criteria: 1st bacteriological count < 100,000 CFU/ml or 2nd bacteriological count > 100,000 CFU/ml but different microorganism comparing with the first one
Interventions	Experimental group: single dose of amoxicillin 3 g, or ampicillin 3.5 g, or trimethoprim 320 mg, or sulfamethoxazole 1600 mg, or cephalexin 3 g. Control group: 2-4 times daily x 1-2 weeks of the antibiotics named in the experiment group
Outcomes	Clinical outcomes: medication side effects. Laboratory outcomes: no cure rate, recurrent asymptomatic bacteriuria
Notes	Type of health provider: not described. Attrition bias: no description of loss to follow-up from experimental group

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Pregazzi 1987 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	D - Not used.

Reeves 1975

Methods	Generation of allocation sequence was by alternation. It was unclear whether the following criteria were met: measurement of contamination of control group, assessment of co-interventions, any deviation from protocol. Blinding of outcome assessment, providers and pregnant women was not done. Consent process not described. No description of sample size or power calculation
Participants	100 women enrolled in study. Setting: antenatal clinics in England. Inclusion criteria: pregnant women attending the bacteriuria clinic; confirmed bacteriuria with 2 consecutive urine cultures of bacterial count greater than or equal to 100,000 colonies/ml urine; urine culture was sensitive to sulphonamides. Exclusion criteria: not described
Interventions	Experiment group: sulphonamide sulfametopyrazine 2 g single dose, orally in 50 ml of water in the clinic. Control group: sulphadimidine 1 g 4 times daily x 7 days.
Outcomes	Clinical outcome: medication side effect. Laboratory outcome: 'no cure', 2 and 6 weeks after the first dose. Growth of different bacteria considered re-infection
Notes	Type of healthcare provider: physicians. Attrition bias: loss to follow-up from experimental group 5/54 (9%); loss to follow-up from control group 6/46 (13%). Unable to abstract data on 'recurrent asymptomatic bacteriuria': Reeves's operational definition of cure rate at 6 weeks was incomparable to the definition of recurrent asymptomatic bacteriuria used for review. No differentiation was made between asymptomatic and symptomatic bacteriuria in methods or results section. However, no indication or description was provided on the presence of any signs or symptoms of urinary tract infection, thus, the study was included in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.

Incomplete outcome data (attrition bias) All outcomes	Low risk	5/54 were lost to follow-up from the experimental arm; 6/46 from the control one

Thoumsin 1990

Methods	Randomized controlled study. Allocation to treatment not described. Pregnant women nor provider were blinded. Informed consent was taken. No description of sample size or power calculation was provided (the study did not conclude). It was unclear whether the following criteria were met: measurement of contamination of control group, assessment of co-interventions, any deviation from protocol
Participants	23 women enrolled in the study. Setting: out-patient clinic in Germany. Inclusion criteria: significant bacteriuria (10,000 CFU/ml or more) without symptoms. Exclusion criteria: not described
Interventions	Experimental group: single dose of fosfomycin trometamol 3 g. Control group: 7-day course of nitrofurantoin 100 mg
Outcomes	Clinical outcome: medication side effect. Laboratory outcomes: rate of no cure.
Notes	Type of healthcare provider: not described. Attrition bias: no description of loss to follow-up. from experimental group nor for control group. This study shows preliminary results. No final results were published

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	D - Not used.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.

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

Study	Reason for exclusion
Adelson 1992	In this study the 66% of the experimental group were determined to have symptomatic bacteriuria as compared to 33% with asymptomatic bacteriuria. Similarly, in the control group 63% of women were determined to have symptomatic bacteriuria as compared to 37% with asymptomatic bacteriuria. Both symptomatic and asymptomatic bacteriuria were combined when outcomes were assessed; therefore, the study is excluded because of the inability to assess asymptomatic bacteriuria separately. Clarification of data is being sought from authors
Bint 1979	In this study 100 pregnant women were screened and randomly allocated in equal numbers to receive either 400 mg pivmecillinam 4 times daily for 7 days or 500 mg ampicillin 4 times daily for 7 days. The treatment did not differ in duration. No distinction was made between asymptomatic and symptomatic bacteriuria. Cure rates were 88% in the pivmecillinam group and 85% in the ampicillin group. Side effects were significantly more frequent in the pivmecillinam group
Brumfitt 1973	This paper includes 2 trials. The first trial compares a 7-day course of treatment with trimethoprim-sulfamethoxazole in 3 different combinations, but of the same duration. In the second trial, 4 drugs were administered at high doses to investigate the possibility that better results might be obtained with high blood levels of antibiotic than smaller dose. There was not a distinction between asymptomatic and symptomatic bacteriuria
Campbell-Brown 1983	This is not a randomized controlled trial. In this study bacteriuria was diagnosed from suprapubic aspiration specimens of urine. All participants received the same treatment: single dose of 3 g cephalexin. There was no distinction between symptomatic and asymptomatic pregnant women. The cure rate achieved was 70%. 30% of the participants who were not cured received a 7-day course of antibacterial according to the sensitivity of the organism isolated. 36% continued with the infection and were given continuous antibacterial therapy
Davies 1975	4 drugs were compared but all were administered during a week. There were 53 women enrolled, 26 (49%) of whom had urinary symptoms at the first clinic attendance
De Cecco 1987	In this study no distinction was made between asymptomatic bacteriuria and symptomatic bacteriuria. The study participants included pregnant women > 8 weeks estimated gestational age who had any bacteriuria > 100,000. The terminology used in the paper to refer to the exposure of interest was 'lower urinary tract infections'. Therefore, this study was excluded. In addition, it was unclear whether randomization was carried out: there was a marked imbalance in the study groups (52 versus 31). If one of the two antimicrobial treatment regimens failed, women were switched to the other treatment regimen; no description was provided on how many or which women crossed over
Harris 1982	86 pregnant women were sequentially assigned to 1 of 4 single-dose, single-antimicrobial treatment groups: ampicillin 2 g, plus probenimide 1 g; keflex 2 g, plus probenimide 1 g; macrodantin 200 mg; or, gantrisin 2 g. All participants were diagnosed as having asymptomatic bacteriuria if they had no symptoms of urinary tract infection and had 2 consecutive urine cultures > 100,000 colonies per ml of the same species of micro-organism. The overall no cure rate was 31%, with a recurrence rate of 3.5%
Jakobi 1987	50 asymptomatic pregnant women were treated with 3 g of amoxicillin or 2 g of cephalexin in accordance with the isolated micro-organism disk sensitivity. The study was not based on randomization. There was no difference in duration of treatment. The immediate cure rate was 84% and the recurrence rate was 12%.

(*Continued*)

	The failure of treatment with single-dose treatment was 16%, these participants were treated with the same drug administered for 7 days and were cured. It is possible that these participants had upper UTI or urinary tract malformations
McFadyen 1987	The main comparison of interest to the present review, single dose versus 3-day regimen, was not based on randomization. 2 3-day regimens that compared cephalexin 1 g with pivmecillinam-pivampicillin in an independent randomized trial (reported separately) were grouped together in this paper and compared with a non-randomized series of pregnant women who received a single dose of cephalexin 3 g orally
Pathak 1969	In this study, participants were randomized to nitrofurantoin or placebo, all of them during a 3-week period
Pedler 1985	In this study no distinction was made between asymptomatic bacteriuria and symptomatic one. Women were randomly allocated to receive either 1 tablet of amoxicillin-clavulanic acid 3 times daily or 250 mg of cephalexin 3 times daily for 7 days. There was no difference in the duration of treatment. The study compared difference of choice of antimicrobial. Differences in cure rates were not statistically significant. No significant difference in the rate of side effects was found. No toxicity to the fetus was seen which could be ascribed to either drug
Robertson 1968	Women were alternately allocated into treatment with a 2-week course of either cycloserine 250 mg 2 times daily or sulphadimidine 0.5 g 4 times daily. There was no difference in the duration of treatment; what was compared was the difference in choice of antimicrobial
Sanderson 1984	This study aimed at reducing reinfection. Participants whose urine was found to be sterile (after 7-day course of pivmecillinam 1 tablet thrice daily), received at random pivmecillinam sachets prophylactically, 100 mg in the evening on alternates days, or were allocated to a control group, who were given no treatment
Whalley 1977	Randomized and non-randomized study participants were combined together. This study was excluded because it was not possible to analyze the results of randomized and non-randomized groups separately
Zinner 1990	Pregnant women with symptomatic and asymptomatic bacteriuria were combined. The majority of women in the study population were described as having symptomatic bacteriuria; therefore, the study is excluded because of the inability to assess asymptomatic bacteriuria separately. An additional concern was the introduction of bias through the sampling method; the sample size of n = 291 was obtained from 25 different study sites in Italy

UTI: urinary tract infection

DATA AND ANALYSES

Comparison 1. Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

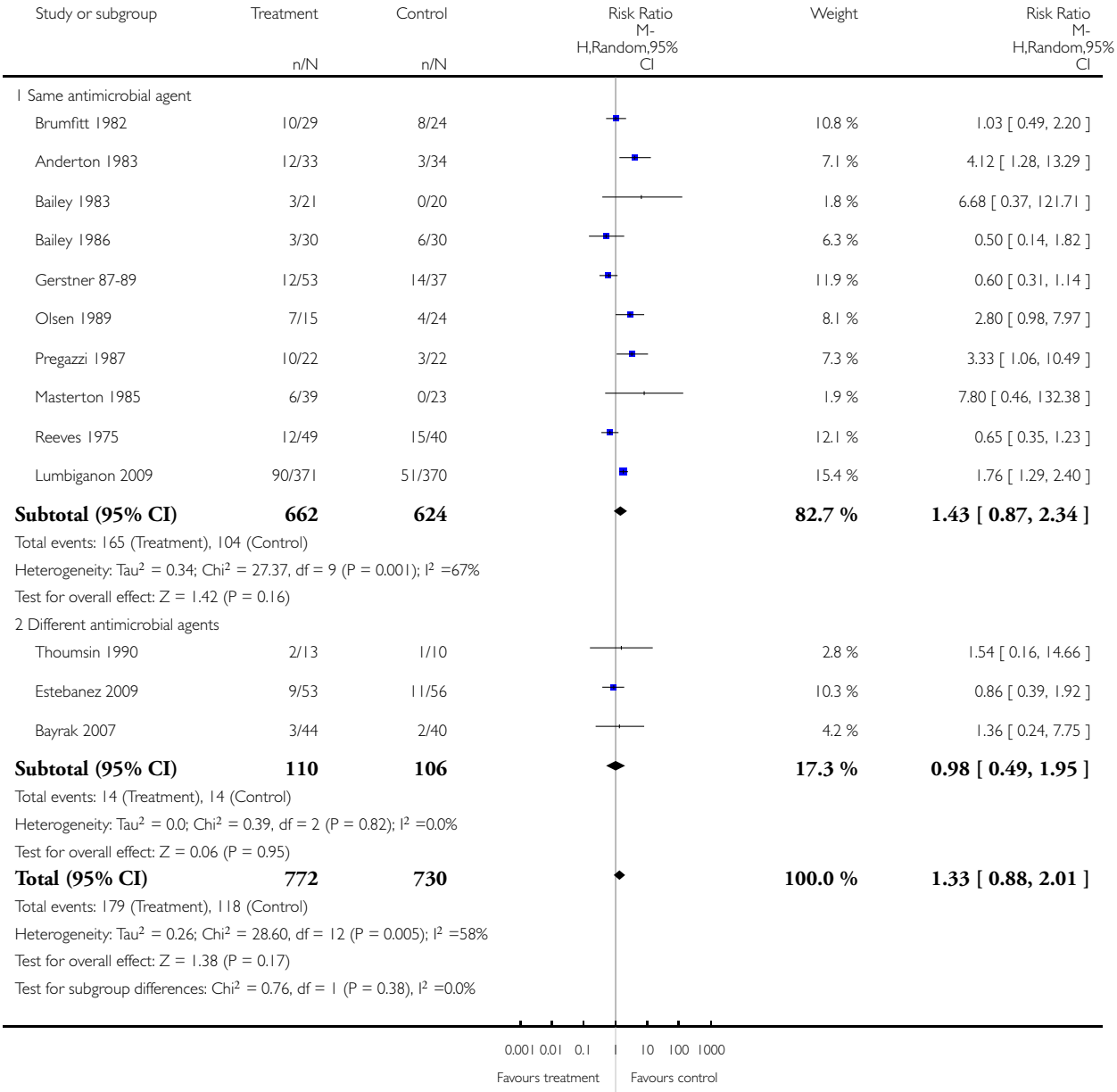
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No cure	13	1502	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.88, 2.01]
1.1 Same antimicrobial agent	10	1286	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.87, 2.34]
1.2 Different antimicrobial agents	3	216	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.49, 1.95]
2 Preterm delivery	3	804	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.52, 2.26]
2.1 Same antimicrobial agent	3	804	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.52, 2.26]
3 Preterm delivery or low birthweight	1	714	Risk Difference (M-H, Random, 95% CI)	0.05 [0.01, 0.10]
3.1 Same antimicrobial agent	1	714	Risk Difference (M-H, Random, 95% CI)	0.05 [0.01, 0.10]
4 Pyelonephritis	2	102	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.51, 17.28]
4.1 Same antimicrobial agent	2	102	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.51, 17.28]
5 Side effects	12	1460	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.56, 0.88]
5.1 Same antimicrobial agent	9	1244	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.61, 0.97]
5.2 Different antimicrobial agents	3	216	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.58]
6 Recurrent asymptomatic bacteriuria	8	445	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.75, 1.60]
6.1 Same antimicrobial agent	6	313	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.74, 1.60]
6.2 Different antimicrobial agents	2	132	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.23, 7.55]
7 Need for repeat treatment	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 1 No cure.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 1 No cure



Analysis 1.2. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 2 Preterm delivery.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 2 Preterm delivery

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Same antimicrobial agent					
Bailey 1983	2/24	4/18		17.7 %	0.38 [0.08, 1.83]
Bailey 1986	3/31	1/28		10.0 %	2.71 [0.30, 24.57]
Lumbiganon 2009	39/354	31/349		72.3 %	1.24 [0.79, 1.94]
Total (95% CI)	**409**	**395**		**100.0 %**	**1.09 [0.52, 2.26]**
Total events: 44 (Treatment), 36 (Control)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 2.61$, df = 2 (P = 0.27); $I^2 = 23\%$					
Test for overall effect: Z = 0.22 (P = 0.83)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 3 Preterm delivery or low birthweight.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 3 Preterm delivery or low birthweight

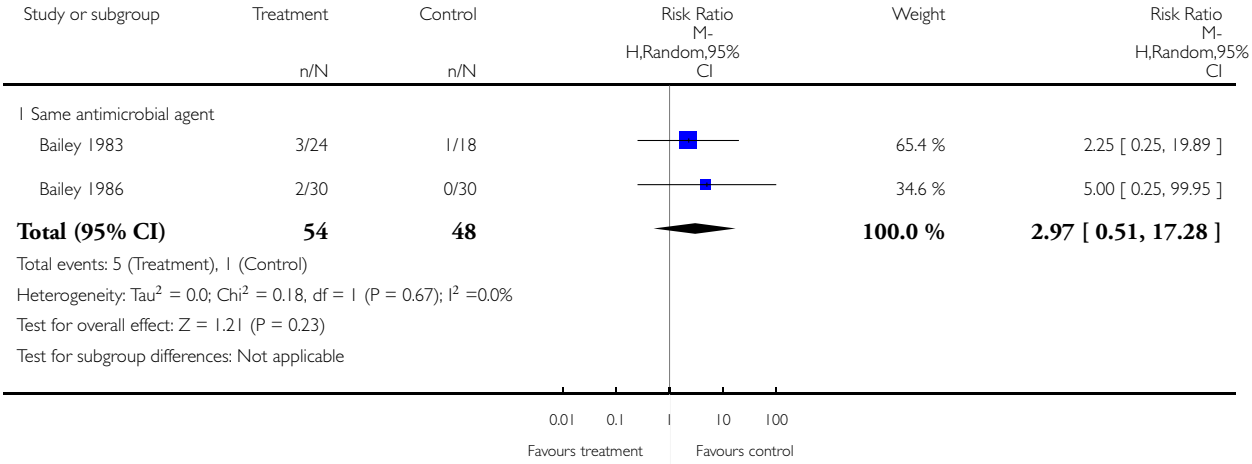
Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Same antimicrobial agent					
Lumbiganon 2009	48/364	28/350		100.0 %	0.05 [0.01, 0.10]
Total (95% CI)	**364**	**350**		**100.0 %**	**0.05 [0.01, 0.10]**
Total events: 48 (Treatment), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.26 (P = 0.024)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 4 Pyelonephritis.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 4 Pyelonephritis



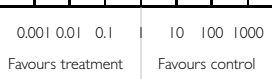
Analysis 1.5. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 5 Side effects.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 5 Side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Same antimicrobial agent					
Brumfitt 1982	3/29	4/24		3.1 %	0.62 [0.15, 2.51]
Anderton 1983	1/33	1/34		0.7 %	1.03 [0.07, 15.80]
Bailey 1983	0/24	0/20			Not estimable
Bailey 1986	1/30	0/30		0.4 %	3.00 [0.13, 70.83]
Gerstner 87-89	2/53	5/37		4.2 %	0.28 [0.06, 1.36]
Olsen 1989	3/15	6/24		3.3 %	0.80 [0.23, 2.73]
Reeves 1975	6/47	13/40		10.0 %	0.39 [0.16, 0.94]
Pregazzi 1987	4/22	6/22		4.3 %	0.67 [0.22, 2.04]
Lumbiganon 2009	75/375	90/385		63.1 %	0.86 [0.65, 1.12]
Subtotal (95% CI)	**628**	**616**		**88.9 %**	**0.77 [0.61, 0.97]**
Total events: 95 (Treatment), 125 (Control)					
Heterogeneity: Chi² = 5.37, df = 7 (P = 0.62); I² =0.0%					
Test for overall effect: Z = 2.19 (P = 0.028)					
2 Different antimicrobial agents					
Thoumsin 1990	0/13	2/10		2.0 %	0.16 [0.01, 2.95]
Estebanez 2009	1/53	11/56		7.6 %	0.10 [0.01, 0.72]
Bayrak 2007	1/44	2/40		1.5 %	0.45 [0.04, 4.82]
Subtotal (95% CI)	**110**	**106**		**11.1 %**	**0.16 [0.04, 0.58]**
Total events: 2 (Treatment), 15 (Control)					
Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 2.76 (P = 0.0059)					
Total (95% CI)	**738**	**722**		**100.0 %**	**0.70 [0.56, 0.88]**
Total events: 97 (Treatment), 140 (Control)					
Heterogeneity: Chi² = 10.93, df = 10 (P = 0.36); I² =9%					
Test for overall effect: Z = 3.03 (P = 0.0024)					
Test for subgroup differences: Chi² = 5.42, df = 1 (P = 0.02), I² =82%					

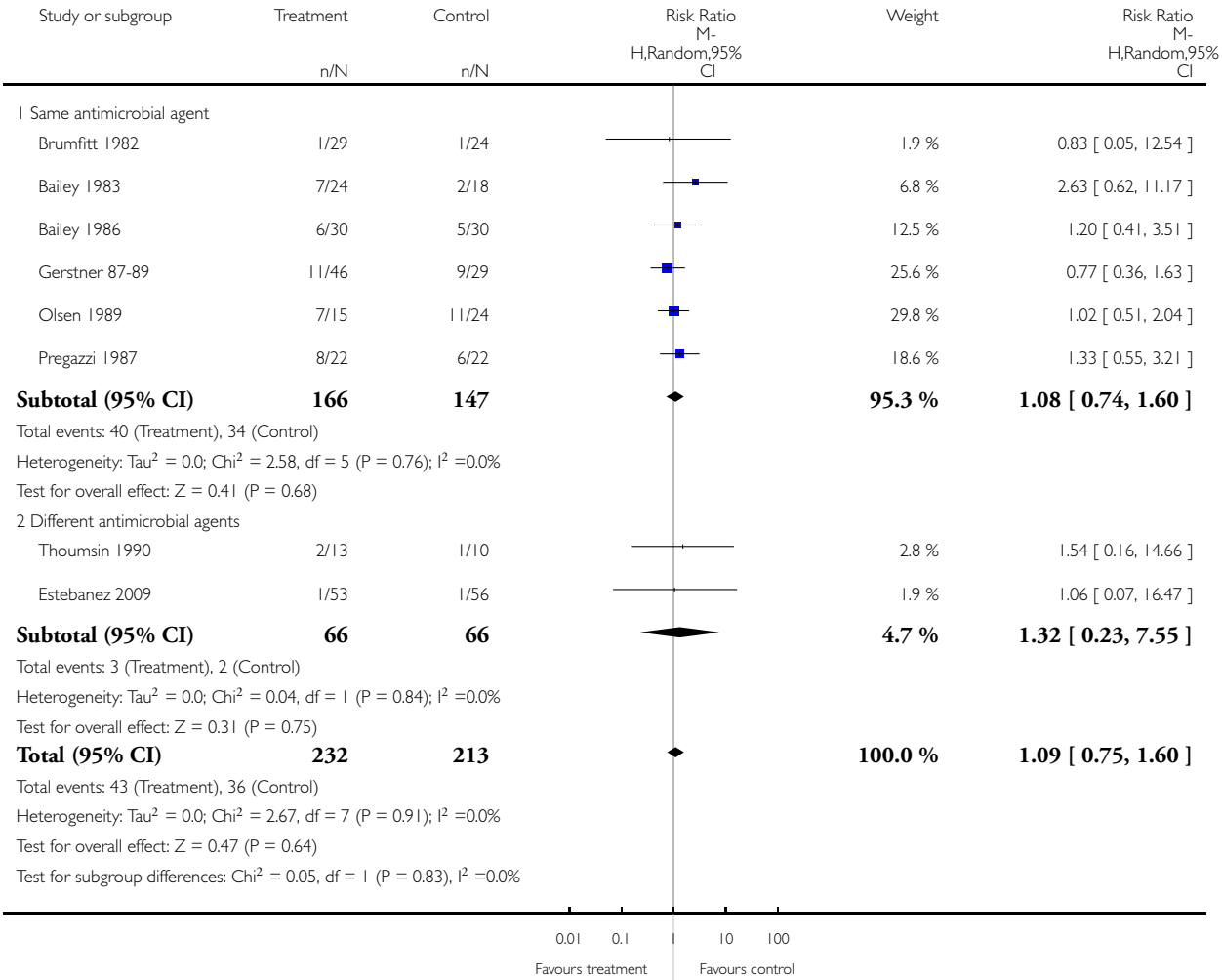


Analysis 1.6. Comparison 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria, Outcome 6 Recurrent asymptomatic bacteriuria.

Review: Duration of treatment for asymptomatic bacteriuria during pregnancy

Comparison: 1 Single dose versus short-course (4-7 day) antibiotic for asymptomatic bacteriuria

Outcome: 6 Recurrent asymptomatic bacteriuria



APPENDICES

Appendix 1. Methods used to assess trials for inclusion in the previous version of the review

We extracted the data from each publication independently and jointly reviewed them before conducting the analysis. We were not blinded to the authors or sources of the articles as the usefulness of blinding has not been confirmed yet (Berlin 1997). We resolved discrepancies by discussion. We divided the included trials into two groups (trials that used the same antimicrobial drug in treatment and control groups, and trials that used different ones). We analyzed outcomes in each group. In addition to the main outcome measures listed above, we systematically extracted the following data for each study:

1. exclusions after randomization;
2. loss to follow-up;
3. size of the trial (numbers enrolled);
4. settings of trials, i.e. country, socioeconomic status, type of clinic, and health provider;
5. detailed description of treatment used.

We used a list of criteria from a methodological review (Villar 1996) and recommendations from the Cochrane Reviewers' Handbook (Clarke 1999). The criteria used were: allocation concealment, blinding of the outcome assessment, blinding of doctor or nurse, blinding of women, contamination in the control groups, attrition bias, co-intervention and protocol deviation. We rated all criteria as 'met', 'unmet' or 'unclear'. We made decisions reached by consensus. We considered the principles related to the evaluation of equivalence trials in assessing the methodological quality of the trials (Jones 1996). The methodological quality assessment is reported in a narrative way in the relevant section of the review.

WHAT'S NEW

Last assessed as up-to-date: 9 November 2011.

Date	Event	Description
31 August 2011	New search has been performed	Search updated. Three new trials included (Bayrak 2007; Estebanez 2009; Lumbiganon 2009).
9 September 2008	New citation required and conclusions have changed	The inclusion of a well-designed trial with a large sample size, published in 2009 (Lumbiganon 2009) contributed significantly to provide a definite answer to this review's question: the one-day antimicrobial treatment is significantly less effective than the seven-day one

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 1, 1999

Date	Event	Description
2 September 2008	Amended	Converted to new review format.
31 July 2006	New search has been performed	Search updated. We identified one new trial report of an ongoing WHO trial
1 May 2004	New search has been performed	We added two new trials to the May 2004 update (Pregazzi 1987; Thoumsin 1990).

CONTRIBUTIONS OF AUTHORS

J Villar and AM Gülmezoglu had the idea for the preparation of this review. MT Lydon-Rochelle and A Roganti worked on the background, data extraction and writing the first version of the review.

M Widmer prepared the 2009 update. AM Gulmezoglu review drafts and provided suggestions for revisions. LE Mignini and A Roganti provided comments to the final draft.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- HRP-UNDP/UNFPA/WHO/WORLD BANK, Switzerland.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage; therapeutic use]; Bacteriuria [*drug therapy]; Drug Administration Schedule; Pregnancy Complications, Infectious [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy