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Smaill FM, Vazquez JC

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[Intervention Review]

Antibiotics for asymptomatic bacteriuria in pregnancy

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ABSTRACT

Background

Asymptomatic bacteriuria occurs in 2% to 10% of pregnancies and, if not treated, up to 30% of mothers will develop acute pyelonephritis. Asymptomatic bacteriuria has been associated with low birthweight and preterm birth.

Objectives

To assess the effect of antibiotic treatment for asymptomatic bacteriuria on the development of pyelonephritis and the risk of low birthweight and preterm birth.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (19 March 2015) and reference lists of retrieved studies.

Selection criteria

Randomized trials comparing antibiotic treatment with placebo or no treatment in pregnant women with asymptomatic bacteriuria found on antenatal screening.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Fourteen studies, involving almost 2000 women, were included. Antibiotic treatment compared with placebo or no treatment reduced the incidence of pyelonephritis (average risk ratio (RR) 0.23, 95% confidence interval (CI) 0.13 to 0.41; 11 studies, 1932 women; *very low quality evidence*). Antibiotic treatment was also associated with a reduction in the incidence of low birthweight babies (average RR 0.64, 95% CI 0.45 to 0.93; six studies, 1437 babies; *low quality evidence*) and preterm birth (RR 0.27, 95% CI 0.11 to 0.62; two studies, 242 women; *low quality evidence*). A reduction in persistent bacteriuria at the time of delivery was seen (average RR 0.30, 95% CI 0.18 to 0.53; four studies; 596 women). There were very limited data on which to estimate the effect of antibiotics on other infant outcomes and maternal adverse effects were rarely described.

Overall, all 14 studies were assessed as being at high or unclear risk of bias. While many studies lacked an adequate description of methods and the risk of bias could only be assessed as unclear, in almost all studies there was at least one domain where the risk of bias was judged as high. The three primary outcomes were assessed with GRADE software and given a quality rating. Evidence for pyelonephritis, preterm birth and birthweight less than 2500 g was assessed as of low or very low quality.

Authors' conclusions

While antibiotic treatment is effective in reducing the risk of pyelonephritis in pregnancy, the estimate of the effect is very uncertain because of the very low quality of the evidence. The reduction in low birthweight and preterm birth with antibiotic treatment is consistent with theories about the role of infection in adverse pregnancy outcomes, but this association should be interpreted with caution given the very poor quality of the included studies.

PLAIN LANGUAGE SUMMARY

Antibiotics for bacterial infection in the urine in pregnancy when there are no symptoms

What is the issue?

Can giving antibiotics in pregnancy to women who have a urinary infection but no symptoms improve the outcomes for women and their babies?

Why is this important?

A bacterial infection of the urine without any of the typical symptoms that are associated with a urinary infection (asymptomatic bacteriuria) occurs in a small number (2% to 10%) of pregnancies. Because of the changes happening in their body, pregnant women are more likely to develop a kidney infection (pyelonephritis) if they have a urinary infection, and the infection may also possibly contribute to having a low birthweight baby or preterm birth (before 37 weeks).

What evidence did we find?

The review of trials on antibiotic treatment for women with no symptoms but bacterial infection in their urine found 14 randomized controlled studies involving almost 2000 women. Antibioitcs were effective in reducing the incidence of kidney infection in the mother (11 studies, 1932 women) and clearing the infection from the urine (four studies, 596 women). The incidence of low birthweight babies (six studies, 1437 babies) and preterm births (two studies, 242 women) seemed also to be reduced. None of the studies adequately assessed any adverse effects of antibiotic treatment for the mother or her baby and often the way the study was done was not well described. The three main outcomes were assessed with GRADE and the evidence to support antibiotic treatment to prevent pyelonephritis, preterm birth and birthweight less than 2500 g was judged to be of low to very low quality.

What does this mean?

Antibiotic treatment can reduce the risk of kidney infections in pregnant women who have a urine infection but show no symptoms of infection. Antibiotics may also reduce the chance a baby will be born too early or have a low birthweight. However, the low quality of the evidence makes it hard to know for certain what the effect of treatment will be and more research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic treatment versus no treatment for asymptomatic bacteriuria in pregnancy

Patient or population: Patients with asymptomatic bacteriuria in pregnancy
Settings: Antenatal clinics predominantly in the US, UK, Ireland and Australia
Intervention: Antibiotic treatment
Comparison: No treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic treatment				
Development of pyelonephritis	Study population[1]		RR 0.23 (0.13 to 0.41)	1932 (11 studies)	⊕○○○ very low[2,3,4]	The rate of pyelonephritis in the control groups ranged from 2.5% to 36%
	208 per 1000[1]	48 per 1000 (27 to 85)				
	Median[1]					
	233 per 1000[1]	54 per 1000 (30 to 96)				
Preterm birth < 37 weeks	221 per 1000	60 per 1000 (24 to 137)	RR 0.27 (0.11 to 0.62)	242 (2 studies)	⊕⊕○○ low[5,6]	Only studies where preterm birth was defined as gestational age < 37 weeks were included in this outcome
Birthweight < 2500 g	Study population[1]		RR 0.64 (0.45 to 0.93)	1437 (6 studies)	⊕⊕○○ low[2,3]	
	136 per 1000[1]	87 per 1000 (61 to 126)				
	Median[1]					

	137 per 1000[1]	**88 per 1000** (62 to 127)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study population baseline risk is the mean baseline risk, calculated as the number in the control group with the outcome divided by the total number of women, from all the included studies. The median of the risk of the outcome of the control groups from all of the included studies is also provided.
[2] Most of the trials contributing outcome data had important design limitations related to lack of allocation concealment (-1).
[3] Most of the trials contributing outcome data had important design limitations related to lack of blinding (-1).
[4] There was significant heterogeneity (I^2 = 64%) which was not explained by the duration of treatment (-1).
[5] There were important design limitations related to allocation and lack of blinding in one of the studies contributing data to this outcome (-1).
[6] The two studies contributing data to this outcome represented very different populations; in one study only women with group B streptococcus bacteriuria were enrolled and treatment was with penicillin (-1).

BACKGROUND

Description of the condition

Asymptomatic bacteriuria, generally defined as true bacteriuria in the absence of specific symptoms of acute urinary tract infection, is a common finding and occurs in 2% to 10% of all pregnancies (Whalley 1967). Rates from more recent studies generally fall within this range (Bandyopadhyay 2005; Celen 2011; Fatima 2006; McIsaac 2005; McNair 2000; Mohammad 2002; Tugrul 2005), although in observational studies from some developing countries higher rates are reported (Ajayi 2012; Rizvi 2011; Tadesse 2014). The prevalence of asymptomatic bacteriuria was reported to be as high as 86.6% in a population from Nigeria that included *Staphylococcus aureus*, a possible contaminant, as a uropathogen (Akerele 2001). Rates were reported to be higher in HIV positive women in Nigeria (Awolude 2010; Ezechi 2013), but not in a study from South Africa (Widmer 2010). In a large retrospective study, the strongest predictor of bacteriuria was an antepartum urinary tract infection (Pastore 1999). A study from an electronics factory in China found an association between urinary tract infections in pregnancy and frequency of voiding, with voiding three or more times a shift being protective (Su 2009), and in a study from Iran, there was an association between infection and frequency of sexual intercourse and genital hygiene practices (Amiri 2009). The prevalence of infection is related to socioeconomic status (Haider 2010; Turck 1962; Whalley 1967), although this may not always apply (Awoleke 2015; Kovavisarach 2009). Other contributing factors recognized as associated with an increased risk for bacteriuria include diabetes and anatomical abnormalities of the urinary tract.

The original criterion for diagnosing asymptomatic bacteriuria was more than 100,000 bacteria/mL on two consecutive clean-catch samples (Kass 1960a). The detection of more than 100,000 bacterial/mL in a single voided midstream urine is accepted as an adequate and more practical alternative, although there is only an 80% probability the woman has true bacteriuria, increasing to 95% if two or more consecutive cultures are positive for the same organism (Kass 1960a). Because the performance of rapid urine screening tests in pregnancy is poor, quantitative culture remains the gold standard for diagnosis (Bachman 1993; Garingalo-Molina 2000; McNair 2000; Mignini 2009; Tincello 1998).

E. coli is the most common pathogen associated with asymptomatic bacteriuria, representing up to 80% of isolates. Other organisms include other gram negative bacteria, e.g. *Klebsiella* spp. and *Proteus mirabilis*, and group B streptococci. These bacteria colonize the vaginal introitus and periurethral area. Uropathogenic gram negative bacteria possess specific virulence factors that enhance both colonization and invasion of the urinary tract, for example, the P-fimbriae of certain strains of *E. coli* that allow for adherence to uroepithelial cells (Eisenstein 1988; Stenqvist 1987). Some strains of *E.coli* isolated from pregnant women with asymptomatic bacteriuria have a similar virulence pattern to strains from women with symptomatic infections (Lavigne 2011), but this does not always hold true (Stenqvist 1987). While *Staphylococcus saprophyticus* is recognized as a urinary pathogen, other species of *Staphylococci* including *Staphylococcus aureus* may reflect contamination rather than a true infection and prevalence data where the number of *Staphylococcus* spp. is high are difficult to interpret. Maternal urinary tract infection with group B streptococci is associated with vaginal colonization with the organism and antibiotic treatment during labor is recommended to prevent early onset neonatal group B streptococcal disease (Allen 2012).

While asymptomatic bacteriuria in non-pregnant women is generally benign (Nicolle 2014), obstruction to the flow of urine in pregnancy leads to stasis and increases the likelihood that pyelonephritis will complicate asymptomatic bacteriuria. If asymptomatic bacteriuria is untreated, up to 30% of mothers develop acute pyelonephritis (Whalley 1967). Mechanical compression from the enlarging uterus is the principal cause of hydroureter and hydronephrosis, but smooth muscle relaxation induced by progesterone may also play a role (Sobel 1995). Differences in urine pH and osmolality and pregnancy-induced glycosuria and aminoaciduria may facilitate bacterial growth. Clinical signs of pyelonephritis include fever, chills, costo-vertebral tenderness, dysuria and frequency. Nausea and vomiting are common and if infection is associated with bacteremia, women may present with high fever, shaking chills and low blood pressure. Maternal complications include maternal respiratory insufficiency, septicemia, renal dysfunction and anemia (Hill 2005; Wing 2014) and in the pre-antibiotic era, acute pyelonephritis was associated with a 20% to 50% incidence of preterm birth. From an 18-year retrospective review in an era of routine screening and treatment for asymptomatic bacteriuria, the incidence of acute pyelonephritis in pregnancy was 0.5% and was associated with preterm birth (odds ratio (OR) 1.3, 95% confidence interval (CI) 1.2 to 1.5) (Wing 2014); women with pyelonephritis were more likely to be black or Hispanic, young, less educated, initiate prenatal care late and smoke. Similar findings of an association between acute pyelonephritis and preterm birth were described in a study from Israel (OR 2.6, 95% CI 1.7 to 3.9) (Farkash 2012).

Since the earliest studies of Kass, an association between asymptomatic bacteriuria and low birthweight and preterm birth has been described (Kass 1960a), but population-based studies have produced conflicting results. A retrospective study from Israel that controlled for confounders showed an association between asymptomatic bacteriuria and preterm birth (OR 1.9, 95% CI 1.7 to 2.0) (Sheiner 2009) but, in contrast, findings from the Cardiff Birth Survey reported that asymptomatic bacteriuria, adjusted for demographic and social factors, was not associated with preterm birth (OR 1.2, 95% CI 0.9 to 1.5) (Meis 1995). However, when preterm births were categorized into those indicated for medical complications of pregnancy (e.g. antepartum hemorrhage, eclampsia or renal disease) or spontaneous preterm births, there was a significant

association between bacteriuria and medically indicated preterm births (OR 2.03, 95% CI 1.5 to 2.8) but not for spontaneous preterm births (OR 1.07, 95% CI 0.78 to 1.46) (Meis 1995a) and the authors concluded that if asymptomatic bacteruria does not progress to pyelonephritis, it is not associated with preterm birth.

Description of the intervention

The goal of treatment for asymptomatic bacteriuria is to treat and clear the infection. The urinary bacterial isolate should be susceptible to the antibiotic chosen, the length of treatment adequate, adherence assured and the drug have favorable pharmacokinetic parameters. The treatment should be safe in pregnancy and for the developing fetus. Many different antibiotic regimens have been used to treat bacteriuria but not all the antibiotics previously evaluated are currently available. Increasing bacterial resistance of urinary pathogens (Assefa 2008; Enayat 2008; Hernandez Blas 2007; Rizvi 2011; Tadesse 2014) can make it difficult to select an appropriate regimen, especially in under-resourced settings where facilities for urine culture and antimicrobial susceptibility testing are limited. There is no evidence that non-pharmacological interventions, e.g. cranberry juice, are effective (Wing 2008), although no data exist to suggest the use of cranberry has any harmful effects on pregnancy (Heitmann 2013).

How the intervention might work

Urinary pathogens causing asymptomatic bacteriuria are similar to those causing pyelonephritis and antibiotic treatment of asymptomatic bacteriuria, with eradication of the infection, is expected to prevent ascending urinary tract infection and the development of clinical pyelonephritis.

The relationship between asymptomatic bacteriuria, low birthweight and preterm birth is controversial and a mechanism for an association between preterm labor and asymptomatic bacteriuria has not been established. Microbial-induced preterm labor is mediated by an inflammatory process (Goldenberg 2000; Romero 2014). Microorganisms and their products are sensed by pattern recognition receptors, such as toll-like receptors (TLRs), which induce the production of chemokines, prostaglandins, and proteases leading to the onset of labor. While this mechanism has been well defined for ascending intra-amniotic infection, there has been no recent research to explore the mechanisms through which asymptomatic bacteriuria might exert adverse pregnancy outcomes.

Why it is important to do this review

Screening for and treatment of asymptomatic bacteriuria in pregnancy has become a standard of obstetric care and most antenatal guidelines include routine screening for asymptomatic bacteriuria. Using a decision analysis, screening for and treatment of asymptomatic bacteriuria to prevent pyelonephritis has been shown to be cost-effective over a wide range of estimates, although the cost-benefit is diminished if the rate of asymptomatic bacteriuria is less than 2% (Rouse 1995; Wadland 1989). The low prevalence of infection in certain populations, the cost of different screening tests, and uncertainty about the benefits of treatment in decreasing adverse outcomes of pregnancy have, however, been used to argue against screening and treatment as universal recommendations, and preventing unnecessary antibiotic use has become an important aspect of programs to decrease the development of antimicrobial resistance. A rigorous evaluation of studies of the effect of treatment of asymptomatic bacteriuria could provide clarity around these issues.

OBJECTIVES

To evaluate the effect of antibiotic treatment for asymptomatic bacteriuria in pregnancy on:

1. the development of symptomatic infection (pyelonephritis);
2. the risk of preterm birth and low birthweight.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials and quasi-randomized trials (e.g. alternation). Cluster-randomized trials were eligible for inclusion. Cross-over trials were not eligible for inclusion.

Types of participants

Pregnant women found on antenatal screening to have asymptomatic bacteriuria, as defined by the study authors, at any stage of pregnancy.

Types of interventions

We included studies if any antibiotic regimen was compared with placebo or no treatment for asymptomatic bacteriuria.

Types of outcome measures

Primary outcomes

1. Development of pyelonephritis
2. Preterm birth less than 37 weeks
3. Birthweight less than 2500 g

Secondary outcomes

1. Persistent bacteriuria
2. Neonatal mortality or other serious adverse neonatal outcome
3. Maternal side effects
4. Costs, as defined by trial authors
5. Birthweight
6. Gestational age
7. Women's satisfaction, as measured by trial authors

Persistent bacteriuria was defined as bacteriuria persisting to the time of delivery.

For the updated version of this review (2015) the World Health Organization's definition of prematurity of less than 37 weeks has been used.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (19 March 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, 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 retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous versions of this review, *see* Smaill 1993 and Smaill 2007.

For this update, we used the following methods to assess the reports that were identified as a result of the updated search, based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. If we had included any new studies, both review authors would have extracted the data using the agreed form. We would have resolved discrepancies through discussion. Data would have been be entered into Review Manager software (RevMan 2014) and checked for accuracy.

If information regarding any of the above had been unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved 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);

- 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.

(3.1) 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 were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We 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.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(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 stated 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 could be supplied by the trial authors, we planned to 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

Where identified, we described bias due to problems not covered elsewhere.

(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 planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using GRADE

For this update, the quality of the evidence was assessed using the GRADE approach (Schunemann 2009). We assessed the quality of the body of evidence relating to the following outcomes, for the main comparison of antibiotic versus no treatment.

1. Development of pyelonephritis
2. Preterm birth less than 37 weeks
3. Birthweight less than 2500 g

We used GRADEprofiler (GRADEpro 2014) to import data from Review Manager (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five con-

siderations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. In future updates, we plan to use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We planned to include cluster-randomized trials in the analyses along with individually-randomized trials, if any were identified. In future updates of this review, if any cluster-randomized trials are included, we will adjust their sample sizes using the methods described in the *Handbook [Section 16.3.4 or 16.3.6]* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore 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 and, where reasonable, we attempted to include all participants randomized to each group in the analyses.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we explored it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not have combined trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analysis and sensitivity analysis. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We carried out the following subgroup analysis to determine whether there was an effect of the duration of antibiotic therapy on the outcomes.

1. Single dose versus no treatment
2. Short course (three to seven days) versus no treatment
3. Intermediate course (three to six weeks) versus no treatment

4. Continuous antibiotic therapy until delivery versus no treatment

The following outcomes were used in subgroup analyses.

1. Development of pyelonephritis
2. Preterm birth less than 37 weeks
3. Birthweight less than 2500 g

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of the subgroup analysis quoting the Chi² statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses and only trials where the overall risk of bias was judged to be low, in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

Results of the search

Twenty-seven reports were identified.

Included studies

Twenty references to 14 studies involving almost 2000 women were included. For details *see* Characteristics of included studies. One study enrolled only women with group B streptococci in the urine (Thomsen 1987). Where there was more than one published reference that in the opinion of the review authors referred to the same study, information was abstracted from whichever reference provided the most detailed information. The earliest published reference was from 1960 (Kass 1960) and the most recent from 1987 (Foley 1987; Thomsen 1987). Most studies enrolled women during the 1960s. No cluster-randomized trials were found.

Participants

All participants were enrolled from hospital-based clinics, most from North America (Elder 1966; Elder 1971; Gold 1966; Kass 1960; Mulla 1960), the United Kingdom and Ireland (Brumfitt 1975; Foley 1987; Little 1966; Williams 1969), and Australia (Furness 1975; Kincaid-Smith 1965, Wren 1969). The majority of studies enrolled women at the first antenatal visit (Brumfitt 1975, Elder 1971, Foley 1987, Kass 1960, Kincaid-Smith 1965, Little 1966; Williams 1969; Wren 1969), but some women were enrolled at the second antenatal visit (Furness 1975), before 24 weeks (Pathak 1969), between 27 and 31 weeks (Thomsen 1987), between 30 and 32 weeks (Mulla 1960), any gestational age < 32 weeks (Elder 1966), or at any prenatal visit (Gold 1966). Two studies did not specify microbiological criteria for enrollment (Brumfitt 1975; Mulla 1960). Where there were microbiological criteria, bacteriuria was usually defined as at least one clean-catch, midstream or catheterized urine specimen with more than 100,000 bacteria/mL on culture. Some studies only required one positive culture of > 100,000 bacteria/ml (Foley 1987; Furness 1975); several studies required confirmation with a second culture (Furness 1975; Gold 1966; Kincaid-Smith 1965; Little 1966; Pathak 1969; Williams 1969; Wren 1969), and some a third culture (Elder 1966; Elder 1971; Kass 1960). One study included women with a lower colony count of more than 10,000 bacteria/mL on two occasions (Furness 1975). and women with any growth of group B streptococcus on a mid-stream urine culture were enrolled in the study from Thomsen 1987.

Interventions

Several different antibiotic regimens were used for treatment (*see* Characteristics of included studies for details), including the study of group B streptococci which compared penicillin to placebo (Thomsen 1987). Treatment was either a single dose (Brumfitt 1975), given for three to seven days (Foley 1987; Mulla 1960; Thomsen 1987; Williams 1969), for three weeks (Pathak 1969), for six weeks (Elder 1971), continued until delivery (Elder 1966; Furness 1975; Gold 1966; Kass 1960; Kincaid-Smith 1965), or until up to six weeks after delivery (Little 1966; Wren 1969). A repeat antibiotic course with the same drug was administered if infection persisted in three studies (Mulla 1960; Pathak 1969; Thomsen 1987). In several studies an alternative agent was used for persisting or resistant organisms (Foley 1987; Kass 1960; Kincaid-Smith 1965; Little 1966; Williams 1969). Most studies used antibiotics that are no longer routinely used for treating bacteriuria, including certain sulfonamides (Brumfitt 1975; Elder 1966; Foley 1987; Gold 1966; Kass 1960; Kincaid-Smith 1965; Little 1966; Mulla 1960), tetracycline (Elder 1971), and methenamine (Furness 1975). Some studies used nitrofurantoin, either first line (Little 1966; Pathak 1969), or for failures (Elder 1971; Kass 1960; Kincaid-Smith 1965; Little 1966; Williams 1969), and in some, ampicillin was used for failures (Kincaid-Smith 1965; Little 1966; Williams 1969). In one study, women received nitrofurantoin, then ampicillin, then sulphurazole and then nalidixic acid in rotation (Wren 1969). In only one study were data on antimicrobial susceptibility used to select the antibiotic (Foley 1987).

Outcomes

Most studies (n = 11) included the outcome of pyelonephritis (Brumfitt 1975; Elder 1971; Foley 1987; Furness 1975; Gold 1966; Kass 1960; Kincaid-Smith 1965; Little 1966; Mulla 1960; Pathak 1969; Williams 1969). The outcome of low birthweight was reported in six studies (Brumfitt 1975; Elder 1971; Kass 1960; Kincaid-Smith 1965; Little 1966; Wren 1969). In many of the studies conducted during the 1960s the standard definition of preterm birth was low birthweight and preterm birth was defined as birthweight less than 2500 g, rather than a gestational age less than 37 weeks. Two studies (Thomsen 1987; Wren 1969), defined preterm birth as a gestational age of less than 37 weeks. One study did not provide a definition of preterm birth (Gold 1966), and Furness 1975 used a definition of less than 38 weeks.

Persistent bacteriuria was defined as a positive culture at delivery or the last prenatal visit in four studies (Elder 1966; Elder 1971; Gold 1966; Pathak 1969), a positive culture at six weeks to three months post-partum by Furness 1975 and Kincaid-Smith 1965, and not defined in the study by Foley 1987, Three studies also measured rates of bacteriuria long term: one between three and nine months postpartum (Pathak 1969), one at six months (Kincaid-Smith 1965), and one at 10 to 14 years (Kass 1960).

No studies reported on women's satisfaction with the intervention.

Excluded studies

Six references to five studies were excluded because they did not meet the inclusion criteria (*see* Characteristics of excluded studies table for details).

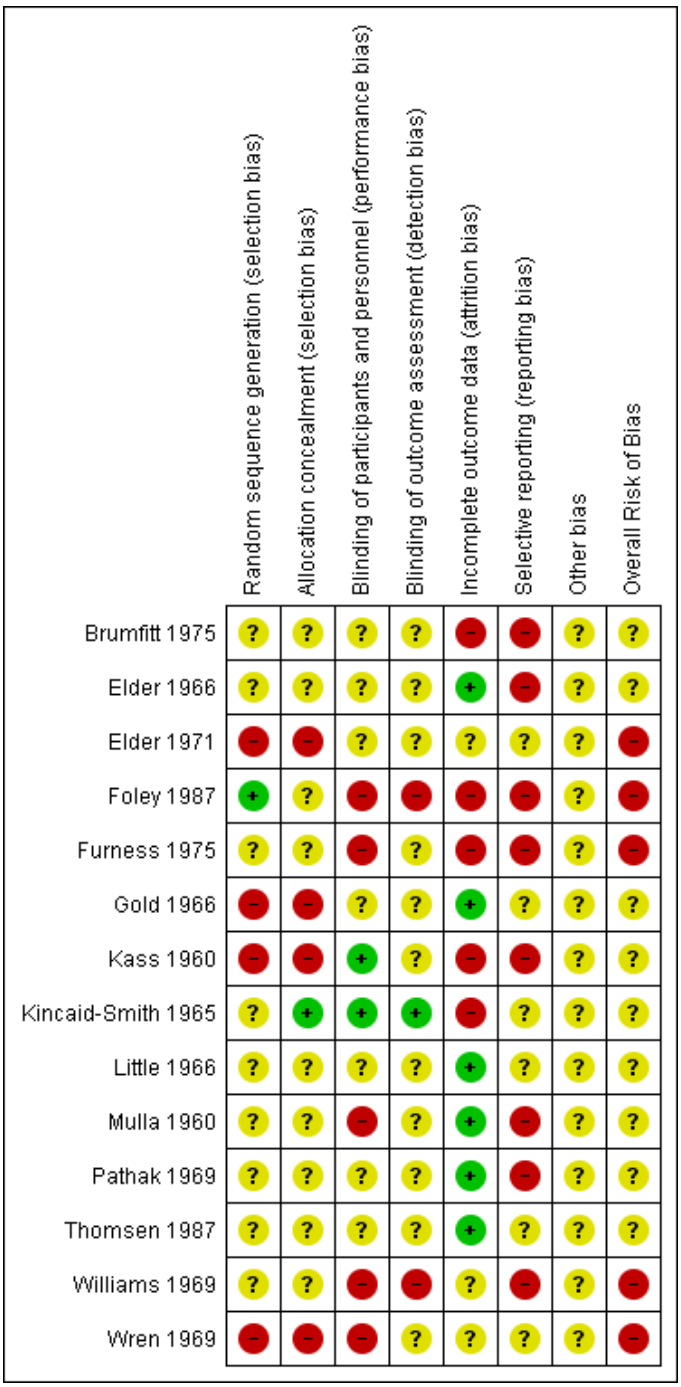
Risk of bias in included studies

For most studies, there was only a brief and incomplete description of the research methods, which made it difficult to assess the methodological quality of the studies.

See Figure 1. The description of the characteristics of the study groups was poor. In only one study (Thomsen 1987), were the similarities in age, parity and socioeconomic status between the treatment and no treatment groups adequately described; in the study from Kass 1960a, the racial distribution of the two groups was described and was comparable; in four other studies (Elder 1966; Elder 1971; Gold 1966; Mulla 1960), the urinary bacterial isolates for the two groups were listed, but otherwise there was no attempt to demonstrate the comparability of the study groups. No study included the rates of maternal smoking, a recognized risk for low birthweight. There was no description of the presence of co-existing genital infections, although one study excluded women with positive serology for syphilis (Pathak 1969). Details on the management of recurrent urinary tract infection or persistent infection, the treatment of symptomatic lower urinary tract infection (cystitis) and concurrent antibiotic administration were incomplete. Some studies included twin deliveries while other studies excluded these.

There was no consistent application of standard definitions for the measured outcomes. Pyelonephritis usually referred to symptoms of loin pain, fever, dysuria or frequency, with or without a significant urine culture. While rates of low birthweight were usually reported, most studies described this as "prematurity". For those studies that reported rates of preterm births, the definition of preterm birth was inconsistent, and there were insufficient data presented in any of the studies to compare gestational ages between treatment and control groups.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Overall, the studies were not methodologically strong and, in the majority of studies, there was inadequate description of concealment of allocation. In only one study was there a random component in the sequence generation described (coin toss) (Foley 1987). There was no statement in any study that allocation was centrally controlled and in the only study that referred to the use of sealed envelopes (Little 1966), the envelope was drawn from a pool of sealed envelopes rather than a consecutively numbered pile. For the other studies, there was no description of the method of randomization or the method was clearly inadequate: in four studies women were allocated to treatment by alternation (Elder 1971; Gold 1966; Kass 1960; Wren 1969).

Blinding

In nine of the 14 studies, the control group received a placebo (Brumfitt 1975; Elder 1966; Elder 1971; Gold 1966; Kass 1960; Kincaid-Smith 1965; Little 1966; Pathak 1969; Thomsen 1987); no treatment was given to the control group in the others (Foley 1987; Furness 1975; Mulla 1960; Williams 1969; Wren 1969). It was unclear in most studies whether the blinding could have been broken. In those studies without placebo, no mention was made that the observer was blinded to treatment allocation, making it more likely that performance and detection biases were also present.

Incomplete outcome data

This was judged high or unclear for eight studies and low for six.

Selective reporting

There was generally insufficient information to judge, but there were studies that failed to include the primary outcome of pyelonephritis (Elder 1966; Thomsen 1987; Wren 1969), or did not report results on all participants randomized to treatment or no treatment.

Other potential sources of bias

Other potential sources of bias not covered elsewhere were judged as unclear for all 14 studies.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic treatment versus no treatment for asymptomatic bacteriuria in pregnancy

See Summary of findings for the main comparison for the comparison of antibiotics versus no treatment.

1. Antibiotic versus no treatment for asymptomatic bacteriuria (Analyses 1.1 to 1.3)

Primary outcomes

Antibiotic treatment was effective in reducing the incidence of pyelonephritis in women with asymptomatic bacteriuria (average risk ratio (RR) 0.23, 95% confidence interval (CI) 0.13 to 0.41; participants = 1932; studies = 11; I^2 = 64%; Analysis 1.1). There was significant heterogeneity among the studies and a random-effects analysis was used. For most studies, however, a substantial benefit effect was seen with treatment; one study with anomalous results (Furness 1975) was responsible for most of the heterogeneity seen for the outcome of pyelonephritis.

There was evidence of a reduction in preterm birth (RR 0.27, 95% CI 0.11 to 0.62; participants = 242; studies = two; I^2 = 10%; Analysis 1.2) when this was defined as a gestational age of less than 37 weeks. Only two studies (Thomsen 1987; Wren 1969) reported this outcome; Thomsen 1987 only enrolled women with group B streptococcal bacteriuria. A reduction in the incidence of birthweight less than 2500 g was seen with treatment (average RR 0.64, 95% CI 0.45 to 0.93; participants = 1437; studies = six; I^2 = 28%; Analysis 1.3). A random-effects meta-analysis was used for the outcome of preterm birth and low birthweight, despite the absence of statistical heterogeneity, because of the clinically significant differences in the study populations and interventions.

Secondary outcomes

Antibiotic treatment is effective in clearing asymptomatic bacteriuria (average RR 0.30, 95% CI 0.18 to 0.53; participants = 596; studies = four; I^2 = 76% Analysis 1.4). Without treatment, asymptomatic bacteriuria persisted in 70% of women. Although there was significant statistical heterogeneity among trials, likely explained by differences in study design and intervention, the direction of the effect was consistent. Treatment with antibiotics had no effect on the incidence of bacteriuria long term (results reported in one study at between three and nine months postpartum, one at six months and one at 10 to 14 years).

Only one study (Elder 1971), reported on serious adverse neonatal outcomes and there was no difference ((RR 2.27, 95% CI 0.42 to 12.16; participants = 273; Analysis 1.5). Information on maternal adverse events was incompletely reported and cannot be analyzed. In the one study that reported the difference in mean birthweights, there was no difference (mean difference (MD) 61.00, 95% CI -56.55 to 178.55; participants = 413; Analysis 1.7).

2. Antibiotic treatment versus no treatment: subgroups by duration of treatment (Analyses 1.1.1 to 1.1.4; 1.2.1 to 1.2.4; 1.3.1 to 1.3.4)

There was a reduction in the incidence of pyelonephritis for all subgroups regardless of duration of treatment and by inspection of the graphs there was no evidence of a clinically important difference by duration of treatment. The interaction test did not suggest a difference between subgroups for the outcome of pyelonephritis (Test for subgroup differences: Chi² = 3.92, df = 3 (P = 0.27), I² = 23.4%).

There were too few studies to make a meaningful interpretation of the effect of duration of treatment on the outcome of preterm birth. On visual inspection of the graphs, it appeared that there was a difference in incidence of low birthweight with duration of treatment and the interaction test did suggest a difference (Test for subgroup differences: Chi² = 2.82, df = 2 (P = 0.24), I² = 29.1%), but there were too few studies to be confident that a longer duration of therapy was associated with a better outcome.

We judged that in none of the studies was the overall risk of bias low; a sensitivity analysis based on trial quality was therefore not performed.

DISCUSSION

Summary of main results

While the results of these studies are consistent, yielding reductions in the incidence of pyelonephritis, low birthweight and preterm birth with treatment of asymptomatic bacteriuria, important methodological considerations limit the strength of the conclusions. There was significant heterogeneity observed among the studies, which may be explained by study design or quality, type of antibiotic used and the long time interval over which the trials were performed.. Duration of antibiotic treatment did not appear to explain any heterogeneity.

The overall incidence of pyelonephritis in the untreated group was 21%, but ranged from 2.5% to 36%. While different definitions of pyelonephritis could explain some of this variation, there may be other factors, for example, type of organism, socioeconomic status, other care given in pregnancy, that, if defined, could identify groups of women with asymptomatic bacteriuria with different risks of developing pyelonephritis. In the absence of this type of information, however, the presence of asymptomatic bacteriuria itself defines a population at risk of pyelonephritis. Overall, treatment of asymptomatic bacteriuria will lead to approximately a 75% reduction in the incidence of pyelonephritis.

Overall completeness and applicability of evidence

The studies reported here (with only three exceptions) date from the 1960s and 1970s; microbiological methodology for the diagnosis of bacteriuria has not significantly changed over this interval. Although not all of the antibiotics used in these studies remain available currently, and the use of tetracycline is now contraindicated in pregnancy, it is valid to assume that the results are applicable to other antibiotics active against urinary pathogens that are safe in pregnancy. A Cochrane review of treatments for symptomatic urinary tract infections during pregnancy concluded that although antibiotic treatment is effective for the cure of urinary tract infections, there are insufficient data to recommend any specific regimen (Vazquez 2011), and there were similar conclusions for the treatment of asymptomatic bacteriuria (Guinto 2010). The choice of a sulfonamide or sulfonamide-containing combination, a penicillin, cephalosporin, fosfomycin or nitrofurantoin, based on the results of susceptibility testing, are appropriate regimens for the management of asymptomatic bacteriuria. Increasing antibiotic resistance, however, complicates the choice of empiric regimens and can make it difficult to select an appropriate regimen (Assefa 2008; Enayat 2008; Hernandez Blas 2007; Tadesse 2014), and a recent report from India described the presence of extended-spectrum ß-lactamases (ESBL) in 47% of isolates of *E. coli* and 36.9% of isolates of *Klebsiella pneumoniae* (Rizvi 2011). Results from surveys of antibiotic susceptibility in pathogens causing community-acquired uncomplicated urinary tract infections demonstrate considerable regional variation: resistance to ampicillin in *E. coli* in a survey of European countries and Canada averaged 29.8% but was as high as 53.9% in Spain (Kahlmeter 2003).

There was an association between treatment and preterm birth, but only two studies reported this outcome, one of which only included women with group B streptococcus bacteriuria, and the other was very poor methodologically. Although we chose to combine data from the two studies, given the very different populations and interventions, the effect of treatment on preterm birth is very uncertain. While preterm births are associated with low birthweight, some low birthweight infants are small-for-gestational age as a consequence of intrauterine growth retardation, for which there are many possible etiologies. The reduction in the incidence of low birthweight with antibiotic treatment is, however, consistent with current theories about the role of infection as a cause of adverse pregnancy outcomes, but a greater understanding of the basic mechanisms by which the treatment of bacteriuria could lead to a reduction in low birthweight is required. Prevention of pyelonephritis, which in early studies prior to the availability of effective antimicrobial therapy was associated with preterm birth, may be a factor, but treatment of bacteriuria with antibiotics may also eradicate organisms colonizing the cervix and vagina that are associated with adverse pregnancy outcomes. The relationship between genital infections such as bacterial vaginosis and preterm labor was not recognized when these studies on the treatment of

asymptomatic bacteriuria were originally designed.

Quality of the evidence

Three outcomes were assessed with GRADE software and given a quality rating. See Summary of findings for the main comparison. Evidence for pyelonephritis was graded as of very low quality; the quality of the evidence was downgraded by important design limitations (including lack of allocation concealment and blinding) and inconsistency (heterogeneity in the results and important differences in the population and intervention). Evidence for preterm birth and for birthweight less than 2500 g was graded as of low quality. For preterm birth there were important differences in the population and intervention and, in one of the studies contributing data, important design limitations. For birthweight less than 2500g, there were important design limitations (including lack of allocation concealment and blinding)

Potential biases in the review process

Many of the studies only contributed data to one or two of the outcomes; for most of the outcomes, data are missing. Most studies did include the outcome of pyelonephritis, but when these studies were being designed there was already an awareness of a possible association between asymptomatic bacteriuria and low birthweight and preterm birth (Kass 1960a). There was no explanation why these outcomes were not systematically collected and reported in most of the trials, and these missing data did contribute to the overall low quality of most of the studies. In none of the studies reviewed were the adverse effects of antibiotics systematically collected. The incidence of allergic reactions, vaginal yeast infections, gastrointestinal side effects and the development of bacterial resistance, were not considered, nor were neonatal outcomes systematically collected. While it is not possible to compare the benefits versus the disadvantages of antibiotic therapy from these studies, it is unlikely that the expected side effects from a short course of antibiotics would be significant although increasingly there are concerns about the effect of antibiotics on the human microbiome and the immune system.

Agreements and disagreements with other studies or reviews

Results of a meta-analysis of 17 cohort studies showed an association between asymptomatic bacteriuria and low birthweight and preterm birth but failed to resolve the question whether or not asymptomatic bacteriuria was merely a marker for low socioeconomic status, which is associated with low birthweight (Romero 1989).

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotic treatment of asymptomatic bacteriuria is indicated to reduce the risk of pyelonephritis in pregnancy. A prospective longitudinal study over a two-year period from 2000 to 2001 reported an incidence of hospitalization for acute pyelonephritis in pregnancy of 1.4% (Hill 2005), and a recent 18-year retrospective study reported that the incidence of acute pyelonephritis was 0.5% (Wing 2014), both less than the 3% to 4% rate reported in the early 1970s before screening for asymptomatic bacteriuria became routine.

The optimal time to perform the urine culture is unknown; it seems reasonable to perform the urine culture and treat, as done in these studies, at the first prenatal visit but a single culture before 20 weeks may miss more than half of women with asymptomatic bacteriuria (McIsaac 2005).

Seven of the studies continued antibiotics until term; one additional study treated women for six weeks, while the majority of the rest gave treatment for three to seven days. Both continuous treatment and short-course therapy strategies show a benefit in the reduction of pyelonephritis. A small randomized study that compared intermittent therapy with continuous treatment confirmed that both strategies were equally effective (Whalley 1977). While short-course therapy of asymptomatic bacteriuria has become accepted practice, the optimal duration of treatment is unknown but a three to seven day treatment regimen is currently recommended (Widmer 2011). The choice of antibiotic for treatment should be guided by antimicrobial susceptibility testing. While it is unlikely that the appropriate use of antibiotics to treat asymptomatic bacteriuria in pregnancy is an important factor in increasing rates of antimicrobial resistance to commonly prescribed antibiotics, it has made the selection of an antibiotic for an individual woman much more difficult.

In the studies included in this review, insufficient data were presented to determine the effectiveness of treatment to prevent recurrent bacteriuria during the pregnancy. Although it is recommended that a urine culture be done following treatment, with retreatment as necessary, the studies did not specifically evaluate the effectiveness of this strategy, and the results of a systematic review concluded there was no optimal intervention to prevent recurrent infection (Schneeberger 2012).

Implications for research

This review has identified several areas where there are implications for research:

Incorporating risk factors for pyelonephritis in a screening algorithm

In an era when routine prenatal screening for asymptomatic bacteriuria has been standard, women with pyelonephritis were more likely to be black or Hispanic, young, less educated, nulliparous, initiate prenatal care late, and smoke during pregnancy (Wing 2014). However, while some of these factors and other risk factors that are associated with asymptomatic bacteriuria may be amenable to interventions or used to identify women at greater risk of an adverse outcome, there has been no evaluation of a screening algorithm incorporating risk factors.

Understanding the pathogenesis of infection

A better understanding of the basic mechanisms by which treatment of asymptomatic bacteriuria could prevent low birthweight is required. Any study of the relationship between other infections and adverse outcomes of pregnancy needs to control for asymptomatic bacteriuria and its treatment but it is unlikely that the particular contribution of asymptomatic bacteriuria to preterm birth and low birthweight will ever be conclusively determined.

The significance of lower colony counts and different urinary pathogens

The studies included in this review generally used a urine colony count of more than 100,000 bacteria/mL to identify patients. Although lower colony counts have been shown to be associated with active infection in other populations (Stamm 1982), their significance in pregnancy has not been established. Treatment of asymptomatic pregnant women with lower colony counts is not currently recommended, but further study of appropriate strategies to manage these women is warranted. *Staphylococcus saprophyticus* is a recognized cause of symptomatic infection in non-pregnant women; however, the importance of this organism in asymptomatic pregnant women has not been established. While *E. coli* remains the predominant organism in most studies, the increasing prevalence of *Proteus mirabilis* and other *Enterobacteriaceae* along with other *Staphylococcus spp.* suggests different variables may be influencing the epidemiology of bacteriuria in developing countries (Nicolle 2014).

Urine screening tests: methods, timing and frequency

Quantitative urine culture of a midstream or clean-catch urine is the gold standard for detecting asymptomatic bacteriuria in pregnancy, but this test is expensive and may not always be available in all clinical settings. Although rapid urine screening tests, for example, urine microscopy and urine dipstick, have not been shown to perform satisfactorily in this population, their use may be cost-beneficial (Rouse 1995). Any new urine screening test that is developed needs to be evaluated in the context of screening for asymptomatic bacteriuria of pregnancy.

None of these studies adequately addressed when the most appropriate time is to perform the initial screening culture, how often to repeat a negative culture and how best to monitor women initially treated for asymptomatic bacteriuria. There is a need to define the appropriate frequency of follow-up cultures and re-treatment strategies.

Adherence to guidelines

Despite almost uniform national guidelines, there is little evidence of adherence to screening recommendations. In Australia, poor adherence with screening for asymptomatic bacteriuria in indigenous communities has been proposed as one explanation for worse pregnancy outcomes in this population; a structural problem related to provision of care in remote communities was identified as the cause (Bookallil 2005). Screening rates from 1% to 96% were reported in a pilot survey of quality indicators of antenatal care in the United Kingdom (Vause 1999). There is an opportunity to evaluate screening for asymptomatic bacteriuria as a measure of quality of care and gain a better understanding of the implementation of screening policies for asymptomatic bacteriuria in the developing world.

Cost-effectiveness

While there are no new data to indicate that women should not be screened for asymptomatic bacteriuria, it is difficult to estimate accurately the cost-effectiveness of screening without up-to-date information on the prevalence of asymptomatic bacteriuria and a more accurate estimate of the reduction in pyelonephritis, low birthweight and preterm births with treatment. A Health Technology Assessment report from the UK on screening to prevent preterm birth estimated that antibiotic treatment for all women without any testing was the most cost-effective option for preventing birth before 37 weeks; however, they did not take into account the side effects of antibiotics or issues such as resistance, and the conclusions were based on the low-quality data associating treatment with a reduction in preterm births (Honest 2009). There needs to be prospective evaluation of cost-effective diagnostic algorithms, that include risk factors and up-to-date outcomes, in different populations.

Research in low-risk populations

Despite the demonstrated association between antibiotic treatment and the prevention of pyelonephritis, there is an opportunity for research to provide better quality data to inform the management of asymptomatic bacteriuria. In a low-risk population, a carefully designed randomized, placebo-controlled trial with close monitoring of outcomes, including the adverse effects of antimicrobial therapy, could be performed and provide useful information on alternative management strategies (Kazemier 2012). Preventing inappropriate antibiotic use has become an important aspect of programs to decrease the development of antimicrobial resistance and this concern gives an impetus to researchers to identify a population of women with asymptomatic bacteriuria in whom antibiotic treatment may not be necessary.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brumfitt 1975

Methods	Placebo-controlled; 2 parallel groups.
Participants	Inclusion criteria: "Significant" bacteriuria (clean-catch urine) at first antenatal visit and 7-10 days later; microbiological criteria not stated. Setting: London and Birmingham, UK. Study period: 1967-1968 (estimated).
Interventions	Sulphonamide (sulphormethoxine 2 g single dose) vs placebo (see Williams 1968 for description of treatment regimen).
Outcomes	Low birthweight (< 2500 g); mean birthweight. Pyelonephritis (loin pain, fever or rigors; fever of at least 100°F; > 100,000 bacteria/mL)
Notes	Outcome of low birthweight (n = 425). Outcome of pyelonephritis in placebo group (55/179). Outcome of pyelonephritis reported for subset of treated women (n = 87): 0/45 successful treatment after 1 course, 4/22 successful after 2 courses; failed (persistent infection) 5/20. Data on persistent bacteriuria provided for treatment group only Outcome reported for women who developed anemia during pregnancy (hemoglobin 70% or less at 32 weeks): 16.8% treated vs 25.9% placebo, P < 0.01 There is no explanation for the difference in numbers in the placebo group (reported as 179 for the outcome of pyelonephritis and 178 for other outcomes) nor the total number of participants in the references to this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The investigators do not describe the sequence generation process: "... were originally assigned to the placebo group ..." There is no description of how women were assigned to treatment or placebo. There is no explanation for the unequal numbers in the treatment and placebo groups
Allocation concealment (selection bias)	Unclear risk	No information provided to judge.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"... were given placebo under double-blind conditions". Method not described in sufficient detail

Brumfitt 1975 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"... were given placebo under double-blind conditions". Method not described in sufficient detail
Incomplete outcome data (attrition bias) All outcomes	High risk	Inconsistencies in total number of women not explained (number of < 2500 g babies provided for 413/426 bacteriuric women); results not provided for outcome of pyelonephritis for all women in treated group
Selective reporting (reporting bias)	High risk	Results not provided for outcome of pyelonephritis for all women allocated to treatment
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Unclear overall.

Elder 1966

Methods	Placebo-controlled; 2 parallel groups.
Participants	Inclusion criteria: bacteriuria (same bacterial species in first 3 uncontaminated clean-voided urine specimens, with 2 samples > 100,000 bacteria/mL and 1 sample > 10,000 bacteria/mL) Exclusion criteria: > 32 weeks' gestation. Setting: Boston City Hospital, US. Study period: June 1965-March 1966.
Interventions	Sulfasymazine 0.5 g daily until delivery (n = 54) or placebo (n = 52)
Outcomes	Persistent bacteriuria (after 3 weeks of treatment) (13/52 treatment vs 48/50 in placebo group) and at last clinic visit before delivery (12/52 vs 30/49)
Notes	2 women were lost to follow-up in the treatment group and 3 women lost to follow-up in the placebo group and have not been included in the analysis. 7/52 women in the placebo group developed "asymptomatic" pyelonephritis (not further defined and not included as an outcome). 1 adverse event reported in treatment group (vomiting); no rash, pruritus or photosensitivity; no newborn kernicterus diagnosed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"... a random sequence"; insufficient information provided to permit judgement

Elder 1966 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information provided to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"... double-blind trial"; no information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"... double-blind trial"; no information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information provided on women lost to follow-up, reasonably balanced between groups
Selective reporting (reporting bias)	High risk	Results not provided for outcome of pyelonephritis for all participants; no pregnancy outcomes (gestational age, birthweight)
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Unclear overall.

Elder 1971

Methods	Placebo-controlled; 2 parallel groups. Quasi-RCT.
Participants	Inclusion criteria: bacteriuria (in clean-voided specimen with 2 samples > 100,000 bacteria/mL and 1 sample > 10,000 bacteria/mL) at first prenatal visit Exclusion: > 32 weeks' gestation; previously treated for a urinary tract infection during the current pregnancy prior to their first obstetrical visit, delivered or aborted after registering but before first obstetric visit, went elsewhere for prenatal care after registering; did not deliver a singleton pregnancy Setting: Boston City Hospital. Number of participants: n = 281. Study period: January 1963-July 1965.
Interventions	Tetracycline 250 mg 4 times a day x 6 weeks (n = 133) vs identically appearing placebo taken similarly (n = 145). If infection did not clear, an alternative drug (usually nitrofurantoin) was given
Outcomes	Persistent bacteriuria (bacteriuria was said to have cleared if the colony count was less than 1000/mL on 2 successive cultures) up to the time of delivery; includes recurrences Pyelonephritis (fever with signs and symptoms localized to the urinary tract, without other explanation) Low birthweight (< 2500 g). Neonatal outcomes (respiratory distress, neonatal jaundice). Mean gestational age (38.46 weeks in treated group n = 107 vs 38.25 weeks in placebo group n = 122 (calculated from numbers in paper))

Elder 1971 (*Continued*)

Notes	Tetracycline associated with staining of teeth in one-third of children No women lost to follow-up for outcome of pyelonephritis: 3 women (1%) lost to follow-up for outcome of persistent bacteriuria and low birthweight. Outcome of persistent bacteriuria in placebo group does not include women who developed pyelonephritis. 7 women moved out of Boston and the outcome of their pregnancies is not known. 4 bacteriuric women delivered twins and are not included Only live births included in outcome of low birthweight. Prematurity was defined as birthweight of < 2500 g regardless of gestational length

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"...alternate bacteriuric ... were assigned".
Allocation concealment (selection bias)	High risk	Participants were allocated by alternation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"identical-appearing placebo"; insufficient information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"identical-appearing placebo"; insufficient information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided to judge.
Selective reporting (reporting bias)	Unclear risk	Unable to judge; twin deliveries were excluded.
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	High risk	Judged at overall high risk of bias.

Foley 1987

Methods	Randomized trial, 2 parallel groups.
Participants	Inclusion: bacteriuric (> 100,000 bacteria/mL x 1; midstream urine) at first prenatal visit. Setting: Dublin, Ireland. Study period: 1985. Number of participants: n = 220.

Foley 1987 (*Continued*)

Interventions	Sulphamethizole 300 mg or nitrofurantoin 150 mg daily x 3 days (based on susceptibility of the organism); re-treatment or maintenance treatment as necessary (n = 100). Control group received no treatment (n = 120)
Outcomes	Persistent bacteriuria (at follow-up, not defined further). Pyelonephritis, only reported as "admitted with pyelonephritis", no definition provided
Notes	Description of study provided in letter to editor; no publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocated to treatment or no treatment by "toss of a coin".
Allocation concealment (selection bias)	Unclear risk	No information was provided to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of any attempt at blinding; not placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	No description of any attempt at blinding; not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 19%; no reasons provided for missing outcome data on these women
Selective reporting (reporting bias)	High risk	No pregnancy outcomes (gestational age, birthweight).
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	High risk	Judged at overall high risk of bias.

Furness 1975

Methods	Randomized trial, 3 parallel groups.
Participants	Inclusion: bacteriuric (> 100,000 bacteria/mL x 1 or > 10,000 bacteria/mL x 2; midstream urine) at second antenatal visit. Setting: South Australia. Enrollment period: not stated. Number of participants: n = 206.

Furness 1975 (*Continued*)

Interventions	Methenamine mandelate or methenamine hippurate 1 g, 4 times a day vs no treatment. Treatment continued until delivery.
Outcomes	Pyelonephritis (frequency and burning on micturition, pyrexia or loin tenderness and significant bacteriuria). Preterm birth (defined as less than or equal to 38 weeks' gestation); treatment 24/139 (17%) vs control 10/67 (15%) Mean birthweight: methenamine hippurate 3273g SE ± 70.7; methenamine mandelate 3303 SE ± 68.2; control 3353g SE ± 73.9; no difference Postnatal bacteriuria at 6 weeks: 26/73 treatment vs 10/27 no treatment
Notes	Women randomized to either methenamine mandelate (n = 69), methenamine hippurate (n = 70) or no treatment (n = 67); for analyses, treatment groups combined. Unable to separate incidence of pyelonephritis during pregnancy and puerperium; results combined

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	" by random allocation"; no additional details provided to permit judgement
Allocation concealment (selection bias)	Unclear risk	No information provided to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	20/226 women withdrawn from trial; no details provided. All women included in outcome of pyelonephritis; 17% loss to follow-up for outcome of low birthweight and gestational age at delivery
Selective reporting (reporting bias)	High risk	Unable to separate incidence of pyelonephritis during pregnancy and puerperium; results combined
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	High risk	Judged at overall high risk of bias.

Gold 1966

Methods	Placebo-controlled, randomized trial; 2 parallel groups. Quasi-RCT
Participants	Inclusion criteria: bacteriuria (> 100,000 bacteria/mL x 2: midstream urine) at any prenatal visit. Setting: New York, NY (85% non-white). Study period: February 1962 - December 1964. Number of participants: n = 65.
Interventions	Sulfadimethoxine 500 mg daily; sulfadiazine 1 g 3 times a day after 36 weeks vs placebo. Treatment continued until delivery.
Outcomes	Persistent bacteriuria at delivery. Pyelonephritis. Preterm birth (not defined further): treatment group 2/35; placebo 0/30 No infants developed jaundice; no toxic manifestations in women in treatment group
Notes	Only antepartum episodes of pyelonephritis included in analysis. There were 2 postpartum episodes of pyelonephritis in the placebo group, none in treatment group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Women allocated to treatment based on study number: odd number treatment, even number control
Allocation concealment (selection bias)	High risk	Allocated to treatment based on study number.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled; no further details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It does not appear that there was any loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No definition provided for prematurity.
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Overall unclear.

Kass 1960

Methods	Placebo-controlled trial, 2 parallel groups. Quasi-RCT.
Participants	Inclusion: bacteriuric (> 100,000 bacteria/mL at first prenatal visit, confirmed x 2). Women were randomized after the second positive sample but only included if the third sample was positive. Exclusion: > 32 weeks' gestation; chronic renal insufficiency. Setting: Boston City Hospital, US (approximately 50% black). Study period: October 1956-April 1960. Number of participants: n = 214 (includes 11 women identified through Renal Clinic)
Interventions	Sulfamethoxypyridazine 500 mg daily with nitrofurantoin for failures (n = 103) or placebo tablet (n = 100) supplied by same manufacturer. Treatment continued until term.
Outcomes	Pyelonephritis (dysuria, frequency and flank pain, fever or chills); however, it was not clear that women were indeed febrile. Low birthweight (< 2500 g); prematurity was defined as birthweight < 2500 g. Long-term persistence of bacteriuria (10-14 years): 18/63 treatment vs 18/71 placebo Mean gestational age: 39.6 ±3.6 SD for treated bacteriurics; 38.6 ± 3.6 SD for placebo bacteriurics There were 2 stillbirths, both in the placebo group; there were 5 neonatal deaths in the placebo group and no neonatal deaths in the treatment group
Notes	For outcome of low birthweight, results are given for total number of deliveries (3 twin deliveries in placebo group vs none in treated group) There are several publications related to this study; where there is a discrepancy in methodology, the most detailed description has been used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Alternate women received a placebo".
Allocation concealment (selection bias)	High risk	Allocation was based on alternation: "Alternate women received a placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used, and "the nature of the treatment was not know to the patient or to the attending obstetrical staff"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although a placebo was used, there are no further details provided to know whether the outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	40 women, initially identified were not enrolled either because they were > 32 weeks before treatment could be started (n = 30)

Kass 1960 (*Continued*)

		or they had already received treatment for symptomatic infection (n = 10) Loss to follow-up: 23 (11%) for outcomes of pyelonephritis and low birthweight; no details provided. 69 (34%) for long-term persistence of bacteriuria
Selective reporting (reporting bias)	High risk	3 women had a subsequent pregnancy in the study period and were reassigned to their original treatment group and included in the analysis In 5 patients in the placebo group, it was assumed they had symptomatic disease but no symptoms were documented. Not all women in the symptomatic group were confirmed to have fever and women treated for infections other that in the urinary tract were also included in the symptomatic group if they were found to have cleared their bacteriuria
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Overall unclear.

Kincaid-Smith 1965

Methods	Randomized, "double-blind" placebo-controlled; 2 parallel groups
Participants	Inclusion criteria: bacteriuria (> 100,000 bacteria/mL x 2, mid-stream urine) at first antenatal visit (< 26 weeks). Women with bacteriuria on the first sample that was not confirmed on the second sample were enrolled and results analyzed separately. Setting: Melbourne, Australia. Study period: 1964-1965. Number of participants: n = 145.
Interventions	Sulphamethoxydiazine 500 mg daily or sulphadimidine 1 g 3 times a day (after 30 weeks) (n = 61) vs placebo (n = 55). Treatment continued until delivery. Ampicillin or nitrofurantoin given if organism known to be resistant
Outcomes	Pyelonephritis (loin pain or tenderness, with or without pyrexia and rigors, with or without dysuria and frequency). Preterm birth (birthweight < 2500 g). Fetal loss: after 28 weeks 4/61 (6.6%) in treatment group and 4/56 (7.2%) in placebo group. Bacteriuria long term: (6 weeks - 3 months after delivery (n = 101) 9/51 treatment vs 18/50 placebo; 6 months after delivery (n = 43) 6/26 treatment vs 6/17 placebo

Kincaid-Smith 1965 (*Continued*)

Notes	29/145 women randomized to treatment but bacteriuria not confirmed on second culture; not included in outcomes reported for this analysis Results for incidence of pyelonephritis and prematurity also provided for women who had bacteriuria at first visit which was not confirmed on second sample (11/72 in treatment group, 18/73 in placebo group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation process.
Allocation concealment (selection bias)	Low risk	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite .... alterations in therapeutic regimen."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite .... alterations in therapeutic regimen."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite .... alterations in therapeutic regimen."
Incomplete outcome data (attrition bias) All outcomes	High risk	240 women initially identified as bacteriuric; no information available on 55 women randomized to treatment (treatment allocation not provided) but not included in the analysis because of poor compliance (attended infrequently or failed to take tablets continuously). For outcome of long-term persistence of bacteriuria (at 6 months), only 43 women were available for follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided to judge.
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Overall unclear.

Little 1966

Methods	Placebo-controlled, randomized; 2 parallel groups.
Participants	Inclusion criteria: bacteriuria (> 100,000 bacteria/mL x 2, midstream urine) at first prenatal visit. Setting: London, England. Study period: 1962-1965. Number of participants: n = 265.
Interventions	Sulphamethoxypyridazine 500 mg or (later) nitrofurantoin 100 mg daily continued until 6 weeks after delivery; ampicillin or nitrofurantoin were alternatives for failures (n = 124) or placebo (n = 141)
Outcomes	Pyelonephritis (loin pain and tenderness, fever and > 100,000 bacteria/mL). Low birthweight (< 2500 g).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Allocation to treatment or control was drawn from "a pool of sealed envelopes containing a slip of paper", but there was no information provided to ensure appropriate safeguards to prevent investigators being aware of treatment group
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants in the control group "were given placebo"; no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided to judge whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge.
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Overall unclear.

Mulla 1960

Methods	Randomized trial, 2 parallel groups.
Participants	Inclusion: bacteriuria at 30-32 weeks; microbiological criteria not stated. Setting: Ohio, US. Study period: not stated. Number of participants: n = 100.
Interventions	Sulfadimethoxine 250 mg twice a day x 7 days, repeated if bacteriuria persisted (n = 50) vs no treatment (n = 50)
Outcomes	Pyelonephritis (criteria for diagnosis not given; described as "acute symptoms of cystopyelitis")
Notes	Half (13/26) infections developed postpartum; only antepartum infections included in analysis No side effects necessitating discontinuation of treatment.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Women were "randomly divided into two groups"; no other details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided to judge whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	No definition for outcome of "cystopyelitis"; no pregnancy outcomes (gestational age, birthweight)
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Judged at overall high risk of bias.

Pathak 1969

Methods	Placebo-controlled; 2 parallel groups.
Participants	Inclusion: bacteriuria (> 100,000 bacteria/mL x 2). Exclusion: > 24 weeks' gestation; BP > 130/90 mmHg. Setting: Kingston, Jamaica. Study period: not stated.
Interventions	Nitrofurantoin 100 mg twice a day x 3 weeks; 400 mg in 4 doses for further 4 days for those who did not respond (6 women) (n = 76) vs identical appearing placebo (n = 76)
Outcomes	Persistence of bacteriuria (at end of pregnancy); pyelonephritis (criteria not described) Postpartum bacteriuria (3-9 months): 6/24 treatment vs 16/45 placebo
Notes	12/88 women in treatment group and 14/90 in control group not included in analysis (treated for positive treponemal serology n = 21; defaulted from clinic n = 5). Rates for preterm birth/fetal loss only presented by bacteriuric status, not treatment group. Rates for postpartum bacteriuria available for 69 women.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"on a random basis". Insufficient information provided to permit further judgement
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced; reasons similar and unlikely to have introduced bias
Selective reporting (reporting bias)	High risk	No pregnancy outcomes (gestational age, birthweight).
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Unclear overall.

Thomsen 1987

Methods	Randomized, placebo-controlled trial; 2 parallel groups.
Participants	Inclusion: positive midstream urine culture for group B streptococcus at 27-31 weeks' gestation. Setting: University Hospital, Denmark. Study period: October 1984-October 1986. Number of participants: n = 69.
Interventions	Penicillin 10 million IU 3 times a day x 6 days, retreated if repeat cultures positive (n = 37) or placebo tablets (n = 32)
Outcomes	Preterm birth (< 37 weeks' gestation). Mean gestational age (39.6 weeks in treatment group (n = 37) vs 36.2 weeks in placebo group (n = 32))
Notes	All mothers positive for group B streptococcus at delivery and their babies were treated with antibiotics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomly allocated" but no description of sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment of allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled, described as "double-blind" but no additional details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double blinded" but no specific information provided to ensure outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided.
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	Unclear risk	Overall unclear.

Williams 1969

Methods	Randomized trial; 2 parallel groups.
Participants	Inclusion: bacteriuria (> 100,000 bacteria/mL x 2, midstream urine) at first antenatal visit. Setting: University Hospital, Cardiff, Wales. Study period: 1967 Number of subjects: n = 163.
Interventions	Sulphadimidine 1 g 3 times a day x 7 days, nitrofurantoin 100 mg twice a day or ampicillin 250 mg 3 times a day x 7 days for failures (n = 85) or no treatment, unless symptoms (frequency, dysuria, fever or loin pain) developed when they were to take sulphadimidine 1 g 3 times a day x 7 days (n = 78)
Outcomes	Pyelonephritis (loin pain with tenderness or fever, or both); includes postpartum infection (n = 6)
Notes	No loss to follow-up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"allocated at random"; no additional information provided to permit judgement
Allocation concealment (selection bias)	Unclear risk	No information provided to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, outcome may have been influenced by lack of blinding. No treatment group was given antibiotics to take if symptoms of infection developed
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, assessment of outcome (pyelonephritis) may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No explanation for unequal group sizes; no information provided on any missing data. An unknown number of women in the control group (no treatment) were given antibiotic treatment if they developed symptoms of urinary tract infection
Selective reporting (reporting bias)	High risk	No pregnancy outcomes (gestational age, birthweight).
Other bias	Unclear risk	Insufficient information to judge.

Williams 1969 (*Continued*)

Overall Risk of Bias	High risk	Judged at high risk of bias.

Wren 1969

Methods	2 parallel groups. Quasi-RCT.
Participants	Inclusion: bacteriuria (midstream urine) x 2 at initial antenatal visits; microbiological criteria not stated. Setting: University Hospital, New South Wales, Australia. Study period: November 1965-December 1968. Number of participants: n = 183.
Interventions	Nitrofurantoin 100 mg twice a day x 2 weeks, then ampicillin 250 mg every 6 hours x 1 week, then sulphurazole 500 mg every 6 hours x 4 weeks, then nalidixic acid 500 mg every 6 hours x 2 weeks, then repeated until 1-6 weeks after delivery (n = 83) or no treatment (n = 90)
Outcomes	Preterm birth (< 37 weeks) or low birthweight (< 2500 g).
Notes	There were no stillbirths or neonatal deaths in the treated group; 6 in the no treatment group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Women "were divided into two groups, alternate patients being treated"
Allocation concealment (selection bias)	High risk	Women "were divided into two groups, alternate patients being treated"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding; knowledge of treatment group may have influenced outcome; women in untreated group who developed clinical urinary tract infection (33/90) were given antibiotics at the choice of the obstetrician, continued to delivery in over 50% of cases
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding; however, outcome of birthweight unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 women not included in outcomes: 2 sets of twins excluded, 6 women moved and only 2 could be traced, 3 women delivered before antibiotics could be started, 1 woman refused treatment

Wren 1969 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient information provided to judge; outcome of pyelonephritis not reported
Other bias	Unclear risk	Insufficient information to judge.
Overall Risk of Bias	High risk	Judged as high risk of bias.

Please attend closely to the study period for patient enrollment (found under 'Method'); in several instances there were significant delays between the enrollment period and the published report.
BP: blood pressure
IU: international unit
RCT: randomized controlled trial
SD: standard deviation
SE standard error
vs: versus

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

Study	Reason for exclusion
Calderon-Jaimes 1989	Women "divided" in 2 groups; no further description of how participants were allocated to treatment or no treatment
LeBlanc 1964	Both asymptomatic and symptomatic women were randomized; results for the asymptomatic bacteriuric women are not provided separately. For the outcome of pyelonephritis in the no treatment group, the outcome for women who were not treated as well as women who discontinued treatment have been combined
Mohammad 2002	Observational study describing incidence of bacteriuria; no details on treatment provided
Rafalskiy 2013	All asymptomatic bacteriuric women were treated with antibiotics (randomized to cefixime or amoxicillin/clavulanate)
Sanderson 1984	All bacteriuric women were treated with antibiotics. Those women successfully treated were randomized to prophylactic pivampicillin or no treatment for up to 3 months

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

Kazemier 2012

Trial name or title	The ASB study.
Methods	Randomized, double-blind, placebo-controlled (part of prospective cohort screening study)
Participants	Women with low-risk singleton pregnancies, positive by urine dipslide without symptoms of a urinary tract infection, between 16 and 22 weeks of gestation
Interventions	Nitrofurantoin or identical appearing placebo 100 mg twice daily for 5 consecutive days
Outcomes	Primary outcome: maternal pyelonephritis and/or preterm birth before 34 weeks. Secondary outcomes: neonatal and maternal morbidity, neonatal weight, time to delivery, preterm birth rate before 32 and 37 weeks, days of admission in neonatal intensive care unit, maternal admission days and costs
Starting date	2011.
Contact information	b.m.kazemier@amc.uva.nl
Notes	This study has been completed and submitted for publication.

DATA AND ANALYSES

Comparison 1. Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Development of pyelonephritis	11	1932	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.13, 0.41]
1.1 Single dose	1	173	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.92]
1.2 Short course (3-7 days)	3	483	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.09, 1.16]
1.3 Intermediate course (3-6 weeks)	2	433	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.08, 0.37]
1.4 Continuous treatment	5	843	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.57]
2 Preterm birth < 37 weeks	2	242	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.62]
2.1 Single dose	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Short course (3-7 days)	1	69	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.03, 0.60]
2.3 Intermediate course (3-6 weeks)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Continuous treatment	1	173	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.95]
3 Birthweight < 2500 g	6	1437	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.45, 0.93]
3.1 Single dose	1	413	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.36, 1.18]
3.2 Short course (3-7 days)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Intermediate course (3-6 weeks)	1	278	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.55, 2.14]
3.4 Continuous treatment	4	746	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.33, 0.87]
4 Persistent bacteriuria	4	596	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.18, 0.53]
5 Serious adverse neonatal outcome	1	273	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.42, 12.16]
6 Serious adverse maternal outcome	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Birthweight	1	413	Mean Difference (IV, Fixed, 95% CI)	61.00 [-56.55, 178.55]
8 Gestational age at delivery	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

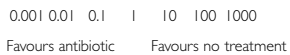
Analysis 1.1. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 1 Development of pyelonephritis.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 1 Development of pyelonephritis

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 Single dose					
Brumfitt 1975	9/87	20/86		13.0 %	0.44 [0.21, 0.92]
Subtotal (95% CI)	**87**	**86**		**13.0 %**	**0.44 [0.21, 0.92]**
Total events: 9 (Treatment), 20 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.18 (P = 0.029)					
2 Short course (3-7 days)					
Foley 1987	3/100	3/120		7.4 %	1.20 [0.25, 5.82]
Mulla 1960	1/50	12/50		5.5 %	0.08 [0.01, 0.62]
Williams 1969	5/85	18/78		11.4 %	0.25 [0.10, 0.65]
Subtotal (95% CI)	**235**	**248**		**24.3 %**	**0.31 [0.09, 1.16]**
Total events: 9 (Treatment), 33 (Control)					
Heterogeneity: Tau^2 = 0.77; Chi^2 = 4.77, df = 2 (P = 0.09); I^2 =58%					
Test for overall effect: Z = 1.74 (P = 0.082)					
3 Intermediate course (3-6 weeks)					
Elder 1971	4/133	27/148		10.8 %	0.16 [0.06, 0.46]
Pathak 1969	3/76	17/76		9.7 %	0.18 [0.05, 0.58]
Subtotal (95% CI)	**209**	**224**		**20.5 %**	**0.17 [0.08, 0.37]**
Total events: 7 (Treatment), 44 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 4.49 (P < 0.00001)					
4 Continuous treatment					
Furness 1975	23/139	17/67		14.2 %	0.65 [0.37, 1.14]
Gold 1966	0/35	2/30		3.0 %	0.17 [0.01, 3.45]
Kass 1960	1/93	26/98		5.6 %	0.04 [0.01, 0.29]
Kincaid-Smith 1965	2/61	20/55		8.3 %	0.09 [0.02, 0.37]
Little 1966	4/124	35/141		11.0 %	0.13 [0.05, 0.36]
Subtotal (95% CI)	**452**	**391**		**42.1 %**	**0.16 [0.04, 0.57]**
Total events: 30 (Treatment), 100 (Control)					
Heterogeneity: Tau^2 = 1.54; Chi^2 = 20.48, df = 4 (P = 0.00040); I^2 =80%					



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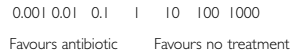
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 2.81 (P = 0.0049)					
Total (95% CI)	**983**	**949**	◆	**100.0 %**	**0.23 [0.13, 0.41]**
Total events: 55 (Treatment), 197 (Control)					
Heterogeneity: Tau^2 = 0.53; Chi^2 = 27.70, df = 10 (P = 0.002); I^2 =64%					
Test for overall effect: Z = 4.97 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.92, df = 3 (P = 0.27), I^2 =23%					



Analysis 1.2. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 2 Preterm birth < 37 weeks.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 2 Preterm birth < 37 weeks

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 Single dose					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Short course (3-7 days)					
Thomsen 1987	2/37	12/32	■	33.5 %	0.14 [0.03, 0.60]
Subtotal (95% CI)	**37**	**32**	◆	**33.5 %**	**0.14 [0.03, 0.60]**
Total events: 2 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.67 (P = 0.0075)					
3 Intermediate course (3-6 weeks)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					

(*Continued* . . .)

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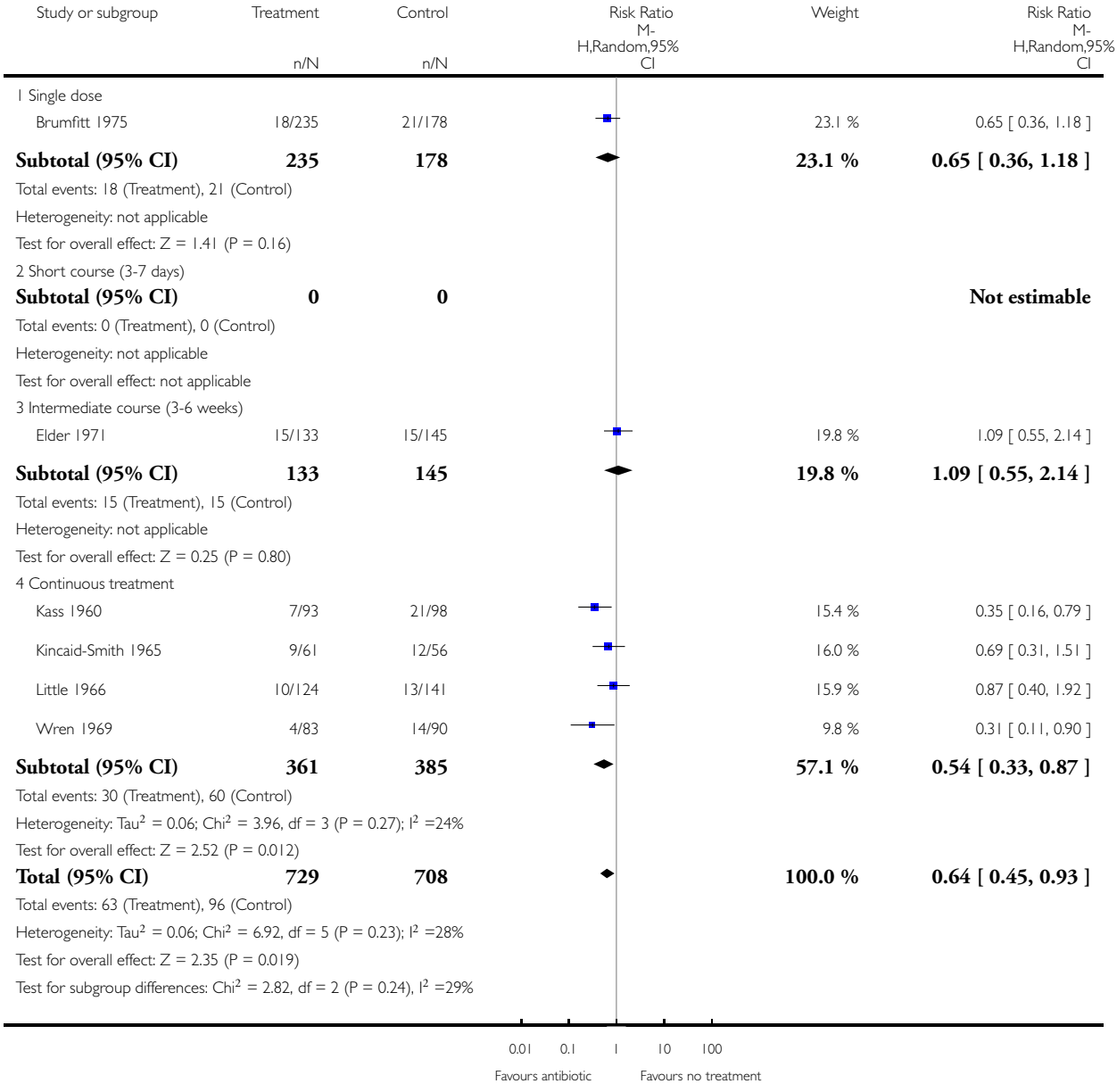
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Continuous treatment					
Wren 1969	5/83	15/90		66.5 %	0.36 [0.14, 0.95]
Subtotal (95% CI)	**83**	**90**		**66.5 %**	**0.36 [0.14, 0.95]**
Total events: 5 (Treatment), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.039)					
Total (95% CI)	**120**	**122**		**100.0 %**	**0.27 [0.11, 0.62]**
Total events: 7 (Treatment), 27 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 1.11, df = 1 (P = 0.29); I^2 =10%					
Test for overall effect: Z = 3.04 (P = 0.0024)					
Test for subgroup differences: Chi^2 = 1.10, df = 1 (P = 0.29), I^2 =9%					

Analysis 1.3. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 3 Birthweight < 2500 g.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 3 Birthweight < 2500 g



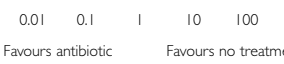
Analysis 1.4. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 4 Persistent bacteriuria.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 4 Persistent bacteriuria

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Elder 1966	12/52	30/49		26.4 %	0.38 [0.22, 0.65]
Elder 1971	33/133	98/145		31.8 %	0.37 [0.27, 0.50]
Gold 1966	12/35	22/30		27.3 %	0.47 [0.28, 0.78]
Pathak 1969	3/76	49/76		14.4 %	0.06 [0.02, 0.19]
Total (95% CI)	**296**	**300**		**100.0 %**	**0.30 [0.18, 0.53]**
Total events: 60 (Treatment), 199 (Control)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 12.52$, df = 3 (P = 0.01); $I^2 = 76\%$					
Test for overall effect: Z = 4.20 (P = 0.000026)					
Test for subgroup differences: Not applicable					

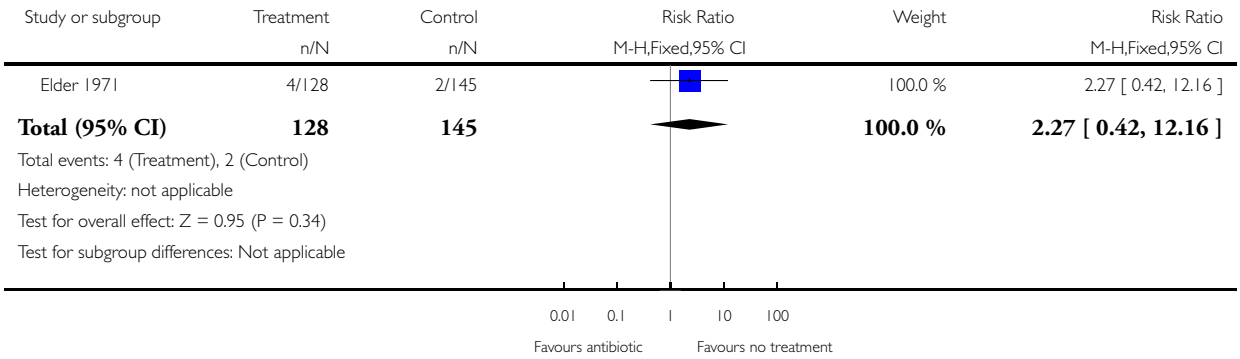


Analysis 1.5. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 5 Serious adverse neonatal outcome.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 5 Serious adverse neonatal outcome

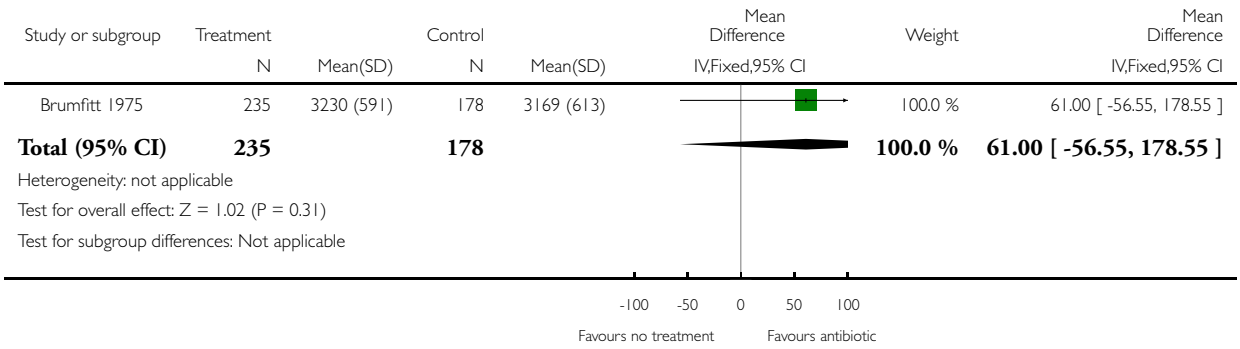


Analysis 1.7. Comparison 1 Antibiotic versus no treatment for asymptomatic bacteriuria, Outcome 7 Birthweight.

Review: Antibiotics for asymptomatic bacteriuria in pregnancy

Comparison: 1 Antibiotic versus no treatment for asymptomatic bacteriuria

Outcome: 7 Birthweight



WHAT'S NEW

Last assessed as up-to-date: 19 March 2015.

Date	Event	Description
19 March 2015	New search has been performed	We updated the search and identified four new studies; two references to a single study were excluded because they did not meet the inclusion criteria (Rafalskiy 2013), one was another reference to a previously included study (Elder 1971), and one was a reference to an ongoing study (Kazemier 2012). Methods and 'Risk of bias' table updated. A 'Summary of findings' table was incorporated
19 March 2015	New citation required but conclusions have not changed	Overall conclusions unchanged, but quality of the evidence in support of an effect of antibiotics for the primary outcomes rated as low to very low

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 1997

Date	Event	Description
1 September 2008	Amended	Converted to new review format.
31 January 2007	New citation required but conclusions have not changed	This review has been extensively rewritten. Low birthweight has been separated from preterm birth as outcomes; subgroup and sensitivity analyses are described and heterogeneity of studies discussed
31 January 2007	New search has been performed	We updated the search and identified two new studies. One additional study (Elder 1966) has been included and another excluded (Mohammad 2002). We have moved the LeBlanc 1964 study to the excluded studies because this study did not meet the inclusion criteria

CONTRIBUTIONS OF AUTHORS

Fiona Smaill had the major responsibility for the preparation of this review. Dr Vazquez reviewed drafts of the review and provided suggestions for revisions.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review substantially rewritten to incorporate current methodology. Primary and secondary outcomes reclassified; definition of prematurity changed to less than 37 weeks; adverse outcomes systematically collected. Discussion rewritten; GRADE tool used to produce a 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Asymptomatic Infections [*therapy]; Bacteriuria [complications; *drug therapy]; Confidence Intervals; Infant, Low Birth Weight; Odds Ratio; Pregnancy Complications, Infectious [*drug therapy]; Pyelonephritis [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy