Screening for Asymptomatic Bacteriuria in Pregnancy:  
Systematic Review & Meta-analysis

October 13, 2017

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# REVISION HISTORY

<table>
<thead>
<tr>
<th>Section</th>
<th>Date</th>
<th>Description/Changes</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Framework and Staged Approach</td>
<td>December 9, 2016*</td>
<td>Added “direct evidence” to Stage 1 and “indirect evidence for KQ1” to Stage 2 and 3 to clarify that KQ4 (treatment) and KQ5 (test accuracy) are encompassed in KQ1 (screening effectiveness), but each component on its own does not provide direct evidence on benefits/harms of screening, and therefore are included as indirect evidence.</td>
<td>To clarify that evidence on each of, treatment and test accuracy, are indirect evidence of screening effectiveness.</td>
</tr>
<tr>
<td>Figure 1. Analytical Framework</td>
<td>December 9, 2016*</td>
<td>Added treatment and no treatment to each arm of ASB+ and ASB-.</td>
<td>To identify that, although unlikely, there is the possibility of a study with treatment and no treatment arms for both patients in the ASB-positive and ASB-negative group.</td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>December 9, 2016*</td>
<td>Added examples of different screening tests (e.g., dipstick vs. Griess test) to illustrate the difference between KQ1a (screening vs. no screening) and KQ1b (different screening tests or algorithms such as frequency of testing or testing criteria).</td>
<td>To clarify the difference between KQ1a and KQ1b.</td>
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<tr>
<td>Eligibility Criteria</td>
<td>December 9, 2016*</td>
<td>Added “maternal and neonatal” to Harms to include both categories are included in serious and non-serious AEs. Added neonatal thrush to list of non-serious AEs as an example of a potential neonatal harm.</td>
<td>To clarify that harms to both mother and neonate are included.</td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>December 9, 2016*</td>
<td>Revised setting to any primary care or clinical setting which provides obstetric/antenatal care to pregnant women.</td>
<td>To avoid precluding care provided in other settings (e.g., obstetric office/clinic).</td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>January 27, 2017**</td>
<td>Revised perinatal mortality to ≥ 20 weeks of gestation.</td>
<td>To capture all perinatal mortality reported, including stillbirths which are reported using different criteria among studies.</td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>February 24, 2017***</td>
<td>Revised PICOTS for KQ1a to examine benefits and harms of a screening program compared to no-screening program, i.e. a screening test as the intervention was removed. Case-control study (Friedman 2012) was excluded for KQ1a.</td>
<td>A screening program is differentiated from a screening test, such that in the former screening would be intended for all women in the intervention group with a majority, but not all, receiving a screening test. This resembles a typical screening trial.</td>
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<tr>
<td>GRADE Assessments</td>
<td>October 6, 2017***</td>
<td>Revised GRADE assessments in KQ4 to no longer downgrade for indirectness due to use of evidence on treatment to infer knowledge about screening interventions; this is considered “linked” evidence. This revision did not lead to any changes to the overall GRADE evaluations or conclusions of our review.</td>
<td>To align with GRADE guidance for interpreting linked evidence and consider the body of evidence (for KQ4) independently from that for KQ1. The “linked” evidence will be considered as such by the CTFPHC when creating the Evidence to Decision framework for their guideline.</td>
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*Revision prior to final study selection and extraction

**Revision prior to data extraction and analyses; Canadian Task Force on Preventive Health Care (CTFPHC) members were blinded to all study reports

***Revision post-hoc, after data extraction and analyses; CTFPHC members were not blinded to study details
Summary

Purpose: This review was produced for the Canadian Task Force on Preventive Health Care (CTFPHC) to inform their recommendations on screening for asymptomatic bacteriuria (ASB) in pregnancy.

Review Approach: Following CTFPHC methods, a staged approach was used based on the quality of evidence when applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods. The quality of evidence was determined for outcomes rated by the CTFPHC, using input from consultations with Canadian women, as important or critical for decision-making. A reduction in the following outcomes would favor screening: maternal mortality, maternal sepsis, pyelonephritis, perinatal mortality, spontaneous abortion, neonatal sepsis, preterm delivery, low birthweight, and serious harms (e.g., fetal abnormalities after antibiotic treatment). Stage 1 examined screening effectiveness on the benefits and harms of any screening program compared with no screening and benefits and harms of different screening methods/algorithms (e.g., detection methods, timing and collection; test for cure after treatment of women found to have significant bacteriuria). Women’s valuation (“weighing”) of the benefits and harms of screening was also examined during this stage, with evidence on outcome valuation related to any antibiotic use in pregnancy considered. Evidence on screening effectiveness was very low quality, therefore we did not review studies on cost-effectiveness of screening programs which would have relied on similar evidence. Based on very low quality evidence from stage 1, stage 2 employing a “linked” evidence approach was undertaken to examine the effectiveness of antibiotic treatment for pregnant women with ASB. Since evidence from stages 1 and 2 considered screening programs and treatment based on the use of urine culture (gold standard), but not point-of-care (rapid) methods, we did not conduct an evidence review of the accuracy of point-of-care screening methods.

Data Sources: Comprehensive searches were conducted in bibliographic databases most relevant for each key question. For evidence on screening effectiveness, we searched MEDLINE (1946-) via Ovid; Embase (1974-) via Ovid; Cochrane Library; CINAHL (1937-present) via EBSCOhost; and PubMed via NCBI Entrez on June 15, 2016 (update searches ran on September 6, 2017). For evidence on women’s outcome valuation, we modified the search (ran on July 4, 2016; update searches ran on September 5, 2017) to include relevant terms and added the database PsycINFO; a search for evidence on cost-effectiveness was not conducted. For evidence on treatment, we searched on October 14, 2016 for systematic reviews using PubMed (1946-) via NCBI Entrez, the Cochrane Database of Systematic Reviews (inception-) and the Database of Abstracts of Reviews of Effects (DARE) (inception-2013) via Wiley Cochrane Library. The authors of the included systematic review on treatment, published in 2015, provided us with the results of their recent search update (using Cochrane Pregnancy and Childbirth Group's Trials Register) in November 2016 and October 2017. We also searched for grey literature and additional studies through internet-based searches, electronic libraries, trial registries, conference proceedings, and contact with experts.

Study Selection: Two reviewers independently screened titles and abstracts of citations from all database searches. Full texts of studies that were classified as “include/unsure” by either reviewer were retrieved and screened independently by two reviewers using a standard form with explicit inclusion and exclusion criteria. Disagreements were resolved through consensus or consultation with a third reviewer. For each key question, the flow of literature and reasons for full-text exclusion are recorded in a PRISMA Flow Chart. For evidence related to treatment effectiveness, systematic reviews were assessed for eligibility based on having conducted a search strategy in more than one database, whether the selection criteria
were reported, and whether the population, intervention, comparator, timing, and setting (PICOTS) criteria closely matched ours.

**Data Abstraction:** For evidence in stage 1, one reviewer independently extracted data, and another reviewer verified all data from each included study on its study design; country of origin, sample size, characteristics of the patients, interventions, and comparator(s); clinical setting; and, outcomes of interest. Authors of included studies were contacted for clarification of study details and outcome data as necessary. For treatment evidence in stage 2, we extracted data from the systemic review on its selection criteria (PICOTS) and its included studies, as well as from an additional trial captured by the review authors’ search update. We verified data from the systematic review, and also examined the primary studies for additional participant characteristics and outcome details relevant to the current review. A narrative summary with accompanying tables is reported for all studies. Two reviewers independently assessed the methodological quality of each included study with the following tools: Newcastle-Ottawa Quality Assessment Scale for observational studies, the Center for Evidence-based Management appraisal tool for cross-sectional studies, and the Cochrane Risk of Bias tool for trials. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.

**Analysis & Interpretation:** We performed meta-analyses for the dichotomous outcomes in the evidence for screening and treatment, using the DerSimonian and Laird random effects model with Mantel-Haenszel method, and report relative risks (RR) with corresponding 95% confidence intervals (CIs). For outcomes having statistically significant effects, we calculated absolute risk reduction (ARR), and number needed to screen (NNS) or number needed to treat (NNT) based on the control group event rates and RR. Where there were at least two studies per category for a variable, we performed subgroup analyses as planned for clinical (patient and intervention) characteristics of interest. We conducted sensitivity analyses for methodological issues (e.g., risk of bias) when substantial heterogeneity was found in meta-analysis. We examined funnel plots and conducted Egger’s test to detect small-study bias when there were at least eight studies in a meta-analysis. When data were not pooled, we provided a narrative summary of findings. Two reviewers independently assessed the quality of the body of evidence using GRADE methodology, with consensus based on discussion and input from a third reviewer.

**Results:** Four non-concurrent cohort studies compared outcomes for groups of pregnant women before and after introduction of a screening program for ASB. All studies used a urine culture for screening, with some variability in the collection methods and treatment protocols. Three studies compared screening with no screening; meta-analysis using data from these studies showed a statistically significant reduction in pyelonephritis (RR 0.28; 95% CI 0.15, 0.54; ARR 1.3%; NNS 77, 95% CI 65, 121). No significant differences were found when comparing screening with no screening for other outcomes of perinatal mortality based on two studies (RR 1.21; 95% CI 0.01, 102.93), spontaneous abortion based on one study (RR 0.96; 95% CI 0.41, 2.27), preterm delivery from two studies (RR 8.70; 95% CI 0.32, 240.07), and fetal abnormalities (neonatal serious harm) from one study (RR 1.50; 95% CI 0.25, 8.87). One study compared frequent screening with one-time (first prenatal visit) screening and found no significant difference for pyelonephritis (RR 1.09; 95% CI 0.27, 4.35) or preterm delivery (RR 1.57; 95% CI 1.11, 2.23). No study provided evidence on how women weigh the benefits and harms of screening for ASB; seven studies provided evidence on sentiments on harms only, and reported conflicting opinions about antibiotic use during pregnancy particularly on teratogenic risks. Fifteen trials examined the effectiveness of antibiotics versus placebo or no antibiotics for women with bacteriuria (≥10^5 colony-forming units of
one organism per mL); only three trials reported that participants were asymptomatic and some trials included high-risk women. Fourteen of the trials reported on outcomes relevant to this review. Meta-analysis from 12 trials found a significant reduction from antibiotic treatment compared with placebo/no treatment in development of pyelonephritis among women with bacteriuria (RR 0.24; 95% CI 0.13, 0.41; ARR 17.6%; NNT 6, 95% CI 5, 7; I²=60%). One of our planned subgroup analysis, for pyelonephritis based on whether or not a confirmatory (second specimen) culture was used (RR 0.19, 95% CI 0.11, 0.31, I²=31% versus RR 0.50, 95% CI 0.19, 1.35, I²=41%), seemed to have some credibility based on visual inspection of the forest plots (indicating possible important difference) and a reduction in heterogeneity within each subgroup; results from testing for a difference between subgroup effects, though, was not statistically significant (p=0.08). Seven studies found that treatment reduced low birth weight (RR 0.63; 95% CI 0.45, 0.90; ARR 4.4%; NNT 23, 95% CI 15, 85). No significant difference between groups was found for all other outcomes: perinatal mortality based on six studies (RR 0.96, 95% CI 0.27, 3.39), spontaneous abortion based on two studies (RR 0.60, 95% CI 0.11, 3.10), neonatal sepsis based on two studies (RR 0.22, 95% CI 0.01, 4.54), preterm delivery based on four studies (RR 0.57, 95% CI 0.21, 1.56), and neonatal harms (fetal abnormalities) from four studies (RR 0.49, 95% CI 0.17, 1.43; no cases of infant hemolytic anemia in one study). No study on screening or treatment reported on maternal mortality, maternal sepsis or maternal harms.

Limitations: Based on our risk of bias tools, the non-concurrent cohort studies examining screening effectiveness were of unclear or low risk of bias; nevertheless, observational studies introduce several potential biases which are not captured in this tool, particularly as related to reporting bias which was suspected for outcomes apart from pyelonephritis. For evidence related to screening effectiveness, studies used a urine culture to detect ASB but the criteria for defining a positive test was not always clear or reported. Many patient and intervention characteristics were not reported, or were inconsistently reported between studies. Outcomes were defined variably among studies. One treatment study only included women who were treated for group B streptococcus based on urine culture, only three of the treatment trials reported that participants were asymptomatic, and four trials included high-risk women. The small sample sizes and event rates for many outcomes led to imprecise effect estimates. Subgroup analyses were few because of the limited reporting on subgroup variables of interest and number of studies contributing to most outcomes; although our findings on pyelonephritis for subgroups based on two (for confirmation) versus one culture specimen appear to have some credibility, these analyses rely on study-level data and are observational (i.e., studies are not randomized) and exploratory in nature. The majority of studies on treatment were published in the 1960s, pre-dating current obstetric practices having, for example, better recognition of risk factors for urinary tract infections and other pregnancy complications, prompt treatment of symptoms, and a broader range of antibiotic options; these factors would suggest a lower control group (baseline) event rate and therefore less absolute benefit in current practice. Much of the evidence came from trials on treatment of bacteriuric women (2-10% of screening population), therefore the results fail to incorporate several effects that would be captured in studies of screening effectiveness (e.g. effects on non-screened women who develop symptoms, or on ASB-negative women; effects from non-adherence to screening protocol). Studies published in languages other than English and French were not included; however, literature suggests language restrictions in systematic reviews of conventional medicine do not appear to bias results of meta-analyses.

Interpretation of Results & Conclusion: This systematic review examined three sets of evidence to inform recommendations on screening for ASB in pregnancy. Using the GRADE approach, we
determined the evidence to be of very low quality for most outcomes from observational studies comparing screening programs using urine culture with no screening; as such, we have no or very little certainty in the effect estimates for these outcomes. Moreover, several outcomes were not reported. Similar interpretations are made about the evidence from one study comparing frequent screening with one-time screening. No direct evidence was found on how women weigh the benefits and harms of screening and/or treatment for ASB and how this might affect their decisions to undergo screening. Antibiotic treatment for women having significant bacteriuria likely reduces the incidence of pyelonephritis in these women and the number of their babies born at low birth weight (both of low quality evidence). We are uncertain if the magnitudes of the effect estimates from treatment are true, and about the extent to which we can apply these results to asymptomatic populations. Very low quality evidence from these trials did not allow us to have any certainty about effects from treatment on other maternal and neonatal benefits and for fetal abnormalities and hemolytic anemia; no evidence was found for other serious harms.

PROSPERO Registration #: CRD42016045263
Chapter 1. Introduction

Background & Purpose

Asymptomatic Bacteriuria in Pregnancy

Asymptomatic bacteriuria (ASB)—synonymous with asymptomatic urinary tract infection (UTI)—signifies a significant quantitative count of bacteria in the urine without symptoms of a lower (acute cystitis) or upper urinary tract/kidney (acute pyelonephritis) infection.1, 2 There is a 2-10% prevalence of ASB in premenopausal, ambulatory women,1 but due to anatomical and physiological changes (e.g., displaced bladder) to the urinary tract in pregnancy there are theoretical reasons to suspect higher rates of ASB during pregnancy and consequently a greater chance of progression to symptomatic UTI and other pregnancy complications (e.g., pyelonephritis, preterm delivery).1, 3 Numerous risk factors for ASB in pregnancy have been identified, with low socioeconomic status, higher parity, a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract most cited.1, 2, 4

Consequences of Untreated Bacteriuria in Pregnancy and Rationale for Review of Screening

There is a potentially greater risk in pregnant women compared to other populations for ASB developing into pyelonephritis3 with its associated inflammation of the renal parenchyma, calices and pelvis,5 although controversy exists. Historical reports pre-19806-8 finding that upwards of 40% of pregnant women with ASB developed pyelonephritis lend support for screening and treatment with antibiotics; current estimates of the incidence of pyelonephritis in ASB positive women are hard to locate because of universal acceptance of this practice (e.g., in Canada for more than two decades). Reports of a reduced incidence of pyelonephritis in pregnant women after introduction of routine screening (e.g., 0.3 to 0.57% vs. 1-2%)9 suggest that these programs have been beneficial.

Recent evidence suggests an association between clinical signs of pyelonephritis and perinatal outcomes. A retrospective cohort study (Wing et al10) of women who delivered in hospitals in the United States from 1993 to 2010 found that pyelonephritis was linked to higher risk of maternal respiratory insufficiency, septicemia, renal dysfunction, and anemia. However, controversy exists over the mechanism linking ASB, pyelonephritis, and adverse perinatal outcomes (e.g., whether ASB affects pregnancy and neonatal outcomes solely through pyelonephritis or also other mechanisms such as prostaglandin activation).2, 4 and therefore also about whether treatment of ASB with antibiotics will reduce the risk of such adverse outcomes. A 2015 Cochrane review4 of fourteen trials found that antibiotic treatment for ASB in pregnancy may reduce the incidence of pyelonephritis, preterm birth, and low birth weight babies. However, the authors’ confidence in the findings was low due to poor quality evidence.

Although the direct link between pyelonephritis and adverse perinatal outcomes may not be easily resolved4, an examination of whether screening of all pregnant women and treatment for significant bacteriuria is effective is of interest. Knowledge of whether screening and treatment offer as much benefit today, when there is more advanced obstetrical care (e.g., for treating acute pyelonephritis) and awareness of risk factors for pregnancy complications, would be valuable information. Knowing that some risk for harm exists from taking antibiotics during pregnancy, the benefit-to-harm ratio may be less favourable than historically thought. This review will examine up-to-date evidence on screening for ASB in pregnancy, for reducing the risks of pyelonephritis and neonatal and maternal complications.
Issues to Consider for Screening Tests

Significant bacteriuria is usually defined by the presence of at least 100 x 10^6 colony-forming units (CFU) per litre of urine of a single organism in two consecutive clean-catch specimens (non-Canadian criteria typically report \( \geq 10^5 \) CFU/mL).\(^4,7\) Acceptable thresholds and repetitions of testing to confirm bacteriuria in pregnancy may vary in practice. The quantitative urine culture is considered to be the gold standard for accurate detection of ASB. However, it is costlier, more labour intensive and more time-consuming compared with rapid urine screening tests (urinalysis, dipstick nitrite tests) which reportedly are less accurate in identifying people with bacteriuria.\(^1,2\) A recent systematic review comparing the accuracy of onsite methods (point-of-care tests that are widely available in resource-limited settings) with urine culture, concluded that point-of-care tests were not reliable in detecting pregnant women with ASB.\(^11\) Further, pregnant women have very active urinary sediment which may contribute to issues with test accuracy. There is no consistent recommendation for urine specimen collection in pregnancy (number of specimens, clean-catch with or without perineal cleansing) or optimal timing and frequency of screening tests or follow-up cultures.\(^2\) It is unclear whether available point-of-care methods for ASB are comparable to the current gold standard (urine culture) for identifying bacteriuric patients. The standard urine culture protocol is evolving with the testing of emerging techniques that may improve the detection of the most clinically relevant uropathogens.\(^12,13\) However, at this time, urine culture is considered the reference standard.

Issues to Consider for Harms of Screening

Patients may have preferences for avoiding harms due to screening with the intention to treat in asymptomatic conditions, particularly when they may otherwise not benefit from the treatment (e.g. in cases where ASB would not lead to complications). Harms from antibiotic treatment need to be considered when making decisions about screening practices for all women with ASB in pregnancy. Some sources have outlined concerns with incidence and reporting on adverse effects of antibiotic treatment for ASB, UTIs, or antibiotic use in general during pregnancy.\(^2,4,14\) Some trials evaluating treatment versus no treatment/placebo of ASB in pregnancy have been critiqued for poorly reporting harms,\(^4\) such that making judgments on the net balance of benefits and harms may be difficult. Increasingly, there are concerns about the effect of antibiotics on the human microbiota and the immune system. Antimicrobial resistance has made the selection of an antibiotic for an individual more difficult.\(^4\) Further, a test-for-cure is increasingly more important and more than one type of antibiotic may be required if sensitivity testing is not performed or accurate.

Recommendations in Other Guidelines and Current Practice

Canadian Organizations

The Society of Obstetricians and Gynecologists of Canada (SOGC) recommends screening during pregnancy using routine testing for ASB with a single quantitative culture in any trimester and treating single-strain colony counts of 10^5 CFU/mL (or 10^8 CFU/L) or greater with appropriate antibiotics to prevent adverse outcomes such as pyelonephritis and preterm birth.\(^15\) They support a single quantitative culture in any trimester as sufficient and recommend re-treatment with antibiotic sensitivity testing for women with recurrent bacteriuria, although they do not make recommendations for timing or frequency of re-testing. As for ASB \( \geq 10^5 \) CFU/mL, similar recommendations apply when group B streptococcal
(GBS) bacteria is detected in the urine; separate recommendations (not relevant for this review) are made for screening and treating GBS (at any colony counts) at time of labor or rupture of membranes for prevention of early-onset neonatal GBS disease.

Guidelines from International Organizations
The U.S. Preventive Services Task Force (USPSTF) 2008 guideline\textsuperscript{16} on screening for ASB in adults recommends with high certainty of substantial net benefit that all pregnant women be screened at 12 to 16 weeks of gestation (or first prenatal visit) for ASB using a urine culture, and that treatment with antibiotics significantly reduces the incidence of pyelonephritis and low birthweight. The evidence informing this reaffirmation of the original USPSTF recommendation from 2004 is mainly drawn from a 2007\textsuperscript{17} Cochrane review of treatment effectiveness. The American Academy of Family Physicians (AAFP)\textsuperscript{18} endorses the recommendations of the USPSTF. The Infectious Diseases Society of America\textsuperscript{19} recommends screening for bacteriuria by urine culture for pregnant women in early pregnancy, and treatment if results are positive, with periodic re-testing for recurrent bacteriuria after therapy. The American Academy of Pediatrics (AAP), jointly with the American College of Obstetricians and Gynecologists (ACOG) recommend to screen and to treat significant bacteriuria and then to test for cure.\textsuperscript{20}

The UK's National Institute for Health and Care Excellence (NICE) states that women should be offered routine screening for ASB by midstream urine culture early in pregnancy to reduce the risk of developing pyelonephritis.\textsuperscript{21}

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that pregnant women be tested for ASB by urine culture at the first antenatal visit and culture-positive patients be treated with an antibiotic.\textsuperscript{22}

Current Practice
Several major healthcare organizations in North America (USPSTF, IDSA, ACOG, AAP, AAFP) recommend screening of pregnant women and treating patients who have been confirmed with ASB using antibiotics. In Canada, the current usual practice is to obtain at least one urine sample (with reported variations in practice on timing such as at first prenatal visit), and potentially with subsequent testing if indicated (e.g., if patient presents with symptoms). Urine samples may be tested with a dipstick, for example, to test for protein or glucose, and may also be used to detect leukocytes, blood and/or nitrites; urine testing in pregnancy may be intended for detecting conditions other than for ASB. Furthermore, there appears to be diversity in urine testing for the presence of significant bacteriuria, with respect to how the sample is collected, what is used to detect presence of bacteriuria (e.g., culture most often but perhaps not always), when sample(s) for ASB is/are collected in pregnancy, and if/when confirmatory tests are used. Because of this screening for ASB may consist of several variations in terms of testing methods, timing, and collection, as well as treatment protocols (duration, test-for-cure, threshold of bacteria for treatment).

The goal of this review is to determine the effectiveness of screening for ASB among pregnant women. This evidence synthesis will inform recommendations on screening for ASB made by the Canadian Task Force on Preventive Healthcare (CTFPHC). As part of the guideline development process, the CTFPHC will also engage patient and organizational stakeholders to gather information on patient preferences and
key implementation considerations, such as strategies to help address potential health inequities and any concerns about the acceptability and feasibility of the guideline.

Chapter 2. Methods

An *a priori* protocol was developed following the methods of the Canadian Task Force on Preventive Health Care (CTFPHC)²³ and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration #CRD42016045263).

Analytic Framework, Review Approach and Key Questions

Figure 1 is an analytical framework that depicts the basic structure used to address the Key Questions (KQs) for evaluating the benefits and harms of screening programs for asymptomatic bacteriuria (ASB) during pregnancy.

**Figure 1. Analytical Framework**

AEs: adverse events; ARDS: acute respiratory distress syndrome; ASB: asymptomatic bacteriuria; g: grams; KQ: key question; NICU: neonatal intensive care unit; UTI: urinary tract infection; wks: weeks

Note: Patient-important outcome ratings by CTFPHC members and patients as critical [7-9, out of 9] or important [4-6, out of 9] are included.
A staged approach was used based on the availability and quality of the body of evidence. Quality of evidence (classified as high, moderate, low, very low) was assessed using methods developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org/), whereby high quality evidence relies on precise and consistent effect estimates from studies having few limitations on internal validity (i.e., low bias) and examining directly relevant populations, interventions, comparators, outcomes, timing, and setting (i.e., PICOTS). Decisions made during the evidence review are based on the information needs of the CTFPHC for making a recommendation in favour of or against screening based on the balance of benefits and harms for critical patient-important outcomes.

Stage 1 focused on identifying and using data from studies directly linking screening programs for ASB to patient-important benefits and harms (KQ1). Study designs providing the highest internal validity (i.e., RCTs) for this KQ were preferred with a hierarchy of evidence used after this point if necessary. After RCTs we planned to consider controlled clinical trials (CCTs; defined for this review as experimental trials without random allocation but where intervention(s) are introduced, standardized, and allocated objectively [e.g., by date of birth, but not using subjective means such as patient or clinician preferences] by investigators and blinding of participants is typically possible) and then prospective and retrospective controlled observational studies. This stage also included examination of women’s valuation of benefits and harms (KQ2) of screening for ASB (and more broadly/indirectly treatment with antibiotics) in pregnancy. The cost-effectiveness of screening for ASB (KQ3) was to be considered only if there was moderate or high quality evidence from KQ1 indicating a favourable benefit-harm ratio. The quality of evidence from cost-effectiveness studies relies on the quality of the data inputs, such that very low quality evidence on effectiveness will not lead to any certainty in the estimates of cost-effectiveness.

If stage 1 did not provide high enough quality of evidence for making a recommendation, the CTFPHC planned to carefully consider pursuing stage 2 with documentation of rationale before proceeding. Stage 2 would commence with examination of effectiveness of treatment (linked evidence) of ASB in pregnancy (KQ4). Moreover, if studies for treatment effectiveness examined the use of point-of-care methods, rather than the current gold standard which is urine culture, an examination of KQ5 on accuracy of these tests would be considered in stage 3. Due to the linked evidence provided by treatment effectiveness (KQ4) and test accuracy (KQ5) for making recommendations on the clinical effectiveness of screening programs for all pregnant women, we would only seek data from study designs offering the greatest potential for high internal validity. That is, for KQ4 (treatment) we planned to focus on RCTs, and for KQ5 (test accuracy) we would exclude case-control designs. Where a high quality systematic review existed examining these evidence linkages to screening effectiveness, we would utilize these when possible.
Key Questions (KQs)

Stage 1 (direct evidence):

Benefits and harms of screening

**KQ1a:** What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences for patient characteristics (e.g., socioeconomic status [SES])?

**KQ1b:** What are the comparative benefits and harms of screening programs with different screening methods or algorithms for asymptomatic bacteriuria in pregnancy?

Outcome valuation

**KQ2a:** How do women weigh the benefits and harms of screening and treatment of asymptomatic bacteriuria in pregnancy?

**KQ2b:** How do women’s valuation of benefits and harms of screening and treatment inform their decisions to undergo screening?

Resource use

**KQ3:** What is the cost-effectiveness of screening for asymptomatic bacteriuria in pregnancy?

Stage 2 (linked evidence):

Treatment

**KQ4:** What are the benefits and harms of antibiotic treatment compared with placebo or no treatment for asymptomatic bacteriuria in pregnancy?

Stage 3 (linked evidence):

Diagnostic accuracy of screening tests

**KQ5:** What is the accuracy of point-of-care screening tests compared with urine culture for asymptomatic bacteriuria in pregnancy?

Search Strategy

The literature search strategies were developed and implemented by a research librarian and peer reviewed. Searches were restricted by language to include full texts published in English and French only; literature suggests language restrictions in systematic reviews in conventional medicine do not appear to bias results from meta-analyses.24, 25 No restrictions were applied to publication dates or study design. Full detailed search strategies for all databases are reported in Appendix 9.

Comprehensive searches were conducted in bibliographic databases most relevant for each KQ. For KQ1 (screening effectiveness), we searched MEDLINE (1946-) via Ovid; Embase (1974-) via Ovid; Cochrane Library; CINAHL (1937-present) via EBSCOhost; and PubMed via NCBI Entrez. For KQ2 (women’s outcome valuation), we modified the search to include relevant terms and added PsycINFO as a database.
We did not search for studies on cost-effectiveness (KQ3) because of the very low quality evidence for KQ1 (see description of staging approach, p.5). We did not search for studies or reviews on test accuracy (KQ5) because there was no evidence from KQ1 or KQ4 that point-of-care tests may replace urine culture as an accurate screening method. Searches for KQ1 and KQ2 are current to September 2017.

For KQ4 (treatment effectiveness), we conducted a database search for systematic reviews, meta-analyses and health technology assessments to ensure all potentially relevant systematic reviews were identified. We searched PubMed (1946-) via NCBI Entrez, the Cochrane Database of Systematic Reviews (inception-) and the Database of Abstracts of Reviews of Effects (DARE) (inception-2013) via Wiley Cochrane Library on October 14, 2016. Our PubMed search utilized a search filter from the Canadian Agency for Drugs and Therapeutics in Health (CADTH).26 The authors of the included systematic review on treatment, published in 2015, provided us with the results of their recent search update (using the Cochrane Pregnancy and Childbirth Group's Trials Register)4 on November 2016 and October 2017.

Grey literature was searched and documented according to CTFPHC methods and included internet-based searches (via adapted CADTH checklists27), electronic libraries (e.g., Health Canada Library, Canadian Electronic Library), and trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform). Based on consultation with clinical experts, the following highly relevant conference proceedings were hand-searched for recent studies not yet published (2014-August 2016): Society of Obstetricians and Gynaecologists of Canada (SOGC, Association of Medical Microbiology and Infectious Disease Canada, ID Week, and American Society for Microbiology meeting (ICAAC). Clinical and content experts identified by the CTFPHC for review of the protocol were invited to identify relevant research reports for consideration. Potentially relevant papers and websites identified by stakeholders and peer reviewers during protocol review were also searched and screened for eligibility: Society for Maternal Fetal Medicine (SMFM), American College of Obstetrics and Gynecology (ACOG) annual meeting, and Infectious Diseases Society of Obstetrics and Gynecology (IDSOG).

Study Selection

Two reviewers independently screened the titles and abstracts of all citations retrieved by the database searches. Full texts of studies that were classified as “include/unsure” were retrieved for review and screened independently by two reviewers using a standard form with explicit inclusion and exclusion criteria. Disagreements were resolved through consensus or consultation with a third reviewer. All decisions for title/abstract screening and full-text review were conducted and documented in DistillerSR.28 For each KQ, the flow of screening and reasons for full-text exclusion are recorded in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart.

We followed methods adopted by the CTFPHC for integrating systematic reviews for KQ4 on treatment (see Appendix 13), where existing systematic review(s) are eligible based on a) searching more than one database, b) reporting selection criteria, and c) using populations, interventions, comparators, timing and setting (PICOTS) criteria that closely match the current review. The included studies were assessed for eligibility to meet our inclusion criteria, incorporating existing data and extracting additional data as necessary, conducting quality assessments, and performing new meta-analyses and GRADE quality assessments.
Eligibility Criteria

We included studies of asymptomatic women at any stage of pregnancy, including populations where a proportion of women may have symptoms or present with risk factors (e.g., kidney infection, recurrent UTI, diabetes), but are considered to represent a routine prenatal care population. Studies that exclusively examined women with risk factors (e.g., high risk for ASB, pyelonephritis, or poor outcomes associated with some conditions such as history of kidney infection, renal anomalies, polycystic kidneys, recurrent UTI, diabetes, or sickle-cell disease) were excluded. Studies that included non-pregnant women were excluded.

The population subgroups of interest included: history of kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection (UTI), diabetes, sickle-cell disease, socioeconomic status (SES; i.e., education, income), ethnicity, and urban/rural setting.

For clinical effectiveness of screening (KQ1a) comparing any screening program with no screening, the screening program could include any screening algorithm for ASB (e.g., different screening methods, collection and timing; treatment duration, test-for-cure). For KQ1b comparing different screening programs, programs could differ by screening method (e.g., culture vs. dipstick) or algorithm (e.g., frequency of screening, urine collection methods); studies that compared differing criteria for a positive urine culture (e.g., threshold $10^3$ CFU/mL versus $10^5$ CFU/mL) were also eligible for inclusion. For the screening studies (KQ1), we did not exclude studies if a treatment protocol was not reported; as part of an overall screening program, it was assumed there was an intent to treat screen-positive cases. For women’s outcome valuation (KQ2), any screening program for ASB during pregnancy was eligible for inclusion; we planned to use indirect evidence about antibiotic treatment during pregnancy broadly if needed. For cost-effectiveness (KQ3), we planned to include any screening program compared with no screening or another screening program. For treatment effectiveness (KQ4), any antibiotic treatment for ASB compared with no treatment or placebo was eligible for inclusion. For diagnostic accuracy (KQ5), we planned to include any index (rapid point-of-care) test compared with a urine culture (reference standard) for detecting bacteriuria. For all KQs, studies that included screening or treatment for group B streptococcus (GBS) at any time of pregnancy for any of the outcomes of interest were included. We excluded studies that screened pregnant women for group B streptococcus near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed above). Studies that exclusively examined urine tests for screening other conditions (e.g., proteinuria, glycosuria), and non-urine screening tests (e.g., vaginal/rectal swab culture for GBS testing) were excluded.

The screening subgroups of interest included: urine collection methods (e.g., clean-catch and/or midstream; excluding catheter methods/samples), frequency of testing, number of samples (e.g., use of confirmatory cultures), criteria for a positive test (bacterial colony count, and specified organism(s)), follow-up testing during pregnancy, and timing during pregnancy.

All outcomes were rated independently by members of the CTFPHC and by women, as per the patient engagement activities of an independent group with expertise in knowledge translation from St. Michael's.
Hospital in Toronto, Ontario. All patient-important outcomes rated as critical (7 to 9 out of 9) or important (4 to 6 out of 9) for decision making were considered for inclusion (See Table 1.0 for list of critical/important outcomes and ratings). From these ratings, the eight outcomes that were rated as critical were included; of three outcomes rated as important, low birth weight (but not hypertension or acute kidney injury) was included because this was conceptualized in older studies to be the same as “preterm birth”, which both the CTFPHC members and patients rated as critical. Considering harms separately, when no evidence was initially found for any of the outcomes (serious adverse events [AEs]), we planned to then include non-serious AEs which are considered important but not critical for decision making by the CTFPHC.

For perinatal mortality, we revised the original criteria of ≥28 weeks of gestation (Statistics Canada’s definition for perinatal mortality including late fetal deaths [stillbirths ≥28 weeks] and early neonatal deaths [deaths of infants <1 week old]) to ≥20 weeks of gestation to allow for inclusion of data from studies that used slight variations in defining this outcome. For preterm delivery defined as <37 weeks of gestation, we included one study that defined preterm birth as <38 weeks of gestation as this was considered inclusive of our criteria. For low birth weight, we included studies where low birth weight was defined as ≤2500 grams (for live births).

Table 1.0 Outcomes and ratings for KQs 1 (screening effectiveness) and 4 (treatment effectiveness)

<table>
<thead>
<tr>
<th>Benefits (reduced incidence for all):</th>
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<tr>
<td>1. maternal mortality (9)*</td>
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<td>2. maternal sepsis (8)</td>
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<td>3. pyelonephritis (7)</td>
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<td>4. perinatal mortality (≥ 20 weeks of gestation [e.g., intrauterine demise, stillbirth, early neonatal death]) (9)</td>
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<td>5. spontaneous abortion/pregnancy loss &lt; 20 weeks of gestation (8)</td>
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<td>6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)</td>
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<td>7. preterm delivery (live fetus passed &lt; 37 weeks of gestation) (7)</td>
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<td>8. low birth weight (≤ 2500g) (6)</td>
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<tr>
<th>Harms (maternal and neonatal):</th>
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<td>1. serious adverse event(s)** associated with antibiotic treatment, including but not limited to: (7)</td>
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<td>a. anaphylaxis,</td>
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<td>b. thrombocytopenia,</td>
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<td>c. hemolytic anemia,</td>
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<td>d. fetal abnormalities; and,</td>
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<td>2. non-serious adverse event(s) associated with treatment, including but not limited to: (4)</td>
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<tr>
<td>a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),</td>
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<td>b. antibiotic-induced diarrhea,</td>
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<td>c. rash,</td>
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<td>d. vomiting,</td>
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<tr>
<td>e. neonatal thrush</td>
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*Bracketed numbers next to each outcome above refer to patient-important outcome ratings by CTFPHC members and patients as critical [7-9, out of 9] or important [4-6, out of 9] are included
Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)

Women’s outcome valuation (KQ2) included several possible outcomes related to the weighing of benefits and harms of screening and treatment (KQs 1 and 4) and how this may affect their decisions to undergo screening (e.g., relative weight/utilities of benefit and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment, anxiety).

Cost-effectiveness (KQ3) outcomes would include cost per quality-adjusted life year (QALYs), incremental cost-effectiveness ratios (ICERs), and net benefit (in dollars from cost-benefit studies).

Diagnostic test accuracy (KQ5) outcomes include: sensitivity, specificity, false positives, false negatives, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.

We included studies conducted in any primary care, or another clinical setting which provides obstetric/antenatal care to pregnant women (e.g., obstetric and hospital outpatient clinics, prisons, remote stations, community health centers, midwifery practice). For KQ3 on cost-effectiveness we planned to limit studies to those conducted using data relevant to Canada, thus within countries having a Very High Human Development Index.

For KQ1 (screening effectiveness), eligible study designs included RCTs, CCTs and controlled observational studies (i.e., prospective and retrospective cohort, non-concurrent cohort (two or more groups identified on basis of common features at different time points), case-control, controlled before-after). For KQ2 (outcome valuation), we included any study where women were asked to balance the benefits and harms of screening and treatment for ASB and/or state their willingness to be screened and treated based on information or reflection on benefits and harms; surveys, experimental designs (e.g., contingent valuation), and qualitative research were eligible examples. For KQ3 (cost-effectiveness), we planned to look at any study comparing effects and costs (e.g., cost-effectiveness, cost-utility, cost-benefit), including modelling of effects and/or costs. For KQ4 (treatment), we planned to include RCTs. For KQ5 (test accuracy), we planned to use prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and reference standard, or where participants are randomized to different index tests but all receive the reference standard; assessment would generally be performed in a cross-sectional manner. For KQs 4 (treatment effectiveness) and 5 (test accuracy), we planned to use existing high-quality systematic review(s) if found.

For all KQs, case reports and case series (i.e., group of patient selected based on particular outcome) were excluded as were non-primary research (e.g. editorials, commentaries, opinion pieces). Conference abstracts were not considered eligible for inclusion, but were planned to be used to identify full study reports and to assess the quality of evidence in relation to potential publication and reporting biases.

For all KQs, studies were included if they were published in English or French. No date restrictions were applied to publications. The inclusion and exclusion criteria for all KQs are detailed in Tables 1.1-1.5.
Table 1.1 - KQ1a, b: Benefits and harms of screening

| Population | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria. Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural Exclude: studies exclusively including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent UTI, diabetes, and sickle cell disease), or with symptoms of UTI |
| Interventions | Any screening program, whereby there is an intent (i.e., clinical algorithm) for all pregnant women to receive a screening test with follow-up of screen-positive cases Screening subgroups/algorithms, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified organism(s)), follow-up testing during pregnancy, timing during pregnancy Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for group B streptococcus (GBS) testing) |
| Comparator | KQ1a: No screening program (but may include indicated testing and/or treatment upon development of symptoms) KQ1b: A different screening test or algorithm (see intervention subgroups) |
| Outcomes | **Benefits (reduced incidence for all):** 1. maternal mortality (9)* 2. maternal sepsis (8) 3. pyelonephritis (7) 4. perinatal mortality (≥ 20 weeks’ gestation [e.g., intrauterine demise, stillbirth, early neonatal death]) (9) 5. spontaneous abortion/pregnancy loss before 20 weeks’ gestation (8) 6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8) 7. preterm delivery (live fetus passed < 37 week’s gestation) (7) 8. low birth weight (< 2500g) (6) **Harms (maternal and neonatal):** 1. serious adverse event(s)** associated with antibiotic treatment, including but not limited to: (7) a. anaphylaxis, b. thrombocytopenia, c. hemolytic anemia, d. fetal abnormalities; and, 2. non-serious adverse event(s) associated with treatment, including but not limited to: (4) a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis), b. antibiotic-induced diarrhea, c. rash, d. vomiting e. neonatal thrush Exclude: screening for GBS near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest in list above) |
| Study Designs | Staged: RCTs, CCTs, controlled observational (i.e., prospective and retrospective cohorts, case-control, controlled before-after) |
| Language | English and French |
| Setting | Any primary care and clinical setting providing obstetric/antenatal care to pregnant women (e.g., obstetric and hospital outpatient clinics, prisons, remote stations, community centers, midwifery practices) |
| Timeframe | No publication date limits |

*Bracketed numbers next to each outcome above refer to patient-important outcome ratings by CTFPHC members and patients as critical [7-9, out of 9] or important [4-6, out of 9] are included ARDS: acute respiratory distress syndrome; CCT: controlled clinical trial; GBS: group B streptococcus; KQ: key question; NICU: neonatal intensive care unit; RCT: randomized controlled trial; UTI urinary tract infection **Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)
<table>
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<tr>
<th><strong>Table 1.2 - KQ2: Outcome valuation</strong></th>
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<td><strong>Population</strong></td>
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<td><strong>Patient subgroups:</strong></td>
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<td><strong>Interventions/Index Test</strong></td>
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<td><strong>Screening subgroups/algorithms, including:</strong></td>
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<td><strong>GBS:</strong></td>
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<th><strong>Table 1.3 - KQ3: Cost-effectiveness of screening</strong></th>
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<td><strong>Population</strong></td>
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<td><strong>Patient subgroups:</strong></td>
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<td><strong>Screening subgroups/algorithms, including:</strong></td>
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GBS: group B streptococcus; ICER: incremental cost-effectiveness ratio; KQ: key question; QALY: quality-adjusted life-years; UTI: urinary tract infection

Table 1.4 - KQ4: Benefits and harms of treatment

| Population | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.
| Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent UTI, diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural
| Exclude: studies exclusively including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent UTI, diabetes, and sickle cell disease), or with symptoms of UTI |
| Interventions/Index Test | Any antibiotic
| Screening subgroups/algorithms, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified organism(s)), follow-up testing during pregnancy, timing during pregnancy
| Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| Comparator/Reference Standard | No treatment or placebo |
| Outcomes* | Benefits (reduced incidence for all):
1. maternal mortality (9)*
2. maternal sepsis (8)
3. pyelonephritis (7)
4. perinatal mortality (≥ 20 weeks’ gestation [e.g., intrauterine demise, stillbirth, early neonatal death]) (9)
5. spontaneous abortion/pregnancy loss before 20 weeks’ gestation (8)
6. neonatal sepsis (if not reported will include surrogate outcomes of ARDS or admission to NICU) (8)
7. preterm delivery (live fetus passed < 37 week’s gestation) (7)
8. low birth weight (< 2500g) (6)
Harms (maternal and neonatal):
1. serious adverse event(s)** associated with antibiotic treatment, including but not limited to: (7)
   a. anaphylaxis,
   b. thrombocytopenia,
   c. hemolytic anemia,
   d. fetal abnormalities; and,
2. non-serious adverse event(s) associated with treatment, including but not limited to: (4)
   a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),
   b. antibiotic-induced diarrhea,
   c. rash,
   d. vomiting
   e. neonatal thrush
| Exclude: screening for group B streptococcus near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed above) |

Study Designs
| RCTs (or systematic review(s)) |

Language
| English and French |

Setting
| Any primary care and clinical setting providing obstetric/antenatal care to pregnant women (e.g., obstetric or hospital outpatient clinics, prisons, remote stations, community centers, midwifery practices) |

Time frame
| No publication date limits |

*Bracketed numbers next to each outcome above refer to patient-important outcome ratings by CTFPHC members and patients as critical [7-9, out of 9] or important [4-6, out of 9] are included.
ARDS: acute respiratory distress syndrome; GBS: group B streptococcus; KQ: key question; NICU: neonatal intensive care unit; RCT: randomized controlled trial; UTI: urinary tract infection

**Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)**

**Table 1.5 - KQ5: Accuracy of screening tests**

| Population | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.  
Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent UTI, diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural  
Exclude: studies exclusively including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary UTI, diabetes, and sickle cell disease), or with symptoms of UTI |
|---|---|
| Interventions/Index Test | Any index test (rapid point-of-care tests)  
Screening subgroups/algorithm, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified organism(s)), follow-up testing during pregnancy, timing during pregnancy  
Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| Comparator/Reference Standard | A urine culture  
Screening subgroups/algorithm, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified organism(s)), follow-up testing during pregnancy, timing during pregnancy  
Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| Outcomes | Sensitivity, specificity, false positives, true positive, false negatives, true negatives, positive and negative likelihood ratios, prevalence/pre-test probability (true positive + false positive)/total number of people |
| Study Designs | Prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and the reference standard, or where participants are randomized to different index tests but all receive the reference standard, and assessment in a cross-sectional manner  
Exclude: case-control studies and studies with longitudinal assessment of the reference standard |
| Language | English and French |

GBS: group B streptococcus; KQ: key question; UTI: urinary tract infection

**Data abstraction and risk of bias assessments**

One reviewer independently extracted data, and another reviewer verified all data from each included study on study design, country of origin, sample size, population and subgroup(s), intervention and comparator, setting, and outcomes of interest. Disagreements were resolved through discussion or a third reviewer. For each KQ, a narrative summary with accompanying tables was produced for all studies including design, country of origin, setting, populations and subgroups, tests, treatment and comparators, and outcome measures. For studies with multiple publications, we extracted data from the primary source and added data reported in associated publications as applicable. We contacted authors of included studies via email (with follow-up as necessary) for clarification of study details (i.e., interventions, outcomes and numerical data). For KQ4 (treatment), we extracted data from the eligible systematic review on its scope (PICOTS), and for the individual studies with specifics related to the population (size and characteristics), outcomes evaluated (including definitions and timing of assessment), and risk of bias (ROB) (by
domain/construct). We conducted data verification on 10% of included studies for quality assurance, and also examined the primary studies for additional participant characteristics and outcome details relevant to the current review.

When using individual studies, we recorded intention-to-treat results whenever possible. For dichotomous outcomes, we reported counts or proportions, and sample size, by study arm. For dichotomous data on harms, each adverse event (AE) was counted as if it represented a unique individual. Only numerical data for AEs were extracted; no assumptions were made on lack or presence of an AE when this was not reported. For patient and intervention subgroups (see Tables 1.1-1.5), we collected data for performing our own subgroup analyses (e.g., stratified analysis, meta-regression) based on study-level data.

Two reviewers independently assessed the ROB of each included study (KQs 1, 2 and 4), with disagreements resolved through discussion or third-party consultation to reach consensus. The results for each study and across studies were reported for each domain and for an overall quality score. For KQ1 (screening effectiveness), all controlled observational studies were appraised using the Newcastle-Ottawa Quality Assessment Scale. The scale comprises eight items that evaluate three domains: sample selection, comparability of cohorts, and assessment of outcomes. Each that is adequately addressed is awarded one star (up to two stars may be awarded for comparability), and the overall score is calculated by tallying the stars. We considered a total score of 7 to 9 to indicate low ROB; 4 to 6 to indicate unclear ROB; and, 3 or lower to indicate high ROB. We included a separate assessment for reporting bias due to suspected selective outcome reporting. For KQ2 (outcome valuation), all cross-sectional studies were appraised using the tool developed by the Center for Evidence-based Management. For KQ4 (treatment effectiveness), all RCTs and CCTs were appraised using the Cochrane Risk of Bias tool. This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and “other” sources of bias [e.g., baseline imbalances between groups]) and a categorization of the overall ROB. The overall assessment is based on the responses to individual domains. If one or more individual domains were assessed as having a high ROB, the overall score was rated as high ROB. The overall ROB was considered low only if all components were rated as having a low ROB. The ROB for all other studies was rated as unclear. Information was collected for each study on the source of funding. We conducted assessments on 10% of included studies in the Cochrane review and found that our methods for assessing ROB were somewhat different: we considered objective outcomes to be at lower ROB than subjective outcomes when assessing the blinding domains; we considered 10-30% loss to follow-up as unclear ROB (rather than high ROB) for incomplete reporting if there appeared to be no imbalances between groups or reasons were provided; we used a default of low ROB (rather than unclear ROB) for selective reporting when this was not detected or not highly suspected; we revised the “other bias” domain to low if no additional bias was detected apart from comparability between groups at baseline; and, we updated the overall ROB to align with guidance (see Chapter 8, Section 8.5.d in the Cochrane Handbook for Systematic Reviews of Interventions) as stated above. To assist with outcome reporting bias assessments, we searched for study protocols and considered reporting by similar studies included.

Data Analysis

Key Question 1 (screening effectiveness)
For pair-wise meta-analysis in KQ1 (screening effectiveness), we employed a random effects model. For dichotomous outcomes, we reported relative risks (RR) using the DerSimonian and Laird random effects model with Mantel-Haenszel method with corresponding 95% CIs. The decision to pool studies was not based on the statistical heterogeneity ($I^2$ statistics were reported), but rather on interpretation of the clinical and methodological differences between studies. We conducted sensitivity analyses when substantial heterogeneity was found and if appropriate (e.g., in the presence of studies with outlying effect sizes, for studies rated as high ROB in some domains such as incomplete outcome data [<80 percent] or lack of allocation concealment). Heterogeneity was also examined for important patient and intervention variables (Tables 1.1-1.5). We did not perform a funnel plot test or Egger’s test to detect small-study bias as there were fewer than eight studies included for KQ1.

Key Question 2 (outcome valuation)

For KQ2 (outcome valuation) results were narratively described, summarizing themes across studies.

Key Question 4 (treatment effectiveness)

For stage 2 examining evidence related to treatment effectiveness, meta-analyses were recalculated with the addition of one new study identified in the search update as well as for subgroups of interest (e.g., for population risk factors, screening/treatment characteristics, ROB and study design). Although we intended to restrict primary studies to RCTs in our protocol, we included and pooled results from CCTs in order to integrate all study designs (RCTs and CCTs) included in the Cochrane systematic review. Where there were at least eight studies in a meta-analysis, we assessed small-study bias both visually using the funnel plot and quantitatively using Egger’s test.35

Key Question 5 (test accuracy)

For this report, we did not examine evidence related to diagnostic test accuracy; this may be conducted and produced in a separate report upon consideration by the CTFPHC based on guideline recommendations following the evidence review for KQs 1 to 4.

Subgroup Analyses

We performed subgroup analyses using study-level data, when possible, using Cochran’s Q ($\alpha=0.05$) to detect statistical heterogeneity and the $I^2$ statistic was used to quantify the magnitude of statistical heterogeneity between studies. When determining whether entire studies fell into a particular subgroup category (e.g., recurrent UTI), we considered ≥80% of the study population meeting the criteria as sufficient. We planned to conduct regression analyses for categorical variables (e.g., history of recurrent UTI), when there were at least three studies for each category level; however, this was not performed due to limited study reporting, variations in size and heterogeneity of effect sizes, and/or insufficient number of studies for each category comprising a subgroup. We did perform some stratification of meta-analyses based on our planned key subgroups, and a minimum of 2 of the following criteria was used to determine credibility of subgroup investigations: a) visual inspection of forest plot showing a meaningful difference between effect estimates (e.g., clinical decision making on the intervention would differ for each
subgroup), b) a reduction in the heterogeneity (I²) for each subgroup from the original meta-analysis, and
c) a statistically significant between-group test for differences.

For outcomes that showed significant effects, we calculated absolute risk reduction (ARR) and number
needed to screen (NNS) or number needed to treat (NNT), as applicable, and reported these in a table
summarizing overview of results. The values for NNS or NNT were calculated using the absolute
numbers presented in the GRADE tables estimated using the control group event rate and RR with the
95% confidence interval (CI) obtained from the meta-analysis (see Chapter 12, Section 12.5.4.2 in the
Cochrane Handbook for Systematic Reviews of Interventions).34

Analyses were performed using Review Manager Version 5.3 and GRADEpro software packages.
Whenever studies did not provide data for pooling, the results were described narratively.

**Assessment of Overall Quality of Evidence Using GRADE**

Two reviewers independently assessed the quality of the body of evidence or confidence in the effect for
each outcome of interest using the GRADE methodology. Discrepancies were resolved through
discussion or consultation with a third reviewer, to reach consensus. Assessments were entered into the
GRADEpro software and summarized in GRADE Evidence Profiles (EP) and Summary of Findings
(SOF) tables. Footnotes to the tables provided explanations for all decisions.

The general approach is outlined here although methods align with GRADE guidance. For evidence
on benefits and harms of screening (KQ1) and treatment (KQ4), as a starting point the quality was
assigned as high for evidence from RCTs and low for evidence from observational studies. Thereafter, we
examined and potentially downgraded the quality based on five core domains: study limitations/ROB,
inconsistency, indirectness, imprecision, and publication/reporting bias.

For the **study limitations (ROB)** domain RCTs and CCTs were downgraded one or two levels depending
on the proportion of trials (e.g., one very large trial may outweigh two very small trials) assessed as
having high ROB for the particular outcome under consideration. Evidence from observational studies
was downgraded when most studies had moderate or high ROB. For **inconsistency** we assessed the
magnitude of the effects of the included studies (e.g., inconsistent when lack of overlap in 95% CIs for
some studies). **Indirectness** of the evidence was based on evaluating the relevance of the studies’
PICOTS compared to those of the current review. We assessed **imprecision** on the basis of Optimal
Information Size (OIS) and a relative risk of under 0.75 to over 1.25. If the OIS criterion was met and
the pooled 95% CI excluded no effect (i.e. CI around RR excluded 1.0), we did not downgrade for
imprecision. If the OIS criterion was met and the 95% CI crossed no effect, we downgraded for precision
if one or more of the limits of the CI crossed a RR of 0.75 or 1.25 (indicating a possibly important benefit
or harm), which suggested lower certainty of no effect. **Reporting bias** (suspected or undetected) was
evaluated with respect to publication bias. When considering the need to balance patient-important
benefits and harms for making a screening recommendation, the CTFPHC may choose to use a different
approach than ours to assess the imprecision domain, taking into account different baseline risks
applicable to specific outcomes and applying clinically meaningful decision thresholds.
Interpretation of Results

We chose to use standard wording to describe our interpretations of the findings and quality of evidence. For findings supported by high, moderate, low, and very low quality evidence (for which we have similar confidence in the results) we use “will”, “probably/likely”, “may/appears to”, and “not known/very uncertain”, respectively, in our textual descriptions of the results.

Chapter 3. Results

Summary of Studies for Review

Key Questions (KQs) 1a, b (screening effectiveness)

The total number of records identified from the literature search, including grey literature, was 2,559. After screening of titles and abstracts, 2,227 were excluded. Of the 332 papers that underwent full text screening, 327 were initially excluded resulting in five studies for inclusion. However, a post-hoc decision was made based on input from the Canadian Task Force on Preventive Health Care (CTFPHC) to clarify criteria for the intervention/comparator to examine screening programs, thereby removing one case-control study (Friedman et al,249 Appendix 10) where the exposure may have been defined by whether or not the women received a screening culture, rather than by whether or not there was the intent to do so; the results reflect an intent to screen all women with some for some reason not receiving the culture, which would also be reflected in the screening arm in other studies.

The search results and study flow and selection are presented in Figure 2.
Figure 2. PRISMA flow diagram of study selection for KQ1 (screening effectiveness)

Characteristics of included studies relevant to KQ1 are summarized in Appendix 1. Detailed study information is reported in Appendix 3.
A total of four studies (7,611 women) examined screening effectiveness for asymptomatic bacteriuria (ASB). One study\(^43\) was published in French. All four studies were non-concurrent cohort studies, comparing outcomes for women before and after introduction of a screening program. The studies were each conducted in France,\(^43\) Spain,\(^44\) Turkey,\(^45\) and the United States (US).\(^46\) None of the studies\(^43-46\) provided details on funding. One enrolled women at a hospital\(^43\), one at a hospital-based midwifery clinic\(^46\) and two at an obstetrics clinic.\(^44,45\)

Among the two studies reporting on the proportion of women with gestational diabetes, Rhode et al\(^46\) reported a relatively high rate of gestational diabetes in their group receiving frequent screening (9% [81 out of 933]) compared with that receiving screening at first prenatal visit only (4% [42 out of 1019]), and another\(^45\) reported approximately 3% of women with gestational diabetes mellitus range (3.8% [7 out of 186] in the screening group compared with 2.7% [5 out of 186] in the no-screening group).

Two studies\(^44,45\) reported gestational age criteria for including women in their study, one at <25 weeks of gestation and the other at <32 weeks of gestation. Two of the four studies\(^43,45\) specified criteria (≥10\(^5\) CFU/mL) as positive for ASB while this was not reported in the other two studies.\(^44,46\) The study by Gérard et al\(^43\) compared outcomes for women in the 10-month period (March to December 1978), when women were only tested if they had clinical signs, before introducing a screening program (January to October 1979) where women were screened at multiple intervals (3, 5, 7 and 9 months). The study by Gratacós et al\(^44\) also compared outcomes of women before (January 1987 to December 1990) and after (January 1991 to December 1992) introduction of a screening program for ASB. Rhode et al\(^46\) compared women who were screened at every prenatal visit, before August 15, 2002 (“routine screening group”) with women who were screened at the first prenatal visit only (“indicated screening group”). The study by Uncu et al\(^45\) compared pregnant women who delivered in the clinic but were not screened for ASB (prior to June 1998), with outcomes of women who were routinely screened for ASB (June 1998 to January 1999).

With regard to treatment protocols, two studies\(^43,44\) reported treating screen-positive women based on antibiotic sensitivity testing, with one study\(^43\) only specifying treatment was provided at the discretion of the treating physician, and the other study\(^44\) detailing 7 days of antibiotics administered 1 to 2 weeks after a second culture was obtained with additional antibiotics 1 to 4 weeks after treatment, and again prior to delivery (as well as additional antibacterial therapy when repeat cultures were positive for bacteriuria). One study\(^45\) reported treating women with antibiotics for 7 to 10 days followed by 7 days of antibiotics for persistent or recurrent bacteriuria. One study\(^44\) did not specify a treatment protocol. One study\(^45\) reported follow-up of women with cultures one week after treatment (test-of-cure), and another study\(^44\) reported re-testing women with urine cultures twice to determine presence of persistent bacteriuria; two studies\(^43,46\) did not report whether women were followed up after treatment to determine test-of-cure.

Outcomes were not uniformly defined among studies. Pyelonephritis was defined as “acute pyelonephritis” by two studies\(^43,44\) with a combination of symptoms including fever, lumbar or flank pain, tenderness in costovertebral angle, dysuria, and at least one positive urine culture. “Pyelonephritis” was not specified by criteria in two studies;\(^45,46\) however, it was clearly differentiated from “ASB”, “cystitis” and “undetermined urinary tract infection (UTI)” in the Rhode study.\(^46\)

Two studies reported on perinatal mortality: Rhode et al\(^46\) used ≥31 weeks of gestation, and Uncu et al\(^45\) defined perinatal mortality as no fetal cardiac activity on ultrasound after 20 weeks of gestation.
Gérard et al.\textsuperscript{43} reported spontaneous abortion, defined as \(\leq 28\) weeks of gestation; since this was distinguished from perinatal mortality, it was included in the analysis for this outcome.

All three studies\textsuperscript{43-45} that reported preterm delivery used \(<37\) weeks of gestation as the criterion. For the study by Uncu et al.\textsuperscript{45}, we were unable to confirm with the authors on eligibility of criteria (i.e., whether women were at risk of, or actual cases of, preterm delivery) and the data for preterm delivery; however, removal of the data would not change overall conclusions for this outcome (see Results below for KQ1a).

One study\textsuperscript{45} reported harms of screening (fetal abnormalities) without a specific definition.

No study reported on maternal mortality, maternal sepsis, neonatal sepsis or low birthweight.

Most studies were of unclear risk of bias (ROB) (rated 6 out of 9 in 3 cohort studies\textsuperscript{43-45}) with one study of low ROB that rated 8 out of 9.\textsuperscript{46} None of the studies\textsuperscript{43-46} reported that pyelonephritis was not present in pregnant women at the outset of the study. Three studies\textsuperscript{43-45} did not demonstrate comparability of baseline characteristics between groups. All of the studies\textsuperscript{43, 44, 46} except one\textsuperscript{45} were suspected of selective outcome reporting due to lack of reporting for neonatal outcomes (e.g., spontaneous abortion, perinatal mortality, preterm delivery and fetal abnormalities) despite following women to delivery. Methodological quality assessments for studies relevant to KQ1 are summarized in Table; detailed assessments for each study are reported in Appendix 6.

**Table 4. Summary of methodological quality\textsuperscript{a} - KQ1 a & b (screening effectiveness)**

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total Score\textsuperscript{a} (max 9)</th>
<th>Selective Outcome Reporting\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representativeness of exposed cohort</td>
<td>Selection of non-exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Outcome not present at start of study (pyelonephritis/other outcomes)</td>
<td>Total</td>
<td>Comparability of cohorts</td>
</tr>
<tr>
<td>Gérard, 1983\textsuperscript{43}</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0/1</td>
<td>3</td>
</tr>
<tr>
<td>Gratacós, 1994\textsuperscript{44}</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0/1</td>
<td>3</td>
</tr>
<tr>
<td>Rhode, 2007\textsuperscript{46}</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0/1</td>
<td>4</td>
</tr>
<tr>
<td>Uncu, 2002\textsuperscript{45}</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0/1</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Assessed using the Newcastle-Ottawa Quality Assessment Scale\textsuperscript{31}

\textsuperscript{b}Assessed due to concern regarding reporting bias in the studies, but assessment not included in the total score

\textsuperscript{c}Did not report on fetal abnormalities

\textsuperscript{d}Did not report on spontaneous abortion, perinatal mortality, preterm delivery or fetal abnormalities

\textsuperscript{e}Did not report on spontaneous abortion, perinatal mortality, preterm delivery and fetal abnormalities

\textsuperscript{f}Reported on all outcomes, including fetal death >20 weeks of gestation (eligible for perinatal mortality)
**KQ1a: What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences for patient characteristics (e.g., socioeconomic status [SES])?**

Three studies (non-concurrent cohort) of unclear ROB\(^43\)-\(^45\) and a combined sample of 5,659 pregnant women addressed the benefits and harms of screening compared with no screening. The results are summarized below; for additional details see Evidence Set 1 for GRADE EP and SOF tables and forest plots.

**Pyelonephritis**

Three studies\(^43\)-\(^45\) of unclear ROB (5,659 women) found a statistically significant difference for screening compared to no screening on the outcome of pyelonephritis (RR 0.28; 95% CI 0.15, 0.54; \(I^2\)=0%; ARR 1.3%; NNS 77, 95% CI 65, 121). The overall quality for this body of observational evidence was rated as very low due to downgrading for study design and ROB.

### 1.1 Pyelonephritis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Universal screening</th>
<th>Targeted screening</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gratacos 1984</td>
<td>9</td>
<td>1552, 98.3%</td>
<td>0.28 [0.15, 0.54]</td>
<td></td>
</tr>
<tr>
<td>Gerard 1983</td>
<td>0</td>
<td>170, 4.8%</td>
<td>0.17 [0.01, 3.23]</td>
<td></td>
</tr>
<tr>
<td>Urca 2004</td>
<td>1</td>
<td>196, 6.3%</td>
<td>0.28 [0.05, 2.22]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2008</td>
<td>3651, 100.0%</td>
<td>0.28 [0.15, 0.54]</td>
<td></td>
</tr>
</tbody>
</table>

*Total events* 10 97  
*Heterogeneity:* Tau\(^2\)=0.90, CHI\(^2\)=0.15, df\(^2\)=2 (\(P=0.93\)), \(I^2\)=0%  
*Total for overall effect:* \(Z=3.60\) (\(P=0.0001\))

**Perinatal mortality**

Two studies\(^43, 45\) (724 women) with unclear ROB but suspected reporting bias\(^43\) found no significant difference (RR 1.21, 95% CI 0.01, 102.93, \(I^2\)=84%) in perinatal mortality. The quality of this body of evidence was rated as very low due to downgrading for study design, ROB, inconsistency, indirectness, and imprecision.

### 1.2 Perinatal mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Universal screening</th>
<th>Targeted screening</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofnerad 1983</td>
<td>6</td>
<td>163, 47.5%</td>
<td>12.74 [7.71, 22.74]</td>
<td></td>
</tr>
<tr>
<td>Urca 2001</td>
<td>1</td>
<td>106, 52.5%</td>
<td>0.14 [0.02, 1.15]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>349</td>
<td>375, 100.0%</td>
<td>1.21 [0.01, 102.93]</td>
<td></td>
</tr>
</tbody>
</table>

*Total events* 6 7  
*Heterogeneity:* Tau\(^2\)=0.87, CHI\(^2\)=8.25, df\(^2\)=1 (\(P=0.01\)), \(I^2\)=54%  
*Total for overall effect:* \(Z=3.06\) (\(P=0.001\))

**Spontaneous abortion**

One study of 370 women\(^43\) with unclear ROB but suspected reporting bias found no significant difference (RR 0.96, 95% CI 0.41, 2.27) in spontaneous abortion at \(\leq28\) weeks of gestation. This body of evidence was rated as very low due to concerns with study design, ROB, inconsistency and imprecision.
1.3 Spontaneous abortion

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>Total</th>
<th>No screening Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gérard 1993</td>
<td>11</td>
<td>157</td>
<td>11</td>
<td>200</td>
<td>100.0%</td>
<td>0.86 [0.41, 2.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>170</td>
<td>200</td>
<td>100.0%</td>
<td>0.86</td>
<td>[0.41, 2.27]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)

Preterm delivery

Two studies\(^{43,45}\) (722 women) with unclear ROB but suspected reporting bias\(^{43}\) found no significant difference (RR 8.70, 95% CI 0.32, 240.07; \(I^2=80\%\)) in preterm delivery before 37 weeks of gestation; this body of evidence was rated as very low due to downgrading for ROB and imprecision.

1.4 Preterm delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>Total</th>
<th>No screening Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gérard 1993</td>
<td>11</td>
<td>151</td>
<td>5</td>
<td>188</td>
<td>57.5%</td>
<td>2.69 [0.93, 7.28]</td>
</tr>
<tr>
<td>Uncu 2001</td>
<td>22</td>
<td>186</td>
<td>0</td>
<td>186</td>
<td>42.5%</td>
<td>45.00 [2.75, 738.38]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>347</td>
<td>375</td>
<td>100.0%</td>
<td>4.70</td>
<td>[0.32, 240.07]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>33</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau\(^2\) = 4.70; Chi\(^2\) = 5.07, df = 1 (P = 0.02); \(I^2=80\%\)
Test for overall effect: Z = 1.28 (P = 0.20)

Fetal abnormalities (harm)

One study\(^{45}\) (372 women) with unclear ROB found no significant difference (RR 1.50, 95% CI 0.25, 8.87) in fetal abnormalities (harm); this body of evidence was rated as very low due to downgrading for study design, ROB, inconsistency, and imprecision.

1.5 Fetal abnormalities (harm)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>Total</th>
<th>No screening Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncu 2001</td>
<td>3</td>
<td>186</td>
<td>2</td>
<td>188</td>
<td>100.0%</td>
<td>1.50 [0.25, 8.87]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>186</td>
<td>186</td>
<td>100.0%</td>
<td>1.50</td>
<td>[0.25, 8.87]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

Subgroup analyses

We did not perform subgroup analyses due to insufficient number of studies contributing to each category comprising our a priori subgroups.
KQ1b. What are the benefits and harms of screening programs using different screening methods or algorithms for asymptomatic bacteriuria in pregnancy?

One non-concurrent cohort study46 (1,952 women) with low ROB compared screening at all prenatal visits with screening at first prenatal visit only. This study only reported on pyelonephritis and preterm delivery. See Evidence Set 2 for GRADE EP and SOF tables and forest plots.

Pyelonephritis

No significant difference was found for pyelonephritis (RR 1.09; 95% CI 0.27, 4.35); this evidence was rated as very low due to downgrading for study design, ROB, inconsistency, indirectness and imprecision.

2.1 Pyelonephritis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Frequent screening</th>
<th>One-time screening</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhode 2007</td>
<td>4</td>
<td>4</td>
<td>1019</td>
<td>1.09 [0.27, 4.35]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4</td>
<td>4</td>
<td>1019</td>
<td>1.09 [0.27, 4.35]</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>1018</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.12 (P = 0.90)

Preterm delivery

A significant difference was found for preterm delivery (RR 1.57; 95% CI 1.11, 2.23) with more preterm deliveries among the group that was screened at all prenatal visits. The study authors did not present a possible hypothesis to explain this result. This body of evidence was rated as very low due to downgrading for study design, ROB, inconsistency, indirectness, and imprecision.

2.2 Preterm delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Frequent screening</th>
<th>One-time screening</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhode 2007</td>
<td>72</td>
<td>50</td>
<td>1019</td>
<td>1.57 [1.11, 2.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>72</td>
<td>60</td>
<td>1019</td>
<td>1.57 [1.11, 2.23]</td>
</tr>
<tr>
<td>Total events</td>
<td>72</td>
<td>1018</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 2.54 (P = 0.01)

Key Question 2 (outcome valuation)

The total number of records identified from database searching, grey literature and hand searching was 6,355; this included searching included studies from KQ1 (screening effectiveness) and KQ4 (treatment effectiveness) for any information regarding women’s valuation of benefits and harms of screening and treatment for ASB. After primary screening of titles and abstracts 6,199 studies were excluded. Of the 156 papers that underwent full text screening 20 were excluded due to study design, 31 due to population, 45 due to the intervention, 47 due to the reported outcomes, 1 was not available in full text and 4 papers did not have full text available in either English or French. No studies were identified that answered the question as to how women weigh the benefits and harms of screening and treatment of asymptomatic bacteriuria in pregnancy or how their valuation of benefits and harms inform their decisions to undergo treatment; however, eight papers (seven studies) focusing only on the harms of antibiotic treatment
(considered indirect evidence) were identified and are analyzed here. The search and study flow and selection are presented in Figure 3.

Figure 3. PRISMA flow diagram of study selection for KQ2 (outcome valuation)
From the eight papers providing indirect evidence, two were from the same study, but reported on different outcomes.\textsuperscript{47, 48} Six of the papers were cross-sectional surveys while one paper was a cross-sectional study using a visual analogue scale.\textsuperscript{49} One study was a multicenter screening cohort of pregnant women with an embedded randomised controlled trial (RCT) of antibiotic treatment for women with significant bacteriuria; cross-sectional findings from the women eligible for treatment are used for this KQ.\textsuperscript{50} The sample sizes ranged from 144 to 4999 participants with three papers\textsuperscript{47, 51, 52} including more than 1000 participants. Six papers reported age ranges from 15 to 45 years.\textsuperscript{47, 48, 50-53} Three studies provide information on drug utilization opinions,\textsuperscript{48, 50, 53} while five papers (four studies) provide information on perceptions of teratogenic risk.\textsuperscript{47, 49, 51, 52, 54} Additional characteristics of these papers are included in Appendix 4.

While all seven studies addressed a focused research question and used a sample representative of this study question, their reported sampling methods could potentially introduce bias and only one of the studies\textsuperscript{47} fully accounted for confounding factors through statistical analysis. None of the papers reported that their sample size was based on pre-study considerations while only two papers used survey questions that were considered valid and reliable. The summary of methodological quality for KQ2 are reported in Table 5; detailed study quality assessments are reported in Appendix 7.

**Table 5. Summary of methodological quality\textsuperscript{a} – KQ2 (outcome valuation)**
KQ2a. How do women weigh the benefits and harms of screening and treatment for asymptomatic bacteriuria in pregnancy?

No study directly examined how women weigh the benefits and harms of screening and treatment for asymptomatic bacteriuria.

KQ2b. How do women’s valuation of benefits and harms of screening and treatment inform their decisions to undergo screening?

No studies were identified that examined women’s valuation of benefits and harms of screening and treatment to inform their decisions to undergo screening.

The included studies herein reported on women’s opinions of antibiotic use and their perception of teratogenic risk related to antibiotics or medication for UTIs.

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Did the study address a clearly focused question / issue?</th>
<th>Is the research method (study design) appropriate for answering the research question?</th>
<th>Is the method of selection of the subjects clearly described?</th>
<th>Could the way the sample was obtained introduce bias?</th>
<th>Was the sample size representative of the population to which the findings will be referred?</th>
<th>Was the sample size based on pre-study considerations of statistical power?</th>
<th>Was a satisfactory response rate achieved?</th>
<th>Are the measurements (questionnaires) likely to be valid and reliable?</th>
<th>Was the statistical significance assessed?</th>
<th>Are confidence intervals given for the main results?</th>
<th>Could there be confounding factors that haven’t been accounted for?</th>
<th>Can the results be applied to your organization?</th>
</tr>
</thead>
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<tr>
<td>Butters, 1990&lt;sup&gt;48&lt;/sup&gt;</td>
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<td>Kazemier, 2015&lt;sup&gt;50&lt;/sup&gt;</td>
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<td>Sanz, 2000&lt;sup&gt;49&lt;/sup&gt;</td>
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<td>Sharma, 2006&lt;sup&gt;53&lt;/sup&gt;</td>
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<td>1</td>
<td>3</td>
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<td>Twigg, 2016&lt;sup&gt;52&lt;/sup&gt;</td>
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<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Assessed using a tool developed by the Center for Evidence-based Management<sup>12</sup> for cross-sectional studies (surveys)

1=Yes, 2=Can’t Tell, 3=No
Opinions on Antibiotic Use During Pregnancy

A questionnaire among recently postpartum women (n=514) in Scotland reported that 49% of participants said they would take a doctor-prescribed antibiotic during pregnancy while 48% said they would not; 3% did not respond to the question. In contrast, a study of 395 pregnant women in North India found that 6.2% believed antibiotics should be used in pregnancy while 46.9% felt they should not be used; 46.9% did not provide a response. The cohort study of screening with embedded treatment trial reported over 61% (n=255) of women who screened positive for ASB opted out of participation in the trial because they did not want to receive antibiotics during pregnancy for an asymptomatic condition.

Perception of Teratogenic Risk

One study addressed the risk perception relating to medication treatment for pregnant women with UTIs. In a web-based study in the United Kingdom (UK) (n=1120), Twigg et al reported that women who were taking medication for a UTI perceived the risk of overuse and harm of medication to be lower and the benefits to be higher than women who were not taking medication (Overuse [mean(SD)]: 11.5 (2.8) vs. 12.6 (2.7), p=0.006; Harm [mean(SD)]: 9.3 (2.7) vs. 10.4 (2.9), p=0.014; Benefit [mean(SD)]: 16.3 (2.2) vs. 14.9 (2.3), p<0.001). Nordeng et al also reported a significant difference in mean risk perception scores for penicillin use during pregnancy between those using the drug and those who were not (n=1793; 3.0 vs. 4.3, p<0.001, on a scale of 0 to 10).

Throughout the included studies there were inconsistencies in opinions of the teratogenic risk perception of antibiotics. An internet study of 4,999 pregnant women across 18 countries reported that 96.2% of participants felt penicillin antibiotics posed a teratogenic risk, whereas an Iranian study (n=400) reported that up to 1.3% of pregnant women felt antibiotics, including penicillin, ampicillin, amoxicillin, metronidazole and cephalosporin, were unsafe for the mother, while 31.3% to 36.8% felt these antibiotics were unsafe for the fetus and 4.5% to 10.0% felt these antibiotics were unsafe for both.

One study using a visual analogue scale also revealed differences in perception of teratogenic risk of some antibiotics between pregnant and non-pregnant women. The authors reported that pregnant women (n=81) have a significantly lower perception of the risk of malformations than non-pregnant women (n=63) for erythromycin (38.7% vs. 55.6%, p<0.001) while there was no significant difference in their risk perception of amoxicillin (40.4% vs. 49.3%, p>0.05).

Key Question 3. What is the cost-effectiveness of screening for asymptomatic bacteriuria in pregnancy?

Evidence on screening effectiveness (KQs 1a and 1b) was very low quality, therefore we did not review studies on cost-effectiveness of screening programs which would have relied on similar evidence.

Key Question 4. What are the benefits and harms of antibiotic treatment compared with placebo or no treatment for asymptomatic bacteriuria in pregnancy?

The total number of records identified from the search for systematic reviews was 112. After screening of titles and abstracts, 97 were excluded. Of the 15 reviews that underwent full text screening, 14 were excluded resulting in one review for inclusion. Contact with the information specialist of the Cochrane Pregnancy and Childbirth Group’s Trials Register confirmed the identification of only one study.
(Kazemier et al50) from their ongoing search updates (to October 2017) relevant for this KQ. The systematic review search results and study flow and selection are presented in Figure 4.

Figure 4. PRISMA flow diagram of study selection for KQ4 (treatment effectiveness)
A summary of the study characteristics for KQ4 is reported in Appendix 2; detailed study information is provided in Appendix 5.

Fifteen studies\(^50, 55-68\) (2,869 women) were included that examined treatment effectiveness for bacteriuria. Most of the included studies were published in the 1960s, and one recent (2015) study\(^50\) was included from the search update. One study\(^56\) included in the Cochrane systematic review\(^4\) only reported on the outcome of persistent bacteriuria and therefore was excluded from analysis and the overall body of evidence relevant to the current review’s outcomes of interest.

The majority of studies were RCTs, with four controlled clinical trials (CCTs) included.\(^57, 60, 61, 68\) Five studies were conducted in the US,\(^56, 57, 60, 61, 64\) three studies were conducted in the UK,\(^55, 63, 67\) and one in Ireland,\(^58\) three studies were conducted in Australia,\(^62, 59, 68\) and one study conducted each in Denmark,\(^65\) Jamaica,\(^65\) and the Netherlands.\(^50\) Seven studies\(^50, 55-57, 60, 61, 67\) were not industry-funded, two studies\(^66, 68\) were industry-funded, four studies\(^59, 62, 63, 65\) were both industry and non-industry funded, and two studies\(^58, 64\) did not report on funding. All pregnant women were enrolled from hospital-based clinics.

The studies varied in reporting of population characteristics. Only four studies\(^50, 56, 64, 67\) (three used in our analysis) specified inclusion criteria for only asymptomatic women. One study\(^62\) included more than 50% (n=117) of patients with radiological renal abnormalities, one study\(^57\) reported previous UTI in its population (36% [n=133] of women in the treatment group and 40% [n=148] in the placebo group), one study\(^63\) reported 23% (of 265 women) with a past history of renal-tract disease, and one study\(^65\) included 18% (9 out of 50) of women with renal abnormalities. One study\(^50\) reported exclusion of women with urogenital anomalies from the study and one study\(^61\) excluded women with chronic renal insufficiency. Two studies\(^55, 66\) reported no differences between groups for socioeconomic status. No study reported whether women were enrolled in an urban or rural setting.

The studies varied in reporting of screening characteristics. Most (n=9) studies\(^50, 55, 57, 58, 61-63, 67, 68\) enrolled women at their first prenatal visit, with one study\(^59\) enrolling women at the second antenatal visit. Five studies\(^55, 56, 58, 60, 64\) followed women until delivery or the postpartum period for outcomes. One study\(^67\) followed women until 10 days post-delivery. Four studies\(^50, 59, 66, 68\) followed women until 6 weeks post-delivery. One study\(^61\) followed women until the post-delivery period but then again 3 to 4 years later. One study\(^62\) followed women until 6 months post-delivery, and one study\(^65\) followed women until 9 months after delivery. Five studies\(^50, 58, 59, 64, 66\) required at least one urine sample to detect bacteriuria, with seven studies\(^55, 60, 62, 63, 65, 67, 68\) requiring confirmation with another sample, and three others\(^56, 57, 61\) requiring three total urine samples. The majority of studies used a routine culture to test for bacteriuria, while two studies\(^56, 59\) used a urine dipslide device.

All studies\(^50, 56-68\) except one\(^55\) treated women with more than 1 dose of antibiotics. Five studies\(^50, 58, 64, 66, 67\) provided up to one week of antibiotics, one study\(^65\) treated women for at least three weeks, one study\(^63\) treated women for at least 30 days, and six studies\(^56, 59-62, 68\) treated women for bacteriuria up to delivery. Most (n=7) studies\(^50, 57, 58, 60, 63, 64, 67\) tested for persistent bacteriuria during pregnancy (with re-treatment as warranted); only one study\(^59\) tested for persistent bacteriuria after delivery and three studies\(^61, 62, 65\) tested for cure during pregnancy and after delivery. The control arm in ten studies\(^50, 55-57, 60-63, 65, 66\) was provided with a placebo; two studies\(^58, 59\) did not provide antibiotics to participants in the control group. Although we would anticipate that studies would treat (initially asymptomatic) women in the control group upon development of symptoms, only three studies\(^54, 67, 68\) reported this.
The outcome reported by the most number of studies (n=1250, 55, 57-65, 67) was pyelonephritis. Most studies used a combination of two or more of the following symptoms to determine development of pyelonephritis: fever (≥100°F or ≥38°C) or pyrexia, nausea, chills or rigours, vomiting, dysuria, frequency of urination, burning during urination, costovertebral tenderness, flank pain, and loin pain and/or tenderness. Three studies did not define criteria for pyelonephritis, and one study used “acute symptoms of cystopyelitis”.

Perinatal mortality was variably defined among the studies that reported this outcome. Two studies used gestation to define perinatal mortality: >20 weeks and >28 weeks. One study defined perinatal death as stillbirth, death during labor or death within 28 days of life. One study did not define “perinatal mortality”. Two studies combined stillbirths with “neonatal death” or “death prior to hospital discharge”.

Spontaneous abortion was reported by two studies that did not specify gestational age.

Of the four studies that reported on preterm delivery, three studies used <37 weeks of gestation as the criteria, and the study by Furness et al used <38 weeks of gestation.

Seven studies reported low birth weight as ≤2500g or <2500g; Kazemier at al used small for gestational age (SGA) at <10th percentile and <5th percentile, and we combined these data for this study.

Neonatal sepsis was reported by one study as confirmed with culture, and without criteria in another study.

For harms (any serious adverse event (AE)), two studies reported congenital/abnormalities, one study reported fetal abnormalities and one study reported anencephaly. Additionally, Elder et al reported no events of hemolytic anemia for infants (“erythroblastosis fetalis”) in either group.

No study reported on maternal mortality, maternal sepsis, or maternal harms (serious AE).

Overall, most of the studies that reported on at least one of the outcomes of interest were assessed as having high ROB, with three studies assessed as having unclear ROB, and only one study assessed at low ROB. The main issues were due to poor reporting of research methods and characteristics of the study population. Groups of studies contributing to each outcome had at least one study with high overall risk. Many studies reported their methodological design as “random” without adequate details, with only one study using a computer-generated random assignment of participants. Many studies did not adequately describe concealment of allocation, with four studies describing allocation by alternation. The Netherlands study used central allocation to support a judgment of low ROB for this domain. Five studies that reported double-blinding were assessed at low ROB for this domain; the remaining ten studies were assessed as unclear ROB for blinding of participants and personnel due to lack of reporting within the context of objective outcomes. Four studies mentioned blinding of assessors or “double-blind” conditions to support a judgment of low ROB, whereas eleven studies assessed as unclear ROB did not report blinding of outcome assessors within the context of subjective outcomes. Two studies were assessed at high ROB for incomplete reporting as there were inconsistent data for low birth weight between groups and missing data on pyelonephritis in the treatment group for one study, and no details on dropouts (20 out of 226 women) as well as 17% loss to follow-up for low birth weight and gestational age at delivery in the other
study. Fifty studies did not provide details on loss to follow-up for pyelonephritis and/or neonatal outcomes; these were assessed at unclear ROB. The majority (n=8) of studies reported on details of dropouts, if any. Six studies were assessed at high ROB for selective reporting due to lack of reporting on pyelonephritis and/or neonatal outcomes. Eight studies were assessed as having unclear ROB due to lack of protocol and ability to assess selective reporting. As no other bias was identified, all the studies were assessed at low ROB for “other sources of bias”.

For the summary of ROB assessments for KQ4, see Table 6; detailed study quality assessments are reported in Appendix 8.

Table 6. Summary of methodological quality - KQ4 (treatment effectiveness)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants and Personnel</th>
<th>Blinding of Outcome Assessors</th>
<th>Incomplete Reporting</th>
<th>Selective Reporting</th>
<th>Other Bias*</th>
<th>Overall Risk of Bias**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brumfitt 1975</td>
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<td></td>
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<td>Low risk</td>
</tr>
<tr>
<td>Elder 1966</td>
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<td></td>
<td></td>
<td></td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Elder 1971</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Foley 1987</td>
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<td></td>
<td></td>
<td>High risk</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Gold 1966</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Kass 1960</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Kazemier 2015</td>
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<td>Mulla 1960</td>
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<td></td>
<td></td>
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</tr>
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</table>

*Assessed as: Low risk of bias if no other sources of bias are identified, High risk of bias if other sources of bias detected such as: participant characteristics (baseline imbalances), study design characteristics (crossover, cluster-randomized, or blocked randomization in trials without blinding); Unclear risk of bias assessment not applicable for this domain.

**Assessed as: Low if all domains are assessed as low, Unclear if at least one domain is assessed as unclear and no domains are assessed as high, or High if at least one domain is assessed as high.

Legend:
- Low risk
- Unclear risk
- High risk

KQ4. What are the benefits and harms of antibiotic treatment compared with placebo or no treatment for asymptomatic bacteriuria in pregnancy?

Results are summarized below by outcome. See Evidence Set 3 for GRADE EP and SOF tables and forest plots. We conducted subgroup analyses to explore possible reasons for heterogeneity among studies, whenever sufficient number of studies (e.g., 2 per subgroup if categorical) reported on the a priori
subgroups for population and screening characteristics. Sensitivity analyses were also carried out for ROB and study design. Only those subgroup findings that were sufficiently credible, as per criteria outlined in method, in explaining inconsistencies between studies are reported here; results for all other subgroup analyses can be obtained by contacting the review authors.

Pyelonephritis

A total of 12 studies\(^50, 55, 57-65, 67\) (2,017 women) with the majority at high ROB examined the effects of antibiotic treatment and found a significant difference in development of pyelonephritis (RR 0.24; 95% CI 0.13, 0.41; \(I^2=60\%\); ARR 17.6%; NNT 6, 95% CI 5, 7). Three of the trials clearly stated that only women without symptoms at baseline were included (other trials may have included some symptomatic women); sensitivity analysis by removing the nine trials did not affect the results (3 trials, RR 0.22; 95% CI 0.10, 0.49; \(I^2=0\%\)). Sensitivity analysis for ROB (removing those studies with overall high risk) and study design (CCTs removed) did not change the results: removal of nine trials did not affect results (1 trials, RR 0.37; 95% CI 0.02, 8.93), and removal of three CCTs did not affect overall results (9 RCTs, RR 0.28; 95% CI 0.16, 0.51; \(I^2=60\%\)). The quality of this body of evidence was rated as low due to concerns with ROB and indirectness (i.e., majority of studies did not report including exclusively asymptomatic women and some included some high-risk women). We have some certainty that treatment will reduce risk for pyelonephritis but are uncertain about the magnitude of the effect.

3.1 Pyelonephritis (overall)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events Total</th>
<th>No treatment or placebo Events Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
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<td>Eklund 1977</td>
<td>4</td>
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<td>26</td>
<td>0.20</td>
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<tr>
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<td>120</td>
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<td>17</td>
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<td>20</td>
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<td>[0.02, 0.37]</td>
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<td>50</td>
<td>12</td>
<td>0.08</td>
<td>[0.01, 0.62]</td>
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<tr>
<td>Palak 1968</td>
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<td>76</td>
<td>17</td>
<td>0.18</td>
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<td>[0.10, 0.66]</td>
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<tr>
<td>Total (95% CI)</td>
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<td>994</td>
<td>100</td>
<td>0.24</td>
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</table>

Heterogeneity: Tau\(^2\) = 0.49, Chi\(^2\) = 27.65, df= 11 (P = 0.004), P = 80%

Test for overall effect: Z = 6.09 (P = 0.00001)

Subgroup analyses considered to have some credibility examined the number of urine samples (e.g. use of confirmatory culture), testing for persistent bacteriuria, and length of follow-up (ES Forest Plots 3.1.1-3.1.3).
3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>No treatment or placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Foley 1987</td>
<td>20</td>
<td>66</td>
<td>0.44 (0.21, 0.92)</td>
</tr>
<tr>
<td>Furness 1975</td>
<td>0</td>
<td>10</td>
<td>1.09 (0.42, 2.78)</td>
</tr>
<tr>
<td>Kozirer 2006</td>
<td>4</td>
<td>15</td>
<td>0.59 (0.11, 2.91)</td>
</tr>
<tr>
<td>Mullis 1989</td>
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<td>3</td>
<td>0.06 (0.01, 0.32)</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>205</td>
<td>0.00 (0.00, 1.0)</td>
</tr>
<tr>
<td>Total events</td>
<td>16</td>
<td>150</td>
<td>0.00 (0.00, 1.0)</td>
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</tbody>
</table>

*The additional culture(s) was used to confirm levels of bacteriuria.

3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria
### 3.1.3 Pyelonephritis subgroup: duration of follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Follow-up to delivery or peripuerium (≤6 weeks post-delivery)</th>
<th>No treatment or placebo Follow-up to delivery or peripuerium (≤6 weeks post-delivery)</th>
<th>Total Follow-up to delivery or peripuerium (≤6 weeks post-delivery)</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunetti 1975</td>
<td>9  87  20</td>
<td>65 12.6%</td>
<td>0.44 0.21 (0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better 1971</td>
<td>4  133  27</td>
<td>148 10.6%</td>
<td>0.19 0.05 (0.46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley 1987</td>
<td>3  100  3</td>
<td>120 7.1%</td>
<td>1.20 0.25 (5.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumes 1975</td>
<td>25  139  17</td>
<td>67 14.1%</td>
<td>0.85 0.57 (1.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold 1989</td>
<td>0  35  2</td>
<td>50 2.6%</td>
<td>0.17 0.04 (1.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazermer 2015</td>
<td>0  40  1</td>
<td>41 2.4%</td>
<td>0.37 0.02 (8.93)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lette 1969</td>
<td>4  124  36</td>
<td>141 10.7%</td>
<td>0.13 0.05 (0.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muller 1980</td>
<td>1  59  12</td>
<td>60 5.3%</td>
<td>0.08 0.01 (0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 1989</td>
<td>5  85  18</td>
<td>78 11.2%</td>
<td>0.25 0.15 (0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>793 765 77.2%</td>
<td></td>
<td>0.34 [0.18, 0.51]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 49 136

### 3.5.3 Follow-up until > 6 weeks post delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>No treatment or placebo Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>Total Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kass 1969</td>
<td>1  83  26</td>
<td>98 5.4%</td>
<td>0.04 0.01 (0.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nance-Smith 1965</td>
<td>2  61  20</td>
<td>55 3.0%</td>
<td>0.09 0.02 (0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pothak 1969</td>
<td>5  78  17</td>
<td>77 9.4%</td>
<td>0.19 0.05 (0.58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>230 229 22.8%</td>
<td></td>
<td>0.11 [0.05, 0.25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 93

### 3.5.3 Follow-up until > 6 weeks post delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>No treatment or placebo Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>Total Follow-up to delivery or peripuerium (&gt;6 weeks post-delivery)</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>1023 994 100.0%</td>
<td></td>
<td>0.24 [0.13, 0.41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 55 196

---

Subgroup analysis for the number of urine samples—studies using one or more additional cultures to confirm ASB compared with just one culture—appeared to explain the heterogeneity among all studies combined (I²=60%) for the outcome of pyelonephritis (RR 0.19, 95% CI 0.11, 0.31; I²=31% versus RR 0.50, 95% CI 0.19, 1.35; I²=41%). The test for subgroup differences did not meet our criteria for statistical significance (p=0.08), but the heterogeneity in each subgroup was reduced and visual inspection of the forest plots suggests there may be an important difference in effect. There was a statistically significant subgroup difference (p=0.001) when testing for persistent bacteriuria was done during pregnancy and after delivery (RR 0.11, 95% CI 0.05, 0.25; I²=0%) compared with testing during pregnancy (RR 0.26, 95% CI 0.15, 0.45; I²=30%) or with testing only after delivery (RR 0.65, 95% CI 0.37, 1.14). The test for subgroup differences for duration of follow-up was statistically significant (p=0.04) between studies that followed women beyond six weeks after delivery (RR 0.11, 95% CI 0.05, 0.25; I²=0%) compared with those that only followed women until delivery or six weeks post-delivery (RR 0.31, 95% CI 0.18, 0.54; I²=53%).

A funnel plot (Figure 5) was performed to visually assess small-study bias, and appeared symmetrical. The Egger’s test was conducted and the result approached significance, but was inconclusive (p=0.065). The twelve studies with small sample sizes limit the ability to detect or exclude the possibility of small-study bias.
Perinatal mortality

A total of six studies (1,104 women) examined the outcome of perinatal mortality; one study was at low ROB, three studies were at high ROB, and two studies were at unclear ROB. There was no significant difference for antibiotics compared with no treatment on perinatal mortality (RR 0.96, 95% CI 0.27, 3.39; I²=56%). This body of evidence was rated as very low due to downgrading for ROB, indirectness, and imprecision.

3.2 Perinatal mortality

[Table and diagram related to the text]
Spontaneous abortion

Two studies\(^59,68\) (379 women) with high ROB reported on spontaneous abortion and found no significant difference between groups (RR 0.60, 95% CI 0.11, 3.10; \(I^2=17\%\)). This body of evidence was downgraded for ROB, indirectness, and imprecision for an overall quality of very low.

### 3.3 Spontaneous abortion

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funes et al 1975</td>
<td>2 139</td>
<td>0</td>
<td>67</td>
<td>26.3%</td>
<td>2.43 [0.12, 49.09]</td>
</tr>
<tr>
<td>Thomsen 1966</td>
<td>2 83</td>
<td>8</td>
<td>90</td>
<td>73.7%</td>
<td>0.38 [0.00, 1.74]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>222</td>
<td>157</td>
<td>379</td>
<td>100.0%</td>
<td>0.60 [0.11, 3.10]</td>
</tr>
</tbody>
</table>

Total events: 2 + 2 = 4

Heterogeneity: \(T^2 = 0.32; \text{Chi}^2 = 1.21; df = 1\) \((P = 0.27); I^2 = 17\%\)

Test for overall effect: \(Z = 0.82\) \((P = 0.41)\)

Neonatal sepsis

Two studies\(^50,66\) (154 women) with low ROB reported on neonatal sepsis and there was no statistically significant difference found between groups. Meta-analysis was not conducted due to there being no events in the study by Thomsen. This body of evidence was downgraded for indirectness, and imprecision for an overall quality of very low.

### 3.4 Neonatal sepsis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazemier 2015</td>
<td>0 40</td>
<td>2</td>
<td>42</td>
<td>100.0%</td>
<td>0.22 [0.01, 4.54]</td>
</tr>
<tr>
<td>Thomsen 1967</td>
<td>0 0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td>77</td>
<td>154</td>
<td>100.0%</td>
<td>0.22 [0.01, 4.54]</td>
</tr>
</tbody>
</table>

Total events: 0 + 0 = 0

Heterogeneity: Not applicable

Test for overall effect: \(Z = 0.97\) \((P = 0.33)\)

Preterm delivery

Two studies\(^50,66\) with low risk of bias and two studies\(^59,68\) with high ROB with a combined total of 533 women found no significant difference between antibiotics and no treatment on preterm delivery (RR 0.57, 95% CI 0.21, 1.56; \(I^2=70\%\)). This body of evidence was rated as very low due to downgrading for ROB, inconsistency, and indirectness.

### 3.5 Preterm delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funes et al 1975</td>
<td>24 139</td>
<td>10</td>
<td>67</td>
<td>32.4%</td>
<td>1.10 [0.59, 2.10]</td>
</tr>
<tr>
<td>Kazemier 2015</td>
<td>3 40</td>
<td>2</td>
<td>45</td>
<td>17.0%</td>
<td>1.09 [0.30, 3.80]</td>
</tr>
<tr>
<td>Thomsen 1967</td>
<td>2 37</td>
<td>12</td>
<td>32</td>
<td>21.7%</td>
<td>0.14 [0.03, 0.60]</td>
</tr>
<tr>
<td>Thomsen 1966</td>
<td>5 83</td>
<td>15</td>
<td>98</td>
<td>20.1%</td>
<td>0.38 [0.14, 0.95]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>299</td>
<td>234</td>
<td>533</td>
<td>100.0%</td>
<td>0.57 [0.21, 1.56]</td>
</tr>
</tbody>
</table>

Total events: 24 + 3 + 2 + 5 = 34

Heterogeneity: \(T^2 = 0.70; \text{Chi}^2 = 9.65; df = 3\) \((P = 0.03); I^2 = 70\%\)

Test for overall effect: \(Z = 1.10\) \((P = 0.27)\)
Low birth weight

A total of seven studies (1,522 women) with two studies\(^{50, 63}\) at low ROB, three\(^{55, 57, 61}\) at high ROB and one\(^{62}\) at unclear ROB examined the effect of treatment on low birth weight. There was a statistically significant difference favoring antibiotic treatment (RR 0.63; 95% CI 0.45, 0.90; I\(^2\)=20%; ARR 4.4%; NNT 23, 95% CI 15, 85). This body of evidence was rated as low quality due to downgrading for ROB and indirectness. The Optimal Information Size did not quite meet our criteria but we did not have serious concerns to warrant downgrading for this domain.

3.6 Low birthweight

Neonatal serious harm: fetal abnormalities

Four studies (821 women) with low ROB in two\(^{50, 63}\) and high ROB in two\(^{57, 59}\) examined the effect of antibiotic treatment on fetal abnormalities (harm). There was no statistically significant difference between groups (RR 0.49, 95% CI 0.17, 1.43; I\(^2\)=0%). This body of evidence was rated as very low due to downgrading for ROB, indirectness, and imprecision.

3.7 Neonatal serious harm: fetal abnormalities

Neonatal serious harm: hemolytic anemia

One study\(^{57}\) (265 women) with high ROB reported no cases of hemolytic anemia (harm) in infants for the intervention and control groups; this body of evidence was downgraded for ROB, inconsistency, indirectness, and imprecision for an overall quality of very low.
Chapter 4. Discussion, Applicability and Conclusion

Overview of Findings

KQ1a. What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences for patient characteristics (e.g., socioeconomic status [SES])?

Three observational studies of unclear risk of bias (ROB) examined the effectiveness of screening with urine culture compared with no screening for asymptomatic bacteriuria (ASB). Timing, collection methods, and treatment protocols differed between studies. None of the studies reported on several of our critical benefit outcomes (maternal mortality, maternal sepsis, neonatal sepsis, and serious maternal harms) or the important benefit of low birthweight. A significant difference was found for pyelonephritis, from three studies (RR 0.28, 95% CI 0.15, 0.54; I²=0%, ARR 1.3%; NNT 77, 95% CI 65, 121). No significant differences were found for the remaining critical benefit outcomes (spontaneous abortion, perinatal mortality, preterm delivery). Only one study reported on serious neonatal harms (fetal abnormalities) and found no differences (although the number of events and overall sample were small). The quality of evidence was very low for all outcomes. Based on the available evidence we are very uncertain about the effects of screening compared with no screening on these outcomes.

KQ1b. What are the benefits and harms of screening programs with different screening methods or algorithms for asymptomatic bacteriuria in pregnancy?

One observational study of low ROB compared frequent screening (using chemical reagent strip, lab urinalysis and urine culture for all visits) with one-time screening (using chemical reagent strip, lab urinalysis and urine culture on first visit) and found a significant difference in preterm delivery but no difference in pyelonephritis; no other outcomes were reported. The study found more preterm deliveries among the group with frequent screening (RR 1.57, 95% CI 1.11, 2.23), a finding for which the authors did not comment on or suggest an explanation. The quality of evidence was very low; therefore, we are very uncertain about the effects of frequent screening compared with one-time screening for these outcomes. The study did not report harms related to the different approaches to screening.

KQ2. How do women weigh the benefits and harms of screening and treatment of asymptomatic bacteriuria in pregnancy? How do women’s valuation of benefits and harms of screening and treatment inform their decisions to undergo screening?

The evidence for women’s outcome valuation was very limited as no studies directly addressed our KQs of weighing benefits versus harms and how this might affect decisions to undergo screening and treatment. Six cross-sectional studies and cross-sectional findings from women being recruited for a treatment trial provided indirect evidence of women’s valuation of benefits and harms of screening and/or treatment of ASB; the findings only reflect valuation on harms, not the balance of benefits and harms, and are not specific to the context of ASB. These studies demonstrated varied opinions on antibiotic use during pregnancy, with nearly half of participants from two studies (47-48%) expressing that antibiotics should not be used during pregnancy. The cross-sectional analysis of patients recruited for a randomised controlled trial (RCT) of treatment for ASB found similar results, with 61% of 255 women with ASB not wanting to be treated for an asymptomatic condition. There was some evidence suggesting that women thought penicillin posed a teratogenic risk and that antibiotics were unsafe during pregnancy particularly for the fetus; these risks may be perceived as greater by women who are pregnant. How these attitudes
may inform the women’s decisions on whether or not to screen for ASB was not reported, nor were
details presented on accuracy or understanding of information regarding potential risks and benefits.

**KQ4. What are the benefits and harms of antibiotic treatment compared with placebo or no
treatment for asymptomatic bacteriuria in pregnancy?**

Fifteen RCTs and controlled clinical trials (CCTs) compared antibiotics with placebo or no treatment for
bacteriuria in pregnancy; the majority were assessed as high ROB. No study reported on maternal
mortality, maternal sepsis or serious maternal harms. The most frequently reported critical benefit
outcome (by 12 studies) was pyelonephritis and overall a significant difference was found showing a
large relative reduction (RR 0.24, 95% CI 0.13, 0.41; I²=60%; ARR 17.6%; NNT 6, 95% CI 5, 7).
However, the quality of evidence for this outcome was low because of ROB and indirectness for concerns
on applicability to asymptomatic and not-at-high risk populations; we have some certainty that treatment
will reduce risk for pyelonephritis but are uncertain about the magnitude of the effect. A significant
difference was also found for low birth weight (important benefit outcome) based on seven RCTs with a
relative risk of 0.63 (95% CI 0.45, 0.90; I²=20%; ARR 4.4%; NNT 23, 95% CI 15, 85). The quality of
evidence for this outcome was also low for the same reasons as pyelonephritis. No significant differences
were found between treatment and placebo/no treatment for spontaneous abortion, perinatal mortality,
neonatal sepsis, preterm delivery, harms (fetal abnormalities and hemolytic anemia), and the quality of
evidence for these outcomes was very low.

Subgroup analyses for pyelonephritis suggested variation in treatment effects based on several factors
including number of urine samples used to confirm ASB, testing for persistent bacteriuria, and length of
follow-up. The treatment effect appeared to be larger for studies where women were tested at least twice
to confirm bacteriuria and initiate treatment, compared with those only testing women with one sample
(and finding no significant difference for this outcome). These findings appear to reflect a reduced
accuracy for one versus two-sample screening, whereby some women in these studies of one sample
would be false positives and thus not having as much potential to gain from treatment (i.e., unnecessarily
treated). Studies where women were tested for persistent bacteriuria (test of cure) during pregnancy or
during pregnancy and post-delivery showed a larger treatment effect than those testing only post-delivery
(although the latter group was represented by only one study). Finally, length of follow-up (>6 weeks
post-delivery vs. ≤6 weeks) showed a greater treatment effect among those followed for more than 6
weeks, although both subgroups benefited from treatment. Relatively higher effects from studies with
follow up >6 weeks post-delivery may indicate that some cases of pyelonephritis only occurred in this
period rather than during pregnancy. These findings should be considered exploratory as they are based
on between-study rather than within-study comparisons (i.e., non-randomized comparisons). Moreover,
some of the subgroups contained few studies.

**Comparison with other reviews**

Similar to our findings, a recent systematic review by Angelescu et al that examined benefits and harms
of screening for ASB in pregnancy found no trials on screening effectiveness. The review authors
included four RCTs focused on treatment of ASB: the recent study from the Netherlands and three
others (Elder et al, Mulla, and Williams et al). These authors chose to limit their inclusion to studies
reporting exclusively on treatment in asymptomatic women. We included studies that likely included
some women with symptoms. In addition to other intervention characteristics (e.g., treatment regimen and
adjunct treatments) and outcomes (e.g., lower urinary tract infection (UTI), infant morbidity, very low birth weight <1500g) that were not included in our review, Angelescu et al also examined population (diabetes, history of UTI, sociodemographic data) and screening (e.g., urine collection method, diagnostic procedures and cutoffs) characteristics, and similar outcomes (pyelonephritis, perinatal mortality, early preterm birth <32 weeks of gestation, adverse events) to ours. These review authors concluded that there was no reliable evidence on the benefits and harms of screening to support routine screening for ASB using urine culture in pregnant women.

Applicability

KQ1 (screening vs. no screening): Some of the included studies may not represent a general population of women who are asymptomatic for bacteriuria. Most studies did not provide descriptive information about their populations’ risk factors. For KQ1b (frequent vs. one-time screening), the included study setting was a hospital-based midwifery practice providing care to predominantly underserved and Hispanic women (72%) and the population had a relatively high rate of gestational diabetes (4 to 9%). All of the studies included in KQ1a and b used a urine culture to screen for bacteriuria.

KQ2 (outcome valuation): No study directly addressed how women weighed the benefits and harms of screening and treatment for ASB. Some information was available on women’s perspectives regarding antibiotic treatment during pregnancy. None of the studies focused on Canadian women. Most studies involved internet surveys to pregnant, antepartum and/or postnatal women.

KQ4 (treatment vs. no treatment): All studies enrolled women from hospital-based clinics, and most enrolled women at their first prenatal visit. Only four studies reported exclusive inclusion of asymptomatic women, and at least four studies included a significant proportion of women that would be considered high-risk for ASB and its sequelae. As women needed to be positive for bacteriuria to be eligible for treatment, this population is not representative of women who undergo screening. Most studies were published in the 1960s; there was only one published post-1990, which was conducted in The Netherlands and published in 2015. The majority of studies used a urine culture to screen for bacteriuria with most using two or more samples, to allow for confirmation of bacteriuria to warrant treatment. Further, the majority tested for persistent bacteriuria during pregnancy and followed women to delivery or six weeks after delivery for outcomes.

Limitations

Methodological limitations were common and heterogeneous across studies. Controlled clinical trials included in the evidence base for treatment may not have allocated participants in an unbiased manner that ensures comparability between groups. Observational study designs do not systematically allocate participants and are therefore at risk of including unknown confounders that may influence outcomes; ratings of low or unclear methodological quality for these studies does not imply that they have comparable validity to RCTs with similar ratings. It is unclear whether poor reporting by many studies is an indicator of true methodological flaws, age of publications, or other potential reasons. Methodological standards for trials have changed over time as empirical evidence becomes available about design features introducing bias; the RCTs examined may have been considered as high quality when conducted although to today’s standards this may not be true. The reporting in the observational screening studies did not demonstrate comparability at baseline or determine whether patients were symptomatic or had pyelonephritis when presenting to the study. Moreover, there were concerns with outcome reporting bias.
as some pregnancy and neonatal outcomes (i.e., perinatal mortality, spontaneous abortion, neonatal sepsis, preterm delivery, low birth weight, and harms) were not reported among studies despite their relevance and high importance to clinicians and patients. While most studies used a urine culture to detect asymptomatic bacteriuria, criteria for defining a positive test were not always clear or reported. One study only included women positive for group B streptococcus with a lower range criterion for bacteriuria warranting treatment (with many considered contaminated specimens, rather than ASB); it is unclear if these women differ from women positive for other organisms. It is unclear whether the variations in definitions of outcomes have any effect on detection and reporting of outcomes. Early stopping due to low incidence of primary outcomes in the Kazemier study\textsuperscript{50} may have biased effects of treatment. The small sample sizes among individual studies and pooled analyses limit the precision of effect size estimates.

Examining evidence on treatment for ASB as linked evidence for benefits and harms of screening programs has limitations. There is a likelihood that the absolute effects from treating bacteriuric women overestimate the effects for the screening population of all pregnant women where an estimated 2-10% will have asymptomatic bacteriuria.\textsuperscript{1} Only three studies contributing to the meta-analyses reported study patients as exclusively asymptomatic pregnant women, while the remaining studies did not specify this criterion; a concern is that among women who are treated, effect of benefit may be larger among symptomatic women compared with women who are asymptomatic for bacteriuria.

The mechanisms of pyelonephritis progressing to adverse maternal and neonatal outcomes are unclear. Multiple factors may influence outcomes; for example, preterm birth may be confounded especially in the older studies by issues such as access to contraception and family planning, treatment of other asymptomatic infections such as chlamydia and bacterial vaginosis, and detection and management of pregnancy complications/conditions. With limited reporting of baseline characteristics among studies, it is difficult to make direct associations between specific risk factors and subsequent outcomes.

Screening and treatment practices have evolved since the 1960s when most of the studies began publishing on asymptomatic bacteriuria. Current obstetric practices have, for example, better recognition of risk factors for urinary tract infections and other pregnancy complications, prompt treatment of symptoms, and a broader range of antibiotic options. These factors would suggest a lower control group (baseline) event rate and therefore less absolute benefit in current practice.

As we did not include studies published in languages other than English and French, it is unknown whether we are missing studies that may provide information on screening and treatment of ASB. There is some evidence showing that meta-analyses from systematic reviews in conventional medicine using language restrictions do not appear to be biased.\textsuperscript{24, 25}

**Future Research**

Although the anticipation of a large relative risk reduction for pyelonephritis appears to limit the clinical equipoise necessary to conduct RCTs on screening for ASB, we think there may be sufficient rationale to consider such trials based on: (1) very low quality evidence from screening studies and an appreciation of the linked nature of treatment evidence, particularly considering there are concerns about the methodological quality and the applicability of these old trials to current practice, and (2) some evidence suggesting that the incidence of pyelonephritis in untreated ASB (e.g., 2.5% in recent screening cohort study\textsuperscript{50}) may be substantially lower than that reported in historical literature and most of the available
treatment trials (median control group incidence of 23%), such that the absolute number of women who actually benefit from screening may be relatively low. Should such RCTs, or some other design valid for evaluating screening programs, be conducted we strongly encourage investigators to capture data accurately on harms and suitable for conducting a cost-effectiveness analysis, in clearly defined populations and using modern definitions for outcomes. Screening for ASB is not currently performed in all settings,\textsuperscript{50} indicating that clinical equipoise exists for enough clinicians to make these trials feasible and informative.

Prior to embarking on designing a trial for screening, but useful in any case, better information is needed to determine whether or not there are important moderating factors for ASB screening, as we attempted to examine in KQ1b. Our subgroup analyses examining moderators of effect, for example based on studies using one urine culture versus at least one additional confirmatory culture, had some credibility but were limited because of the need to rely on between-study effects. Studies directly examining this, and other factors such as different thresholds for treatment when particular organisms are detected, could provide high-quality data and be informative for how to maximize benefit. Enhanced culture protocols (e.g. expanded spectrum) for detecting the most clinically relevant uropathogens are emerging,\textsuperscript{12, 13} and if found to consistently provide better detection of these microorganisms than standard urine culture, studies comparing screening programs differing by these methods are encouraged to determine if they also predict how well treatment reduces the risk for pyelonephritis and other pregnancy complications in women without symptoms.

More evidence or information about how women, especially those living in Canada, weigh the benefits and harms of screening (including treatment when screened positive) for ASB in pregnancy would be valuable. Understanding the difficulties in providing patients with results on benefits and harms in easily understood formats (particularly in absolute numbers), and because of low-quality evidence to support such information, it is hard to know how well some forms of additional research (e.g., population surveys) could answer this question. It may be useful to use deliberative processes or focus group research, to facilitate understanding and in-depth considerations on this question. Regardless of whether this information influences recommendations to screen or not for ASB on a population level, this information may be informative to determine whether it is critical to better engage patients in decision-making on their care.

Conclusions

This systematic review examined three sets of evidence to inform recommendations on screening for ASB in pregnancy. Using the GRADE approach, we determined the evidence to be very low quality for most outcomes from observational studies comparing screening programs using urine culture with no screening; as such, we have no or very little certainty in the effect estimates for these outcomes. Moreover, several outcomes were not reported. Similar interpretations are made about the evidence from one study comparing frequent screening with one-time screening with culture. No direct evidence was found on how women weigh the benefits and harms of screening and/or treatment for ASB and how this might affect their decisions to undergo screening. Antibiotic treatment for women having significant bacteriuria may reduce the incidence of pyelonephritis in these women and the number of their babies born at low birth weight. We are uncertain if the magnitudes of the effect estimates from treatment are true. Very low quality evidence from these trials did not allow us to have any certainty in effects on other...
maternal and neonatal benefits and for fetal abnormalities and hemolytic anemia; no evidence was found for other serious harms.
## Evidence Sets 1 - 3

Evidence Set 1. Table 1.1 GRADE Summary of Findings – KQ1a: Benefits and harms of screening compared to no screening

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with no screening</td>
<td>Risk with screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0 per 1,000 (0 to 0)</td>
<td>0 per 1,000 (0 to 0)</td>
<td>not estimable (0 studies)</td>
<td>-</td>
<td>No study reported on maternal mortality.</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>0 per 1,000 (0 to 0)</td>
<td>0 per 1,000 (0 to 0)</td>
<td>not estimable (0 studies)</td>
<td>-</td>
<td>No study reported on maternal sepsis.</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Median</td>
<td>RR 0.28 (0.15 to 0.54)</td>
<td>5659 (3 observational studies&lt;sup&gt;43, 44, 45&lt;/sup&gt;)</td>
<td>⬤◯◯◯ VERY LOW &lt;sup&gt;1, a&lt;/sup&gt;</td>
<td>We are very uncertain about the effects of screening on pyelonephritis.</td>
</tr>
<tr>
<td></td>
<td>18 per 1,000</td>
<td>13 fewer per 1,000 (from 8 fewer to 16 fewer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>Median</td>
<td>RR 1.21 (0.01 to 102.93)</td>
<td>724 (2 observational studies&lt;sup&gt;43, 45&lt;/sup&gt;)</td>
<td>⬤◯◯◯ VERY LOW &lt;sup&gt;1, b&lt;/sup&gt;</td>
<td>We are very uncertain about the effects of screening on perinatal mortality.</td>
</tr>
<tr>
<td></td>
<td>19 per 1,000</td>
<td>4 more per 1,000 (from 19 fewer to 1,000 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>55 per 1,000</td>
<td>2 fewer per 1,000 (from 32 fewer to 70 more)</td>
<td>RR 0.96 (0.41 to 2.27)</td>
<td>⬤◯◯◯ VERY LOW &lt;sup&gt;1, c&lt;/sup&gt;</td>
<td>We are very uncertain about the effects of screening on spontaneous abortion.</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>0 per 1,000 (0 to 0)</td>
<td>not estimable (0 studies)</td>
<td>-</td>
<td>No study reported on neonatal sepsis.</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Screening compared to no screening for asymptomatic bacteriuria in pregnant women

Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

Comparison: no screening

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with no screening</td>
<td>Risk with screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk with no screening</td>
<td>13 per 1,000</td>
<td>102 more per 1,000</td>
<td>RR 8.70 (0.32 to 240.07)</td>
<td>722 (2 observational studies)</td>
<td>⊗◯◯◯</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 9 fewer to 1,000 more)</td>
<td></td>
<td></td>
<td>VERY LOW 1, d We are very uncertain about the effects of screening on preterm delivery.</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>0 per 1,000</td>
<td>0 per 1,000 (0 to 0)</td>
<td>not estimable</td>
<td>(0 studies)</td>
<td>-</td>
</tr>
<tr>
<td>Maternal serious harm(s)</td>
<td>0 per 1,000</td>
<td>0 per 1,000 (0 to 0)</td>
<td>not estimable</td>
<td>(0 studies)</td>
<td>-</td>
</tr>
<tr>
<td>Neonatal serious harm: fetal abnormalities</td>
<td>11 per 1,000</td>
<td>5 more per 1,000</td>
<td>RR 1.50 (0.25 to 8.87)</td>
<td>372 (1 observational study)</td>
<td>⊗◯◯◯</td>
</tr>
<tr>
<td></td>
<td>(from 8 fewer to 85 more)</td>
<td></td>
<td></td>
<td></td>
<td>VERY LOW 1, e We are very uncertain about the effects of screening on fetal abnormalities.</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 The imprecision domain is assessed using GRADE guidance relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

Pyelonephritis [a] ➔ Very Low Quality Evidence: Three non-concurrent cohort studies (Gérard 1983, Gratacós 1994, Uncu 2001) reported this outcome (n=5,659). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics. The optimal information size is met (sample size >5600).
therefore downgrading for imprecision is not warranted. There were no serious concerns to warrant downgrading for inconsistency, indirectness, or other considerations.

**Perinatal mortality [b] → Very Low Quality Evidence:** Two non-concurrent cohort studies (n=724; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on perinatal mortality. Further downgrading is warranted for imprecision due to optimal information size not being met with a small sample size. There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

**Spontaneous abortion [c] → Very Low Quality Evidence:** One non-concurrent cohort study reported this outcome (n=370; Gérard 1983). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for indirectness or other considerations.

**Preterm delivery [d] → Very Low Quality Evidence:** Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for imprecision for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

**Neonatal serious harm: fetal abnormalities (harm) [e] → Very Low Quality Evidence:** One non-concurrent cohort study reported this outcome (n=370; Uncu 2001). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on this outcome so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to the optimal information size not being met for rare events. There were no serious concerns to warrant downgrading for indirectness or other considerations.
Evidence Set 1. Table 1.2 GRADE Evidence Profile – KQ1a: Benefits and harms of screening compared to no screening

**Question:** Screening compared to no screening for asymptomatic bacteriuria in pregnant women

**Setting:** Any primary or clinical care setting providing care to pregnant women

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0</td>
<td>observational studies(^43, 44, 45)</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>0</td>
<td>observational studies(^43, 44, 45)</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>3</td>
<td>observational studies(^43, 44, 45)</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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</tr>
<tr>
<td>2</td>
<td>observational studies(^{43, 45})</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>1</td>
<td>observational studies(^{43})</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

### Spontaneous abortion

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients screening</th>
<th>No screening</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
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<td>0</td>
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</table>

### Neonatal sepsis

<table>
<thead>
<tr>
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<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients screening</th>
<th>No screening</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>observational studies(^{43, 45})</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>33/347 (9.5%)</td>
<td>1.3%</td>
<td>RR 8.70 (0.32 to 240.07)</td>
<td>102 more per 1,000 (from 9 fewer to 1,000 more)</td>
<td>(\text{ ultimo })</td>
<td>VERY LOW 1, d</td>
</tr>
</tbody>
</table>

## Preterm delivery
<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision ¹</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>screening</td>
<td>no</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
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<td></td>
<td></td>
<td>screening</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>no</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
</tbody>
</table>

### Quality assessment

#### Low birthweight

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</table>

Not estimable

**IMPORTANT**

#### Maternal serious harm(s)

<p>| | | | | | | | | | | | |</p>
<table>
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<tr>
<td>0</td>
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</tbody>
</table>

Not estimable

**CRITICAL**

### Neonatal serious harm: fetal abnormalities

#### Pyelonephritis [a] → Very Low Quality Evidence:

Three non-concurrent cohort studies (Gérard 1983, Gratacós 1994, Uncu 2001) reported this outcome (n=5,659). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics. The optimal information size is met (sample size >5600), therefore downgrading for **imprecision** is not warranted. There were no serious concerns to warrant downgrading for **inconsistency**, **indirectness**, or **other considerations**.

#### Perinatal mortality [b] → Very Low Quality Evidence:

Two non-concurrent cohort studies (n=724; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on perinatal mortality.

---

1. The imprecision domain is assessed using GRADE guidance relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

**CI:** Confidence interval; **RR:** Risk ratio
Further downgrading is warranted for **imprecision** due to optimal information size not being met with a small sample size. There were no serious concerns to warrant downgrading for **inconsistency**, **indirectness** or **other considerations**.

**Spontaneous abortion [c]** → **Very Low Quality Evidence**: One non-concurrent cohort study reported this outcome (n=370; Gérard 1983). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for **inconsistency**. Further downgrading for **imprecision** is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for **indirectness** or **other considerations**.

**Preterm delivery [d]** → **Very Low Quality Evidence**: Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for **imprecision** for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for **inconsistency**, **indirectness** or **other considerations**.

**Neonatal serious harm: fetal abnormalities [e]** → **Very Low Quality Evidence**: One non-concurrent cohort study reported this outcome (n=370; Uncu 2001). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on this outcome so this warrants downgrading for **inconsistency**. Further downgrading for **imprecision** is warranted due to the optimal information size not being met for rare events. There were no serious concerns to warrant downgrading for **indirectness** or **other considerations**.
Evidence Set 1. Forest Plots 1.1-1.5 – KQ1a: Benefits and harms of screening compared to no screening

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Effect size (Risk Ratio; M-H, Random, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Pyelonephritis</td>
<td>3</td>
<td>5659</td>
<td>0.28 [0.15, 0.54]</td>
</tr>
<tr>
<td>1.2 Perinatal mortality &gt;=20 wks GA note: Gérard &gt;=31 wks; Uncu &gt;20 wks</td>
<td>2</td>
<td>724</td>
<td>1.21 [0.01, 102.93]</td>
</tr>
<tr>
<td>1.3 Spontaneous abortion &lt;20 wks GA note: 1 study &lt;=28 wks (all occurred 7-21 wks)</td>
<td>1</td>
<td>370</td>
<td>0.96 [0.41, 2.27]</td>
</tr>
<tr>
<td>1.4 Preterm delivery &lt;37 wks GA</td>
<td>2</td>
<td>722</td>
<td>8.70 [0.32, 240.07]</td>
</tr>
<tr>
<td>1.5 Neonatal serious harm: fetal abnormalities</td>
<td>1</td>
<td>372</td>
<td>1.50 [0.25, 8.87]</td>
</tr>
</tbody>
</table>

CI: confidence interval; GA: gestational age; M-H: Mantel-Haenszel; No.: number; wks: weeks

1.1 Pyelonephritis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>No screening Events</th>
<th>Total</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grotzcz 1994</td>
<td>9</td>
<td>552</td>
<td>651</td>
<td>66.3%</td>
<td>0.30 [0.15, 0.53]</td>
</tr>
<tr>
<td>Gérard 1983</td>
<td>0</td>
<td>170</td>
<td>170</td>
<td>4.9%</td>
<td>0.17 [0.01, 3.23]</td>
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<tr>
<td>Uncu 2001</td>
<td>1</td>
<td>185</td>
<td>186</td>
<td>8.8%</td>
<td>0.25 [0.03, 2.22]</td>
</tr>
</tbody>
</table>

Total (95% CI): 2085/3651 (100.0%)
Risk Ratio: 0.28 [0.15, 0.54]

1.2 Perinatal mortality (>=20 wks GA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>No screening Events</th>
<th>Total</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gérard 1983</td>
<td>6</td>
<td>133</td>
<td>139</td>
<td>47.5%</td>
<td>12.74 [0.71, 228.74]</td>
</tr>
<tr>
<td>Uncu 2001</td>
<td>1</td>
<td>185</td>
<td>186</td>
<td>62.5%</td>
<td>0.14 [0.02, 1.15]</td>
</tr>
</tbody>
</table>

Total (95% CI): 349/375 (100.0%)
Risk Ratio: 1.21 [0.01, 102.93]

1.3 Spontaneous abortion (<20 wks GA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>No screening Events</th>
<th>Total</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gérard 1983</td>
<td>9</td>
<td>170</td>
<td>209</td>
<td>100.0%</td>
<td>0.96 [0.41, 2.27]</td>
</tr>
</tbody>
</table>

Total (95% CI): 170/200 (100.0%)
Risk Ratio: 0.96 [0.41, 2.27]
1.4 Preterm delivery (<37 wks GA)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>No screening Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gérard 1993</td>
<td>11</td>
<td>181</td>
<td>5</td>
<td>169</td>
<td>2.66 [0.92, 7.29]</td>
</tr>
<tr>
<td>Uncu 2001</td>
<td>22</td>
<td>186</td>
<td>0</td>
<td>166</td>
<td>45.00 [2.75, 736.39]</td>
</tr>
</tbody>
</table>

Total (95% CI): 347 375 100.0% 8.70 [0.32, 240.07]

Total events 33 5

Heterogeneity: Tau² = 4.70, Ch² = 5.07, df = 1 (P = 0.02), I² = 80%

Test for overall effect: Z = 1.26 (P = 0.20)

1.5 Neonatal serious harm: fetal abnormalities

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Screening Events</th>
<th>No screening Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncu 2001</td>
<td>3</td>
<td>186</td>
<td>2</td>
<td>188</td>
<td>1.50 [0.25, 8.87]</td>
</tr>
</tbody>
</table>

Total (95% CI): 180 180 100.0% 1.50 [0.25, 8.87]

Total events 3 2

Heterogeneity: Not applicable

Test for overall effect: Z = 0.45 (P = 0.65)
### Evidence Set 2. Table 2.1 GRADE Summary of Findings - KQ1b: Benefits and harms of frequent screening compared to one-time screening

**Frequent screening compared to one-time screening for asymptomatic bacteriuria**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Nº of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with one-time screening</td>
<td>Risk difference with frequent screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>4 per 1,000</td>
<td>0 fewer per 1,000 (from 3 fewer to 13 more)</td>
<td>RR 1.09 (0.27 to 4.35)</td>
<td>1952 (1 observational study46)</td>
<td>⬤◯◯◯ VERY LOW 1,a</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>49 per 1,000</td>
<td>28 more per 1,000 (from 5 more to 60 more)</td>
<td>RR 1.57 (1.11 to 2.23)</td>
<td>1952 (1 observational study46)</td>
<td>⬤◯◯◯ VERY LOW 1,b</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (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:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

---

1 The imprecision domain is assessed using GRADE guidance42 relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

CI: Confidence interval; RR: Risk ratio

**Pyelonephritis [a] ➔ Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias associated with: 1) no demonstration that pyelonephritis was not present at start of study, 2) no demonstration of comparability between frequent and one-time screening groups, and 3) no adjustment to analyses to account for risk factors or other patient characteristics. Only one study provided data for this outcome so downgrading is warranted for inconsistency. Further downgrading is warranted for indirectness as the women
are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The optimal information size is not met (8 events) with sample size (n=1952), therefore this warrants downgrading for **imprecision**. There were no serious concerns to warrant downgrading for **other considerations**.

**Preterm delivery [b] → Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to very serious **risk of bias** associated with: 1) no demonstration of comparability between frequent and one-time screening groups, 2) no adjustment to analyses to account for risk factors or other patient characteristics, and 3) suspected reporting bias among outcomes reported by studies (did not report on spontaneous abortion, perinatal mortality or fetal abnormalities). Only one study provided data for this outcome so downgrading is warranted for **inconsistency**. Further downgrading is warranted for **indirectness** as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The event rate is low (122 events) without meeting optimal information size, so this is downgraded for **imprecision**. There were no serious concerns to warrant downgrading for **other considerations**.
Evidence Set 2. Table 2.2 GRADE Evidence Profile - KQ1b: Benefits and harms of frequent screening compared to one-time screening

**Question:** Frequent screening compared to one-time screening for asymptomatic bacteriuria

**Setting:** Any primary clinical care setting providing care to pregnant women

### Bibliography:

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>observational studies</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td></td>
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<tr>
<td>1</td>
<td>observational studies</td>
<td>serious</td>
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<td>serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval; **RR:** Risk ratio

1 The imprecision domain is assessed using GRADE guidance relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).
**Pyelonephritis [a]** → **Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias associated with: 1) no demonstration that pyelonephritis was not present at start of study, 2) no demonstration of comparability between frequent and one-time screening groups, and 3) no adjustment to analyses to account for risk factors or other patient characteristics. Only one study provided data for this outcome so downgrading is warranted for inconsistency. Further downgrading is warranted for indirectness as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The optimal information size is not met (8 events) with sample size (n=1952), therefore this warrants downgrading for imprecision. There were no serious concerns to warrant downgrading for other considerations.

**Preterm delivery [b]** → **Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to very serious risk of bias associated with: 1) no demonstration of comparability between frequent and one-time screening groups, 2) no adjustment to analyses to account for risk factors or other patient characteristics, and 3) suspected reporting bias among outcomes reported by studies (did not report on spontaneous abortion, perinatal mortality or fetal abnormalities). Only one study provided data for this outcome so downgrading is warranted for inconsistency. Further downgrading is warranted for indirectness as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The event rate is low (122 events) without meeting optimal information size, so this is downgraded for imprecision. There were no serious concerns to warrant downgrading for other considerations.
Evidence Set 2. Forest Plots 2.1-2.2 - KQ1b: Benefits and harms of frequent screening compared to one-time screening

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Effect size (Risk Ratio; M-H, Random, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Pyelonephritis</td>
<td>1</td>
<td>1952</td>
<td>1.09 [0.27, 4.35]</td>
</tr>
<tr>
<td>2.2 Preterm delivery &lt;37 wks GA</td>
<td>1</td>
<td>1952</td>
<td>1.57 [1.11, 2.23]</td>
</tr>
</tbody>
</table>

CI: confidence interval; GA: gestational age; M-H: Mantel-Haenszel; No.: number; wks: weeks

2.1 Pyelonephritis

2.2 Preterm delivery (<37 wks GA)
### Evidence Set 3. Table 3.1 GRADE Summary of Findings – KQ4: Benefits and harms of treatment compared to no treatment

#### Treatment compared to no treatment for asymptomatic bacteriuria

**Patient or population:** asymptomatic bacteriuria  
**Setting:** Any primary or clinical care setting providing care to pregnant women  
**Intervention:** treatment  
**Comparison:** no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with no treatment Risk with treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0 per 1,000 0 per 1,000 (0 to 0)</td>
<td>not estimable</td>
<td>(0 studies)</td>
<td>-</td>
<td>No study reported on maternal mortality.</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>0 per 1,000 0 per 1,000 (0 to 0)</td>
<td>not estimable</td>
<td>(0 studies)</td>
<td>-</td>
<td>No study reported on maternal sepsis.</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Median 176 fewer per 1,000 (from 137 fewer to 202 fewer)</td>
<td>RR 0.24 (0.13 to 0.41)</td>
<td>2017 (12 RCTs50, 55, 57-65, 67)</td>
<td>✭✭◯◯ LOW 1, a</td>
<td>There may be a reduction in pyelonephritis from treatment.</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>Median 2 fewer per 1,000 (from 29 fewer to 97 more)</td>
<td>RR 0.96 (0.27 to 3.39)</td>
<td>1104 (6 RCTs50, 57, 61-63, 68)</td>
<td>✭✭✭✭ VERY LOW 1, b</td>
<td>We are very uncertain about the effects of treatment on perinatal mortality.</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>Median 13 fewer per 1,000 (from 30 fewer to 70 more)</td>
<td>RR 0.60 (0.11 to 3.10)</td>
<td>379 (2 RCTs59, 68)</td>
<td>✭✭✭✭ VERY LOW 1, c</td>
<td>We are very uncertain about the effects of treatment on spontaneous abortion.</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>Median 17 fewer per 1,000 (from 22 fewer to 79 more)</td>
<td>RR 0.22 (0.01 to 4.54)</td>
<td>154 (2 RCTs50, 66)</td>
<td>✭✭✭✭ VERY LOW 1, d</td>
<td>We are very uncertain about the effects of treatment on neonatal sepsis.</td>
</tr>
</tbody>
</table>
### Treatment compared to no treatment for asymptomatic bacteriuria

**Patient or population:** asymptomatic bacteriuria

**Setting:** Any primary or clinical care setting providing care to pregnant women

**Intervention:** treatment

**Comparison:** no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Risk with no treatment</strong></td>
<td><strong>Risk with treatment</strong></td>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>Median</td>
<td>RR 0.57 (0.21 to 1.56)</td>
<td>533</td>
<td>⬤◯◯◯</td>
<td>VERY LOW 1.e We are very uncertain about the effects of treatment on preterm delivery.</td>
</tr>
<tr>
<td></td>
<td>158 per 1,000</td>
<td>68 fewer per 1,000</td>
<td>(from 125 fewer to 88 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Median</td>
<td>RR 0.63 (0.45 to 0.90)</td>
<td>1522</td>
<td>⬤◯◯◯</td>
<td>LOW 1.f There may be a reduction in low birth weight from treatment.</td>
</tr>
<tr>
<td></td>
<td>118 per 1,000</td>
<td>44 fewer per 1,000</td>
<td>(from 12 fewer to 65 fewer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal serious harm(s)</td>
<td>0 per 1,000</td>
<td>0 per 1,000</td>
<td>(0 to 0)</td>
<td>not estimable</td>
<td>- No study reported on maternal serious harms.</td>
</tr>
<tr>
<td>Neonatal serious harm: fetal abnormalities</td>
<td>Median</td>
<td>RR 0.49 (0.17 to 1.43)</td>
<td>821</td>
<td>⬤◯◯◯</td>
<td>VERY LOW 1.g We are very uncertain about the effects of treatment on harms (fetal abnormalities).</td>
</tr>
<tr>
<td></td>
<td>19 per 1,000</td>
<td>9 fewer per 1,000</td>
<td>(from 15 fewer to 8 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal serious harm: hemolytic anemia</td>
<td>0 per 1,000</td>
<td>0 per 1,000</td>
<td>(0 to 0)</td>
<td>not estimable</td>
<td>VERY LOW 1.h We are very uncertain about the effects of treatment on harms (hemolytic anemia).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (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
Treatment compared to no treatment for asymptomatic bacteriuria

**Patient or population:** asymptomatic bacteriuria

**Setting:** Any primary or clinical care setting providing care to pregnant women

**Intervention:** treatment

**Comparison:** no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Risk with no treatment | Risk with treatment | Grade Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

---

1 The imprecision domain is assessed using GRADE guidance relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

CI: Confidence interval; RR: Risk ratio

**Pyelonephritis, overall [a] → Low Quality Evidence:** Twelve trials (Brumfitt 1975, Elder 1971, Foley 1987, Furness 1975, Gold 1966, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Mulla 1960, Pathak 1969, Williams 1969) reported this outcome (n=2,017). Quality of evidence is downgraded from high to moderate due to serious **risk of bias** associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for **indirectness** due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for **imprecision**. There were no concerns with **inconsistency** or other considerations to warrant further downgrading.

**Perinatal mortality [b] → Very Low Quality Evidence:** Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious **risk of bias** associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment effectiveness is downgraded for **indirectness** due to studies that did not explicitly include asymptomatic women as well as studies that included high-risk women. Further downgrading is warranted for **imprecision** due to the samples size not being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for **inconsistency** or other considerations.

**Spontaneous abortion [c] → Very Low Quality Evidence:** Two trials (n=379; Furness 1975, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious **risk of bias** associated with use of alternation (Wren 1969) and incomplete reporting (Furness 1975). Further downgrading from moderate to low is warranted for **indirectness** due to studies that did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size not met (10 events) to warrant downgrading twice from low to very low for **imprecision**. There were no concerns to warrant downgrading for **inconsistency** or other considerations.

**Neonatal sepsis [d] → Very Low Quality Evidence:** Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this outcome. Quality of evidence is downgraded for **indirectness** due to studies that did not explicitly include exclusively asymptomatic women. The sample size (<2000) is
not met with only 2 events to warrant downgrading twice for imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations.

**Preterm delivery [e]** → **Very Low Quality Evidence**: Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and incomplete reporting (Furness 1975). There is substantial heterogeneity (I²=70%) with point estimates on both sides of the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to warrant downgrading for imprecision or other considerations.

**Low birth weight [f]** → **Low Quality Evidence**: Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

**Neonatal serious harm: fetal abnormalities [g]** → **Very Low Quality Evidence**: Four trials (n=821; Elder 1971, Furness 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations.

**Neonatal serious harm: hemolytic anemia [h]** → **Very Low Quality Evidence**: One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for imprecision. There were no concerns to warrant downgrading for other considerations.
Evidence Set 3. Table 3.1 GRADE Evidence Profile – KQ4: Benefits and harms of treatment compared to no treatment

**Question:** Treatment compared to no treatment for asymptomatic bacteriuria

**Setting:** Any primary or clinical care setting providing care to pregnant women

**Bibliography:**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maternal sepsis</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>12</td>
<td>randomised trials(^{50, 55, 57-65, 67})</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality assessment</td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>2</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>2</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

Preterm delivery
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serious serious not serious very serious none</td>
<td>34/299 (11.4%)</td>
<td>15.8%</td>
<td>RR 0.57 (0.21 to 1.56)</td>
<td>68 fewer per 1,000 (from 125 fewer to 88 more)</td>
</tr>
<tr>
<td><strong>Maternal serious harm(s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>not estimable</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neonatal serious harm: fetal abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serious not serious serious not serious very serious none</td>
<td>4/425 (0.9%)</td>
<td>1.9%</td>
<td>RR 0.49 (0.17 to 1.43)</td>
<td>9 fewer per 1,000 (from 15 fewer to 8 more)</td>
</tr>
<tr>
<td><strong>Neonatal serious harm: hemolytic anemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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There were no concerns to warrant downgrading for imprecision or other considerations.

### Pyelonephritis, overall [a] → Low Quality Evidence

Twelve trials (Brumfitt 1975, Elder 1971, Foley 1987, Furness 1975, Gold 1966, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Mulla 1960, Pathak 1969, Williams 1969) reported this outcome (n=2,017). Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for indirectness due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for imprecision. There were no concerns with inconsistency or other considerations to warrant further downgrading.

### Perinatal mortality [b] → Very Low Quality Evidence

Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment effectiveness is downgraded for indirectness due to studies that did not explicitly include asymptomatic women as well as studies that included high-risk women. Further downgrading is warranted for imprecision due to the sample size not being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for inconsistency or other considerations.

### Spontaneous abortion [c] → Very Low Quality Evidence

Two trials (n=379; Furness 1975, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969) and incomplete reporting (Furness 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size not met (10 events) to warrant downgrading twice from low to very low for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

### Neonatal sepsis [d] → Very Low Quality Evidence

Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this outcome. Quality of evidence is downgraded for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size (<2000) is not met with only 2 events to warrant downgrading twice for imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations.

### Preterm delivery [e] → Very Low Quality Evidence

Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and incomplete reporting (Furness 1975). There is substantial heterogeneity (I²=70%) with point estimates on both sides of the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to warrant downgrading for imprecision or other considerations.

---

1 The imprecision domain is assessed using GRADE guidance relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

CI: Confidence interval; RR: Risk ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>0/122 (0.0%)</td>
<td>0/143 (0.0%)</td>
<td>not estimable</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

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Low birth weight \[f\]  \rightarrow \textbf{Low Quality Evidence:} Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: fetal abnormalities \[g\]  \rightarrow \textbf{Very Low Quality Evidence:} Four trials (n=821; Elder 1971, Furness 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: hemolytic anemia \[h\]  \rightarrow \textbf{Very Low Quality Evidence:} One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for imprecision. There were no concerns to warrant downgrading for other considerations.
Evidence Set 3: Forest Plots 3.1-3.8 - KQ4: Benefits and harms of treatment compared to no treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Effect size (Risk Ratio; M-H, Random, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Pyelonephritis</td>
<td>12</td>
<td>2017</td>
<td>0.24 [0.13, 0.41]</td>
</tr>
<tr>
<td>3.2 Perinatal mortality (≥20 wks, including intrauterine demise, stillbirth, early neonatal death)</td>
<td>6</td>
<td>1104</td>
<td>0.96 [0.27, 3.39]</td>
</tr>
<tr>
<td>3.3 Spontaneous abortion (&lt;20 wks)</td>
<td>2</td>
<td>379</td>
<td>0.60 [0.11, 3.10]</td>
</tr>
<tr>
<td>3.4 Neonatal sepsis</td>
<td>2</td>
<td>154</td>
<td>0.22 [0.01, 4.54]</td>
</tr>
<tr>
<td>3.5 Preterm delivery (&lt;38 wks)</td>
<td>4</td>
<td>533</td>
<td>0.57 [0.21, 1.56]</td>
</tr>
<tr>
<td>3.6 Low birth weight (≤2500g; SGA &lt;10th percentile &amp; &lt;5th percentile)</td>
<td>7</td>
<td>1522</td>
<td>0.63 [0.45, 0.90]</td>
</tr>
<tr>
<td>3.7 Neonatal serious harm: fetal abnormalities</td>
<td>4</td>
<td>821</td>
<td>0.49 [0.17, 1.43]</td>
</tr>
<tr>
<td>3.8 Neonatal serious harm: hemolytic anemia</td>
<td>1</td>
<td>265</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

CI: confidence interval; g: grams; M-H: Mantel-Haenszel; No.: number; SGA: small for gestational age; wks: weeks

3.1 Pyelonephritis

3.2 Perinatal mortality
### 3.3 Spontaneous abortion

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumese 1975</td>
<td>2</td>
<td>139</td>
<td>0</td>
<td>67</td>
<td>93.7%</td>
<td>2.42 [1.12, 4.99]</td>
</tr>
<tr>
<td>Wrin 1969</td>
<td>2</td>
<td>83</td>
<td>0</td>
<td>90</td>
<td>73.7%</td>
<td>0.39 [0.08, 1.74]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>222</strong></td>
<td><strong>157</strong></td>
<td><strong>6</strong></td>
<td><strong>90</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.60 [0.11, 3.10]</strong></td>
</tr>
</tbody>
</table>

Total events: 4
Heterogeneity: Tau² = 0.33; Chi² = 1.21, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 0.02 (P = 0.54)

### 3.4 Neonatal sepsis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazemier 2015</td>
<td>0</td>
<td>40</td>
<td>2</td>
<td>45</td>
<td>100.0%</td>
<td>0.22 [0.01, 4.54]</td>
</tr>
<tr>
<td>Thornson 1987</td>
<td>0</td>
<td>37</td>
<td>0</td>
<td>37</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>77</strong></td>
<td><strong>2</strong></td>
<td><strong>77</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.22 [0.01, 4.54]</strong></td>
</tr>
</tbody>
</table>

Total events: 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.33)

### 3.5 Preterm delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumese 1975</td>
<td>24</td>
<td>139</td>
<td>10</td>
<td>67</td>
<td>32.4%</td>
<td>1.16 [0.59, 2.20]</td>
</tr>
<tr>
<td>Kazemier 2015</td>
<td>3</td>
<td>40</td>
<td>2</td>
<td>45</td>
<td>17.9%</td>
<td>1.69 [0.30, 9.59]</td>
</tr>
<tr>
<td>Thornson 1987</td>
<td>2</td>
<td>37</td>
<td>12</td>
<td>50</td>
<td>21.7%</td>
<td>0.14 [0.03, 0.60]</td>
</tr>
<tr>
<td>Wrin 1969</td>
<td>5</td>
<td>83</td>
<td>15</td>
<td>98</td>
<td>28.1%</td>
<td>0.39 [0.14, 0.96]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>269</strong></td>
<td><strong>234</strong></td>
<td><strong>39</strong></td>
<td><strong>234</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.57 [0.21, 1.50]</strong></td>
</tr>
</tbody>
</table>

Total events: 39
Heterogeneity: Tau² = 0.70, Chi² = 9.95, df = 9 (P = 0.02); I² = 70%
Test for overall effect: Z = 1.10 (P = 0.27)

### 3.6 Low birthweight

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunner 1975</td>
<td>10</td>
<td>228</td>
<td>21</td>
<td>178</td>
<td>23.0%</td>
<td>0.65 [0.36, 1.16]</td>
</tr>
<tr>
<td>Elder 1971</td>
<td>15</td>
<td>133</td>
<td>15</td>
<td>145</td>
<td>19.4%</td>
<td>1.08 [0.55, 2.14]</td>
</tr>
<tr>
<td>Koss 1965</td>
<td>7</td>
<td>88</td>
<td>21</td>
<td>98</td>
<td>14.8%</td>
<td>0.35 [0.16, 0.76]</td>
</tr>
<tr>
<td>Kazemier 2015</td>
<td>1</td>
<td>40</td>
<td>4</td>
<td>44</td>
<td>2.5%</td>
<td>0.28 [0.03, 2.41]</td>
</tr>
<tr>
<td>Kinsella-Smith 1955</td>
<td>9</td>
<td>51</td>
<td>12</td>
<td>63</td>
<td>15.5%</td>
<td>0.99 [0.31, 1.51]</td>
</tr>
<tr>
<td>Little 1988</td>
<td>10</td>
<td>124</td>
<td>13</td>
<td>141</td>
<td>15.4%</td>
<td>0.97 [0.40, 1.92]</td>
</tr>
<tr>
<td>Wrin 1969</td>
<td>4</td>
<td>83</td>
<td>14</td>
<td>97</td>
<td>3.3%</td>
<td>0.31 [0.11, 0.90]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>769</strong></td>
<td><strong>753</strong></td>
<td><strong>100</strong></td>
<td><strong>753</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.63 [0.45, 0.90]</strong></td>
</tr>
</tbody>
</table>

Total events: 100
Heterogeneity: Tau² = 0.04; Chi² = 7.52, df = 6 (P = 0.29); I² = 20%
Test for overall effect: Z = 2.57 (P = 0.01)
3.7 Neonatal serious harm: fetal abnormalities

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elder 1971</td>
<td>2</td>
<td>122</td>
<td>6</td>
<td>142</td>
<td>46.4%</td>
<td>0.39 [0.09, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Furness 1975</td>
<td>0</td>
<td>139</td>
<td>1</td>
<td>140</td>
<td>7.1%</td>
<td>0.19 [0.01, 3.92]</td>
<td></td>
</tr>
<tr>
<td>Kazemi 2015</td>
<td>0</td>
<td>40</td>
<td>1</td>
<td>42</td>
<td>11.5%</td>
<td>0.37 [0.02, 8.03]</td>
<td></td>
</tr>
<tr>
<td>Little 1966</td>
<td>2</td>
<td>124</td>
<td>2</td>
<td>142</td>
<td>30.7%</td>
<td>1.14 [0.16, 7.06]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>425</strong></td>
<td><strong>396</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>425</strong></td>
<td><strong>40</strong>%</td>
<td><strong>0.49 [0.17, 1.43]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4
Heterogeneity: Tau² = 0.00, Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

3.8 Neonatal serious harm: hemolytic anemia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elder 1971</td>
<td>0</td>
<td>122</td>
<td>0</td>
<td>122</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>122</strong></td>
<td><strong>143</strong></td>
<td></td>
<td><strong>143</strong></td>
<td><strong>0</strong>%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Evidence Set 3. Forest Plots for Subgroup Analyses 3.1.1-3.1.4 – KQ4: Benefits and harms of treatment compared to no treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Effect size (Risk Ratio; M-H, Random, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1 Pyelonephritis (overall)</strong></td>
<td>12</td>
<td>2017</td>
<td>0.24 [0.13, 0.41]</td>
</tr>
<tr>
<td><strong>3.1.1 Subgroup analysis: no. of urine samples before confirming bacteriuria and giving treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One urine sample</td>
<td>4</td>
<td>611</td>
<td>0.50 [0.19, 1.35]</td>
</tr>
<tr>
<td>Two or more urine samples</td>
<td>8</td>
<td>1406</td>
<td>0.19 [0.11, 0.31]</td>
</tr>
<tr>
<td><strong>3.1.2 Subgroup analysis: testing for persistent bacteriuria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested for persistent bacteriuria during pregnancy</td>
<td>8</td>
<td>1352</td>
<td>0.26 [0.15, 0.45]</td>
</tr>
<tr>
<td>Testing for persistent bacteriuria post-delivery only</td>
<td>1</td>
<td>206</td>
<td>0.65 [0.37, 1.14]</td>
</tr>
<tr>
<td>Tested for persistent bacteriuria during pregnancy and post-delivery</td>
<td>3</td>
<td>459</td>
<td>0.11 [0.05, 0.25]</td>
</tr>
<tr>
<td><strong>3.1.3 Subgroup analysis: follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up until delivery or puerperium (≤6 wks post-delivery)</td>
<td>9</td>
<td>1558</td>
<td>0.31 [0.18, 0.54]</td>
</tr>
<tr>
<td>Follow-up until &gt;6 wks post-delivery</td>
<td>3</td>
<td>459</td>
<td>0.11 [0.05, 0.25]</td>
</tr>
</tbody>
</table>

CI: confidence interval; M-H: Mantel-Haenszel; No.: number; wks: weeks

### 3.1 Pyelonephritis (overall)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>No treatment or placebo</th>
<th>Total</th>
<th>Events</th>
<th>Total Weight</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brummitt 1975</td>
<td>9 B7</td>
<td>20</td>
<td>96</td>
<td>32</td>
<td>0.44 [0.21, 0.92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elder 1971</td>
<td>4 133</td>
<td>27</td>
<td>148</td>
<td>71</td>
<td>0.16 [0.06, 0.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley 1967</td>
<td>3 108</td>
<td>3</td>
<td>120</td>
<td>60</td>
<td>1.20 [0.25, 5.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fumawo 1975</td>
<td>23 150</td>
<td>17</td>
<td>97</td>
<td>46</td>
<td>0.95 [0.37, 1.14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold 1968</td>
<td>0 35</td>
<td>2</td>
<td>30</td>
<td>15</td>
<td>0.17 [0.01, 3.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kass 1960</td>
<td>1 26</td>
<td>26</td>
<td>98</td>
<td>49</td>
<td>0.04 [0.01, 0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazemi 2015</td>
<td>0 45</td>
<td>1</td>
<td>45</td>
<td>22</td>
<td>0.37 [0.02, 0.93]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kicinska-Smith 1995</td>
<td>2 55</td>
<td>20</td>
<td>55</td>
<td>27</td>
<td>0.09 [0.02, 0.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little 1988</td>
<td>4 124</td>
<td>35</td>
<td>141</td>
<td>69</td>
<td>0.13 [0.05, 0.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulla 1960</td>
<td>1 50</td>
<td>12</td>
<td>50</td>
<td>26</td>
<td>0.08 [0.01, 0.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathak 1968</td>
<td>3 71</td>
<td>17</td>
<td>76</td>
<td>38</td>
<td>0.18 [0.05, 0.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 1969</td>
<td>5 85</td>
<td>18</td>
<td>78</td>
<td>39</td>
<td>0.25 [0.10, 0.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1023</strong></td>
<td><strong>196</strong></td>
<td><strong>994</strong></td>
<td><strong>494</strong></td>
<td><strong>0.24 [0.13, 0.41]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 55 Heterogeneity: Tau² = 0.40, Chi² = 27.66, df=11 (P = 0.004), I² = 66%
Test for overall effect: Z = 5.08 (P = 0.00001)
### 3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1.1 One urine sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley 1987</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>120</td>
<td>7.1%</td>
<td>1.20 (0.25, 5.92)</td>
<td></td>
</tr>
<tr>
<td>Furness 1975</td>
<td>25</td>
<td>139</td>
<td>17</td>
<td>67</td>
<td>14.1%</td>
<td>0.05 (0.57, 1.14)</td>
<td></td>
</tr>
<tr>
<td>Kozier 1986</td>
<td>4</td>
<td>40</td>
<td>1</td>
<td>45</td>
<td>2.6%</td>
<td>0.67 (0.02, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Mulia 1983</td>
<td>1</td>
<td>59</td>
<td>12</td>
<td>62</td>
<td>5.3%</td>
<td>0.69 (0.01, 0.92)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>329</td>
<td>282</td>
<td>29.1%</td>
<td>0.50</td>
<td>(0.19, 1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>27</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.42; Chi² = 5.11, df = 3 (P = 0.18); P = 41%
Test for overall effect: Z = 1.39 (P = 0.17)

### 3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.2 Two or more urine samples</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brunner 1975</td>
<td>9</td>
<td>87</td>
<td>20</td>
<td>66</td>
<td>12.6%</td>
<td>0.44 (0.21, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Elder 1987</td>
<td>4</td>
<td>133</td>
<td>27</td>
<td>140</td>
<td>10.6%</td>
<td>0.16 (0.06, 0.48)</td>
<td></td>
</tr>
<tr>
<td>Gold 1989</td>
<td>0</td>
<td>35</td>
<td>2</td>
<td>33</td>
<td>2.9%</td>
<td>0.17 (0.01, 0.44)</td>
<td></td>
</tr>
<tr>
<td>Kings 1989</td>
<td>1</td>
<td>93</td>
<td>26</td>
<td>68</td>
<td>5.4%</td>
<td>0.49 (0.01, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Liddle-Smith 1965</td>
<td>2</td>
<td>81</td>
<td>20</td>
<td>61</td>
<td>9.6%</td>
<td>0.09 (0.02, 0.37)</td>
<td></td>
</tr>
<tr>
<td>Little 1987</td>
<td>4</td>
<td>124</td>
<td>36</td>
<td>160</td>
<td>10.7%</td>
<td>0.13 (0.05, 0.36)</td>
<td></td>
</tr>
<tr>
<td>Paton 1989</td>
<td>3</td>
<td>75</td>
<td>17</td>
<td>76</td>
<td>9.4%</td>
<td>0.19 (0.05, 0.59)</td>
<td></td>
</tr>
<tr>
<td>Williams 1989</td>
<td>6</td>
<td>85</td>
<td>18</td>
<td>73</td>
<td>11.2%</td>
<td>0.25 (0.05, 0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>694</td>
<td>712</td>
<td>70.9%</td>
<td>0.19</td>
<td>(0.11, 0.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>26</td>
<td>165</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.18; Chi² = 10.22, df = 7 (P = 0.18); P = 31%
Test for overall effect: Z = 0.59 (P < 0.03961)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.3 Three or more urine samples</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brunner 1975</td>
<td>9</td>
<td>87</td>
<td>20</td>
<td>66</td>
<td>12.6%</td>
<td>0.44 (0.21, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Elder 1987</td>
<td>4</td>
<td>133</td>
<td>27</td>
<td>140</td>
<td>10.6%</td>
<td>0.16 (0.06, 0.48)</td>
<td></td>
</tr>
<tr>
<td>Gold 1989</td>
<td>0</td>
<td>35</td>
<td>2</td>
<td>33</td>
<td>2.9%</td>
<td>0.17 (0.01, 0.44)</td>
<td></td>
</tr>
<tr>
<td>Kings 1989</td>
<td>1</td>
<td>93</td>
<td>26</td>
<td>68</td>
<td>5.4%</td>
<td>0.49 (0.01, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Liddle-Smith 1965</td>
<td>2</td>
<td>81</td>
<td>20</td>
<td>61</td>
<td>9.6%</td>
<td>0.09 (0.02, 0.37)</td>
<td></td>
</tr>
<tr>
<td>Little 1987</td>
<td>4</td>
<td>124</td>
<td>36</td>
<td>160</td>
<td>10.7%</td>
<td>0.13 (0.05, 0.36)</td>
<td></td>
</tr>
<tr>
<td>Mulia 1983</td>
<td>1</td>
<td>59</td>
<td>12</td>
<td>50</td>
<td>5.3%</td>
<td>0.09 (0.01, 0.52)</td>
<td></td>
</tr>
<tr>
<td>Williams 1989</td>
<td>5</td>
<td>85</td>
<td>16</td>
<td>79</td>
<td>11.2%</td>
<td>0.25 (0.05, 0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>654</td>
<td>698</td>
<td>63.1%</td>
<td>0.26</td>
<td>(0.15, 0.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>26</td>
<td>118</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.17; Chi² = 9.89, df = 7 (P = 0.10); P = 36%
Test for overall effect: Z = 4.90 (P < 0.0001)

*The additional culture(s) was used to confirm levels of bacteriuria.

### 3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>No treatment or placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.4 One urine sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furness 1975</td>
<td>25</td>
<td>139</td>
<td>17</td>
<td>67</td>
<td>14.1%</td>
<td>0.05 (0.57, 1.14)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>139</td>
<td>139</td>
<td>100.0%</td>
<td>0.24</td>
<td>(0.13, 0.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>25</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.17; Chi² = 7.79, df = 1 (P = 0.0014); P = 59%
Test for overall effect: Z = 3.89 (P < 0.0001)
Test for subgroup differences: Chi² = 3.65, df = 1 (P = 0.05), P = 67.3%

---

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3.1.3 Pyelonephritis subgroup: duration of follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>No treatment or placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Weight</td>
<td>M.H. Random, 95% CI</td>
</tr>
<tr>
<td>Follow-up to delivery or peripuerum (≤6 weeks post delivery)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brummitt 1975</td>
<td>9</td>
<td>67</td>
<td>12.6%</td>
</tr>
<tr>
<td>Elder 1977</td>
<td>4</td>
<td>133</td>
<td>10.6%</td>
</tr>
<tr>
<td>Foley 1987</td>
<td>3</td>
<td>100</td>
<td>7.1%</td>
</tr>
<tr>
<td>Furness 1975</td>
<td>23</td>
<td>139</td>
<td>14.1%</td>
</tr>
<tr>
<td>Gold 1986</td>
<td>0</td>
<td>35</td>
<td>2.9%</td>
</tr>
<tr>
<td>Kozinet 2006</td>
<td>0</td>
<td>40</td>
<td>2.6%</td>
</tr>
<tr>
<td>Liang 1989</td>
<td>4</td>
<td>124</td>
<td>10.7%</td>
</tr>
<tr>
<td>Muller 1980</td>
<td>1</td>
<td>50</td>
<td>5.3%</td>
</tr>
<tr>
<td>Williams 1980</td>
<td>5</td>
<td>85</td>
<td>11.2%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>793</td>
<td>765</td>
<td>77.2%</td>
</tr>
<tr>
<td>Total events</td>
<td>49</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Tau² = 0.33; Chi² = 17.17, df = 8 (P = 0.03); I² = 53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 4.07 (P &lt; 0.0001)</td>
<td></td>
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</table>

3.5.3 Follow-up until > 6 weeks post delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>No treatment or placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Weight</td>
<td>M.H. Random, 95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauss 1969</td>
<td>1</td>
<td>83</td>
<td>5.4%</td>
</tr>
<tr>
<td>Khane-Cox 1966</td>
<td>2</td>
<td>51</td>
<td>3.6%</td>
</tr>
<tr>
<td>Patihic 1989</td>
<td>3</td>
<td>76</td>
<td>4.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>230</td>
<td>229</td>
<td>22.8%</td>
</tr>
<tr>
<td>Total events</td>
<td>6</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Tau² = 0.00; Chi² = 1.79, df = 2 (P = 0.41); I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 5.29 (P &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1823 994 100.0% 0.24 [0.13, 0.41] |
Total events 55 196 Heterogeneity Tau² = 0.49; Chi² = 27.89, df = 11 (P = 0.004); I² = 60% Test for overall effect Z = 5.09 (P < 0.0001) Test for subgroup differences: Chi² = 4.23, df = 1 (P = 0.04); I² = 76.4%
Author Contributions
LH, AW, JP, RF, MS, KS and BV critically reviewed and contributed to drafts of the report. AW, JP, MG, MS and KS conducted screening, quality assessments, data extraction and analysis. AW, JP, LH, MS, KS and BV contributed to interpretation of results. All of the authors approved the final version of this report.

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**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAFP</td>
<td>American Academy of Family Physicians</td>
</tr>
<tr>
<td>AAP</td>
<td>American Academy of Physicians</td>
</tr>
<tr>
<td>ACOG</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AMSTAR</td>
<td>Assessing the Methodological Quality of Systematic Reviews</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute Risk Reduction</td>
</tr>
<tr>
<td>ASB</td>
<td>Asymptomatic Bacteriuria</td>
</tr>
<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
</tr>
<tr>
<td>CCT</td>
<td>Controlled Clinical Trial</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony-Forming Units</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CTFPHC</td>
<td>Canadian Task Force on Preventive Healthcare</td>
</tr>
<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effects</td>
</tr>
<tr>
<td>EP</td>
<td>Evidence Profile</td>
</tr>
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<td>ES</td>
<td>Evidence Set</td>
</tr>
<tr>
<td>GBS</td>
<td>Group B Streptococcus</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>IDSOG</td>
<td>Infectious Diseases Society of Obstetrics and Gynecology</td>
</tr>
<tr>
<td>KQ</td>
<td>Key Question</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>NNS</td>
<td>Number Needed to Screen</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NOS</td>
<td>Newcastle-Ottawa Quality Assessment Scale</td>
</tr>
<tr>
<td>OIS</td>
<td>Optimal Information Size</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>PICOTS</td>
<td>Population, Intervention, Comparator, Timing and Setting</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PROSPERO</td>
<td>International Prospective Register of Systematic Reviews</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Year</td>
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<tr>
<td>RCT</td>
<td>Randomized Clinical Trial</td>
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<td>ROB</td>
<td>Risk of Bias</td>
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<td>RR</td>
<td>Risk Ratio</td>
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<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
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<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<td>SMFM</td>
<td>Society for Maternal-Fetal Medicine</td>
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<tr>
<td>SOF</td>
<td>Summary of Findings</td>
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<td>SOGC</td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
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<tr>
<td>USPSTF</td>
<td>US Preventive Services Task Force</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
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</tbody>
</table>
References

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Appendices

1. Summary of Study Characteristics - KQ1a & b
2. Summary of Characteristics of SR and Studies - KQ4
3. Characteristics of Included Studies – KQ1a & b
4. Characteristics of Included Studies – KQ2
5. Characteristics of Included Studies – KQ4
6. Quality Assessments for Included Studies – KQ1a & b
7. Quality Assessments for Included Studies – KQ2
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9. Search Strategies, Grey Literature
10. Excluded Studies – KQ1a & b
11. Excluded Studies – KQ2
12. Excluded Systematic Reviews – KQ4
13. Methods for Integrating Systematic Reviews
### Appendix 1. Summary of Study Characteristics – KQ1a & b: Benefits and harms of screening

<table>
<thead>
<tr>
<th>Study; Design; Setting</th>
<th>Sample</th>
<th>Population characteristics (risk factors of interest)</th>
<th>Screening timing, frequency &amp; details</th>
<th>Comparator</th>
<th>Treatment protocol</th>
<th>Definition of outcomes</th>
</tr>
</thead>
</table>
| Gérald 1983            |        | NR; all women screened vs. not screened (reason for screening NR) | All women 3, 5, 7 and 9 months Midstream with cleansing and culture (positive at ≥10^5 CFU/mL) | Screening with culture if clinical signs | • Treatment after sensitivity testing, but at discretion of physician  
• Follow-up confirmation of treatment effect NR | Acute pyelonephritis: Clinical signs (fever, lumbar pain, dysuria) and positive culture  
Spontaneous abortion: ≤28 weeks of gestation  
Perinatal mortality: “stillbirth” as either death in utero or during delivery, all ≥31 weeks of gestation  
Preterm delivery: <37 weeks of gestation |
| Gratacos 1994          |        | NR; all women seen at clinic <25 weeks of gestation and who delivered at study site | <25 weeks of gestation Assume 1 screen  
2 consecutive positive cultures of same species; midstream after cleansing | No routine screening (details NR) | • Offered 7-day course after sensitivity testing (70/77 ASB+ received)  
• Repeat culture 2X and treatment if positive | Acute pyelonephritis: fever, flank pain, tenderness in costovertebral angle, ≥1 positive culture |
| Rhode 2007             |        | All pregnant women receiving prenatal care at midwifery clinic (33% becoming ineligible based on risk factors/spontaneous abortion/preterm delivery) | First (mean 20 weeks) visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical | First (mean 20 weeks) visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical | ND | Pyelonephritis: ND; however, clearly differentiated from ASB, cystitis and undetermined UTI  
Preterm delivery: <37 weeks of gestation |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Funding</th>
<th>Population</th>
<th>Gestational Age</th>
<th>Urinary Test</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-based midwifery practice; USA</td>
<td></td>
<td>NR</td>
<td>Predominantly medically underserved and Hispanic women (72%)</td>
<td>GDM: routine 9% vs. indicated 4%</td>
<td>reagent strips, culture or urinalysis as indicated&lt;sup&gt;1&lt;/sup&gt;</td>
<td>one of the criteria was present (risk factors for UTI, GDM). Follow-up of culture or lab urinalysis as indicated&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Uncu 2001</td>
<td>Turkey</td>
<td>NR</td>
<td>All pregnant women ≤32 weeks of gestation</td>
<td>GDM: ~3%</td>
<td>First visit (&lt;32 weeks of gestation)</td>
<td>No screening with culture</td>
<td>ASB+ treated 7-10 days after sensitivity testing • Follow-up cultures 1 week post-treatment- 5/23 (22%) recurrence</td>
</tr>
</tbody>
</table>

ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; DM: diabetes mellitus; GDM: gestational diabetes mellitus; n: number; ND: no description; NR: not reported; USG: ultrasound/ultrasonography; UTI: urinary tract infection

<sup>1</sup>lab urinalysis may be used instead of culture due to presence of blood in urine; culture typically done to confirm reagent strip unless reagent strip was used to test for elevated blood pressure (information provided by study author)

<sup>2</sup>criteria for outcomes were confirmed by study author
### Appendix 2a. Summary of Characteristics of Systematic Review – KQ4: Benefits and harms of treatment

<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Population; No. of studies (no. of participants)</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Outcome(s)</th>
<th>Study Design</th>
<th>QA; Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaill 2015</td>
<td>Pregnant women found via antenatal screening to have asymptomatic bacteriuria, as defined by the study authors, at any stage of pregnancy 7 (1932)</td>
<td>Any antibiotic regimen</td>
<td>Placebo or no treatment</td>
<td>Primary: 1) Development of pyelonephritis 2) Preterm birth &lt;37 wks of gestation 3) Birthweight &lt;2500g Secondary: 1) Persistent bacteriuria (bacteriuria persisting to time of delivery) 2) Neonatal mortality or other serious adverse neonatal outcome 3) Maternal side effects 4) Costs, as defined by study authors 5) Birthweight 6) Gestational age 7) Women’s satisfaction, as measured by trial authors</td>
<td>RCTs and CCTs</td>
<td>Exclusion: Cross-over trials 1) Cochrane ROB tool for individual studies; and, 2) GRADE approach for the quality of the body of evidence – for primary outcomes</td>
</tr>
</tbody>
</table>

* Studies included in the Cochrane Review (Smaill 2015)

CCT: controlled clinical trial; g: gram(s); GRADE: Grading of Recommendations Assessment, Development and Evaluation; QA: quality assessment; RCT: randomised controlled trial; ROB: Risk of Bias; wks: weeks
### Appendix 2b. Summary of Study Characteristics – KQ4: Benefits and harms of treatment

<table>
<thead>
<tr>
<th>Study; Design; Setting; Funding</th>
<th>Sample</th>
<th>Population characteristics (risk factors of interest)</th>
<th>Screening &amp; Treatment details</th>
<th>Comparator details</th>
<th>Definition of outcomes</th>
<th>ROB (overall)</th>
</tr>
</thead>
</table>
| **Brumfitt 1975** (Partial data obtained from Condie 1968 & Williams, 1968, preliminary reports) | Treated: 247, Not treated/placebo-treated: 179 | • Patients attending the antenatal clinics for the first time.  
• Asian or West Indian: treatment 20.8%, placebo 14.1%  
• No difference in SES between groups  
Excluded home delivery, abortions, treatment before confirmation of ASB, other complicating factors. | **Screening test:** clean-catch x 2; microbiological criteria NR  
**Treatment:** sulphonamide  
**Follow-up:** until delivery  
**Persistent bacteriuria:** subset of treated women (n=87) retested after 1-2 courses of treatment (as applicable) | Placebo | Pyelonephritis: presence of loin pain and tenderness together with a temperature of ≥100 degrees F and >10⁵ CFU/mL  
Prematurity*: ≤2500g | High |
| **Elder 1966** | Treated: 54, Not treated: 52 | • Patients registering at the outpatient department for antenatal care; ≤32 wks GA.  
Excluded those too advanced in pregnancy, included in other bacteriuria studies, given treatment in error, or who moved away. | **Screening test:** clean-voided x 3; ≥10⁴ CFU/mL of same organism in one sample and ≥10⁵ CFU/mL in the other two samples  
**Treatment:** sulfasymazine, nitrofurantoin  
**Follow-up:** until delivery  
**Persistent bacteriuria:** retested after 1 wk of | Placebo | **No relevant results reported (pyelonephritis reported only for the placebo group; some non-serious adverse events) – Smaill included this study for persistent bacteriuria outcome | High |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Screening test</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Pyelonephritis</th>
<th>Perinatal mortality</th>
<th>Prematurity*</th>
<th>Infant respiratory distress</th>
</tr>
</thead>
</table>
| Elder 1971   | Quasi-RCT; 4 groups; some patients may have participated for >1 pregnancy | 133 | 148 | • Prenatal care, ≤32 wks GA.  
• Non-white: treatment 66.2%, placebo 54.7%  
• Previous UTI: treatment 35.9%, placebo 40.1%  
Excluded those treated for UTI prior to first obstetric visit, >32 wks GA, had delivered or had aborted before the first obstetric visit, went elsewhere for prenatal care, delivered twins: | Placebo | Pyelonephritis: temperature of ≥100 degrees F with signs and symptoms localized to the urinary tract and not otherwise explained  
Perinatal mortality: stillbirth or neonatal death prior to hospital discharge  
Prematurity*: ≤2500g  
Infant respiratory distress: respiratory distress syndrome and other causes of 'respiratory embarrassment' | High |
<p>| Foley 1987   | RCT | 100 | 120 | • First antenatal visit. | No treatment | Pyelonephritis: ND; 'admitted with pyelonephritis' | High |
| Furness 1975 | RCT; 3 groups | 139 | 67 | • Second antenatal visit. | No treatment | Pyelonephritis: frequency and burning on micturition | High |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Funded</th>
<th>Type</th>
<th>Subjects</th>
<th>Inclusion Criteria</th>
<th>Screening Test</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Persistent Bacteriuria</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queen Victoria Hospital, Adelaide, Australia</td>
<td>Industry and non-industry funded</td>
<td></td>
<td></td>
<td></td>
<td>Treatment: methenamine mandelate, methenamine hippurate</td>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Persistent bacteriuria: retested for postnatal bacteriuria at 6 wks post-partum (excludes those who developed pyelonephritis)</td>
<td>accompanied by pyrexia or loin tenderness, with presence of a significant number of bacteria in urine</td>
<td>Spontaneous abortion: ND; ‘abortions’</td>
<td>Fetal abnormalities: major fetal abnormality (anencephaly)</td>
</tr>
<tr>
<td>Gold 1966</td>
<td>Quasi-RCT (odd and even number assignment)</td>
<td>Non-industry funded</td>
<td></td>
<td></td>
<td>Prenatal visit. 85% nonwhite, 6% Puerto Rican, 9% other white</td>
<td>MSU x2; &gt;10^5 CFU/mL</td>
<td>Sulfadimethoxine, sulfadiazine</td>
<td>Follow-up: until the 'post-partum period' (exact time ND)</td>
<td>Persistent bacteriuria: retested at each clinic visit until delivery (either for initial diagnosis or persistent bacteriuria); persistent bacteriuria defined as at delivery</td>
<td>Pyelonephritis: ND</td>
</tr>
<tr>
<td>Kass 1960</td>
<td>(data obtained from updated report: Savage, 1967)</td>
<td></td>
<td></td>
<td></td>
<td>First prenatal visit (registration); &lt;32 wks GA</td>
<td>MSU x2; first prenatal visit with 10^3-10^5 CFU/mL, followed by 10^6 CFU/mL in 2 cultures of the same organism</td>
<td>Placebo</td>
<td>Pyelonephritis: dysuria, frequency, and flank pain or other localizing evidence of inflammation, with either documented High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quasi-RCT, double-blind, some patients participated for >1 pregnancy; 4 groups
Boston City Hospital, USA
Non-industry funded

<table>
<thead>
<tr>
<th>Kazemier 2015</th>
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</thead>
<tbody>
<tr>
<td>Cohort (screening vs. no screening), with embedded RCT</td>
<td></td>
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<tr>
<td>40</td>
<td>45 placebo; 163 untreated</td>
<td></td>
</tr>
</tbody>
</table>

- About 50% of the treated population and slightly <50% of placebo population is Black
- Diabetes: 2 (group distribution NR)
- History of UTI: ~15% (group distribution NR)
- 2 bacteriuric women with cesarean section had uterine abnormalities; prevalence in remaining population NR

Excluded those >32 wks GA, with chronic renal insufficiency, given treatment in error, without further prenatal care, whose records were inadequate or unobtainable, urine samples were contaminated, were unable to void or found to not be pregnant.

| Treatment: | sulphamethoxypyridazine, nitrofurantoin | | |
| --- | --- | --- | |
| Follow-up: | until the post-delivery period and up to 12 months postpartum; records reviewed 3-4 years later | | |

Persistent bacteriuria: Treated patients retested within the 4 wks preceding delivery. A subset of women retested at 3-12 months postpartum (Kass, 1960)

Perinatal mortality: 'perinatal death' and loss >20 wks

Prematurity*: <2500g
<table>
<thead>
<tr>
<th>Kincaid-Smith 1965</th>
<th>61</th>
<th>56</th>
</tr>
</thead>
</table>
| **RCT, “double-blind”** | **First antenatal visit at <26 wks GA**  
  All from lowest income category in community | **Screening:** MSU x 2; $>10^5$ CFU/mL  
  **Treatment:**  
  sulphamethoxydiazine, sulphadimidine, ampicillin, nitrofurantoin | **Placebo**  
  **Pyelonephritis:** loin pain and tenderness, with or without pyrexia, and rigors, with or without symptoms of dysuria and frequency  
  **Prematurity***: fetal weight <2500g (“many | **Unclear** |

- ≥18yrs, singleton pregnancy at 16-22 wks GA (median GA 20 wks at screening)
- Asymptomatic (all)
- Non-white participants: 3 (8%) treated vs. 36 (17%) placebo/untreated
- Low education (≤pre-vocational): 6 (15%) treated vs. 21 (10%) placebo/untreated

Excluded women with history or high risk of preterm delivery, fetal congenital malformations, antibiotic use within 2 wks of screening, glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI

*screening not routinely available to women outside of study

**Treatment:** nitrofurantoin

**Follow-up:** until 6 wks post-delivery

**Persistent bacteriuria:** Retested after the first round of treatment. This was repeated for a maximum of two rounds.

- vomiting, chills, costovertebral tenderness) and positive urine culture for bacteria

**Neonatal sepsis:** confirmed with culture

**Preterm birth:** spontaneous 32-37 wks GA

**Low birth weight:** <10th or 5th percentile

**Perinatal mortality:** neonatal death before discharge

**Congenital abnormalities:** ND

8 hospitals and 5 ultrasound centres, Netherlands
Non-industry funded

Non-white participants: 3 (8%) treated vs. 36 (17%) placebo/untreated

Low education (≤pre-vocational): 6 (15%) treated vs. 21 (10%) placebo/untreated

Excluded women with history or high risk of preterm delivery, fetal congenital malformations, antibiotic use within 2 wks of screening, glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI

**Screening** not routinely available to women outside of study

**Treatment:** nitrofurantoin

**Follow-up:** until 6 wks post-delivery

**Persistent bacteriuria:** Retested after the first round of treatment. This was repeated for a maximum of two rounds.

- vomiting, chills, costovertebral tenderness) and positive urine culture for bacteria

**Neonatal sepsis:** confirmed with culture

**Preterm birth:** spontaneous 32-37 wks GA

**Low birth weight:** <10th or 5th percentile

**Perinatal mortality:** neonatal death before discharge

**Congenital abnormalities:** ND
<table>
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<th>Industry and non-industry funded</th>
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<tr>
<td>&gt;50% patients had radiological renal abnormalities</td>
<td>&gt;50% patients had radiological renal abnormalities</td>
<td>&gt;50% patients had radiological renal abnormalities</td>
<td>&gt;50% patients had radiological renal abnormalities</td>
<td>&gt;50% patients had radiological renal abnormalities</td>
<td>&gt;50% patients had radiological renal abnormalities</td>
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<td>5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction</td>
<td>5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction</td>
<td>5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction</td>
<td>5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction</td>
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<td>5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction</td>
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<td>Follow-up: until 6 months post-delivery</td>
<td>Follow-up: until 6 months post-delivery</td>
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<td>Follow-up: until 6 months post-delivery</td>
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<td>Follow-up: until 6 months post-delivery</td>
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<tr>
<td>Persistent bacteriuria: Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum</td>
<td>Persistent bacteriuria: Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum</td>
<td>Persistent bacteriuria: Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum</td>
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<td>Persistent bacteriuria: Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum</td>
<td>Persistent bacteriuria: Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum</td>
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<td>babies born after the 36th wk of gestation“</td>
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<td>babies born after the 36th wk of gestation“</td>
<td>babies born after the 36th wk of gestation“</td>
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<td>First antenatal visit</td>
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<td>First antenatal visit</td>
<td>First antenatal visit</td>
<td>First antenatal visit</td>
</tr>
<tr>
<td>Past history of renal-tract disease: 62 (23.4%) with bacteriuria</td>
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</tr>
<tr>
<td>Screening: MSU x 2; &gt;10⁵ CFU/mL</td>
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<td>Screening: MSU x 2; &gt;10⁵ CFU/mL</td>
</tr>
<tr>
<td>Treatment: sulphonmethoxypyridazine, nitrofurantoin, ampicillin</td>
<td>Treatment: sulphonmethoxypyridazine, nitrofurantoin, ampicillin</td>
<td>Treatment: sulphonmethoxypyridazine, nitrofurantoin, ampicillin</td>
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<tr>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Follow-up: until 6 wks post-delivery</td>
<td>Follow-up: until 6 wks post-delivery</td>
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<tr>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
<td>Persistent bacteriuria: Treatment group retested monthly until delivery</td>
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<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
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<tr>
<td>Pyelonephritis: loin pain and tenderness, a fever &gt;100 degrees F, &gt;10⁵ CFU/mL, and often frequency, dysuria, rigors and hematuria</td>
<td>Pyelonephritis: loin pain and tenderness, a fever &gt;100 degrees F, &gt;10⁵ CFU/mL, and often frequency, dysuria, rigors and hematuria</td>
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</tr>
<tr>
<td>Prematurity*: birth weight &lt;2500g</td>
<td>Prematurity*: birth weight &lt;2500g</td>
<td>Prematurity*: birth weight &lt;2500g</td>
<td>Prematurity*: birth weight &lt;2500g</td>
<td>Prematurity*: birth weight &lt;2500g</td>
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<tr>
<td>Fetal abnormalities: ND</td>
<td>Fetal abnormalities: ND</td>
<td>Fetal abnormalities: ND</td>
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<td>St. Elizabeth Hospital, Ohio, USA</td>
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<td>Funding not reported</td>
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<td>30-32 wks GA</td>
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<tr>
<td>Screening: culture, microbiological criteria NR</td>
<td>Screening: culture, microbiological criteria NR</td>
<td>Screening: culture, microbiological criteria NR</td>
<td>Screening: culture, microbiological criteria NR</td>
<td>Screening: culture, microbiological criteria NR</td>
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<tr>
<td>Treatment: sulfadimethoxine</td>
<td>Treatment: sulfadimethoxine</td>
<td>Treatment: sulfadimethoxine</td>
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<td>Treatment: sulfadimethoxine</td>
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<tr>
<td>Follow-up: to delivery and immediately after</td>
<td>Follow-up: to delivery and immediately after</td>
<td>Follow-up: to delivery and immediately after</td>
<td>Follow-up: to delivery and immediately after</td>
<td>Follow-up: to delivery and immediately after</td>
<td>Follow-up: to delivery and immediately after</td>
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<tr>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
<td>Persistent bacteriuria: Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment</td>
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<tr>
<td>No treatment</td>
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<tr>
<td>Pyelonephritis: Clinical evidence of active infection, including acute symptoms of cystopyelitis and premature labour that subsided with treatment; urine was tested</td>
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<td><strong>Pathak 1969</strong></td>
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<tr>
<td>RCT</td>
<td></td>
<td>University College Hospital and Kingston Public Hospital, Jamaica</td>
<td>Industry and non-industry funded</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≤24 wks GA</td>
<td>Screening: clean-voided x 2; &gt;10^2 CFU/mL</td>
<td>Placebo</td>
<td>Pyelonephritis: ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 18/84 (21.4%) ASB+ positive for sickle-cell trait (“sickling”), had approx. twice rate of bacteriuria as patients without trait</td>
<td>Treatment: nitrofurantoin</td>
<td>Preterm delivery: &lt;37 wks GA (mean 39.6 wks GA treated vs. 36.2 wks GA placebo-treated)</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On postpartum intravenous pyelogram:</td>
<td>Follow-up: until 9 months post-delivery (bacteriuria)</td>
<td>Neonatal sepsis: ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 9/50 (18%) patients had radiological renal abnormalities; however, no major differences between groups for developing pyelonephritis</td>
<td>Persistent bacteriuria: Retested weekly during treatment, then every 2 wks until delivery, and at 3-9 months postpartum</td>
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<tr>
<td></td>
<td></td>
<td>Excluded women &gt;24 wks GA, or with blood pressure &gt;130 mmHg, did not re-attend the clinic, early abortions (6/217), clinical pyelonephritis (9/217), ’mentally defective’</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| **Thomsen 1987** | | | | | |
| RCT, “double-blind” |        | 27-31 wks GA | Screening: MSU x 1; 10^2-10^6 CFU/mL (group B streptococci) | Placebo | Preterm delivery: <37 wks GA (mean 39.6 wks GA treated vs. 36.2 wks GA placebo-treated) |
| University Hospital, Denmark |        | Screening for Group B streptococci | Treatment: penicillin | | Neonatal sepsis: ND |
| Industry-funded |        | All patients White | Follow-up: until delivery (one infant found to have group-B streptococcal sepsis at 6 wks post-delivery) | | Unclear |
| Study | Year | RCT | Hospital/Location | Funding | 85 | 78 | Persistent bacteriuria: Retested weekly until delivery | Screening | Treatment | Follow-up | Persistent bacteriuria: Treatment group retested 2-3 wks after the first course of treatment, and each subsequent course of treatment | No treatment | Pyelonephritis: loin pain with tenderness, with or without fever | Prematurity*: birth weight <2501g | Perinatal mortality: stillbirths and neonatal deaths | Spontaneous abortion: ND | Preterm delivery: <37 wks GA | High |
|-------|------|-----|-------------------|---------|----|----|--------------------------------------------------|----------|-----------|-----------|---------------------------------------------------------------|-------------|---------------------------------------------------------------|---------------------|---------------------------------------------------------------|-------------------|---------------------------------------------------------------|-------------------|---------------------|
| Williams 1969 | 1969 | RCT | Maternity Hospital and St. David’s Hospital, Wales, England | Non-industry funded | 85 | 78 | • First antenatal visit<br>• <30 wks GA | MSU x 2; >10⁵ CFU/mL | Sulphadimidine, ampicillin, nitrofurantoin | until 10 days post-delivery | No treatment | | | | |
| Wren 1969 | 1969 | Quasi-RCT (alternation) | Royal Hospital for Women, New South Wales, Australia | Industry-funded | 83 | 90 | • First antenatal visit | MSU x 2; microbiological criteria NR | Nitrofurantoin, ampicillin, sulphurazole, nalidixic acid | until up to 6 wks post-delivery | No treatment | | | | | | | | | | | | | | | | | |
Prematurity defined by study authors as low birth weight; data will be used for low birth weight only
### Appendix 3. Characteristics of Included Studies - KQ1a & b: Benefits and harms of screening

<table>
<thead>
<tr>
<th><strong>Gérard, Blazquez &amp; Mounac, 1983</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td>To determine if a routine screening program for ASB can reduce the incidence of pyelonephritis and other adverse pregnancy outcomes, and if such a program would be economically feasible</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td>Design: Non-concurrent cohort</td>
</tr>
<tr>
<td>Inclusion criteria: All pregnant women followed at the Centre Hospitalier de Corbeil-Essonnes (prospective). Controls were all women who were not involved in the screening program (retrospective).</td>
</tr>
<tr>
<td>Exclusion criteria: NR</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td>Setting: Centre Hospitalier de Corbeil-Essonnes (a Hospital)</td>
</tr>
<tr>
<td>Study period: January-October 1979 (and 10 previous months for the control group)</td>
</tr>
<tr>
<td>Sample: n=370 pregnant women; n=170 in study group; n=200 in control group</td>
</tr>
<tr>
<td>Mean age, y (SD): NR</td>
</tr>
<tr>
<td>Risk factors: NR</td>
</tr>
<tr>
<td>Length of follow-up: until delivery, and for 3-6 months after in those with ≥2 instances of ASB; loss to follow-up: n=0.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td>Implementation of a routine screening and treatment program for ASB:</td>
</tr>
<tr>
<td>1) Screening of all women at 3, 5, 7 and 9 months of pregnancy, and treatment of those diagnosed with ASB</td>
</tr>
<tr>
<td>2) Controls only screened after presenting with clinical signs</td>
</tr>
<tr>
<td>Urine testing characteristics:</td>
</tr>
<tr>
<td>Urine collection: Midstream urine sample with cleansing of the vulva before micturition</td>
</tr>
<tr>
<td>Urine testing: Microscopy, urine culture and Gram staining</td>
</tr>
<tr>
<td>Criteria for positive test: ≥10⁵ CFU/mL</td>
</tr>
<tr>
<td>Gestational age (weeks) at first prenatal visit: ~3 months for the treatment group; NR for the control group</td>
</tr>
<tr>
<td>Number of prenatal visits: at least 4 (every 2 months) for the treatment group; NR for control group</td>
</tr>
<tr>
<td>Treatment: Treatment based on antibiotic sensitivity and at the discretion of the prescribing physician</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>Acute pyelonephritis: Clinical signs (fever, lumbar pain, dysuria, pollakiuria (urinary frequency)) and positive urine culture of 10⁵ CFU/mL</td>
</tr>
<tr>
<td>Spontaneous abortion: ≤28 wks GA</td>
</tr>
<tr>
<td>Preterm delivery: Delivery at &lt;37 wks GA</td>
</tr>
<tr>
<td>Birth weight: Reported means for ASB vs. non-ASB in study group; symptomatic + positive culture vs. asymptomatic in controls</td>
</tr>
<tr>
<td>Perinatal mortality: “stillbirth” as either death in utero or during delivery, all ≥31 wks GA</td>
</tr>
<tr>
<td>Adverse event(s): NR</td>
</tr>
</tbody>
</table>
### Notes
Study is descriptive, no between-group associations tested

ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; GA: gestational age; n: number; NR: not reported; SD: standard deviation; wks: weeks; y: year

### Gratacós et al., 1994

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To determine the incidence of pyelonephritis in pregnant women before and after the introduction of a screening program for ASB</th>
</tr>
</thead>
</table>
| **Methods**   | Design: Non-concurrent cohort  
Inclusion criteria: Study group were women who were seen at the clinic at <25 wks GA who subsequently delivered January 1991-December 1992. Controls were women who were seen at the clinic at <25 wks GA and delivered January 1987-December 1990.  
Exclusion criteria: NR |
| **Participants** | Setting: An obstetrics clinic in Barcelona, Spain  
Sample: n=4,917 pregnant women; n=1,652 in study group, n=3,265 in control group  
Mean age, y (SD): NR  
Risk factors: NR  
Length of follow-up: until delivery; loss to follow-up: n=10 |
| **Interventions** | Implementation of a routine screening and treatment program for ASB:  
1) Screening of all women <25 wks pregnant and treatment of those diagnosed with ASB  
2) Controls: no routine screening  
Urine testing characteristics:  
Urine collection: Midstream morning urine sample. Women with positive culture returned within 1-2 wks for a second midstream urine culture, after stressing the importance of cleansing the vulva before micturition.  
Urine testing: Urine culture following the guidelines of the National Committee for Clinical Laboratory Standards  
Criteria for positive test: Two consecutive positive urine cultures (number of organisms NR) with growth of the same species  
Gestational age (wks), at first prenatal visit: <25  
Number of prenatal visits: study group: NR; controls: NR  
Treatment: 7-day course of antibiotics based on antibiotic sensitivity testing, started 1-2 wks after the second culture. At 1-4 wks after treatment and at least once more before delivery, additional midstream urine samples were obtained. If repeat cultures were positive, antibacterial therapy was repeated until cultures were negative for ASB. |
| **Outcomes** | Pyelonephritis: fever, flank pain, tenderness in costovertebral angle, ≥1 positive culture  
Adverse event(s): NR |
Rhode, 2007

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To determine if urinary tract infection, high blood pressure, and gestational diabetes mellitus are underdiagnosed when prenatal urine testing is done on a clinically indicated basis versus a routine basis</th>
</tr>
</thead>
</table>
| **Methods**   | Design: Non-concurrent cohort  
Inclusion criteria: Routine screening group were all pregnant women who enrolled for care and delivered before August 15, 2002. Indicated screening group were all women who enrolled for care and delivered after August 15, 2002.  
Exclusion criteria: Women who were in the transitional urine screening group (enrollment prior to and delivery after August 15, 2002), who received both screening techniques (n=570) |
| **Participants** | Setting: Hospital-based nurse-midwifery practice, Aurora, Colorado; provides care to predominantly medically underserved and Hispanic women  
Study period: Charts of patients enrolled for care and delivered November 2000-March 2004  
Sample: n= 1,952 pregnant women; n=933 in routine screening group; n=1019 in indicated screening group  
Mean age, y (SD): Routine screening= 24.4 (5.6); Indicated screening= 24.9 (5.1)  
Risk factors:  
Gestational diabetes: routine screening=81 (9.3%), indicated screening=42 (4.2%)  
Race (ethnicity): Hispanic; routine screening=669 (72.1%), indicated screening=783 (76.9%)  
Length of follow-up: until delivery or patient left the practice; loss to follow-up (n=112; 4.6%); total ineligible=459 (19%), due to: spontaneous abortion (n=58), transfer of care (n=218), transfer to high risk care (n=71) |
| **Interventions** | Routine urine screening (enrollment and delivery before August 15, 2002): first visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent strips, culture or urinalysis as indicated¹  
Indicated urine screening (enrollment on and delivery after August 15, 2002): first visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent strip only if one of the criteria was present (risk factors for UTI, GDM). Follow-up of culture or lab urinalysis as indicated¹  
Urine testing characteristics:  
Urine collection: midstream morning urine sample, first visit  
Urine testing: chemical reagent strip test, lab urinalysis and culture;  
Mean number of strip tests performed (SD): Routine screening= 7.8 (3.4), range 0-19; Indicated screening= 1.4 (1.3), range 0-16  
Criteria for positive test: NR |

Notes: Also investigated prevalence of ASB and response to treatment in the study group, but this was not compared to the controls who did not receive routine screening

ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; wks: weeks; y: year(s)
<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine the incidence of asymptomatic bacteriuria during pregnancy and its relation to pregnancy complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Design: Non-concurrent cohort</td>
</tr>
<tr>
<td>Inclusion criteria: Screened group were pregnant women ≤32 wks GA seen at the antenatal outpatient clinic. Controls were women who delivered in clinic before study and were not screened for ASB; formed in retrospective manner from first day of study</td>
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<tr>
<td>Exclusion criteria: Patients who were followed-up at clinic due to prior renal disease, positive for ASB or were taking antibiotics</td>
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<tr>
<td>Participants</td>
<td>Setting: Antenatal outpatient clinic, Uludag University Faculty of Medicine, Department of Obstetrics and Gynecology, Turkey</td>
</tr>
<tr>
<td>Study period: June 1998-January 1999</td>
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<tr>
<td>Sample: Screened= 186; Controls= 186</td>
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<tr>
<td>Mean age, y (SD): Screened= 27.7 (5.1); Controls= 27.7 (4.6)</td>
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<tr>
<td>Risk factors: Gestational diabetes mellitus: Screened=7 (3.8%); Controls= 5 (2.7%) Socioeconomic status: lower SES correlated with high prevalence of ASB*</td>
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<tr>
<td>Length of follow-up: NR; loss to follow-up: NR</td>
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<tr>
<td>Interventions</td>
<td>Determine incidence of asymptomatic bacteriuria during pregnancy and relation to pregnancy complications: 1) Screening group: All pregnant women routinely screened at first visit with whole blood count, total urine analysis and urine culture. 2) Controls: Formed in a retrospective manner from the first day of the study with pregnant women who delivered in the clinic and who were not routinely screened.</td>
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<tr>
<td><strong>Urine testing characteristics:</strong></td>
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<tr>
<td>Urine collection: midstream morning urine sample, first visit</td>
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<tr>
<td>Urine testing: whole blood count, total urine analysis, and urine culture</td>
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<tr>
<td>Criteria for positive test: &gt;10⁵ CFU/mL of the same organism</td>
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<tr>
<td>Gestational age (wks), at time of urine culture: beginning of pregnancy</td>
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<tr>
<td>Number of prenatal visits: NR</td>
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<tr>
<td>Treatment: n=23 [7-10 days of antibiotics, Follow-up 7-days of antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)</td>
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</table>

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<thead>
<tr>
<th><strong>Outcomes</strong></th>
<th>Pyelonephritis: ND</th>
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</thead>
<tbody>
<tr>
<td>Intrauterine death²: no fetal cardiac activity by USG, after 20 weeks’ gestation</td>
<td></td>
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<tr>
<td>Prematurity²: &lt;37 wks of gestation</td>
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<tr>
<td>Adverse event(s): NR</td>
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<tr>
<td>Fetal abnormalities: ND</td>
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</tbody>
</table>

| **Notes** | Total screened for ASB=270 → with urine cultures=247 → sufficient delivery records=186 (61 excluded) |

*statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: gestational age; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrasonography; wks: weeks; y: year(s) |
² Criteria for outcomes were confirmed by study author(s)
### Appendix 4. Characteristics of Included Studies – KQ2: Women’s outcome valuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Objective</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butters, 1990</td>
<td>Awareness among pregnant women of the effect on the fetus of commonly used drugs</td>
<td>To determine the level of knowledge of the effects of commonly used drugs on a fetus</td>
<td>Design: Cross-sectional (self-completed questionnaire) &lt;br&gt;Recruitment: Participants were recruited from postnatal wards of the hospitals on a weekly basis</td>
<td>Setting: Two maternity hospitals: one serves a white urban and semirural population, the other serves a wider population mix from rural to urban and includes ethnic minorities. Both are located in Glasgow, Scotland. &lt;br&gt;Inclusion criteria: Postnatal women who were still in hospital after delivering. They had to be given the questionnaire in person (i.e. they were either in their bed or in the sitting room when the questionnaire was distributed). &lt;br&gt;Exclusion criteria: Women who had vaginal delivery on the day of the study, women one or two days post-delivery by caesarean section, and women who were unable to read English.</td>
<td>Anonymous short questionnaire with mostly tick boxes.</td>
<td>-254 (49%) said they would take an antibiotic prescribed by their doctor, 246 (48%) said they would not, and 14 (3%) did not respond. &lt;br&gt;-The responses were similar for all ages and social class groups. &lt;br&gt;-There was a strong relationship between the women that would avoid taking an analgesic (n=80, 74%) and those that would avoid taking an antibiotic (187, 45%), p&lt;0.0001.</td>
</tr>
<tr>
<td>Kazemier, 2015</td>
<td>Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomized controlled trial</td>
<td>To investigate the consequences of treated and untreated ASB in pregnancy</td>
<td>Design: Prospective cohort (screening vs. no screening) with embedded RCT (decision on entry into the study considered cross-sectional) &lt;br&gt;Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available)</td>
<td>Setting: 8 hospitals and 5 ultrasound centres, the Netherlands</td>
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</tbody>
</table>
dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI (e.g., pre-gestational DM, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract).

Study period: October 11, 2011-August 22, 2014

Sample: n=248

Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)

Gestational age (wks + days at screening (SE)): treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)

Parity (% nulliparous): treated=50%, placebo or untreated=42%

Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)

Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (10%)

Interventions

Women who were positive for ASB were invited to participate in a treatment RCT. Reasons for declining participation were recorded.

Outcomes

Most women (155/163 positive for ASB, 94%) who did not want to participate made this choice because they did not want to receive antibiotics during pregnancy for an asymptomatic condition.

ASB: asymptomatic bacteriuria; DM: diabetes mellitus; GA: gestational age; NA: not applicable; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

Lupattelli, 2014

Health literacy and its association with perception of teratogenic risks and health behavior during pregnancy

Objective

To investigate the association between health literacy and perception of medication risk, beliefs about medications, use and non-adherence to prescribed pharmacotherapy during pregnancy.

Methods

Design: Cross-sectional internet-based questionnaire

Recruitment: Banners announcing the study were placed on one to four websites per country and/or social networks commonly visited by pregnant women that had a high number of daily users.

Participants

Setting: Anonymous internet questionnaire with participants from 18 countries: Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, The Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and United States as well as some South American countries.

Inclusion criteria: Pregnant women at any stage of gestation.

Exclusion criteria: Women who were not currently pregnant.

Study period: October 1 2011 to February 29, 2012

Sample: n=4999

Mean age (SD): NR overall

Gestational age in weeks, mean (SD): 22.4 (10.3)

Race/ethnicity: Multinational

Interventions

Health literacy was measured using a self-assessment scale of 0 to 4 for three questions. Perceived risk of medications was measured using 13 agents on a scale of 0 to 10. Beliefs about medications were measured using a 5-point agreement scale for three questions. Participants were asked standardized questions about medication use for specific illnesses, non-adherence and over-the-counter medication use with free text entry.

Outcomes

-96.2% of participants felt penicillin antibiotics posed a teratogenic risk.

NR: not reported; SD: standard deviation
| **Mashayekhi, 2009**  
*Study of awareness among pregnant women of the effects of drugs on the fetus and mother in Iran* |
<table>
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</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods** | Design: Cross sectional, questionnaire  
Recruitment: Women in the postnatal and prenatal wards were invited. |
| **Participants** | Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.  
Inclusion criteria: Antenatal and postnatal women.  
Exclusion criteria: Women who had a complicated labor.  
Study period: August 2006 and May 2007  
Sample: n=400  
Median age (SD or SE), range: 26 (4.90), 15 to 44 years  
Gestational age: NA  
Gravidiy: None – 183 (45.8%), one – 118 (29.5%), two – 69 (17.3%), more than two – 30 (7.5%)  
Parity: None – 200 (50.0%), one – 127 (31.8%), two (54, 13.5%), more than two – 19 (4.8%)  
Race/ethnicity: Iranian  
Education level: High school or lower – 184 (46.0%), diploma – 147 (36.8%), University education – 69 (17.3%) |
| **Interventions** | Face-to-face questionnaire divided into three sections: demographic information, drug use before and during pregnancy including drug safety, source of information regarding drugs safety during pregnancy. Majority of response options were tick boxes. |
| **Outcomes** | - Specific antibiotics the women felt were safe: penicillin – 51 (12.8%), ampicillin – 36 (9.0%), amoxicillin – 66 (16.5%), metronidazole - 20 (5.0%), cephalosporin - 10 (2.5%), other antibiotics - 6 (1.5%).  
- For penicillin use none felt it was unsafe for the mother, 143 (35.8%) felt it was unsafe for the fetus, 40 (10.0%) felt it was unsafe for both.  
- For ampicillin use 4 (1.0%) felt it was unsafe for the mother, 145 (36.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both.  
- For amoxicillin use 5 (1.3%) felt it was unsafe for the mother, 147 (36.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.  
- For metronidazole use none felt it was unsafe for the mother, 129 (32.3%) felt it was unsafe for the fetus, 21 (5.3%) felt it was unsafe for both.  
- For cephalosporin use none felt it was unsafe for the mother, 127 (31.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.  
- For other antibiotic use none felt it was unsafe for the mother, 125 (31.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both. |

NA: not applicable; SE: standard error; SD: standard deviation

| **Nordeng, 2010**  
*Perception of risk regarding the use of medications and other exposures during pregnancy* |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods** | Design: Retrospective web-based questionnaire  
Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers. |
### Participants

**Setting:** Internet  
**Inclusion criteria:** Pregnant woman or a mother of a child less than 5 years old.  
**Exclusion criteria:** NR  
**Study period:** September 16, 2008 to October 25, 2008  
**Sample:** n=1793; 866 (48.3%) pregnant, 927 (51.7%) mothers  
**Mean age (median, range):** 30, 17 to 45 years  
**Gestational age:** NR  
**Parity:** primiparous – 689 (38.4%), one or more previous children – 1104 (61.6%)  
**Race/ethnicity:** Norwegian  
**Education level:** Basic school level – 88 (4.9%), upper secondary education – 390 (21.8%), tertiary education (<4 years) – 810 (45.2%), tertiary education (>4 years) – 421 (23.5%), other education – 84 (4.7%)  

### Interventions

Questionnaire consisted of open-ended questions and numeric rating scales from 0 to 10 relating to teratogenic risk of 17 drugs, foods, chemicals and radiation.

### Outcomes

- There was a significant difference in mean risk perception scores between non-users of the indicated drugs and users of 4.3 vs. 3.0 (p<0.001) with a ratio between non-users/users of 1.4.

NR: not reported

---

### Sanz, 2001  
**Perception of teratogenic risk of common medicines**

### Objective

To assess the perception of the teratogenic risk of common medication by professionals and the public

### Methods

**Design:** Cross-sectional  
**Recruitment:** Pregnant women attending a regular obstetric follow up in an out-patient clinic at a University hospital; non-pregnant women from an obstetric and gynecological out-patient clinic in the hospital and in a randomized manner from four different neighborhoods. Medical staff (general physicians, gynecologists and medical students were also recruited and interviewed, their data are not included here).

### Participants

**Setting:** Outpatient clinic at a University hospital, home setting  
**Inclusion criteria:**  
Currently pregnant for the pregnant women group, not pregnant for the comparison group  
**Exclusion criteria:** NR  
**Study period:** NR  
**Sample:** n=81 pregnant women, n=63 non-pregnant women  
**Median age:** NR  
**Gestational age:** NR  
**Gravidity:** NR  
**Parity:** NR  
**Race/ethnicity:** Spanish
**Interventions**

A visual analogue scale with a 10 cm horizontal line with a short vertical line at each end, with a scale of 0 to 100%. Participants were asked to mark on the scale what they thought was the potential risk for fetal malformations and malformations in non-pregnant women given exposure to a particular drug.

**Outcomes**

- The mean value of the perceived teratogenic risk by non-pregnant women was higher than that perceived by pregnant women for erythromycin (55.6 vs. 38.7) but not amoxicillin (49.3 vs. 40.4) (Mann-Whitney U Test).
- The median value of the perceived teratogenic risk by non-pregnant women was higher than that perceived by pregnant women for erythromycin (50.0 vs. 30.0) but not amoxicillin (50.5 vs. 34.0) (Mann-Whitney U Test).
- In comparison to the “true” limits, risk from antibiotics was rated higher by pregnant women (erythromycin chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).

---

**Sharma, 2006**

**Drug utilization pattern during pregnancy in North India**

**Objective**

To evaluate the drug utilization pattern in pregnant women and the effect of education and economic status.

**Methods**

**Design:** Retrospective cross-sectional study

**Recruitment:** Medical students interviewed pregnant women visiting the antenatal clinic.

**Participants**

**Setting:** Antenatal clinic of a medical college in North India

- **Inclusion criteria:** Pregnant women
- **Exclusion criteria:** NR
- **Study period:** June 2005 to December 2005
- **Sample:** n=405
- **Age range:** Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22%)
- **Gestational age:** First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.90%)
- **Gravidity:** 243 primigravida; 152 multigravida
- **Race/ethnicity:** Indian
- **Education level:** Undergraduates – 220 (54.32%), graduates - 185 (45.68%)

**Interventions**

98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants’ statements were confirmed by their records if available.

**Outcomes**

- 190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used.

NR: not reported

---

**Twigg, 2016**

**Women’s beliefs about medication use during their pregnancy: a UK perspective**

**Objective**

To describe beliefs and risk perception associated with medicines for treatment of common acute conditions.

**Methods**

**Design:** Cross-sectional internet-based questionnaire

**Recruitment:** Advertisements announcing the study were placed on two commonly visited by pregnant women or new mothers

**Participants**

**Setting:** Anonymous internet questionnaire with participants from across the United Kingdom (England, Scotland, Wales and Northern Ireland).
<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Women who were pregnant or within one year of giving birth.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria:</td>
<td>NR</td>
</tr>
<tr>
<td>Study period:</td>
<td>November 15, 2011 to January 15, 2012</td>
</tr>
<tr>
<td>Sample:</td>
<td>n=1120</td>
</tr>
<tr>
<td>Mean age (SD):</td>
<td>30.5 (5.2) years</td>
</tr>
<tr>
<td>Gestational age:</td>
<td>442 (39.5%) were currently pregnant</td>
</tr>
<tr>
<td>Parity (95% CI):</td>
<td>No previous children – 48.0% (45.1-50.9%)</td>
</tr>
<tr>
<td>Race/ethnicity:</td>
<td>NR</td>
</tr>
<tr>
<td>Education level (95% CI):</td>
<td>Less than high school – 0.6% (0.14-1.05), high school – 27.9% (25.3-30.5), more than high school – 52.1% (49.2 – 55.0), other – 19.3% (17.0-21.6).</td>
</tr>
</tbody>
</table>

**Interventions**
Health literacy was measured using a self-assessment scale of 0 to 4 for three questions. General beliefs about medicine were obtained using the validated Beliefs about Medicines Questionnaire (BMQ-General) with an additional four questions regarding the benefit of medications on a scale of 1 to 5.

**Outcomes**
Women with a UTI using medication for treatment had lower mean risk perception scores relating to the overuse and harm of medication and a higher mean risk score relating to the benefits of medication compared to women with a UTI who did not undergo treatment with medication.

- **Overuse [mean(SD)]:** 11.5 (2.8) vs. 12.6 (2.7), p=0.006
- **Harm [mean(SD)]:** 9.3 (2.7) vs. 10.4 (2.9), p=0.014
- **Benefit [mean(SD)]:** 16.3 (2.2) vs. 14.9 (2.3), p<0.001

**Notes**
Sub-study of the Multinational Medication Use in Pregnancy Study which was reported by Lupattelli et al. and another paper from that study is included in this review.

CI: confidence interval; NR: not reported; SD: standard deviation; UK: United Kingdom; UTI: urinary tract infection
### Appendix 5. Characteristics of Included Studies – KQ4: Benefits and harms of treatment

<table>
<thead>
<tr>
<th>Brumfitt, 1975</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>
| **Methods** | Design: RCT (randomization ND); placebo controlled  
Recruitment: Pregnant women attending one of three antenatal clinics for the first time  
Inclusion criteria: Pregnant women who were screened and found to be positive for ‘significant bacteriuria’ at their first antenatal visit and 7-10 days later  
Exclusion criteria: Home delivery, abortions, treatment before confirmation of bacteriuria and other complicating factors |
| **Participants** | Setting: Birmingham (1 clinic) and London (2 clinics), UK; urban  
Study period: NR; ~1967-1968  
Sample: n=426; treated (n=235), placebo (n=179)  
Mean age (SD), years: Treated=26.5 (6.8); Placebo=26.2 (6.9)  
Risk factors: Ethnicity (Asian and West Indian): Treated n=49 (20.8%); Placebo n=35 (14.1%)  
Length of follow-up: until delivery and the postpartum period for perinatal mortality  
Loss to follow-up: NR; outcome of pyelonephritis reported only for a subset (n=173); n=413 for outcome of low birth weight. |
| **Interventions** | Screening characteristics:  
Timing: First antenatal visit  
Urine collection: Clean-catch urine sample  
Urine testing method: Urine culture  
Criteria for positive test: Two positive tests; women with one positive test were recalled for a second test 7-10 days later and ‘detailed documentation’. Microbiological criteria NR.  
Treatment characteristics (Williams, 1968):  
Type of antibiotic and length of treatment: 2g sulphonamide in a single dose; additional courses of treatment for persistent bacteriuria  
Control group: Received placebo under ‘double-blind conditions’  
Follow-up testing: Subset of treated women (n=87) retested after 1 and 2 courses of treatment (as applicable) |
| **Outcomes** | Benefits:  
Pyelonephritis: Presence of loin pain and tenderness together with a temperature of $\geq 100^\circ F$ and $>10^3$ CFU/mL (Condie, 1968)  
Low birth weight (reported as prematurity): $\leq 2500$g  
Harms: NR |
### Notes

Study also included a non-bacteriuric control group. There are two preliminary reports associated with this study (Condie, 1968; Williams, 1968). Brumfitt, 1975 reported outcome of pyelonephritis for the placebo group only (55/179), comparison between groups only available for a subset of treatment group (Condie, 1968). No explanation for variation in number of participants across reports for this study, nor for the various outcomes.

---

### Elder, 1966

**Objective**
To evaluate the effectiveness of sulfasymazine for the treatment of ASB in pregnant women

**Methods**
Design: RCT; placebo-controlled

Recruitment: Pregnant women registering for prenatal care

Inclusion criteria: Pregnant women ≤32 wks GA with bacteriuria at registration confirmed in two additional samples

Exclusion criteria: >32 wks GA, included in other bacteriuria studies, given treatment in error, moved away

**Participants**
Setting: Boston City Hospital, Boston, US; urban

Study period: June 9, 1965-March 9, 1966

Sample: n=106; treated (n=54); placebo (n=52)

Mean age (SD): NR

Risk factors: NR

Length of follow-up: Until delivery

Loss to follow-up: 5 (5%) lost; 2(4%) treated patients left the community, 3 (6%) placebo-treated patients dropped out of the study

**Interventions**
Screening characteristics:
Timing: At registration for prenatal care
Urine collection: Clean-voided urine sample
Urine testing method: Urine culture
Criteria for a positive test: Three uncontaminated urine specimens containing the same species of bacteria with ≥10⁴ CFU/mL in one and ≥10⁵ CFU/mL in the other two.

Treatment characteristics
Type of antibiotic and length of treatment: 0.5g sulfasymazine once daily until delivery; if there was evidence of persistent bacteriuria, another treatment was given according to clinical judgment (usually nitrofurantoin)
Control group: Received placebo
Follow-up testing: Retested after one week of treatment, and at each clinic visit (at least weekly for the first 3 wks, then at least biweekly until 36 wks GA, then weekly until delivery)
Outcomes

Benefits: NR
Harms: NR

Notes

There are no relevant results reported in this study. Study also included non-bacteriuric control patients. 7/52 (13%) of women in the placebo group developed ‘asymptomatic pyelonephritis’, but not information provided for the treated group.

ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; g: gram(s); GA: gestational age; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

Elder, 1971

Objective

To assess the effect of treatment of ASB on pregnancy outcomes

Methods

Design: Quasi-RCT; placebo-controlled

Recruitment: Patients registering for prenatal care

Inclusion criteria: Pregnant women ≤32 wks GA, with confirmed bacteriuria at the first prenatal visit

Exclusion criteria: Treated for UTI during the current pregnancy and before the first obstetric appointment, >32 wks GA, delivered or had aborted before the first obstetric visit, went elsewhere for prenatal care, delivered twins

Participants

Setting: Boston City Hospital, Boston, US; urban

Study period: January 28, 1963-July 2, 1965

Sample: n=281; treated (n=133), placebo (n=148)

Mean age (SE), years: Treated=24.8 (0.60); Placebo=25.3 (0.46)

Risk factors:
Ethnicity (non-white): Treated=66.2%; Placebo=54.7%
Previous UTI: Treated=35.9%; Placebo=40.1%

Length of follow-up: Until delivery, and postpartum (time frame ND) for complications

Loss to follow-up: Of original n=289, 8 (3%) were excluded because they moved away. No loss to follow-up for pyelonephritis; 3 (1%) patients in the placebo group lost for low birthweight because they were treated for reasons other than UTI; 8 (3%) lost for perinatal mortality, 11 (4%) for neonatal sepsis, and 16 (6%) fetal abnormalities and hemolytic anemia, reasons NR.

Interventions

Screening characteristics:
Timing: Upon registration at the clinic
Urine collection: Clean-voided urine sample
Urine testing method: Urine culture
Criteria for a positive test: Three samples (two at registration and one at the first obstetric visit); colony count from 2 of 3 specimens $\geq 10^5$ CFU/mL and no specimens with $< 10^4$ CFU/mL, with the same species predominating in all 3 specimens.

Treatment characteristics:
Type of antibiotic and length of treatment: 250mg tetracycline, 4 times daily for 6 wks; if infection did not clear in 2 wks, another antibiotic (usually nitrofurantoin) was given until it cleared.
Control group: Given identically appearing placebo to be taken similarly.
Follow-up testing: Retested at each clinic visit until delivery (includes recurrence and excludes those who became symptomatic); colony count $< 10^3$ CFU/mL on two successive cultures considered cleared.

Outcomes
Benefits:
Pyelonephritis: Temperature of $\geq 100^\circ$ F with signs and symptoms localized to the urinary tract and not otherwise explained.
Perinatal mortality: Stillbirth or neonatal death prior to hospital discharge.
Respiratory distress: Respiratory distress syndrome and other causes of 'respiratory embarrassment'.
Low birth weight (defined as prematurity): $\leq 2500$ g

Harms:
Serious adverse events: Congenital malformations of bone, genitourinary system, other; hemolytic anemia (erythroblastosis fetalis).

Notes
Study also included a non-bacteriuric control group. Some patients may have participated more than once if they had more than one pregnancy during the study period (treatment assigned by alternation regardless of assignment for previous pregnancy). Outcomes of low birth weight, fetal abnormalities and hemolytic anemia reported for live births only. 4 bacteriuric women delivered twins and are not included.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; $^\circ$ F: degrees Fahrenheit; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; US: United States; UTI: urinary tract infection; wks: weeks

Foley, 1987

Objective
Test of treatment vs. non-treatment of ASB for the prevention of symptomatic UTI in pregnancy.

Methods
Design: RCT
Recruitment: Pregnant women attending an antenatal clinic for the first time
Inclusion criteria: Pregnant women with bacteriuria at the first prenatal visit
Exclusion criteria: NR

Participants
Setting: National Maternity Hospital, Dublin, Ireland; urban
Study period: 1985
| Sample: n=220; treated (n=100); not treated (n=120) |
| Mean age (SD), years: NR |
| Risk factors: NR |
| Length of follow-up: Until delivery (patients interviewed post-delivery) |
| Loss to follow-up: Reported follow-up rate of 81%, unclear if these were from treatment or control groups (total n used in analysis). |

<table>
<thead>
<tr>
<th>Interventions</th>
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</thead>
<tbody>
<tr>
<td><strong>Screening characteristics:</strong></td>
</tr>
<tr>
<td><strong>Timing:</strong> First antenatal visit</td>
</tr>
<tr>
<td><strong>Urine collection:</strong> Midstream urine sample</td>
</tr>
<tr>
<td><strong>Urine testing method:</strong> NR</td>
</tr>
<tr>
<td><strong>Criteria for a positive test:</strong> One urine sample with $&gt;10^5$ CFU/mL</td>
</tr>
<tr>
<td><strong>Treatment characteristics:</strong></td>
</tr>
<tr>
<td><strong>Type of antibiotic and length of treatment:</strong> 300mg sulphamethizole or 150mg nitrofurantoin daily for 3 days, on the basis of sensitivity testing; further treatment, including maintenance treatment, provided if needed to render urine sterile</td>
</tr>
<tr>
<td><strong>Control group:</strong> Received no treatment</td>
</tr>
<tr>
<td><strong>Follow-up testing:</strong> Retested ‘at follow-up’; not further defined</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits:</strong></td>
</tr>
<tr>
<td>Pyelonephritis: ND; ‘admitted with pyelonephritis’</td>
</tr>
<tr>
<td><strong>Harms:</strong> NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
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<tbody>
<tr>
<td>Reported as a letter to the editor, not a full publication.</td>
</tr>
</tbody>
</table>

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; mg: milligram(s); ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection

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**Furness, 1975**

<table>
<thead>
<tr>
<th>Objective</th>
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<tbody>
<tr>
<td>To examine the effectiveness of urinary antiseptics in preventing pyelonephritis and adverse among pregnant women with ASB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design:</strong> RCT</td>
</tr>
<tr>
<td><strong>Recruitment:</strong> Pregnant women attending their initial prenatal visit</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Pregnant women with ‘significant’ bacteriuria at the second prenatal visit</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting:</strong> Queen Victoria Hospital, Adelaide, Australia; urban</td>
</tr>
<tr>
<td><strong>Study period:</strong> NR</td>
</tr>
<tr>
<td>Sample: n=206; treated (n=139); not treated (n=67)</td>
</tr>
<tr>
<td>Mean age (SD), years: NR</td>
</tr>
<tr>
<td>Risk factors: NR</td>
</tr>
<tr>
<td>Length of follow-up: Until 6 wks postpartum</td>
</tr>
<tr>
<td>Loss to follow-up: None reported</td>
</tr>
</tbody>
</table>

**Interventions**

- Screening characteristics:
  - Timing: At the second antenatal visit
  - Urine collection: Midstream urine sample
  - Urine testing method: Dipslide
  - Criteria for a positive test: One specimen with $>10^5$ CFU/mL or two specimens each with $10^4$ to $10^5$ CFU/mL

- Treatment characteristics
  - Type of antibiotic and length of treatment: 1g methenamine mandelate 4 times daily or 1g methenamine hippurate twice daily until delivery; if pyelonephritis developed the patient was treated with the appropriate antibiotic and no further antiseptics were given
  - Control group: Received no treatment
  - Follow-up testing: A postnatal urine specimen was obtained at the 6-week postnatal visit from women who did not develop clinical pyelonephritis during pregnancy or the puerperium

**Outcomes**

- Benefits:
  - Pyelonephritis: Frequency and burning on micturition accompanied by pyrexia or loin tenderness, with presence of a significant number of bacteria in urine
  - Spontaneous abortion: ND; ‘abortions’
  - Preterm delivery: <38 wks GA

- Harms:
  - Serious adverse events: Major fetal abnormality (anencephaly)

**Notes**

- The treatment group received one of two antiseptics, the two groups were combined for reporting of outcomes. Outcome of pyelonephritis includes both during pregnancy and the puerperium. Three intrauterine deaths reported but it is unclear which group the patients belonged to. GA at delivery reported for 118 treated and 52 placebo untreated patients with no explanation given, total n used as denominator in analysis.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

**Gold, 1966**

**Objective**

To determine whether chemotherapy for ASB, continued throughout the rest of the prenatal period, reduces the incidence of prematurity

**Methods**

- Design: Quasi-RCT; placebo-controlled
- Recruitment: Pregnant women registering at a prenatal clinic
### Inclusion criteria:
Pregnant women with two consecutive positive tests for bacteriuria at any prenatal visit

### Exclusion criteria:
Failed to return to the clinic, aborted, delivered at other hospitals, found to not be pregnant, ectopic pregnancy, transferred to other care, delivered by a private physician

### Participants
**Setting:** Prenatal clinic at a hospital in New York, NY, US; urban

**Study period:** February 2, 1962-December 21, 1964

**Sample:** n=65; treated (n=35); placebo (n=30)

**Mean age (SD), years:** NR

**Risk factors:**
Ethnicity: 85% non-white, 6% Puerto-Rican, 9% other white (distribution among groups NR)

**Length of follow-up:** Until the ‘postpartum period’ (exact time NR)

**Loss to follow-up:** None reported

### Interventions
**Screening characteristics:**
Timing: First prenatal visit and each visit thereafter
Urine collection: Clean-voided midstream urine sample
Urine testing method: Urine culture
Criteria for a positive test: Two consecutive laboratory reports with >10⁵ CFU/mL of the same species

**Treatment characteristics**
Type of antibiotic and length of treatment: 0.5g sulfadimethoxine once per day until 36 wks GA, 1g sulfadiazine 3 times daily thereafter until delivery
Control group: Received placebo tablets taken in the same manner
Follow-up testing: Each patient had repeat tests at each antenatal visit until delivery (either for diagnosis or persistent bacteriuria); data presented for persistent bacteriuria at delivery.

### Outcomes
**Benefits:**
Pyelonephritis: ND

**Harms:** NR

### Notes
Also reported delivery data for non-bacteriuric patients. Only antepartum pyelonephritis included in the analysis (postpartum excluded). 'Preterm delivery' reported for 2/35 treated and 0/30 placebo patients, but this is not further defined.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; NY: New York; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

**Kass, 1960**
### Objective
To assess the effect of early detection and eradication of bacteriuria on excessive morbidity in pregnant women

### Methods
**Design:** Quasi-RCT; placebo controlled  
**Recruitment:** Pregnant women ≤32 wks GA registering for a prenatal clinic  
**Inclusion criteria:** Pregnant women with bacteriuria at the first prenatal visit and confirmed on two repeat cultures  
**Exclusion criteria:** >32 wks GA, chronic renal insufficiency, given treatment in error, did not have further prenatal care, records were inadequate or unobtainable, urine samples were contaminated, unable to void, found to not be pregnant

### Participants
**Setting:** Boston City Hospital, Boston, US; urban  
**Study period:** October 1956-April 1960  
**Sample:** n=214 (n=11 recruited via renal clinic); treatment (n=93); placebo (n=98)  
**Mean age (SD), years:** NR; similar distribution between treated and placebo groups  
**Risk factors:**  
- Ethnicity (black): Treated (~50%); placebo (slightly <50%)  
- History of UTI: ~15% (distribution by group NR)  
- Diabetes: n=2 (distribution by group NR)  
- Uterine abnormalities: reported for n=2 bacteriuric women with cesarean section; prevalence in rest of population NR  
**Length of follow-up:** Until the post-delivery period and up to 12 months postpartum; records reviewed 3-4 years later  
**Loss to follow-up:** n=23 (11%) lost; 13 (12%) in the treatment group (7 not seen in last 4 wks before delivery, 5 delivered out of state, 1 incorrectly assigned), 10 (9%) in the placebo group (8 cleared spontaneously or false positive, 2 lost)

### Interventions
**Screening characteristics:**  
- **Timing:** At the time of registration for the clinic  
- **Urine collection:** Clean-voided urine sample  
- **Urine testing method:** Urine culture  
- **Criteria for a positive test:** $10^3$-$10^5$ CFU/mL at registration, then two additional cultures with $>10^5$ CFU/mL of the same species  
**Treatment characteristics:**  
- **Type of antibiotic and length of treatment:** 0.5g sulfamethoxypyridazine daily until delivery; if infection did not clear in one week, the patient was given 100mg nitrofurantoin 3 times daily until delivery  
- **Control group:** Received a placebo tablet supplied by the same manufacturer  
**Follow-up testing:** Treated patients were retested within the 4 wks preceding delivery. Data for 3-12 months postpartum bacteriuria presented for a subset of women (n=91) (Kass, 1960).
Outcomes

Benefits:
- Pyelonephritis: dysuria, frequency, and flank pain or other localizing evidence of inflammation, with either documented temperature of 100°F or above or a history of chills and fever. When patients were seen outside the clinic (e.g., accident floor or emergency department), it was not always clear that patients were indeed febrile.
- Perinatal mortality: ND; ‘perinatal death’ and fetal loss >20 wks GA
- Low birth weight (defined as prematurity): <2500g

Harms: NR

Notes

Kass, 1960 is a preliminary report, updated and more complete data retrieved from Savage, 1967 are presented. The study also includes a group of non-bacteriuric women. Some patients participated for >1 pregnancy, and were reassigned to the same treatment they received in the first pregnancy. Outcome of pyelonephritis reported only for the antenatal period, postpartum excluded. Outcome of low birth weight given for the total number of deliveries (3 twin deliveries in the placebo group and none in the treated group).

Kazemier, 2015

Objective

To investigate the consequences of treated and untreated ASB in pregnancy

Methods

Design: Prospective cohort (screening vs. no screening) with embedded RCT

Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available)

Inclusion criteria: Pregnant women aged ≥18 years with a singleton pregnancy who were between 16 and 22 wks GA, tested positive for ASB, and did not have symptoms of UTI

Exclusion criteria: History of preterm delivery <34 wks, warning signs of imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 wks of screening, known glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI (e.g., pre-gestational DM, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract)

Participants

Setting: 8 hospitals and 5 ultrasound centres, the Netherlands

Study period: October 11, 2011-August 22, 2014

Sample: n=248; treated (n=40); placebo (n=45), untreated (n=163)

Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)

Risk factors:
- Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)
- Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (10%)

Length of follow-up: Until 6 wks postpartum
Loss to follow-up: n=12 (5%) lost, all from the untreated or placebo group; 5 women could not be contacted for outcomes because of errors in their contact information. Missing data were imputed (see notes).

### Interventions

**Screening characteristics:**
- **Timing, median (IQR) wks + days GA:** treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)
- **Urine collection:** Midstream urine sample
- **Urine testing method:** Dipslide
- **Criteria for a positive test:** $\geq 10^5$ CFU/mL of a single microorganism or when two different colony types were present but one had a concentration of $\geq 10^5$ CFU/mL

**Treatment characteristics:**
- **Type of antibiotic and length of treatment:** 100mg nitrofurantoin twice daily for 5 days; if bacteriuria did not clear the treatment was repeated for a maximum of two rounds
- **Control group:** Received identical placebo capsules on the same dose and schedule as treated patients, or no treatment
- **Follow-up testing:** All participants provided a follow-up dipslide 1 week after the end of treatment; those who remained positive were retested after each new round of treatment, for a maximum of two rounds

### Outcomes

**Benefits:**
- **Pyelonephritis:** Hospital admission with $\geq 2$ of the following: fever (body temperature $\geq 38^\circ$C), symptoms of pyelonephritis (nausea, vomiting, chills, and costovertebral tenderness), and a positive urine culture indicating the presence of bacteria in the urine.
- **Perinatal mortality:** Neonatal death before discharge from the neonatal ward
- **Preterm delivery:** Spontaneous birth between 32 and 37 wks GA
- **Low birth weight:** $< 10^{th}$ or $5^{th}$ percentile
- **Neonatal sepsis:** Confirmed with culture, includes group B streptococcal sepsis

**Harms:**
- **Serious adverse events:** Congenital abnormalities (ND)

### Notes

Cohort study addressed screening, results reported here for treatment RCT only. Study included both placebo and untreated groups who were combined in the analysis. When data were missing, these were imputed taking into account patient characteristics and outcomes. Differences in outcomes between groups were controlled for potential confounders (smoking, low education, conception through in-vitro fertilization or intracytoplasmic sperm injection, pre-existing hypertension). 5 women originally assigned to treatment group were later found to not have ASB, but remained in their assigned group (intention-to-treat analysis).

ASB: asymptomatic bacteriuria; C: Celsius; CFU/mL: colony forming units per millilitre; DM: diabetes mellitus; g: gram(s); GA: gestational age; IQR: interquartile range; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

### Kincaid-Smith, 1965

**Objective**
- To assess the effectiveness of antibacterial drugs for pregnant women with bacteriuria in preventing pyelonephritis, perinatal mortality, and low birth weight
<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT; placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Pregnant women attending their first antenatal visit before 26 wks GA</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Pregnant women &lt;26 wks GA with ASB at the first antenatal visit and confirmed by a subsequent positive test</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Setting: Queen Victoria Hospital, Melbourne, Australia; urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study period</td>
<td>1964-1965</td>
</tr>
<tr>
<td>Sample</td>
<td>n=145; treated (n=61), placebo (n=56) (see notes)</td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>NR</td>
</tr>
<tr>
<td>Risk factors</td>
<td>(see notes)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>All from lowest income category in community, but the community has a high standard of living</td>
</tr>
<tr>
<td>Urogenital anomalies</td>
<td>At post-delivery testing, 51.4% of patients had an abnormal intravenous pyelogram and 5 patients had poorly functioning or non-functioning kidneys on one side due to ureteric obstruction.</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>Until 6 months postpartum</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>Of initial 240 women with completed pregnancies, no outcomes reported for 95 women for various reasons (6 aborted before treatment, 20 developed symptoms before treatment, 22 attended infrequently, 33 failed to take tablets continuously, 14 had coagulase-negative staphylococcal bacteriuria); further information on non-compliant patients NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Screening characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>First antenatal visit</td>
</tr>
<tr>
<td>Urine collection</td>
<td>Midstream urine sample; the second test was clean-voided (first was not)</td>
</tr>
<tr>
<td>Urine testing method</td>
<td>Urine culture</td>
</tr>
<tr>
<td>Criteria for a positive test</td>
<td>&gt;10⁵ CFU/mL on two occasions</td>
</tr>
<tr>
<td>Treatment characteristics:</td>
<td>Type of antibiotic and length of treatment: 0.5g sulphamexyldazine daily, changing to 1g sulphadimidine 3 times daily in the 13th week of gestation, continuing until delivery; if resistance to sulphonamides was indicated by sensitivity tests, 500mg ampicillin 3 times daily or 50mg nitrofurantoin 4 times daily was prescribed instead.</td>
</tr>
<tr>
<td>Control group</td>
<td>Received identical placebo capsules and tablets</td>
</tr>
<tr>
<td>Follow-up testing</td>
<td>Patients re-examined at monthly intervals, on any hospital admission, and at delivery. Retesting at 6 wks-3 months and 6 months postpartum ongoing at the time of publication. These subsequent samples involved cleansing of the periurethral area and insertion of a vaginal tampon to avoid contamination.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Benefits:</th>
</tr>
</thead>
</table>

| **Pyelonephritis:** | Loin pain and tenderness, with or without pyrexia, and rigors, with or without symptoms of dysuria and frequency  
| **Perinatal mortality:** | >28 wks GA  
| **Low birth weight (reported as preterm delivery):** | <2500g  
| **Harms:** | NR |

**Notes**
- Study also included a non-bacteriuric group. 29/145 (20%) patients were given treatment or placebo prior to confirmation of ASB (before the second culture was analyzed); outcomes for these patients were reported separately, leaving 116 in the current analysis. 11 fetal losses reported but group assignment NR.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; mg: milligram(s); NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

### Little, 1966

**Objective**
- To assess the effect of antibiotic treatment for pregnant women with ASB on incidence of pyelonephritis and adverse pregnancy outcomes

**Methods**
- **Design:** RCT; placebo-controlled
  - **Recruitment:** Pregnant women attending their first antenatal visit
  - **Inclusion criteria:** Pregnant women with bacteriuria at the first antenatal visit and confirmed with a subsequent culture
  - **Exclusion criteria:** NR

**Participants**
- **Setting:** Charing Cross Hospital and Fulham Maternity Hospital, London, England; urban
  - **Study period:** 1962-1965
  - **Sample:** n=265; treated (n=124), placebo (n=141)
  - **Mean age (SD), years:** NR; 6.89% 10-20, 4.99% 21-30, 4.62% 31-40, 4.25% ≥40
  - **Risk factors:**
    - Past history of urinary tract disease: 62 (23.4%) recalled a past episode (both groups combined)
  - **Length of follow-up:** Until 6 wks postpartum
  - **Loss to follow-up:** None reported.

**Interventions**
- **Screening characteristics:**
  - **Timing:** First antenatal visit, usually ~12th week of gestation
  - **Urine collection:** Clean-voided midstream urine sample
  - **Urine testing method:** Urine culture
  - **Criteria for a positive test:** Two consecutive urine cultures with >10⁵ CFU/mL

- **Treatment characteristics:**
Type of antibiotic and length of treatment: At start of trial, patients were given 0.5g sulphamethoxypyridazine daily for 30 days; if bacteriuria did not clear, 1.5g ampicillin daily was given for 1 week, then a maintenance dose of 1g daily until delivery. Because treatment with ampicillin was generally not successful, later in the trial, a single dose of 100mg nitrofurantoin became the first form of treatment.
Control group: Received placebo tablets
Follow-up testing: Retested monthly throughout pregnancy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Benefits:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyelonephritis: Loin pain and tenderness, a fever &gt;100°F, &gt;10⁵ CFU/mL. Usually there was also frequency and dysuria, and sometimes rigors and hematuria</td>
</tr>
<tr>
<td></td>
<td>Perinatal mortality: ND</td>
</tr>
<tr>
<td></td>
<td>Low birth weight (reported as prematurity): &lt;2500g</td>
</tr>
<tr>
<td>Harms:</td>
<td>Serious adverse events: fetal abnormalities, ND</td>
</tr>
</tbody>
</table>

Notes: ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; F: Fahrenheit; g: gram(s); mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation

Mulla, 1960

<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate the clinical results of treatment of bacteriuria in pregnant women with long-acting sulfonamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Design: RCT</td>
</tr>
<tr>
<td></td>
<td>Recruitment: Pregnant women attending the obstetrical clinic</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: Pregnant women with ASB at their 30-32 wks GA obstetric visit</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: NR</td>
</tr>
<tr>
<td>Participants</td>
<td>Setting: St. Elizabeth Hospital, Ohio, US; urban</td>
</tr>
<tr>
<td>Study period:</td>
<td>NR</td>
</tr>
<tr>
<td>Sample:</td>
<td>n=100; treated (n=50), not treated (n=50)</td>
</tr>
<tr>
<td>Mean age (SD), years:</td>
<td>NR</td>
</tr>
<tr>
<td>Risk factors:</td>
<td>NR</td>
</tr>
<tr>
<td>Length of follow-up:</td>
<td>Until delivery and immediately after</td>
</tr>
<tr>
<td>Loss to follow-up:</td>
<td>None reported.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Screening characteristics:</td>
</tr>
<tr>
<td>Timing:</td>
<td>Obstetric visit at 30-32 wks GA</td>
</tr>
<tr>
<td><strong>Urine collection:</strong></td>
<td>Catheter urinalysis (antimicrobial jelly used on the catheter)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Urine testing method:</strong></td>
<td>Urine culture</td>
</tr>
<tr>
<td><strong>Criteria for a positive test:</strong></td>
<td>NR</td>
</tr>
</tbody>
</table>

**Treatment characteristics:**
- Type of antibiotic and length of treatment: 250mg sulfadimethoxine twice daily for 1 week; the regimen was repeated if bacteriuria persisted
- Control group: Received no medication until symptoms appeared
- Follow-up testing: Followed at weekly intervals until delivery; were re-tested at least once, after the first course of treatment.

<table>
<thead>
<tr>
<th><strong>Outcomes</strong></th>
<th><strong>Benefits:</strong> Pyelonephritis: Clinical evidence of active infection, including acute symptoms of cystopyelitis; urine was tested at the time of the episode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Harms:</strong> NR</td>
</tr>
</tbody>
</table>

| **Notes** | Pyelonephritis after delivery was reported, but this was excluded from the present analysis. |

**ASB:** asymptomatic bacteriuria; **GA:** gestational age; **mg:** milligram(s); **n:** number; **NR:** not reported; **RCT:** randomized controlled trial; **SD:** standard deviation; **US:** United States; **wks:** weeks

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### Pathak, 1969

**Objective**
To determine the effect of short-term antibacterial therapy on eradication of bacteriuria during pregnancy, and its effects on pregnancy outcomes

**Methods**
- **Design:** RCT; placebo-controlled
- **Recruitment:** Pregnant women attending antenatal clinics
- **Inclusion criteria:** Pregnant women ≤24 wks GA with confirmed bacteriuria on two consecutive tests
- **Exclusion criteria:** Confirmation of bacteriuria at >24 wks GA, blood pressure >130/90mmHg at the initial antenatal visit, did not re-attend after first examination (wrong dates or could not be traced), early abortions, clinical pyelonephritis, ‘mentally defective’

**Participants**
- **Setting:** University College Hospital and Kingston Public Hospital, Jamaica; urban
- **Study period:** NR
- **Sample:** n=178; treated (n=76); placebo (n=76)
- **Mean age (SD), years:** NR
- **Risk factors:**
  - Sickle-cell trait: 18/24 (21.4%) in bacteriuric patients, incidence by group NR
  - Urogenital anomalies: 9/50 (18%) of bacteriurics had abnormalities on postpartum intravenous pyelogram (1 bilateral hydroureret with hydronephrosis, 1 localized calyceal clubbing, 1 bifid pelvis, 2 had changes consistent with papillary necrosis, 4 showed evidence of chronic pyelonephritis).
Length of follow-up: Until delivery (all) and 3-9 months postpartum for a subset

Loss to follow-up: n=26 (15%) lost; 12 (14%) treated (9 antibiotic received for positive serology, 3 defaulted from the clinic and could not be traced), 14 (16%) placebo (12 antibiotic received, 3 defaulted from the clinic)

Interventions

Screening characteristics:
Timing: NR; ≤24 wks GA
Urine collection: clean-voided urine sample
Urine testing method: NR
Criteria for a positive test: >10^5 CFU/mL on two consecutive specimens

Treatment characteristics:
Type of antibiotic and length of treatment: 100mg nitrofurantoin twice daily for 3 wks; patients who did not respond received 400mg nitrofurantoin daily for a further 4 days
Control group: Received placebo identical in appearance
Follow-up testing: Retested at weekly intervals during treatment (or placebo), then every 2 wks until delivery, and a subset (n=69, 24 treated and 45 placebo) at 3-9 months postpartum

Outcomes

Benefits:
Pyelonephritis: ND

Harms: NR

Notes

Reported preterm birth/fetal loss only by bacteriuric status, not by treatment group.

ASB: asymptomatic bacteriuria; CFU: colony forming units per millilitre; GA: gestational age; mg: milligram; mmHg: millimetre of mercury; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

Thomsen, 1987

Objective
To assess the effect of treatment for group-B streptococcal bacteriuria in pregnant women on the incidence of preterm labour

Methods
Design: RCT; placebo-controlled

Recruitment: Pregnant women attending Statens Seruminstitut

Inclusion criteria: Pregnant women 27-31 wks GA who were positive for group-B streptococcal bacteriuria

Exclusion criteria: NR; <27 or >31 wks GA

Participants
Setting: University Hospital, Denmark; urban

Study period: October 1, 1984-October 1, 1986

Sample: n=69; treated (n=37), placebo (n=32)

Mean age, years: 28.1, similar for both groups
### Risk factors:
- Ethnicity: All patients were white
- Socioeconomic status: Similar for both groups

### Interventions
**Screening characteristics:**
- **Timing:** NR; 27-31 wks GA
- **Urine collection:** Midstream urine sample
- **Urine testing method:** Urine culture
- **Criteria for a positive test:** $10^2$-$10^6$ CFU/mL of group-B streptococci bacteria

**Treatment characteristics:**
- **Type of antibiotic and length of treatment:** $10^6$ IU penicillin 3 times daily for 6 days; treatment was repeated if bacteriuria persisted
- **Control group:** Received placebo tablets
- **Follow-up testing:** Retested weekly until delivery for persistent bacteriuria or recurrence

### Outcomes
**Benefits:**
- Preterm delivery: <37 wks GA (mean wks GA for treated: 39.6, placebo: 36.2)
- Neonatal sepsis: ND

**Harms:** NR

### Notes
Patients positive for streptococci at delivery were treated with 2g ampicillin intravenously followed by 1g intravenously every 4 hours from the start of labour. Infants were given ampicillin (50mg/kg) intramuscularly every 12 hours to avoid sepsis. Umbilical cord blood was tested from group-B streptococci and babies with positive cultures were treated for 6 days. One infant tested positive for sepsis at 6 wks post-delivery.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age; IU: international unit; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; wks: weeks

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**Williams, 1969**

### Objective
To investigate the effect of treatment of ASB in pregnancy on urine concentrating ability and the development of symptomatic UTI

### Methods
**Design:** RCT

**Recruitment:** Pregnant women attending their first antenatal visit

**Inclusion criteria:** Pregnant women <30 wks GA with significant ASB at the first antenatal visit, confirmed by a second positive test within 10 days

**Exclusion criteria:** NR

### Participants
**Setting:** Maternity Hospital and St. David’s Hospital, Cardiff, Wales, England; urban
Study period: 1967

Sample: n=163; treated (n=85), untreated (n=78)

Mean age (SE), years: 24.82 (0.49) for all bacteriurics, differences between groups NR

Risk factors: NR

Length of follow-up: Until 10 days postpartum

Loss to follow-up: None reported

Interventions

Screening characteristics:
Timing: First antenatal visit; mean (SE) 20.78 (0.45) wks GA
Urine collection: Clean-voided midstream urine sample
Urine testing method: Urine culture
Criteria for a positive test: >10^5 gram-negative CFU/mL in at least two consecutive urine specimens; if the first specimen was positive, patients were recalled for a second specimen within 10 days

Treatment characteristics:
Type of antibiotic: 1g sulphadimidine 3 times daily for 7 days; if bacteriuria persisted, patients received 100mg nitrofurantoin twice daily for 7 days; if bacteriuria still persisted, patients received 250mg ampicillin 3 times daily for 7 days (ampicillin repeated as necessary)
Control group: received no treatment until symptoms presented
Follow-up testing: Retested 2-3 wks after the first course of treatment, and each subsequent course of treatment

Outcomes

Benefits:
Pyelonephritis: loin pain and tenderness with or without fever (no record of fever in antenatal patients)

Harms: NR

Notes

The study also included a non-bacteriuric and a non-pregnant group. Data for pyelonephritis includes postpartum infections (n=6) because group assignment NR.

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; mg: milligram(s); n: number; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

Wren, 1969

Objective
To evaluate the effect of treatment of pregnant women with ASB on the incidence of premature deliveries and other adverse pregnancy outcomes

Methods
Design: Quasi-RCT

Recruitment: Pregnant women booking at an antenatal clinic

Inclusion criteria: Pregnant women with ASB at their first antenatal visit
<table>
<thead>
<tr>
<th><strong>Exclusion criteria:</strong></th>
<th>NR</th>
</tr>
</thead>
</table>

| **Participants** | Setting: Royal Hospital for Women, New South Wales, Australia; urban  
Study period: November 1968-December 1968  
Sample: n=183; treated (n=83), untreated (n=90)  
Mean age (SD): NR  
Risk factors: NR  
Length of follow-up: Until 6 wks postpartum  
Loss to follow-up: Of original n=183, 10 (5%) women lost; 2 sets of twins, 4 moved away and could not be traced, 3 received antibiotics before the trial started, 1 refused to take the treatment |

| **Interventions** | Screening characteristics:  
Timing: First antenatal visit  
Urine collection: Midstream urine sample  
Urine testing method: NR  
Criteria for a positive test: NR  
Treatment characteristics:  
Type of antibiotic and length of treatment: Rotational therapy with 100mg nitrofurantoin twice daily for 2 wks, 250mg ampicillin 4 times daily for 1 week, 500mg sulphurazole 4 times daily for 4 wks, and nalidixic acid 4 times daily for 2 wks. Each new patient started with one of the four drugs, then rotated through the remaining drugs in order. Every 9 wks, patients began a new course of rotational therapy until 1-6 wks after delivery.  
Control group: Untreated until clinical evidence of UTI developed  
Follow-up testing: Patients were retested one per month when possible, until the last month of pregnancy |

| **Outcomes** | Benefits:  
Spontaneous abortion: ND; ‘abortion’  
Perinatal mortality: Stillbirth and neonatal death  
Preterm delivery: <37 wks GA  
Low birth weight (reported as prematurity): <2501g  
Harms: NR |

| **Notes** | The study also included a control group of non-bacteriuric women. |

ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection; wks: weeks
### Appendix 6. Quality Assessments for Included Studies - KQ1a & b

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gérard, 1983 (cohort)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>1</td>
<td>Included all pregnant women who visited the clinic at &lt;25 wks GA.</td>
</tr>
<tr>
<td>Selection of the non-exposed cohort</td>
<td>1</td>
<td>Formed retrospectively, pregnant women attending the clinic in the 10 previous months (before implementation of screening).</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>0</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Outcome not present at start of study (pyelonephritis/other outcomes)</td>
<td>0/1</td>
<td>Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.</td>
</tr>
<tr>
<td>Comparability of the cohorts</td>
<td>0</td>
<td>No evidence of comparability.</td>
</tr>
<tr>
<td>Assessment of outcome</td>
<td>1</td>
<td>Appear to have used a chart review.</td>
</tr>
<tr>
<td>Adequacy of length of follow-up</td>
<td>1</td>
<td>Follow-up until delivery and for 3-6 months post-partum for those with ≥2 instances of asymptomatic bacteriuria.</td>
</tr>
<tr>
<td>Adequacy of follow-up of cohorts</td>
<td>1</td>
<td>No loss to follow-up.</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>suspected</td>
<td>Did not report on fetal abnormalities.</td>
</tr>
<tr>
<td>Total score (maximum 10)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Gratacós, 1944 (cohort)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>1</td>
<td>All pregnant women presenting to the clinic at &lt;25 wks GA between January 1991 and December 1992.</td>
</tr>
<tr>
<td>Selection of the non-exposed cohort</td>
<td>1</td>
<td>Women who visited the same clinic in years (January 1987 to December 1990) before implementation of the screening program.</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>0</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Outcome not present at start of study (pyelonephritis/other outcomes)</td>
<td>0/1</td>
<td>Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.</td>
</tr>
<tr>
<td>Comparability of the cohorts</td>
<td>0</td>
<td>No evidence of comparability.</td>
</tr>
<tr>
<td>Assessment of outcome</td>
<td>1</td>
<td>Used a chart review – ‘was recorded for 6 years’.</td>
</tr>
<tr>
<td>Adequacy of length of follow-up</td>
<td>1</td>
<td>Followed-up until delivery.</td>
</tr>
<tr>
<td>Adequacy of follow-up of cohorts</td>
<td>1</td>
<td>10 (6.9%) lost to follow-up.</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>suspected</td>
<td>Did not report on spontaneous abortion, perinatal mortality, preterm delivery or fetal abnormalities.</td>
</tr>
<tr>
<td>Total score (maximum 10)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Rhode, 2007 (cohort)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>1</td>
<td>All pregnant women who enrolled for care and delivered after August 15, 2002.</td>
</tr>
<tr>
<td>Domain</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Selection of the non-exposed cohort</td>
<td>1</td>
<td>All pregnant women who enrolled for care at the same practice and delivered before August 15, 2002.</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>1</td>
<td>Used delivery records.</td>
</tr>
<tr>
<td>Outcome not present at start of study (pyelonephritis/other outcomes)</td>
<td>0/1</td>
<td>Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.</td>
</tr>
<tr>
<td>Comparability of the cohorts</td>
<td>1</td>
<td>Compared 10 demographic factors, showing that groups were similar.</td>
</tr>
<tr>
<td>Assessment of outcome</td>
<td>1</td>
<td>Used a chart review.</td>
</tr>
<tr>
<td>Adequacy of length of follow-up</td>
<td>1</td>
<td>Followed-up until delivery of the patient left the practice.</td>
</tr>
<tr>
<td>Adequacy of follow-up of cohorts</td>
<td>1</td>
<td>112 (4.6%) lost to follow-up.</td>
</tr>
<tr>
<td>Selective outcome reporting&lt;sup&gt;b&lt;/sup&gt;</td>
<td>suspected</td>
<td>Did not report on spontaneous abortion, perinatal mortality or fetal abnormalities.</td>
</tr>
<tr>
<td>Total score (maximum 10)</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

 Uncu, 2002 (cohort)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>1</td>
<td>All pregnant women &lt;32 wks GA seen at an antenatal outpatient clinic.</td>
</tr>
<tr>
<td>Selection of the non-exposed cohort</td>
<td>1</td>
<td>Women who visited the clinic prior to the start of the screening study.</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>1</td>
<td>Used delivery records.</td>
</tr>
<tr>
<td>Outcome not present at start of study (pyelonephritis/other outcomes)</td>
<td>0/1</td>
<td>Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.</td>
</tr>
<tr>
<td>Comparability of the cohorts</td>
<td>0</td>
<td>No evidence of comparability.</td>
</tr>
<tr>
<td>Assessment of outcome</td>
<td>1</td>
<td>Used delivery records.</td>
</tr>
<tr>
<td>Adequacy of length of follow-up</td>
<td>1</td>
<td>Follow-up until post-delivery.</td>
</tr>
<tr>
<td>Adequacy of follow-up of cohorts</td>
<td>0</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Selective outcome reporting&lt;sup&gt;b&lt;/sup&gt;</td>
<td>not suspected</td>
<td>Reported on all outcomes, including fetal death &gt;20 wks GA (eligible for perinatal mortality).</td>
</tr>
<tr>
<td>Total score (maximum 10)</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

GA: gestational age; wks: weeks
<sup>a</sup>Assessed using the Newcastle-Ottawa Quality Assessment Scale
<sup>b</sup>Assessed due to concern regarding reporting bias in the studies, but assessment not included in the total score
## Appendix 7. Quality Assessments for Included Studies – KQ2*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement*</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Butters, 1990 (cross-sectional survey)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly focused question/issue</td>
<td>1</td>
<td>Awareness of the effects of commonly used drugs, cigarettes and alcohol on the fetus</td>
</tr>
<tr>
<td>Appropriate research method (study design)</td>
<td>1</td>
<td>Cross-sectional survey of women in postnatal wards</td>
</tr>
<tr>
<td>Selection of subjects clearly described</td>
<td>1</td>
<td>Provides inclusion and exclusion criteria, outlines selection methods</td>
</tr>
<tr>
<td>Sampling method introduces bias</td>
<td>2</td>
<td>Sampling was not random, may be consecutive</td>
</tr>
<tr>
<td>Sample of subjects representative of the population</td>
<td>1</td>
<td>Included women who were recently post-partum</td>
</tr>
<tr>
<td>Sample size based on pre-study considerations of statistical power</td>
<td>2</td>
<td>Not reported</td>
</tr>
<tr>
<td>Satisfactory response rate</td>
<td>1</td>
<td>Response rate was 87%</td>
</tr>
<tr>
<td>Questionnaires are likely to be valid and reliable</td>
<td>2</td>
<td>Validation of survey questions was not reported</td>
</tr>
<tr>
<td>Statistical significance assessed</td>
<td>1</td>
<td>Chi-square analysis</td>
</tr>
<tr>
<td>Confidence intervals for main results</td>
<td>3</td>
<td>No confidence intervals reported</td>
</tr>
<tr>
<td>Confounding factors not accounted for</td>
<td>1</td>
<td>Confounders were not addressed with study design or analysis</td>
</tr>
<tr>
<td>Applicability of the results</td>
<td>1</td>
<td>Identifies areas for further education in this population</td>
</tr>
<tr>
<td><strong>Kazemier, 2015 (Prospective multi-centre screening cohort with embedded treatment RCT; valuation of outcomes obtained/reported in cross-sectional manner)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly focused question/issue</td>
<td>2</td>
<td>To assess maternal and neonatal consequences of treating and not treating asymptomatic bacteriuria in pregnancy; however, no direct examination of outcome valuation set out in protocol or study methods</td>
</tr>
<tr>
<td>Appropriate research method (study design)</td>
<td>2</td>
<td>Appears to be cross-sectional for information regarding why eligible women did not consent to participate in treatment trial</td>
</tr>
<tr>
<td>Selection of subjects clearly described</td>
<td>1</td>
<td>Clear inclusion and exclusion criteria for screening cohort and treatment RCT, with study flow documented</td>
</tr>
<tr>
<td>Sampling method introduces bias</td>
<td>3</td>
<td>Various clinics, hospitals and ultrasound centres in the Netherlands</td>
</tr>
<tr>
<td>Sample of subjects representative of the population</td>
<td>1</td>
<td>Women 18 years or older with singleton pregnancy without symptoms of urinary tract infection.</td>
</tr>
<tr>
<td>Sample size based on pre-study considerations of statistical power</td>
<td>2</td>
<td>Sample size estimates reported in statistical analysis, but none specified for cross-section of women for outcome valuation</td>
</tr>
<tr>
<td>Satisfactory response rate</td>
<td>2</td>
<td>Authors did not report response rate specifically for cross-section of women who declined treatment. Of 255 ASB-positive women, 163 received no treatment (of whom 155 did not want treatment for specified reason), but</td>
</tr>
<tr>
<td>Questionnaires are likely to be valid and reliable</td>
<td>2</td>
<td>Validation of reason(s) for dissenting not reported</td>
</tr>
<tr>
<td>Statistical significance assessed</td>
<td>3</td>
<td>Fisher’s exact test for outcomes from screening cohort and treatment trial; no significance for outcome valuation data</td>
</tr>
<tr>
<td>Confidence intervals for main results</td>
<td>3</td>
<td>CI’s reported for outcomes from screening cohort and treatment trial; no CI’s for outcome valuation data</td>
</tr>
<tr>
<td>Confounding factors not accounted for</td>
<td>2</td>
<td>Assessed confounders for outcomes from screening cohort and treatment trial, but not for outcome valuation data</td>
</tr>
<tr>
<td>Applicability of the results</td>
<td>3</td>
<td>Medication avoidance for asymptomatic conditions in pregnancy among Dutch women acknowledged by study authors to align with Dutch guidelines (not routinely screening and treating women with ASB); may be more applicable for the Netherlands but not for Canada where routine screening and treatment is standing practice</td>
</tr>
</tbody>
</table>

**Lupattelli, 2014 (cross-sectional survey)**
- Clearly focused question/issue: 1
  - Association of health literacy and risk perception
- Appropriate research method (study design): 1
  - Cross-sectional survey of pregnant women
- Selection of subjects clearly described: 1
  - Self-selection, voluntary internet survey
- Sampling method introduces bias: 1
  - Informal sampling method – self-selection was not random or consecutive
- Sample of subjects representative of the population: 1
  - Pregnant women with internet access
- Sample size based on pre-study considerations of statistical power: 2
  - Not reported
- Satisfactory response rate: 2
  - Large n, no response rate reported
- Questionnaires are likely to be valid and reliable: 2
  - Validation of survey questions was not reported
- Statistical significance assessed: 1
  - Mann-Whitney U test, Spearman’s rank correlation coefficient, logistic regression
- Confidence intervals for main results: 1
  - Reported in Table 3
- Confounding factors not accounted for: 3
  - Adjusted for confounders in statistical analysis
- Applicability of the results: 1
  - Health literacy is significantly associated with adherence to pharmacotherapy in pregnant women

**Mashayekhi, 2009 (cross-sectional survey)**
- Clearly focused question/issue: 1
  - Awareness of pregnant women on the effects of drugs during pregnancy
- Appropriate research method (study design): 1
  - Cross-sectional survey of pre and postnatal women
- Selection of subjects clearly described: 1
  - Reports selection methods
- Sampling method introduces bias: 1
  - Sampling was not random or consecutive
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample of subjects representative of the population</td>
<td>Included pre and postnatal women in hospital wards</td>
<td></td>
</tr>
<tr>
<td>Sample size based on pre-study considerations of statistical</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory response rate</td>
<td>Large n, no response rate reported</td>
<td></td>
</tr>
<tr>
<td>Questionnaires are likely to be valid and reliable</td>
<td>Validation of survey questions was not reported</td>
<td></td>
</tr>
<tr>
<td>Statistical significance assessed</td>
<td>Chi-square, Student’s t-test, Pearson correlations, ANOVA</td>
<td></td>
</tr>
<tr>
<td>Confidence intervals for main results</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Confounding factors not accounted for</td>
<td>Confounders were not addressed with study design or analysis</td>
<td></td>
</tr>
<tr>
<td>Applicability of the results</td>
<td>Identifies roles for pharmacists in education of this population</td>
<td></td>
</tr>
<tr>
<td><strong>Nordeng, 2010 (cross-sectional survey)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly focused question/issue</td>
<td>Women’s perception of risk during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Appropriate research method (study design)</td>
<td>Cross-sectional survey of pregnant women and mothers</td>
<td></td>
</tr>
<tr>
<td>Selection of subjects clearly described</td>
<td>Self-selection, voluntary internet survey</td>
<td></td>
</tr>
<tr>
<td>Sampling method introduces bias</td>
<td>Informal sampling method – self-selection was not random or</td>
<td></td>
</tr>
<tr>
<td>Sample of subjects representative of the population</td>
<td>Pregnant women and young mothers (child less than 5 years) with</td>
<td></td>
</tr>
<tr>
<td>Sample size based on pre-study considerations of statistical</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory response rate</td>
<td>Large n, no response rate reported</td>
<td></td>
</tr>
<tr>
<td>Questionnaires are likely to be valid and reliable</td>
<td>Validation of survey questions was not reported</td>
<td></td>
</tr>
<tr>
<td>Statistical significance assessed</td>
<td>Linear regression, ANOVA, Student’s t-test</td>
<td></td>
</tr>
<tr>
<td>Confidence intervals for main results</td>
<td>Confidence intervals were available in graph format only</td>
<td></td>
</tr>
<tr>
<td>Confounding factors not accounted for</td>
<td>Addressed in limitations</td>
<td></td>
</tr>
<tr>
<td>Applicability of the results</td>
<td>Indicates women overestimate risks and more education in this</td>
<td></td>
</tr>
<tr>
<td></td>
<td>area is needed.</td>
<td></td>
</tr>
<tr>
<td><strong>Sanz, 2000 (cross-sectional)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly focused question/issue</td>
<td>Drug utilization in pregnant women</td>
<td></td>
</tr>
<tr>
<td>Appropriate research method (study design)</td>
<td>Cross-sectional, visual analogue scale</td>
<td></td>
</tr>
<tr>
<td>Selection of subjects clearly described</td>
<td>Selection methods are not reported for all populations</td>
<td></td>
</tr>
<tr>
<td>Sampling method introduces bias</td>
<td>Not reported for all populations</td>
<td></td>
</tr>
<tr>
<td>Sample of subjects representative of the population</td>
<td>Pregnant women attending out-patient clinic at a hospital</td>
<td></td>
</tr>
<tr>
<td>Sample size based on pre-study considerations of statistical</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory response rate</td>
<td>Small n, no response rate reported</td>
<td></td>
</tr>
<tr>
<td>Questionnaires are likely to be valid and reliable</td>
<td>Validation of VAS questions was not reported</td>
<td></td>
</tr>
<tr>
<td>Statistical significance assessed</td>
<td>1</td>
<td>Mann-Whitney U, Kruskal Wallis, Chi-squared</td>
</tr>
<tr>
<td>Confidence intervals for main results</td>
<td>3</td>
<td>Only in graph format</td>
</tr>
<tr>
<td>Confounding factors not accounted for</td>
<td>1</td>
<td>Confounders were not addressed with study design or analysis</td>
</tr>
<tr>
<td>Applicability of the results</td>
<td>1</td>
<td>Pregnant women have high perceptions of teratogenic risk</td>
</tr>
</tbody>
</table>

**Sharma, 2006 (cross-sectional survey)**

| Clearly focused question/issue | 1 | Drug utilization in pregnant women |
| Appropriate research method (study design) | 1 | Cross-sectional survey of pregnant women |
| Selection of subjects clearly described | 3 | Selected from an antenatal clinic but no sampling methods |
| Sampling method introduces bias | 2 | Not reported |
| Sample of subjects representative of the population | 1 | Pregnant women |
| Sample size based on pre-study considerations of statistical power | 2 | Not reported |
| Satisfactory response rate | 2 | Large n, no response rate reported |
| Questionnaires are likely to be valid and reliable | 1 | Women’s statements were confirmed through medical records when available |
| Statistical significance assessed | 1 | Chi-squared test |
| Confidence intervals for main results provided | 3 | Not reported |
| Confounding factors not accounted for | 1 | Confounders were not addressed with study design or analysis |
| Applicability of the results | 1 | Education of women of child-bearing age regarding benefits and harms of drug use during pregnancy is needed |

**Twigg, 2016 (cross-sectional survey)**

| Clearly focused question/issue | 1 | Risk perception of medications in pregnant women and relationship with use |
| Appropriate research method (study design) | 1 | Cross-sectional survey of pregnant women and new mothers |
| Selection of subjects clearly described | 1 | Self-selection, voluntary internet survey |
| Sampling method introduces bias | 1 | Informal sampling method – self-selection was not random or consecutive |
| Sample of subjects representative of the population | 1 | Pregnant women or women <1 year post-natal with internet access |
| Sample size based on pre-study considerations of statistical power | 2 | Not reported |
| Satisfactory response rate | 2 | Large n, no response rate reported |
| Questionnaires are likely to be valid and reliable | 1 | Used validated BMQ-General questionnaire |
| Statistical significance assessed | 1 | Chi-square, Fisher’s exact test, Mann-Whitney U, Independent t-test |
| Confidence intervals for main results | 3 | No confidence intervals for the main results, descriptive statistics only |
| Confounding factors not accounted for | 1 | Adjustment for confounding not reported in design or analysis |
| Applicability of the results | 1 | Medication use by pregnant women is impacted by beliefs about risk |

*Assessed using a tool developed by the Center for Evidence-based Management for cross-sectional studies*
* 1=Yes, 2=Can’t Tell, 3=No

ANOVA: analysis of variance; ASB: asymptomatic bacteriuria; BMQ: beliefs about medicine questionnaire; n: sample size; RCT: randomized clinical trial; VAS: visual analogue scale
## Appendix 8. Quality Assessments for Included Studies - KQ4

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author's judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brumfitte, 1975</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Unclear</td>
<td>No description of the sequence generation process, how women were assigned to treatment or placebo, unequal numbers in treatment and placebo groups.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No information provided to judge.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>&quot;...were given placebo under double-blind conditions&quot;. Method not described in sufficient detail. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low</td>
<td>&quot;...were given placebo under double-blind conditions&quot;. Method not described in sufficient detail. Objective outcomes.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High</td>
<td>Inconsistencies in total number of women not explained (number of &lt;2500g babies provided for 413/326 bacteriuric women); results not provided for pyelonephritis for all women in treated group (only subset).</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High</td>
<td>Results not provided for pyelonephritis for all women allocated to treatment.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Elder, 1966</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Unclear</td>
<td>&quot;...a random sequence&quot;. Insufficient information to judge.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No information provided to judge.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>&quot;...double-blind trial&quot;; no information provided to judge. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low</td>
<td>&quot;...double-blind trial&quot;; no information provided to judge. Objective outcomes.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low</td>
<td>Information provided on women lost to follow-up, reasonably balanced between groups.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High</td>
<td>Result not provided for pyelonephritis for all participants; no pregnancy outcomes (GA, birthweight).</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Elder, 1971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>High</td>
<td>&quot;...alternate bacteriuric...were assigned.”</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High</td>
<td>Participants were allocated by alternation.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>“identical-appearing placebo”; insufficient information to judge.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>“identical-appearing placebo”; insufficient information to judge.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>Unable to judge; twin deliveries were excluded.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Foley, 1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domain</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Low</td>
<td>Allocated to treatment or no treatment by “toss of a coin”.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No information to judge.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>No description of any attempt at blinding; not placebo-controlled. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>No description of any attempt at blinding; not placebo-controlled. Objective outcomes.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>Loss to follow-up: 19%; no reasons provided for missing outcome data.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High</td>
<td>No pregnancy outcomes (GA, birthweight).</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

**Furness, 1975**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear</td>
<td>“by random allocation”; no additional information to judge.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No information to judge.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>Not placebo-controlled. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>No information to judge.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High</td>
<td>20/226 women withdrawn from trial, no details provided. All women included in outcome of pyelonephritis, 17% loss to follow-up or low birthweight and GA at delivery.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>Unable to separate incidence of pyelonephritis during pregnancy and puerperium; results combined.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

**Gold, 1966**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>High</td>
<td>Women allocated to treatment based on study number: odd number treatment, even number control.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High</td>
<td>Allocated to treatment based on study number.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>Placebo-controlled; no further details provided. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>No information to judge.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low</td>
<td>Does not appear to be any loss to follow-up.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>No definition provided for prematurity.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

**Kass, 1960**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Author’s judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>High</td>
<td>“alternate women received a placebo”.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High</td>
<td>Allocation based on alternation: “alternate women received a placebo”.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>Placebo was used and “the nature of the treatment was not known to the patient or to the attending obstetrical staff”.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>Although a placebo was used, no further details are provided on blinding of outcome assessment. Objective outcomes.</td>
</tr>
<tr>
<td>Domain</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>40 (21%) women were not enrolled either because they were &gt;32 weeks GA before treatment could be started (n=30), or already received treatment for symptomatic infection (n=10). Loss to follow-up: 23 (11%) for pyelonephritis and low birthweight, no details provided; 69 (34%) for long-term persistent bacteriuria.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>3 women had subsequent pregnancy and were reassigned to their original treatment group included in the analysis. In 5 placebo patients, symptomatic disease was assumed but no symptoms were documented. Not all women in symptomatic group were confirmed to have fever. Women treated for infections other than that in the urinary tract were included in the symptomatic group if they had cleared their bacteriuria.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>Kazemier, 2015</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Low</td>
<td>Random assignment in 1:1 ratio; computer-generated list with random block sizes of 2/4/6 participants.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low</td>
<td>Women, treating physicians and researchers remained unaware of bacteriuria status and treatment allocation. Central allocation - unmasking of treatment allocation was possible by 24h telephone service.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>Double-blinded. Women, treating physicians and researchers remained unaware of bacteriuria status and treatment allocation. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low</td>
<td>Outcomes recorded by participants on questionnaires, and from data provided by hospitals and midwives up to 6 weeks post-delivery.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low</td>
<td>ITT and dropout rate &lt;10% (12/255 ASB-positive)</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low</td>
<td>Cost-effectiveness was outlined in protocol but not reported in final study methods or results.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>No other sources of bias identified.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Kincaid-Smith, 1965</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Unclear</td>
<td>No description of sequence generation process.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low</td>
<td>“a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen”.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>“a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen”.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low</td>
<td>“a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen”.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>240 women initially identified as bacteriuric; no information available on 55 (23%) women randomized to treatment but not included in the analysis because of poor compliance (attended infrequently or failed to take tablets continuously).</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Domain</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Little, 1966</td>
<td></td>
<td><strong>Random sequence generation</strong> Unclear No information to judge.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Allocation concealment</strong> Unclear Allocation to treatment or control was drawn for “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 the treatment group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of participants and personnel</strong> Unclear Participants in the control group “were given placebo”; no further details provided. Objective outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of outcome assessment</strong> Unclear No information to judge. Objective outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Incomplete outcome data</strong> Low No missing outcome data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Selective reporting</strong> Unclear Insufficient information to judge.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other bias</strong> Low Insufficient information to judge.</td>
</tr>
<tr>
<td></td>
<td><strong>Overall risk of bias</strong> Unclear</td>
<td></td>
</tr>
<tr>
<td>Mulia, 1960</td>
<td></td>
<td><strong>Random sequence generation</strong> Unclear No description of sequence generation process.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Allocation concealment</strong> Unclear Women were “randomly divided into two groups”; no other details provided Objective outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of participants and personnel</strong> Unclear Not placebo-controlled. Objective outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of outcome assessment</strong> Unclear No information to judge. Objective outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Incomplete outcome data</strong> Low No missing outcome data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Selective reporting</strong> High No definition for outcome of cystopyelitis; no pregnancy outcomes (GA, birthweight).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other bias</strong> Low Insufficient information to judge.</td>
</tr>
<tr>
<td></td>
<td><strong>Overall risk of bias</strong> High</td>
<td></td>
</tr>
<tr>
<td>Pathak, 1969</td>
<td></td>
<td><strong>Random sequence generation</strong> Unclear “on a random basis”. Insufficient information provided to permit further judgement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Allocation concealment</strong> Unclear Method of concealment not described.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of participants and personnel</strong> Unclear No information to judge.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of outcome assessment</strong> Unclear No information to judge.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Incomplete outcome data</strong> Low Missing outcome data balanced; reasons similar and unlikely to have introduced bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Selective reporting</strong> High No pregnancy outcomes (GA, birthweight).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other bias</strong> Low Insufficient information to judge.</td>
</tr>
<tr>
<td></td>
<td><strong>Overall risk of bias</strong> High</td>
<td></td>
</tr>
<tr>
<td>Thomsen, 1987</td>
<td></td>
<td><strong>Random sequence generation</strong> Unclear Described as “randomly allocated” but no description of the sequence generation process.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Allocation concealment</strong> Unclear Method of concealment of allocation not described.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Blinding of participants and personnel</strong> Unclear Placebo-controlled, described as “double-blinded” but no additional data. Objective outcomes.</td>
</tr>
<tr>
<td>Domain</td>
<td>Author’s judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>Described as “double-blinded” but no specific information provided to ensure outcome assessment was blinded. Objective outcomes.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low</td>
<td>No missing outcome data.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td><strong>Williams, 1969</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Unclear</td>
<td>“allocation at random”; no additional information to judge.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No information to judge.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>No blinding, outcome may have been influenced by lack of blinding. No treatment group was given antibiotics to take if symptoms of infection developed. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>No blinding; assessment of outcome (pyelonephritis) may have been influenced by knowledge of treatment allocation. Objective outcomes.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>No explanation for unequal group sizes; no information provided on any missing data. An unknown number of women in the control group were given antibiotic treatment if they developed symptoms of UTI.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High</td>
<td>No pregnancy outcomes (GA, birthweight).</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>Wren, 1969</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>High</td>
<td>Women “were divided into two groups, alternate patients being treated”.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High</td>
<td>Women “were divided into two groups, alternate patients being treated”.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear</td>
<td>No blinding; knowledge of treatment group may have influenced outcome; women in untreated group who developed clinical UTI (33/90) were given antibiotics at the choice of the obstetrician, continued to delivery in 50% of cases. Objective outcomes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>No blinding; however, outcome of birthweight unlikely to be influenced by lack of blinding.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low</td>
<td>10 (6%) women not included in outcomes: 2 sets of twins excluded, 6 moved and 2 could not be traced, 3 delivered before antibiotics could be started, 1 refused treatment.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear</td>
<td>Insufficient information to judge; outcome of pyelonephritis not reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Insufficient information to judge.</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

*Assessed using the Cochrane Risk of Bias tool

ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; UTI: urinary tract infection
Appendix 9. Search Strategy

KQ1: Screening Effectiveness

Database: Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date Searched: 13 June 2016
Records Retrieved: 1437

1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.
2. Bacteriuria/
3. exp Cystitis/
4. Dysuria/
5. Pyelonephritis/
6. Urinary Tract Infections/
7. bacilluria*.tw,kf.
8. bacteriuria*.tw,kf.
9. cystiti*.tw,kf.
10. (cysto-pyeliti* or cystopyeliti*).tw,kf.
11. dysuria*.tw,kf.
12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.
13. (pyelo-cystiti* or pyelocystiti*).tw,kf.
14. (pyelo-nephriti* or pyelonephriti*).tw,kf.
15. (UTI or UTIs).tw,kf.
16. or/1-15 [Combined MeSH & text words for bacteriuria]
17. Antibody-Coated Bacteria Test, Urinary/
18. *Bacteriuria/di, pc, mi, ur
19. exp *Cystitis/di, pc, mi, ur
20. Mass Screening/
21. Microbial Sensitivity Tests/
22. Microscopy/
23. Predictive Value of Tests/
24. *Pyelonephritis/di, pc, mi, ur
25. Reagent Kits, Diagnostic/
26. Reagent Strips/
27. "Sensitivity and Specificity"/
28. Urinalysis/
29. *Urinary Tract Infections/di, pc, mi, ur
30. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw,kf.
31. diagnostic accurac*.tw,kf.
32. culture*.tw,kf.
33. (detect* or predict* or screen*).tw,kf.
34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.
35. (microscopy or microscopy).tw,kf.
36. (microb* adj2 test*).tw,kf.
37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.
38. strip* test*.tw,kf.
39. urine test*.tw,kf.
KQ1: Screening Effectiveness

Database: Ovid Embase 1974 to 2016 Week 24
Date Searched: 13 June 2016
Records Retrieved: 1613

1. acute pyelonephritis/
2. asymptomatic bacteriuria/
3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.
4. bacteriuria/
5. exp cystitis/
6. dysuria/
7. kidney infection/
8. pyelonephritis/
9. urinary tract infections/
10. bacilluria*.tw.
11. bacteriuria*.tw.
12. cystiti*.tw.
13. (cysto-pyeliti* or cystopyeliti*).tw.
14. dysuria*.tw.
15. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw.
16. (pyelo-cystiti* or pyelocystiti*).tw.
17. (pyelo-nephriti* or pyelonephriti*).tw.
18. (UTI or UTIs).tw.
19. or/1-18 [Combined Emtree & text words for bacteriuria]
20. *asymptomatic bacteriuria/di, pc
21. *acute pyelonephritis/di, pc
22. *bacteriuria/di, pc
23. exp *cystitis/di, pc
24. diagnostic kit/
25. fluorescent antibody technique/
26. *kidney infection/di, pc
27. mass screening/
28. microbial sensitivity test/
29. microscopy/
30. predictive value/
31. *pyelonephritis/di, pc
32. "sensitivity and specificity"/
33. screening/
34. test strip/
35. exp urinalysis/
36. *urinary tract infection/di, pc
37. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw.
38. diagnostic accurac*.tw.
39. culture*.tw.
40. (detect* or predict* or screen*).tw.
41. (dip slide* or dipslide* or dip stick* or dipstick*).tw.
42. (microscopy or microscopy).tw.
43. (microb* adj2 test*).tw.
44. ((re-agent* or reagent) adj3 (strip* or test*)).tw.
45. strip* test*.tw.
46. urine test*.tw.
47. (urinalys* or urine analys*).tw.
48. uriscreen.tw.
49. or/20-48 [Combined Emtree & text words for screening]
50. exp pregnancy/
51. pregnancy complication/
52. pregnant woman/
53. prenatal care/
54. prenatal diagnosis/
55. prenatal screening/
56. (antenatal* or pre-natal* or prenatal*).mp.
57. (expect* adj (female? or mother? or wom#n)).tw.
58. pregnan*.mp.
59. or/50-58 [Combined Emtree & text words for pregnancy]
60. and/19,49,59 [Combined Emtree & text words for pregnancy]
61. Male/ not (Female/ and Male/)  
62. 60 not 61 [Male only records excluded]
63. animals/ not (animals/ and humans/)  
64. 62 not 63 [Animal only records excluded]
65. (conference* or editorial or letter).pt.
66. 64 not 65 [Excluded publication types – RF note: will search conference proceedings separately with different strategy]
67. case report/ or case report*.ti.
68. 66 not 67 [Case reports excluded]
69. limit 68 to (english or french)
70. remove duplicates from 69

KQ1: Screening Effectiveness
Database: Wiley Cochrane Library
Date Searched: 13 June 2016
Records Retrieved: 11 in Cochrane Database of Systematic Reviews
Records Retrieved: 1 in Database of Abstracts of Reviews of Effects (DARE)
Records Retrieved: 112 in Cochrane Central Register of Controlled Trials (CENTRAL)
Records Retrieved: 1 in Health Technology Assessment Database

#1 [mh ^"Asymptomatic Infections"] and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw
#2 [mh ^Bacteriuria]
#3 [mh Cystitis]
#4 [mh ^Dysuria]
#5 [mh ^Pyelonephritis]
#6 [mh ^"Urinary Tract Infections"]
#7 bacilluria*:ti,ab,kw
#8 bacteriuria*:ti,ab,kw
#9 cystiti*:ti,ab,kw
#10 (cysto-pyeliti* or cystopyeliti*):ti,ab,kw
#11 dysuria*:ti,ab,kw
#12 (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw
#13 (pyelo-cystiti* or pyelocystiti*):ti,ab,kw
#14 (pyelo-nephriti* or pyelonephriti*):ti,ab,kw
#15 (UTI or UTIs):ti,ab,kw
#16 [or #1-#15]
#17 [mh ^"Antibody-Coated Bacteria Test, Urinary"]
#18 [mh ^Bacteriuria [mj]/DI,PC,MI,UR]
#19 [mh Cystitis [mj]/DI,PC,MI,UR]
#20 [mh ^"Mass Screening"]
#21 [mh ^"Microbial Sensitivity Tests"]
#22 [mh ^Microscopy]
#23 [mh ^"Predictive Value of Tests"]
#24 [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]
#25 [mh "Reagent Kits, Diagnostic"]
#26 [mh "Reagent Strips"]
#27 [mh ^"Sensitivity and Specificity"]
#28 [mh ^Urinalysis]
#29 [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]
KQ1: Screening Effectiveness

Database: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost

Date Searched: 13 June 2016
Records Retrieved: 249

S1. (MH "Bacteriuria")
S2. (MH "Cystitis+")
S3. (MH "Dysuria")
S4. (MH "Pyelonephritis")
S5. (MH "Urinary Tract Infections")
S6. bacilluria*
S7. bacteriuria*
S8. cystiti*
S9. "cysto-pyeliti*" or cystopyeliti*
S10. dysuria*
S11. (infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))
S12. "pyelo-cystiti*" or pyelocystiti*
S13. "pyelo-nephriti*" or pyelonephriti*
S14. UTI or UTIs
S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16. (MM "Bacteriuria/DI/PC/MI/UR")
S17. (MM "Cystitis+/DI/MI/PC/UR")
S18. (MH "Fluorescent Antibody Technique")
S19. (MH "Health Screening")
S20. (MH "Microbial Culture and Sensitivity Tests")
S21. (MH "Microscopy")
S22. (MH "Predictive Value of Tests")
S23. (MM "Pyelonephritis/DI/PC/MI/UR")
S24. (MH "Reagent Kits, Diagnostic+")
S25. (MH "Sensitivity and Specificity")
S26. (MH "Urinalysis")
S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")
S28. (accurac* or diagnostic) N5 (algorithm* or test*)
S29. "diagnostic accurac**
S30. culture*
S31. detect* or predict* or screen*
S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*
S33. "micro-scopy" or microscopy
S34. microb* N2 test*
S35. ("re-agent*" or reagent) N3 (strip* or test*)
S36. "strip* test**
S37. "urine test**
S38. urinals* or "urine analys**
S39. uriscreen
S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39
S41. (MH "Expectant Mothers")
S42. (MH "Pregnancy+)")
S43. (MH "Pregnancy Complications, Infectious")
S44. (MH "Prenatal Care")
S45. (MH "Prenatal Diagnosis")
S46. antenatal* or "pre-natal*" or prenatal*
S47. expect* N1 (female? or mother? or wom?n)
S48. pregnan*
S49. S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48
S50. S15 AND S40 AND S49
S51. MH "Male" NOT ((MH "Female") AND (MH "Male"))
S52. S50 NOT S51
S53. ((MH "Vertebrates+") NOT MH Human)
S54. S52 NOT S53
S55. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter
S56. S54 NOT S55
S57. S56 Narrow by Language: - english [RF: No French records in results to include]

KQ1: Screening Effectiveness
Database: PubMed via NCBI Entrez (1946 to Present)
Date Searched: 14 June 2016
Records Retrieved: 1246
> limit to English or French

KQ2: Women’s Outcome Valuation
Database: Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date Searched: 4 July 2016
Records Retrieved: 2965

1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.
2. Bacteriuria/
3. exp Cystitis/
4. Dysuria/
5. Pyelonephritis/
6. Urinary Tract Infections/
7. bacilluria*.tw,kf.
8. bacteriuria*.tw,kf.
9. cystiti*.tw,kf.
10. (cysto-pyeliti* or cystopyeliti*).tw,kf.
11. dysuria*.tw,kf.
12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.
13. (pyelo-cystiti* or pyelocystiti*).tw,kf.
14. (pyelo-nephriti* or pyelonephriti*).tw,kf.
15. (UTI or UTIs).tw,kf.
16. or/1-15 [Combined MeSH & text words for bacteriuria]
17. Antibody-Coated Bacteria Test, Urinary/
18. *Bacteriuria/di, pc, mi, ur
19. exp *Cystitis/di, pc, mi, ur
20. Mass Screening/
21. Microbial Sensitivity Tests/
22. Microscopy/
23. Predictive Value of Tests/
24. *Pyelonephritis/di, pc, mi, ur
25. Reagent Kits, Diagnostic/
26. Reagent Strips/
27. "Sensitivity and Specificity"/
28. Urinalysis/
29. *Urinary Tract Infections/di, pc, mi, ur
30. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw,kf.
31. diagnostic accurac*.tw,kf.
32. culture*.tw,kf.
33. (detect* or predict* or screen*).tw,kf.
34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.
35. (micro-scopy or microscopy).tw,kf.
36. (microb* adj2 test*).tw,kf.
37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.
38. strip* test*.tw,kf.
39. urine test*.tw,kf.
40. (urinalys* or urine analys*).tw,kf.
41. uriscreen.tw,kf.
42. or/17-41 [Combined MeSH & text words for screening]
43. and/16,42 [Combined searches for ASB and screening]
44. Anti-Bacterial Agents/
45. Antibiotic Prophylaxis/
46. Anti-Infective Agents, Urinary/
47. Asymptomatic Infections/dt, th
48. *Bacteriuria/dt, th
49. Drug Therapy, Combination/
50. Norfloxacin/
51. exp Penicillins/
52. exp Sulfonamides/
53. *Urinary Tract Infections/dt, th
54. amoxicillin*.mp.
55. ampicillin*.mp.
56. (anti-bacteria* or antibacteria*).tw,kf.
57. (anti-biotic* or antibiotic*).tw,kf.
58. aztreonam*.mp.
59. cefadroxil*.mp.
60. cefepime*.mp.
61. ceftibuten*.mp.
63. cefuroxime*.mp.
64. cephaalexin*.mp.
65. cephalosporin*.mp.
66. cephadine*.mp.
67. clindamycin*.mp.
68. (co-trimoxazole* or cotrimoxazole*).mp.
69. cycloserine*.mp.
70. fosfomycin*.mp.
71. gentam###cin*.mp.
72. nalidixic acid*.mp.
73. nitrofurantoin*.mp.
74. penicillin*.mp.
75. piperacillin*.mp.
76. pivampicillin*.mp.
77. pivmecillinam*.mp.
78. sulfadimethoxine*.mp.
79. sulfadiazine*.mp.
80. sulfamethizole*.mp.
81. sulfamethoxazole*.mp.
82. sulfamethoxypyridazine*.mp.
83. sulfonamide*.mp.
84. sulphadimidine*.mp.
85. sulphonamide*.mp.
86. tetracycline*.mp.
87. vancomycin*.mp.
88. or/44-87 [Combined MeSH & text words for antibiotic treatment]
89. exp Pregnancy/
90. Pregnancy Complications, Infectious/
91. Pregnant Women/
92. Prenatal Care/
93. Prenatal Diagnosis/
94. (antenatal* or pre-natal* or prenatal*).mp.
95. (expect* adj (female? or mother? or wom#n)).tw,kf.
96. pregnan*.mp.
97. or/89-96 [Combined MeSH & text words for pregnancy]
98. and/88,97 [Combined searches for antibiotic treatment and pregnancy]
99. Choice Behavior/
100. *Consumer Behavior/
101. exp Consumer Participation/
102. Cooperative Behavior/
103. exp Decision Making/
104. Focus Groups/
105. Health Care Surveys/
106. exp Informed Consent/
107. Interviews as Topic/
108. Patient Acceptance of Health Care/
109. exp Patient Education as Topic/
110. Patient Participation/
111. Patient Preference/
112. Social Values/
113. "Surveys and Questionnaires"/
114. Treatment Refusal/
115. (15D* and (HRQoL or QoL or "quality of life")).mp.
116. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or opinion* or participat* or perceiv* or percep* or perspective? or prefer* or refus* or respons* or valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).tw,kf.
117. ((analys* or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf.
118. (choice? adj2 (behavi?r* or discrete or experiment*)).tw,kf.
119. ((choice? or choos* or consent* or decision*) adj1 informed).tw,kf.
120. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or support*)).tw,kf.
121. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.
122. (focus group? or interview* or questionnaire? or survey*).tw,kf.
123. gambl*.tw,kf.
KQ2: Women's Outcome Valuation
Database: Ovid Embase 1974 to 2016 Week 27
Date Searched: 4 July 2016
Records Retrieved: 3922

1. acute pyelonephritis/
2. asymptomatic bacteriuria/
3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.
4. bacteriuria/
5. exp cystitis/
6. dysuria/
7. kidney infection/
8. pyelonephritis/
9. urinary tract infections/
10. bacilluria*.tw.
11. bacteriuria*.tw.
12. cystiti*.tw.
13. (cysto-pyeliti* or cystopyeliti*).tw.
14. dysuria*.tw.
15. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw.
16. (pyelo-cystiti* or pyelocystiti*).tw.
17. (pyelo-nephriti* or pyelonephriti*).tw.
18. (UTI or UTIs).tw.
19. or/1-18 [Combined Emtree & text words for bacteriuria]
20. *asymptomatic bacteriuria/di, pc
21. *acute pyelonephritis/di, pc
22. *bacteriuria/di, pc
23. exp *cystitis/di, pc
24. diagnostic kit/
25. fluorescent antibody technique/
26. *kidney infection/di, pc
27. mass screening/
28. microbial sensitivity test/
29. microscopy/
30. predictive value/
31. *pyelonephritis/di, pc
32. "sensitivity and specificity"/
33. screening/
34. test strip/
35. exp urinalysis/
36. *urinary tract infection/di, pc
37. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw.
38. culture*.tw.
39. (detect* or predict* or screen*).tw.
40. diagnostic accurac*.tw.
41. (dip slide* or dipslide* or dip stick* or dipstick*).tw.
42. (micro-scopy or microscopy).tw.
43. (microb* adj2 test*).tw.
44. ((re-agent* or reagent) adj3 (strip* or test*)).tw.
45. strip* test*.tw.
46. urine test*.tw.
47. (urinalys* or urine analys*).tw.
48. uriscreen.tw.
49. or/20-48 [Combined Emtree & text words for screening]
50. and/19,49 [Combined searches for ASB and screening]
51. antibiotic agent/
52. antibiotic prophylaxis/
53. antiinfective agent/
54. *asymptomatic bacteriuria/dt, th
55. *asymptomatic infection/dt, th
56. *bacteriuria/dt, th
57. exp *cystitis/dt, th
58. drug combination/
59. *kidney infection/dt, th
60. norfloxacin/
61. penicillin derivative/
62. *pyelonephritis/dt, th
63. sulfonamide/
64. urinary tract antiinfective agent/
65. *urinary tract infection/dt, th
66. amoxicillin*.mp.
67. ampicillin*.mp.
68. (anti-bacteria* or antibacteria*).tw.
69. (anti-biotic* or antibiotic*).tw.
70. aztreonam*.mp.
71. cefadroxil*.mp.
72. cefepime*.mp.
73. ceftibuten*.mp.
74. ceftriaxone*.mp.
75. cefuroxime*.mp.
76. cephalaxin*.mp.
77. cephalosporin*.mp.
78. cephradine*.mp.
79. clindamycin*.mp.
80. (co-trimoxazole* or cotrimoxazole*).mp.
81. cycloserine*.mp.
82. fosfomycin*.mp.
83. gentamicin*.mp.
84. nalidixic acid*.mp.
85. nitrofurantoin*.mp.
86. penicillin*.mp.
87. piperacillin*.mp.
88. pivampicillin*.mp.
89. pivmecillinam*.mp.
90. sulfadimethoxine*.mp.
91. sulfadiazine*.mp.
92. sulfamethizole*.mp.
93. sulfamethoxazole*.mp.
94. sulfamethoxypyridazine*.mp.
95. sulfonamide*.mp.
96. sulphadimidine*.mp.
97. sulphonamide*.mp.
98. tetracycline*.mp.
99. vancomycin*.mp.
100. or/51-99 [Combined Emtree & text words for antibiotic treatment]
101. exp pregnancy/
102. pregnancy complication/
103. pregnant woman/
104. prenatal care/
105. prenatal diagnosis/
106. prenatal screening/
107. (antenatal* or pre-natal* or prenatal*).mp.
108. (expect* adj (female? or mother? or wom#.n)).tw.
109. pregnan*.mp.
110. or/101-109 [Combined Emtree & text words for pregnancy]
111. and/100,110 [Combined searches for antibiotic treatment and pregnancy]
112. cooperation/
113. *consumer attitude/
114. exp decision making/
115. health care survey/
116. informed consent/
117. exp interview/
118. exp patient attitude/
119. patient education/
120. exp questionnaire/
121. social psychology/
122. treatment refusal/
123. (15D* and (HRQoL or QoL or "quality of life").mp.
124. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).tw,kw.
125. (choice? adj2 (behavi?r* or discrete or experiment*)).tw,kw.
126. ((choice? or choos* or consent* or decision*) adj1 informed).tw,kw.
127. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or support*)).tw,kw.
128. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.
129. (focus group? or interview* or questionnaire? or survey*).tw,kw.
130. gambi*.tw,kw.
131. health utilit*.tw,kw.
132. HUI.tw,kw.
134. (preference? adj1 (elicit* or scor* or state*)).tw,kw.
135. prospect theor*.tw,kw.
136. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.
137. (trade off? or tradeoff?).tw,kw.
138. (willing* adj2 pay*).tw,kw.
139. or/112-138 [Combined Emtree & text words for patient preferences & values]
140. and/50,139 [Combined searches for patient preferences & ASB screening]
141. and/111,139 [Combined searches for patient preferences & antibiotic treatment and pregnancy]
142. or/140-141 [Combined sets of patient preferences for ASB screening & patient preferences for antibiotic treatment in pregnancy]
143. Male/ not (Female/ and Male/)
144. 142 not 143 [Male only records excluded]
145. animals/ not (animals/ and humans/)
146. 144 not 145 [Animal only records excluded]
147. (conference* or editorial or letter).pt.
148. 146 not 147 [Excluded publication types – RF note: will search conference proceedings separately with different strategy]
149. case report/ or case report*.ti.
150. 148 not 149 [Case reports excluded]
151. limit 150 to (english or french)
152. remove duplicates from 151
KQ2: Women's Outcome Valuation
Database: Wiley Cochrane Library
Date Searched: 5 July 2016
Records Retrieved: 45 in Cochrane Database of Systematic Reviews
Records Retrieved: 1 in Database of Abstracts of Reviews of Effects (DARE)
Records Retrieved: 321 in Cochrane Central Register of Controlled Trials (CENTRAL)
Records Retrieved: 4 in Cochrane Methodology Register
Records Retrieved: 14 in Economic Evaluations Database

#1 [mh ^"Asymptomatic Infections"] and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelonephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw
#2 [mh ^Bacteriuria]
#3 [mh Cystitis]
#4 [mh ^Dysuria]
#5 [mh ^Pyelonephritis]
#6 [mh ^"Urinary Tract Infections"]
#7 bacilluria*:ti,ab,kw
#8 bacteriuria*:ti,ab,kw
#9 cystiti*:ti,ab,kw
#10 (cysto-pyeliti* or cystopyeliti*):ti,ab,kw
#11 dysuria*:ti,ab,kw
#12 (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw
#13 (pyelo-cystiti* or pyelocystiti*):ti,ab,kw
#14 (pyelo-nephriti* or pyelonephriti*):ti,ab,kw
#15 (UTI or UTIs):ti,ab,kw
#16 {or #1-#15}
#17 [mh ^"Antibody-Coated Bacteria Test, Urinary"]
#18 [mh ^Bacteriuria [mj]/DI,PC,MI,UR]
#19 [mh Cystitis [mj]/DI,PC,MI,UR]
#20 [mh ^"Mass Screening"]
#21 [mh ^"Microbial Sensitivity Tests"]
#22 [mh ^Microscopy]
#23 [mh ^"Predictive Value of Tests"]
#24 [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]
#25 [mh "Reagent Kits, Diagnostic"]
#26 [mh "Reagent Strips"]
#27 [mh ^"Sensitivity and Specificity"]
#28 [mh ^Urinalysis]
#29 [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]
#30 ((accurac* or diagnostic) near/5 (algorithm* or test*)):ti,ab,kw
#31 "diagnostic accurac*":ti,ab,kw
#32 culture*:ti,ab,kw
#33 (detect* or predict* or screen*):ti,ab,kw
#34 ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw
#35 (micro-scopy or microscopy):ti,ab,kw
#36 (microb* near/2 test*):ti,ab,kw
#37 ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw
"strip* test":ti,ab,kw
"urine test":ti,ab,kw
(urinalys* or "urine analys*"):ti,ab,kw
uriscreen:ti,ab,kw
{or #17-#41}
#16 and #42
[mh "Anti-Bacterial Agents"]
[mh "Antibiotic Prophylaxis"]
[mh "Anti-Infective Agents, Urinary"]
[mh "Asymptomatic Infections"/DT,TH]
[mh Bacteriuria [mj]/DT,TH]
[mh "Drug Therapy, Combination"]
[mh Norfloxacin]
[mh Penicillins]
[mh Sulfonamides]
[mh "Urinary Tract Infections" [mj]/DT,TH]
amoxicillin*:ti,ab,kw
ampicillin*:ti,ab,kw
("anti-bacteria*" or antibacteria*):ti,ab,kw
("anti-biotic*" or antibiotic*):ti,ab,kw
aztreonam*:ti,ab,kw
cefadroxil*:ti,ab,kw
cefepime*:ti,ab,kw
ceftibuten*:ti,ab,kw
ceftri?xone*:ti,ab,kw
cefuroxime*:ti,ab,kw
cephalexin*:ti,ab,kw
cephradine*:ti,ab,kw
clindamycin*:ti,ab,kw
("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw
cycloserine*:ti,ab,kw
fosfomycin*:ti,ab,kw
gentam?cin*:ti,ab,kw
"nalidixic acid*":ti,ab,kw
nitrofurantoin*:ti,ab,kw
penicillin*:ti,ab,kw
piperacillin*:ti,ab,kw
 pivampicillin*:ti,ab,kw
 pivmecillinam*:ti,ab,kw
 sulfadimethoxine*:ti,ab,kw
 sulfadiazine*:ti,ab,kw
 sulfadimethoxazole*:ti,ab,kw
 sulfadiazine*:ti,ab,kw
 sulfadimidine*:ti,ab,kw
 sulphonamide*:ti,ab,kw
 sulfamethoxypyridazine*:ti,ab,kw
 sulfonamide*:ti,ab,kw
 sulphadimidine*:ti,ab,kw
 sulphonamide*:ti,ab,kw
KQ2: Women's Outcome Valuation
Database: Ovid PsycINFO 1806 to June Week 5 2016
Date Searched: 5 July 2016
Records Retrieved: 113

1. Bacterial Disorders/ and (bladder* or genitourin* or kidney* or urin* or urogenita*).mp.
2. Infectious Disorders/ and (bladder* or genitourin* or kidney* or urin* or urogenita*).mp.
3. Urinary Function Disorders/ and infection*.mp.
4. Urogenital Disorders/ and infection*.mp.
5. bacilluria*.mp.
6. bacteriuria*.mp.
7. cystit*.mp.
8. (cysto-pyeliti* or cystopyeliti*).mp.
9. dysuria*.mp.
10. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).mp.
11. (pyelo-cystiti* or pyelocystiti*).mp.
12. (pyelo-nephriti* or pyelonephriti*).mp.
13. (UTI or UTIs).mp.
14. or/1-13 [Combined subject headings & text words for bacteriuria]
15. Health Screening/
16. Screening/
17. Screening Tests/
18. Test Reliability/
19. exp Test Validity/
20. Urinalysis/
21. ((accurac* or diagnostic) adj5 (algorithm* or test*)).ti,ab.
22. diagnostic accurac*.ti,ab.
23. culture*.ti,ab.
24. (detect* or predict* or screen*).ti,ab.
25. (dip slide* or dipslide* or dip stick* or dipstick*).ti,ab.
26. (micro-scopy or microscopy).ti,ab.
27. (microb* adj2 test*).ti,ab.
28. ((re-agent* or reagent) adj3 (strip* or test*)).ti,ab.
29. strip* test*.ti,ab.
30. urine test*.ti,ab.
31. (urinalys* or urine analys*).ti,ab.
32. uriscreen.ti,ab.
33. or/15-32 [Combined subject headings & text words for screening]
34. and/14,33 [Combined searches for ASB and screening]
35. antibiotics/
36. penicillins/
37. amoxicillin*.mp.
38. ampicillin*.mp.
39. (anti-bacteria* or antibacteria*).mp.
40. (anti-biotic* or antibiotic*).mp.
41. aztreonam*.mp.
42. cefadroxil*.mp.
43. cefepime*.mp.
44. ceftibuten*.mp.
45. ceftriaxone*.mp.
46. cefuroxime*.mp.
47. cephalaxin*.mp.
48. cephalosporin*.mp.
49. cephadrine*.mp.
50. clindamycin*.mp.
51. (co-trimoxazole* or cotrimoxazole*).mp.
52. cycloserine*.mp.
53. fosfomycin*.mp.
54. gentamycin*.mp.
55. nalidixic acid*.mp.
56. nitrofurantoin*.mp.
57. penicillin*.mp.
58. piperacillin*.mp.
59. pivampicillin*.mp.
60. pivmecillinam*.mp.
61. sulfadimethoxine*.mp.
62. sulfadiazine*.mp.
63. sulfamethizole*.mp.
64. sulfamethoxazole*.mp.
65. sulfamethoxypyridazine*.mp.
66. sulfonamide*.mp.
67. sulphadimidine*.mp.
68. sulphonamide*.mp.
69. tetracycline*.mp.
70. vancomycin*.mp.
71. or/35-70 [Combined subject headings & text words for antibiotic treatment]
72. adolescent pregnancy/
73. pregnancy/
74. prenatal care/
75. (antenatal* or pre-natal* or prenatal*).ti,ab.
76. (expect* adj (female? or mother? or wom*n)).ti,ab.
77. pregnancy*.mp.
78. or/72-77 [Combined subject headings & text words for pregnancy]
79. and/71,78 [Combined searches for antibiotic treatment and pregnancy]
80. Choice Behavior/
81. Client Attitudes/
82. Client Participation/
83. Client Rights/
84. Cooperation/
85. Decision Making/
86. *Consumer Behavior/
87. Informed Consent/
88. Interviews/
89. Preferences/
90. Questionnaires/
91. Social Values/
92. Surveys/
93. Treatment Barriers/
94. Treatment Refusal/
95. (15D* and (HRQoL or QoL or "quality of life")).mp.
96. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).ti,ab.
97. (analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).ti,ab.
98. (choice? adj2 (behandio?r* or discrete or experiment*)).mp.
99. ((choice? or choos* or consent* or decision*) adj1 informed).ti,ab.
100. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or support*)).ti,ab.
101. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.
102. (focus group? or interview* or questionnaire? or survey*).ti,ab.
103. gambli*.ti,ab.
104. health utilit*.ti,ab.
105. HUI.mp.
107. (preference? adj1 (elicit* or scor* or state*)).mp.
108. prospect theor*.ti,ab.
109. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.
110. (trade off? or tradeoff?).ti,ab.
111. (willing* adj2 pay*).ti,ab.
112. or/80-111 [Combined subject & text words for patient preferences & values]
113. and/34,112 [Combined searches for patient preferences & ASB screening]
114. and/79,112 [Combined searches for patient preferences & antibiotic treatment and pregnancy]
115. or/113-114 [Combined sets of patient preferences for ASB screening & patient preferences for antibiotic treatment in pregnancy]
116. (boy* or male* or men).ti.
117. 115 not 116 [Male records excluded]
118. (case report* or comment* or editorial or letter).ti.
119. 117 not 118 [Opinion pieces & case reports excluded]
120. limit 119 to (english or french)
121. remove duplicates from 120

KQ2: Women's Outcome Valuation
Database: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost
Date Searched: 5 July 2016
Records Retrieved: 872

S1. (MH "Bacteriuria")
S2. (MH "Cystitis+")
S3. (MH "Dysuria")
S4. (MH "Pyelonephritis")
S5. (MH "Urinary Tract Infections")
S6. bacilluria*
S7. bacteriuria*
S8. cystiti*
S9. "cysto-pyeliti*" or cystopyeliti*
S10. dysuria*
S11. (infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))
S12. "pyelo-cystiti**" or pyelocystiti*
S13. "pyelo-nephriti**" or pyelonephriti*
S14. UTI or UTIs
S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16. (MM "Bacteriuria/DI/PC/MI/UR")
S17. (MM "Cystitis+/DI/MI/PC/UR")
S18. (MH "Fluorescent Antibody Technique")
S19. (MH "Health Screening")
S20. (MH "Microbial Culture and Sensitivity Tests")
S21. (MH "Microscopy")
S22. (MH "Predictive Value of Tests")
S23. (MM "Pyelonephritis/DI/PC/MI/UR")
S24. (MH "Reagent Kits, Diagnostic+")
S25. (MH "Sensitivity and Specificity")
S26. (MH "Urinalysis")
S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")
S28. (accurac* or diagnostic) N5 (algorithm* or test*)
S29. "diagnostic accurac**
S30. culture*
S31. detect* or predict* or screen*
S32. "dip slide**" or dipslide* or "dip stick**" or dipstick*
S33. "micro-scopy" or microscopy
S34. microb* N2 test*
S35. ("re-agent**" or reagent) N3 (strip* or test*)
S36. "strip* test**
S37. "urine test**
S38. urinalys* or "urine analys**
S39. uriscreen
S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39
S41. S15 AND S40 [Combined searches for ASB and screening]
S42. (MH "Antibiotic Prophylaxis")
S43. (MH "Antibiotics")
S44. (MH "Antibiotics, Combined")
S45. (MH "Antiiinfective Agents, Urinary+")
S46. (MM "Bacteriuria/DT/TH")
S47. (MH "Penicillins")
S48. (MH "Sulfonamides")
S49. (MM "Urinary Tract Infections/DT/TH")
S50. amoxicillin*
S51. ampicillin*
S52. ("anti-bacteria** or antibacteria")
S53. ("anti-biotic** or antibiotic")
S54. aztreonam*
S55. cefadroxil*
S56. cefepime*
S57. ceftibuten*
S58. ceftriaxone*
S59. cefuroxime*
S60. cephalexin*
S61. cephalosporin*
S62. cephradine*
S63. clindamycin*
S64. ("co-trimoxazole** or cotrimoxazole")
S65. cycloserine*
S66. fosfomycin*
S67. gentamicin*
S68. "nalidixic acid**"
S69. nitrofurantoin*
S70. penicillin*
S71. piperacillin*
S72. pivampicillin*
S73. pivmecillinam*
S74. sulfadimethoxine*
S75. sulfadiazine*
S76. sulfamethizole*
S77. sulfamethoxazole*
S78. sulfamethoxypyridazine*
S79. sulfonamide*
S80. sulphadimidine*
S81. sulphonamide*
S82. tetracycline*
S83. vancomycin*
S84. S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83
S85. (MH "Expectant Mothers")
S86. (MH "Pregnancy+")
S87. (MH "Pregnancy Complications, Infectious")
S88. (MH "Prenatal Care")
S89. (MH "Prenatal Diagnosis")
S90. antenatal* or "pre-natal** or prenatal*
S91. expect* N1 (female? or mother? or wom?n)
S92. pregnan*
S93. S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92
S94. S84 AND S93
S95. (MH "Consumer Participation")
S96. (MH "Consensus")
S97. (MH "Consent")
S98. (MH "Cooperative Behavior")
S99. (MH "Decision Making")
S100. (MH "Decision Making, Patient")
S101. (MH "Dissent and Disputes")
S102. (MH "Focus Groups")
S103. (MH "Interviews")
S104. (MH "Patient Education")
S105. (MH "Quality of Health Care")
S106. (MH "Questionnaires")
S107. (MH "Self Report")
S108. (MH "Social Values")
S109. (MH "Surveys")
S110. (MH "Treatment Refusal")
S111. (15D* and (HRQoL or QoL or "quality of life"))
S112. ((accept* or consider* or choice* or choos* or chose* or decid* or decis* or input* or involv* or opinion* or participat* or perceiv* or percepti* or perspective* or prefer* or refus* or respons* or valuation or value* or valuing or view*) N3 (citizen* or client* or consumer* or female* or male* or men or patient* or public or "stake-holder*" or stakeholder* or user* or wom?n))
S113. ((analys?s or valuation* or value* or valuing) N3 (conjoint or contingent))
S114. (choice* N2 (behavio* or discrete or experiment*))
S115. ((choice* or choos* or consent* or decision*) N1 informed)
S116. ((choice* or choos* or decision*) N2 (made or make or makes or making or shar* or support*))
S117. ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D)
S118. ("focus group*" or interview* or questionnaire* or survey*)
S119. gambl*
S120. "health utilit*"
S121. HUI
S122. ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria)
S123. (preference* N1 (elicit* or scor* or state*))
S124. "prospect theor*"
S125. ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D)
S126. ("trade off*" or tradeoff*)
S127. (willing* N2 pay*)
S128. S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127
S129. S41 AND S128
S130. S94 AND S128
S131. S129 OR S130
S132. MH "Male" NOT ((MH "Female") AND (MH "Male"))
S133. S131 NOT S132
amoxicillin OR ampicillin OR "anti-bacteria" AND "anti-bacterial" OR "anti-bacterials" AND "anti-biotic" OR "anti-biotics" OR antibiotic OR antibiotics OR antibacteria OR antibacterial OR antibiotic OR antibiotics OR aztreonam OR cefadroxil OR cefepime OR ceftibuten OR ceftiraxone OR cefuroxime OR cephalixin OR cephalosporin OR cephalosporins OR cephradine OR clindamycin OR "co-trimoxazole" OR cotrimoxazole OR cycloserine OR cycloserines OR fosfomycin OR gentamicin OR gentamycin OR "naldixic acid" OR nitrofurantoin OR penicillin OR penicillins OR piperacillin OR pivampicillin OR pivmecillinam OR sulfamethoxazole OR sulfamethoxypridazine OR sulfonamide OR sulphonamide OR sulphadimidine OR sulphamethoxazole OR tetracycline OR tetracyclines OR vancomycin AND ("Pregnancy" OR "Pregnancy Complications, Infectious" OR "Pregnant Women" OR "Prenatal Care" OR "Prenatal Diagnosis" OR antenatal OR "pre-natal" OR prenatal OR "expectant mother" OR "expectant mothers" OR "expecting mothers" OR "expectant woman" OR "expectant women" OR "expecting women" OR pregnancies OR pregnancy OR pregnant) AND ("Consumer Participation" OR "Cooperative Behavior" OR "Decision Making" OR "Focus Groups" OR "Health Care Surveys" OR "Informed Consent" OR "Interviews as Topic" OR "Patient Acceptance of Health Care" OR "Patient Education as Topic" OR "Patient Participation" OR "Patient Preference") OR (accept OR accepted OR accepting OR accepts OR consider OR consideration OR considers OR choice OR choices OR choose OR chooses OR choosing OR chose OR chosen OR decide OR decided OR deciding OR decides OR decision OR decisionmaker OR decisionmaking OR decisions OR decisive OR input OR involve OR involution OR opinion OR opinionated OR opinions OR participate OR participated OR participating OR participation OR participates OR perceive OR perceived OR perceiving OR perceives OR perception OR perceptions OR perceptive OR persuasive OR perspective OR perspectives OR preference OR preferences OR preferred OR preferring OR refusal OR refuse OR refused OR refusing OR refuses OR response OR responses OR valuation OR value OR valued OR values OR valuing OR view OR viewed OR viewing OR viewpoint OR viewpoints OR views OR (analyses OR analysis OR valuation OR valuations OR value OR values OR valuation OR valuing) AND (conjoint OR contingent)) OR "choice behavior" OR "choice behaviour" OR "discrete choice" OR "EQ 5D" OR EQ5D OR "EuroQol 5D" OR EuroQol5D OR "focus group" OR "focus groups" OR gamble OR gambled OR gambling OR gambles OR "health utilities" OR "health utility"
KQs4,5: Systematic Review & HTA Search

Database: PubMed via NCBI Entrez (1946 to Present)

Date Searched: 14 October 2016

Records Retrieved: 104


KQs4,5: Systematic Review & HTA Search

Database: Wiley Cochrane Library
Date Searched: 14 October 2016

Records Retrieved: 19 in Cochrane Database of Systematic Reviews
Records Retrieved: 4 in Database of Abstracts of Reviews of Effects (DARE)
Records Retrieved: 1 in Health Technology Assessment Database
Records Retrieved: 3 in Economic Evaluations Database

#1 [(mh "Asymptomatic Infections") and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw]
#2 [mh Bacteriuria]
#3 [mh Cystitis]
#4 [mh Dysuria]
#5 [mh Pyelonephritis]
#6 [mh "Urinary Tract Infections"]
#7 bacilluria*:ti,ab,kw
#8 bacteriuria*:ti,ab,kw
#9 cystiti*:ti,ab,kw
#10 (cysto-pyeliti* or cystopyeliti*):ti,ab,kw
#11 dysuria*:ti,ab,kw
#12 (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw
#13 (pyelo-cystiti* or pyelocystiti*):ti,ab,kw
#14 (pyelo-nephriti* or pyelonephriti*):ti,ab,kw
#15 (UTI or UTIs):ti,ab,kw
#16 {or #1-#15}
Antibody-Coated Bacteria Test, Urinary

Bacteriuria

Cystitis

Mass Screening

Microbial Sensitivity Tests

Microscopy

Predictive Value of Tests

Pyelonephritis

Reagent Kits, Diagnostic

Reagent Strips

Sensitivity and Specificity

Urinalysis

Urinary Tract Infections

Diagnostic accurac*

Culture

Detect or predict or screen

"dip slide" or dipslide or "dip stick" or dipstick

Microscopy

Microbial test

Reagent strip test

Urine test

Urinalysis

Urinary Tract Infections

Anti-Bacterial Agents

Antibiotic Prophylaxis

Anti-Infective Agents, Urinary

Asymptomatic Infections

Bacteriuria

Drug Therapy, Combination

Norfloxacin

Penicillins

Sulfonamides

Urinary Tract Infections

Amoxicillin

Ampicillin

"anti-bacteria" or antibacteria

"anti-biotic" or antibiotic

Aztreonam

Cefadroxil

Cefepime

Ceftibuten

Ceftriaxone

Cefuroxime

Cephalexin

Cephalosporin
#65 cephradine*:ti,ab,kw
#66 clindamycin*:ti,ab,kw
#67 ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw
#68 cycloserine*:ti,ab,kw
#69 fosfomycin*:ti,ab,kw
#70 gentam?cin*:ti,ab,kw
#71 "nalidixic acid*":ti,ab,kw
#72 nitrofurantoin*:ti,ab,kw
#73 penicillin*:ti,ab,kw
#74 piperacillin*:ti,ab,kw
#75 pivampicillin*:ti,ab,kw
#76 pivmecillinam*:ti,ab,kw
#77 sulfadimethoxine*:ti,ab,kw
#78 sulfadiazine*:ti,ab,kw
#79 sulfamethizole*:ti,ab,kw
#80 sulfamethoxazole*:ti,ab,kw
#81 sulfamethoxypyridazine*:ti,ab,kw
#82 sulphonamide*:ti,ab,kw
#83 sulphadimidine*:ti,ab,kw
#84 sulphonamide*:ti,ab,kw
#85 tetracycline*:ti,ab,kw
#86 vancomycin*:ti,ab,kw
#87 (or #43-#86)
#88 #16 and (#42 or #87)
#89 [mh Pregnancy]
#90 [mh ^"Pregnancy Complications, Infectious"]
#91 [mh ^"Pregnant Women"]
#92 [mh ^"Prenatal Care"]
#93 [mh ^"Prenatal Diagnosis"]
#94 (antenatal* or "pre-natal*" or prenatal*):ti,ab,kw
#95 (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw
#96 pregnan*:ti,ab,kw
#97 (or #89-#96)
#98 #88 and #97
### Appendix 10. Excluded Studies – KQ1 a & b (screening effectiveness)

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Authors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm labor: Diagnostic and therapeutic options are not all alike.</td>
<td>Abies AZ, Chauhan SP.</td>
<td>J. 2005;54(3):245-52.</td>
</tr>
</tbody>
</table>


Studies Excluded Due to Population (56)


Studies Excluded due to Comparator (56)


Studies Excluded Due to Language (3)


Studies Excluded as Full Text was Unavailable (7)
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies Excluded as they were Duplicates (1)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: no studies were excluded due to outcome
### Appendix 11. Excluded Studies – KQ2 (women’s outcome valuation)

<table>
<thead>
<tr>
<th>Studies Excluded Due to Study Design (20)</th>
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### Studies Excluded Due to Population (31)

<table>
<thead>
<tr>
<th>Studies Excluded Due to Population (31)</th>
</tr>
</thead>
</table>


Studies Excluded Due to Intervention (45)


65. Forrester MB, Stanley SK. Exposures and treatments among women of childbearing age and pregnant women reported to Texas poison centers. Veterinary and Human Toxicology. 2004;46(4):210-2.


Studies Excluded Due to Outcome (47)


Studies Excluded Due to Language (4)


## Appendix 12. Excluded Studies – KQ4 (treatment effectiveness)

<table>
<thead>
<tr>
<th>Studies Excluded Due to Study Design (5)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
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<th>Studies Excluded Due to Population (3)</th>
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<table>
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<th>Studies Excluded Due to Intervention (5)</th>
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<table>
<thead>
<tr>
<th>Studies Excluded due to Comparator (1)</th>
<th></th>
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</thead>
</table>
Appendix 13. Methods for Integrating Existing Systematic Reviews into New Reviews

One or more systematic reviews may exist that align with one or more key questions (KQs) of the reviews undertaken to inform CTFPHC guidelines. The CTFPHC and ERSCs have considered the manner in which new reviews conducted for CTFPHC guidelines can benefit from efficiencies by incorporating existing systematic reviews, while maintaining methodological rigor in their own systematic review conduct, closely aligning existing reviews within their review scope (i.e., inclusion/exclusion criteria), and maintaining consistency with other CTFPHC Methods. They have based their approach on work conducted by a methods working group composed of investigators from the Evidence-based Practice Center Program funded by the U.S. Agency for Healthcare Research and Quality.1,2 A summary of the way the ERSCs will operationalize the 12 AHRQ recommendations (Box 1) to meet their needs is outlined below. This approach differs from situations when “updating” a single existing systematic review is deemed suitable, that is, in some cases a high-quality review will be used to answer one or more of the CTFPHC KQs in entirety, usually without revisions to the review’s scope, search for evidence (apart from updating to present), methodological quality/risk of bias assessments, data extraction, or data analysis.

Summary of CTFPHC Approach

The recommendations developed by AHRQ (Box 1) will serve as an overall framework for ERSC reviews, although in most cases existing systematic reviews will be used to build efficiencies in discrete steps within the review process—mainly search and selection of literature, and data extraction—which will not generally include refinement of the scope or data analysis and interpretation. Moreover, we will not in most circumstances include a systematic review itself as a study design for inclusion (unless the intention is to specifically conduct an overview of reviews). The ability to use any given systematic review will largely depend on how it aligns with the CTFPHC review’s scope (PICOTS). A further primary consideration will be the comprehensiveness of its search strategy and reporting of literature flow. It is important to note that some CTFPHC reviews need to be complex with multiple stages (e.g., a review of screening effectiveness for patient-important benefits and harms may require including evidence on indirect evidence of test accuracy and treatment) such that existing systematic reviews may exist for one or more discrete stages but not for others. Some key points on the operationalization, and minor revision, by the ERSCs of these recommendations are provided below.

1. **Choosing systematic reviews**: Following the identification of relevant reviews (a search for systematic reviews may be undertaken for some topics), the evidence for each will be mapped to the PICOTS elements and the quality of the review will be assessed (e.g., using the AMSTAR tool which has been evaluated and found effective to discriminate reviews with high and low quality of methods and reporting).3 Some of the CTFPHC KQs may only have a single existing systematic review for possible incorporation, while others may have more than one; if suitable, a decision between systematic reviews will be based on methodological quality, comprehensiveness and quality of its literature search and reporting (e.g., assessed using PRESS checklist), comprehensiveness of reporting on included studies, and the best fit within the CTFPHC scope and methods. In some cases two or more reviews may be integrated because, together, they capture the full scope of the CTFPHC KQ(s). Rationale will be provided for choices made.
Note: If no review is deemed a good fit for purpose for integration (i.e., de novo process all together appears to be best option) we will at minimum examine available reviews for their search strategies (to ensure that our search strategies are comprehensive) and review their reference lists for identification of studies.

2. **Searching**: Various strategies will be considered. If one or more reviews are fit for purpose (but do not meet criteria for classification as a systematic review update) and cover a scope that is *very similar or broader* than the CTFPHC topic, we may update the search(es) if the last search date was prior to 6 months before commencing our review. When there are multiple reviews being considered, updating the literature to present may involve a new comprehensive search strategy to identify studies published after the date of the earliest existing review; this may reduce complexities when trying to implement, document, and remove duplicates from multiple searches. Alternatively, if the scope of the existing review(s) is *narrower* (e.g., missing an element in PICOTS) or the search *deemed sub-optimal in some manner* (e.g., missing key terms, additional database viewed as highly relevant) we may re-run the existing review’s search concurrent with an original (e.g., broader) search and remove the citations previously screened for the other review. If more appropriate, we may update the other review’s search and use a new search for the missing PICO element(s) (e.g., one additional intervention) for a longer time period to meet our timeframe. In cases where we feel screening excluded studies lists is appropriate we will also undertake this. Careful consideration will be used to ensure a comprehensive search is conducted regardless of approach taken; moreover, the ERSC librarians will help determine on a case-by-case basis what approach would be feasible for implementation to ensure aims of building efficiencies are possible.

3. **Screening and selection**: We will assess articles included in all relevant reviews (based on full text if necessary) to determine if they meet our inclusion criteria.

4. **Data extraction and methodological quality assessments**: We will consider incorporating the data on study and participant characteristics rather than extracting these data anew; we may also use the review author’s risk of bias assessments if the tools/methods are consistent with CTFPHC methods. These steps will create efficiencies but because they are dependent on the quality of the systematic review and extent of reporting, the ERSC staff will verify the data on at least 5 to 10% of studies.¹

5. **Data analysis**: We will consider using quantitative outcome data from reviews (with verification), but will not typically use meta-analyses or quality (GRADE) assessments of existing reviews.

6. **Reporting**: Transparent reporting of all integration steps used will be included in the evidence review report.
Box 1. Recommendations developed by AHRQ EPCs*1,2

*Strength of evidence refers to AHRQ’s slightly modified approach to the GRADE quality of evidence approach

1. Existing reviews should be confirmed as systematic reviews through the application of a minimum set of eligibility criteria. We propose that the minimum eligibility criteria for systematic reviews include an explicit and adequate search, application of predefined eligibility criteria to select studies, risk of bias assessment for included studies, and synthesis of results.

2. Criteria to assess the relevance, in terms of question elements and currency, and quality of existing systematic reviews under consideration for inclusion in reviews should be predefined.

3. The quality of relevant existing systematic reviews should be assessed in an explicit manner with a minimum set of quality criteria that include search of multiple sources, use of a generally accepted tool for risk of bias assessment, and sufficient information to assess the strength of the body of evidence that includes the major domains of risk of bias, directness, consistency, precision, and reporting bias.

4. The risk of bias assessments from the existing systematic review may be used when the review described an explicit process, including the use of a tool or method that is compatible with the approach of the current review and that assessed the key sources of potential bias.

5. We suggest that risk of bias assessment be repeated in a sample of studies from an existing review under consideration for inclusion in a new review to confirm concordance with current review team approach.

6. We recommend that at a minimum, reviews should narratively describe findings of the prior review(s), including the number and types of studies included, and the overall findings.

7. We recommend that newly identified studies be clearly distinguished from studies in the existing review(s) when presented in the narrative and any tables (eg, separate tables).

8. Summary tables should include sufficient information to support ratings for overall strength of evidence, including ratings for individual strength of evidence domains (study limitations, consistency, precision, directness, reporting bias). The strength of evidence ratings should be based on the underlying primary evidence, not the number or quality of existing systematic reviews.

9. Using strength of evidence domains as a framework (study limitations, consistency, precision, directness, and reporting bias), review authors should consider how new evidence would change estimates of effect or ratings for strength of evidence. A new quantitative synthesis (ie, pooled estimate) is needed if new studies would change conclusions or strength of evidence judgements, or to obtain a more precise or more up-to-date estimate.

10. In cases where the existing systematic review(s) did not complete strength of evidence grading for a comparison and outcome of interest, the strength of evidence should be assessed for the body of evidence, considering primary studies from prior review(s) and any new studies identified.

11. In cases where no new studies are added to the body of evidence, the strength of evidence assessment from the existing systematic review may be used if conducted using an acceptable grading approach consistent with current review context. In these cases, we suggest that the overall strength of evidence assessment be reviewed, considering the strength of evidence domains, to confirm consistency with current review team assessments.

12. In cases where new studies are added to the body of evidence, the strength of evidence may need to be reassessed on the basis of all studies/evidence.
Appendix 8 References

