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

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REVISION HISTORY

Section	Date	Description/Changes	Reason for Change
Analytical Framework and Staged Approach	December 9, 2016*	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.	To clarify that evidence on each of, treatment and test accuracy, are indirect evidence of screening effectiveness.
Figure 1. Analytical Framework	December 9, 2016*	Added treatment and no treatment to each arm of ASB+ and ASB-.	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.
Eligibility Criteria	December 9, 2016*	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).	To clarify the difference between KQ1a and KQ1b.
Eligibility Criteria	December 9, 2016*	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.	To clarify that harms to both mother and neonate are included.
Eligibility Criteria	December 9, 2016*	Revised setting to any primary care or clinical setting which provides obstetric/antenatal care to pregnant women.	To avoid precluding care provided in other settings (e.g., obstetric office/clinic).
Eligibility Criteria	January 27, 2017**	Revised perinatal mortality to ≥ 20 weeks of gestation.	To capture all perinatal mortality reported, including stillbirths which are reported using different criteria among studies.
Eligibility Criteria	February 24, 2017***	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.	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.
GRADE Assessments	October 6, 2017***	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.	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.

*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 ($\geq 10^5$ 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; I^2=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, I^2=31% versus RR 0.50, 95% CI 0.19, 1.35, I^2=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 pyelonephritis[3] with its associated inflammation of the renal parenchyma, calices and pelvis,[5] although controversy exists. Historical reports pre-1980[6-8] 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 al[10]) 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 review[4] 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 resolved[4], 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 ≥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 ≥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[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[17] Cochrane review of treatment effectiveness. The American Academy of Family Physicians (AAFP)[18] endorses the recommendations of the USPSTF. The Infectious Diseases Society of America[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.[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.[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.[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.

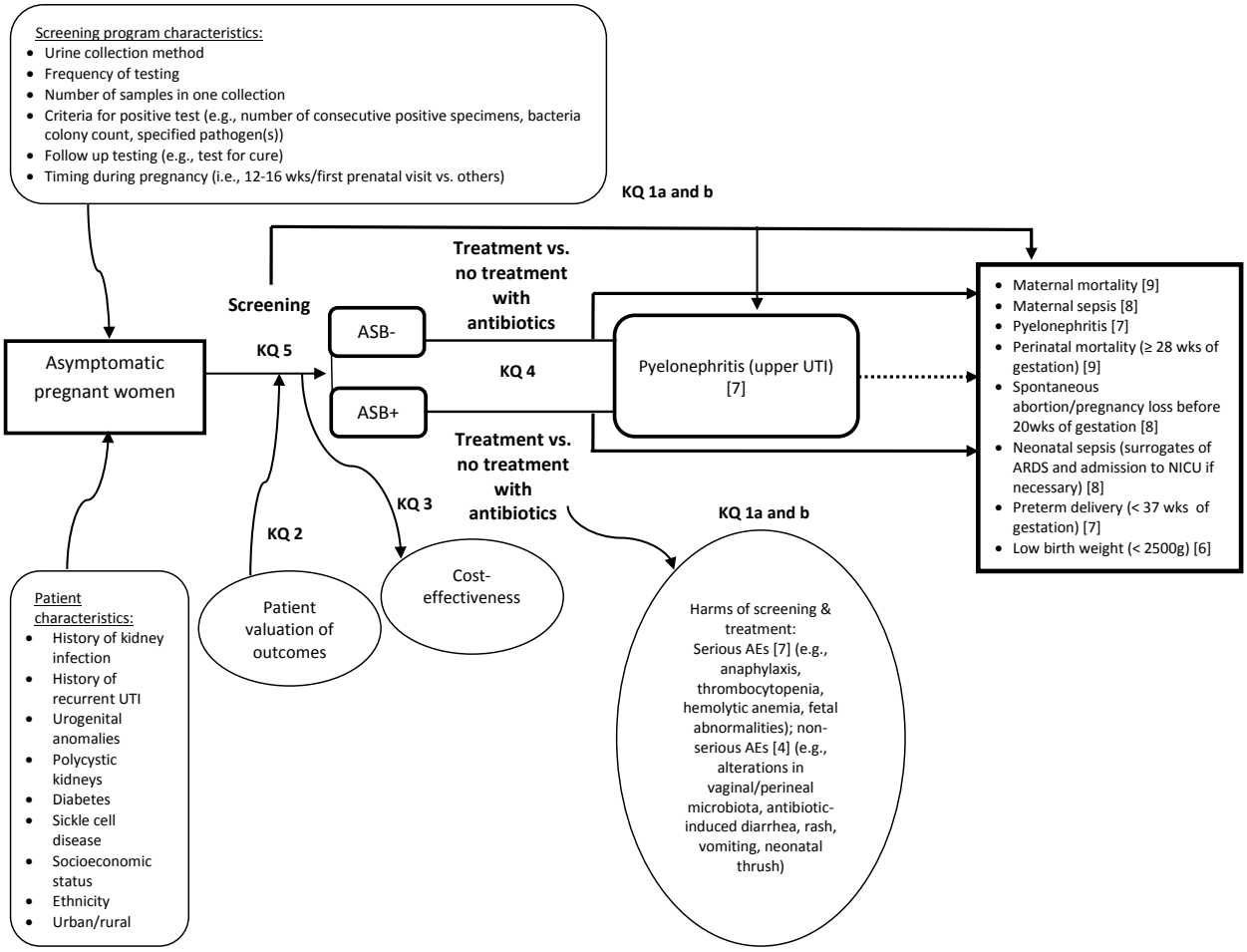
Chapter 2. Methods

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 checklists[27]), 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[29] 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)

Benefits (reduced incidence for all):

1. maternal mortality (9)*
2. maternal sepsis (8)
3. pyelonephritis (7)
4. perinatal mortality (≥ 20 weeks of gestation [e.g., intrauterine demise, stillbirth, early neonatal death]) (9)
5. spontaneous abortion/pregnancy loss < 20 weeks of 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 weeks of 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

*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.[30]

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 1.2 - KQ2: Outcome valuation

Population	Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria; will also accept asymptomatic women who are not pregnant if necessary 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 screening program or test, and any antibiotic; will accept studies on treatment for any bacterial condition in pregnancy Screening subgroups/algorithms, including: urine collection method, frequency of testing, criteria for a positive test (including number of consecutive positive specimens, bacteria 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), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)
Comparator/Reference Standard	Not applicable
Outcomes	Several possible outcomes (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)
Study Designs	Qualitative, mixed methods, surveys/cross-sectional
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)
Time frame	No publication date limits

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

Table 1.3 - KQ3: Cost-effectiveness 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 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 screening program 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, 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 screening (but may include indicated testing and/or treatment upon development of symptoms), or a different screening algorithm (see intervention subgroups)
Outcomes	Cost per quality-adjusted life-years (cost per QALY), incremental cost-effectiveness ratio (ICER), net benefit/cost
Study Designs	Economic evaluations
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); limited to countries rated as having very high Human Development Index[30]
Time frame	No publication date limits

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.[31] 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.[32] For KQ4 (treatment effectiveness), all RCTs and CCTs were appraised using the Cochrane Risk of Bias tool.[33] 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[4] 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*[34]) 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 (α=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 (I^2) 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.[36, 37] Discrepancies were resolved through discussion or consultation with a third reviewer, to reach consensus. Assessments were entered into the GRADEpro software[38] and summarized in GRADE Evidence Profiles (EP) and Summary of Findings (SOF) tables.[39] Footnotes to the tables provided explanations for all decisions.

The general approach is outlined here although methods align with GRADE guidance.[36, 37] 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.[40] 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).[41] *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.[42] 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

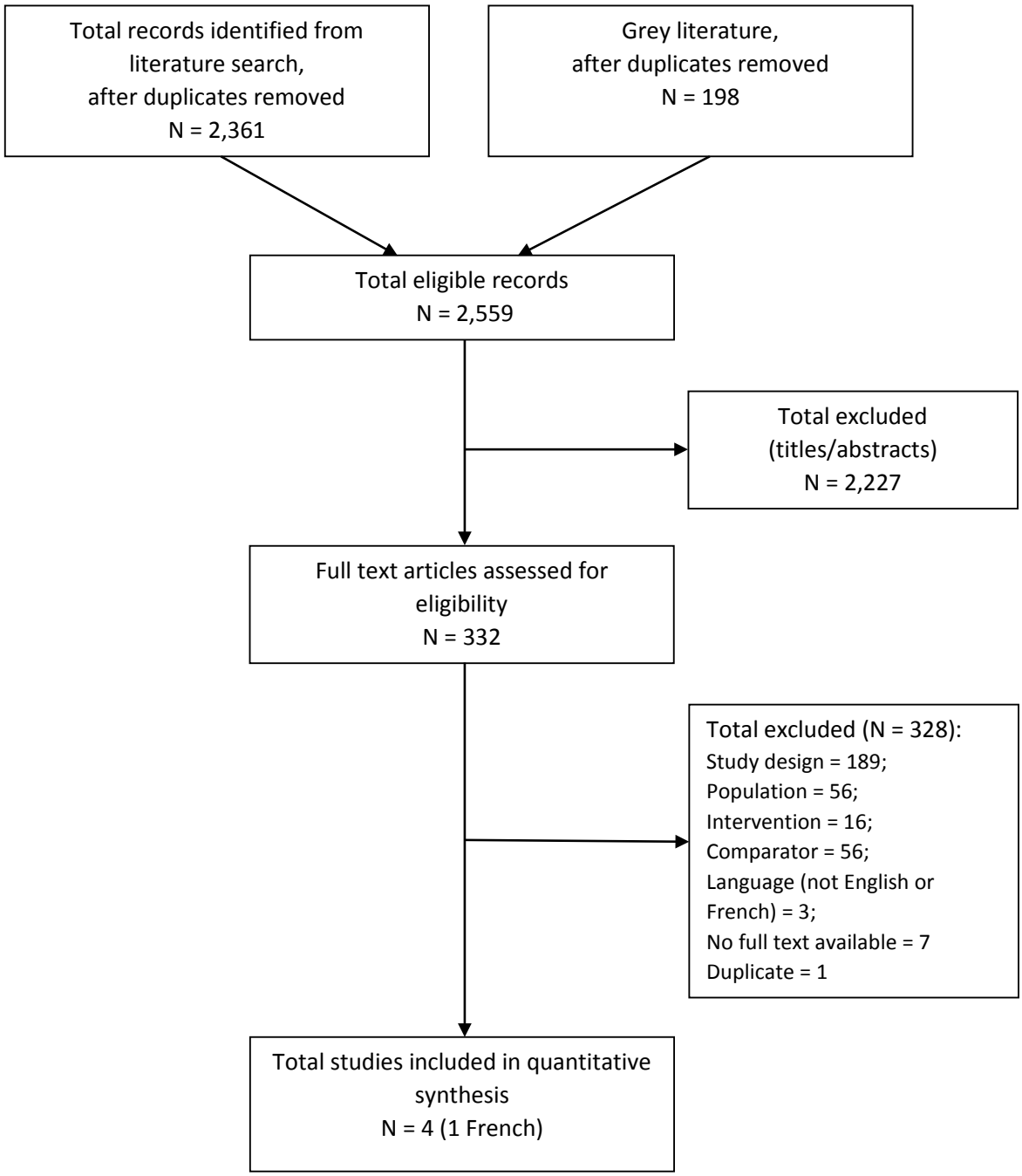
Summary of Studies for Review

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 ($\geq 10^5$ 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[43] reported spontaneous abortion, defined as ≤28 weeks of gestation; since this was distinguished from perinatal mortality, it was included in the analysis for this outcome.

All three studies[43-45] that reported preterm delivery used <37 weeks of gestation as the criterion. For the study by Uncu et al[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[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[43-45]) with one study of low ROB that rated 8 out of 9.[46] None of the studies[43-46] reported that pyelonephritis was not present in pregnant women at the outset of the study. Three studies[43-45] did not demonstrate comparability of baseline characteristics between groups. All of the studies[43, 44, 46] except one[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[a] - KQ1 a & b (screening effectiveness)

First Author, Year	Selection					Comparability		Outcome				Total Score[a] (max 9)	Selective Outcome Reporting[b]
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study (pyelonephritis/ other outcomes)	Total	Comparability of cohorts	Total	Assessment of outcome	Adequacy of length of follow-up	Adequacy of follow-up of cohorts	Total		
Gérard, 1983[43]	1	1	0	0/1	3	0	0	1	1	1	3	6	Suspected[c]
Gratacós, 1994[44]	1	1	0	0/1	3	0	0	1	1	1	3	6	Suspected[d]
Rhode, 2007[46]	1	1	1	0/1	4	1	1	1	1	1	3	8	Suspected[e]
Uncu, 2002[45]	1	1	1	0/1	4	0	0	1	1	0	2	6	Not suspected[f]

[a]Assessed using the Newcastle-Ottawa Quality Assessment Scale[31]

[b]Assessed due to concern regarding reporting bias in the studies, but assessment not included in the total score

[c]Did not report on fetal abnormalities

[d]Did not report on spontaneous abortion, perinatal mortality, preterm delivery or fetal abnormalities

[e]Did not report on spontaneous abortion, perinatal mortality, or fetal abnormalities

[f]Reported on all outcomes, including fetal death >20 weeks of gestation (eligible for perinatal mortality)

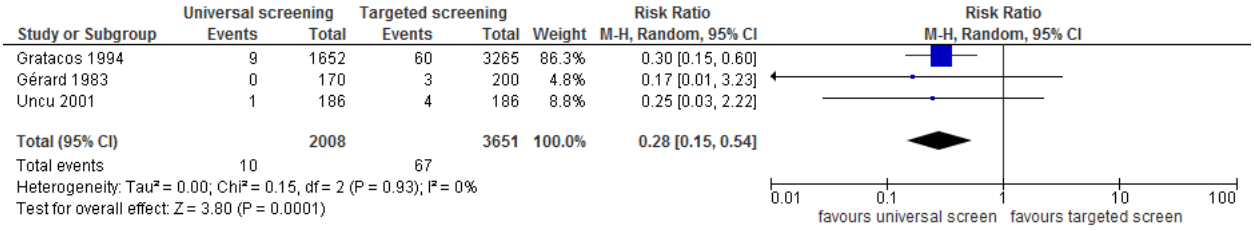
KQ1a: What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences for patient characteristics (e.g., socioeconomic status [SES])?

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.

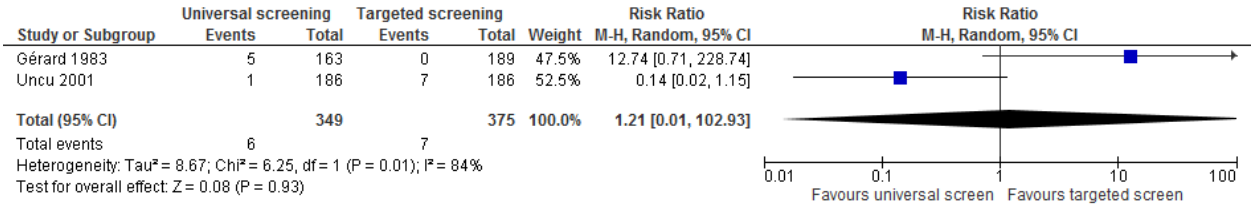
1.1 Pyelonephritis



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.

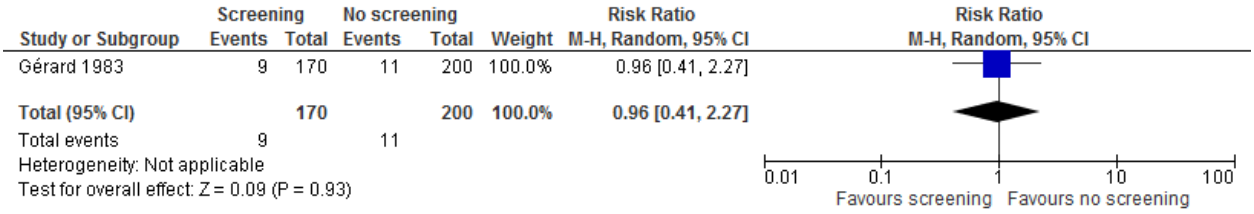
1.2 Perinatal mortality



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 ≤28 weeks of gestation. This body of evidence was rated as very low due to concerns with study design, ROB, inconsistency and imprecision.

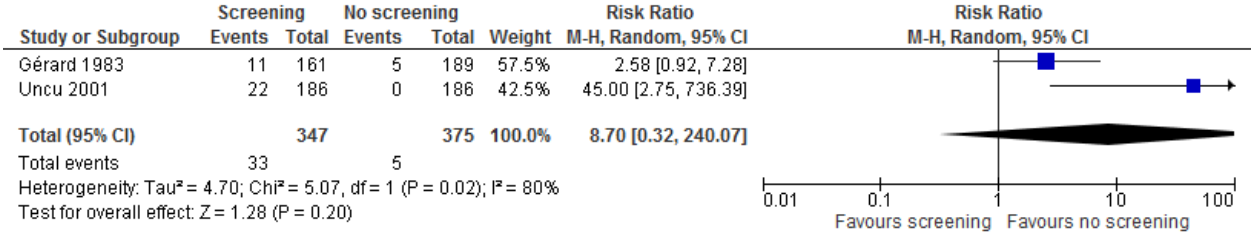
1.3 Spontaneous abortion



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.

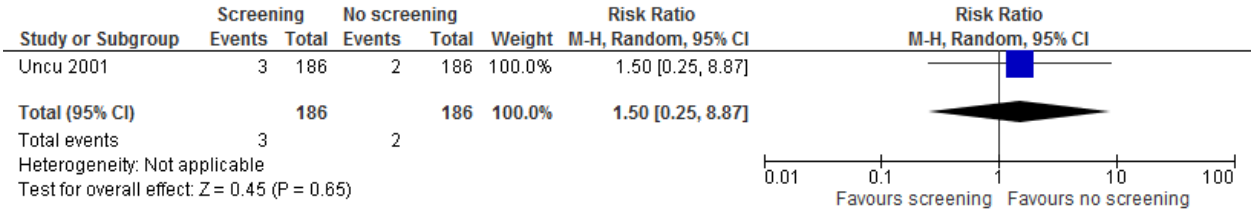
1.4 Preterm delivery



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)



Subgroup analyses

We did not perform subgroup analyses due to insufficient number of studies contributing to each category comprising our *a priori* subgroups.

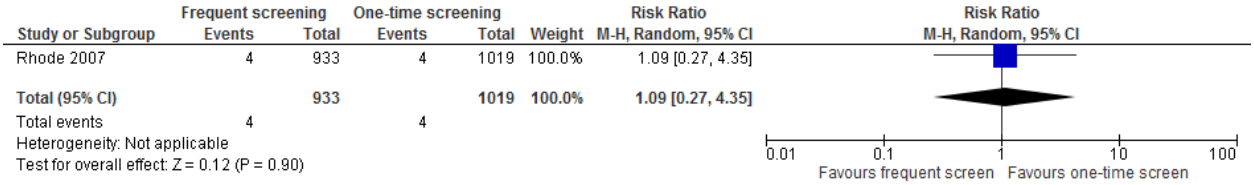
KQ1b. What are the benefits and harms of screening programs using different screening methods or algorithms for asymptomatic bacteriuria in pregnancy?

One non-concurrent cohort study[46] (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.

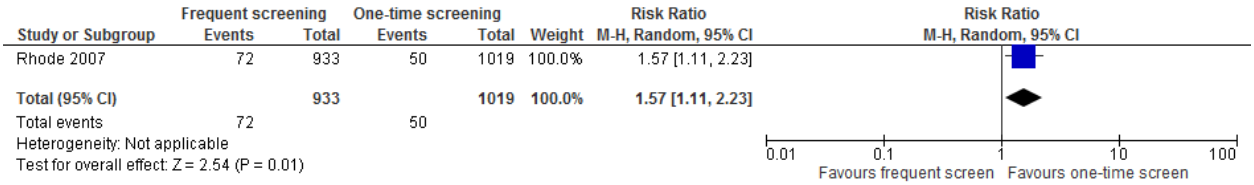
2.1 Pyelonephritis



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

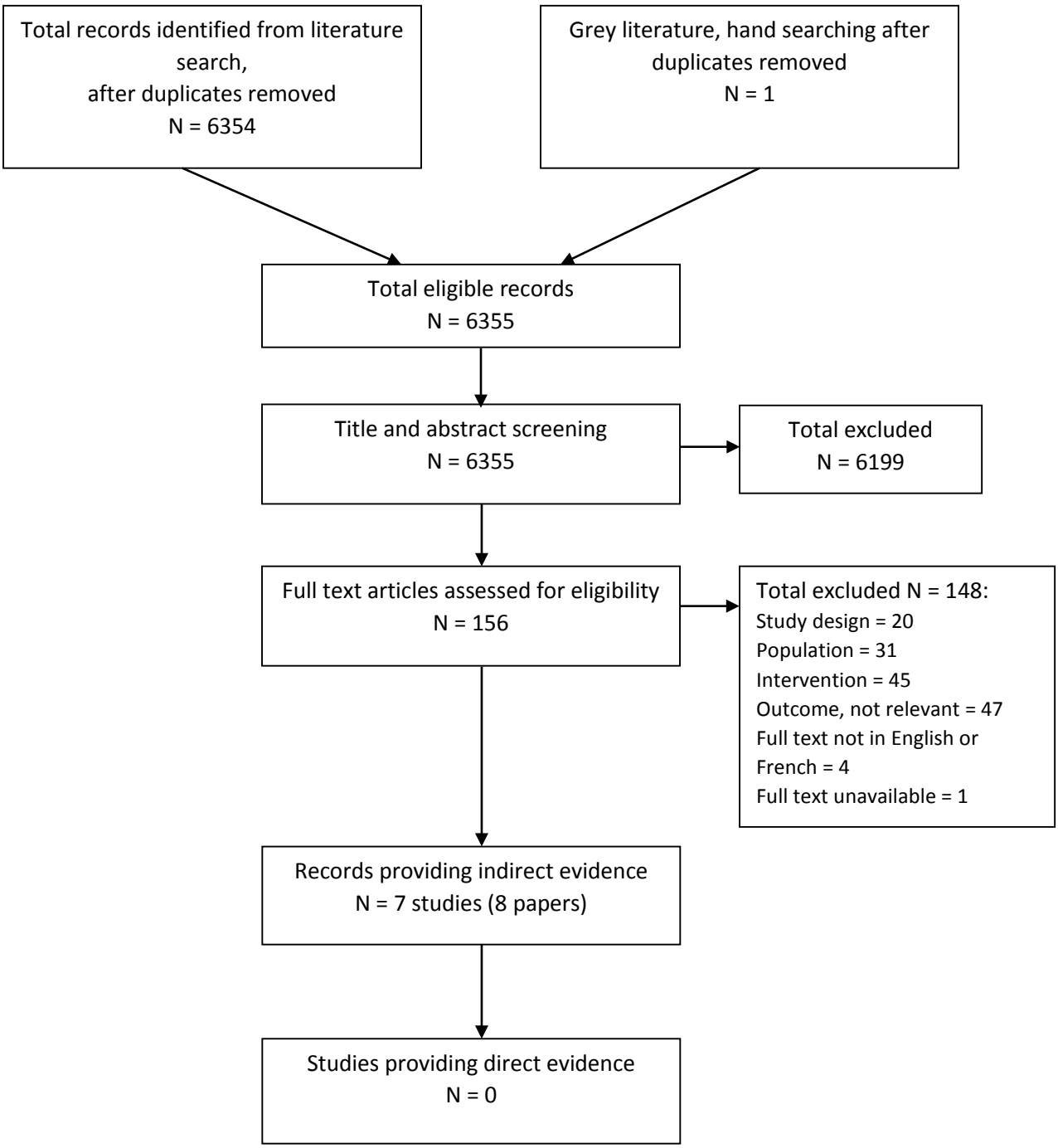


Key Question 2 (outcome valuation)

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.[47, 48] Six of the papers were cross-sectional surveys while one paper was a cross-sectional study using a visual analogue scale.[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.[50] The sample sizes ranged from 144 to 4999 participants with three papers[47, 51, 52] including more than 1000 participants. Six papers reported age ranges from 15 to 45 years.[47, 48, 50-53] Three studies provide information on drug utilization opinions,[48, 50, 53] while five papers (four studies) provide information on perceptions of teratogenic risk.[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[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[a] – KQ2 (outcome valuation)

First Author, Year	Did the study address a clearly focused question / issue?	Is the research method (study design) appropriate for answering the research question?	Is the method of selection of the subjects clearly described?	Could the way the sample was obtained introduce bias?	Was the sample of subjects representative of the population to which the findings will be referred?	Was the sample size based on pre-study considerations of statistical power?	Was a satisfactory response rate achieved?	Are the measurements (questionnaires) likely to be valid and reliable?	Was the statistical significance assessed?	Are confidence intervals given for the main results?	Could there be confounding factors that haven't been accounted for?	Can the results be applied to your organization?
Butters, 1990[48]	1	1	1	2	1	2	1	2	1	3	1	1
Kazemier, 2015[50]	2	2	1	3	1	2	2	2	3	3	2	3
Lupattelli, 2014[47]	1	1	1	1	1	2	2	2	1	1	3	1
Mashayekhi, 2009[54]	1	1	1	1	1	2	2	2	1	3	1	1
Nordeng, 2010[51]	1	1	1	1	1	2	2	2	1	3	2	1
Sanz, 2000[49]	1	1	3	2	1	2	2	2	1	3	1	1
Sharma, 2006[53]	1	1	3	2	1	2	2	1	1	3	1	1
Twigg, 2016[52]	1	1	1	1	1	2	2	1	1	3	1	1

[a]Assessed using a tool developed by the Center for Evidence-based Management[32] for cross-sectional studies (surveys)
1=Yes, 2=Can't Tell, 3=No

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.

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.[48] 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.[53] The cohort study of screening with embedded treatment trial[50] 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[52] 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[51] 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,[47] 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.[54]

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).[49]

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

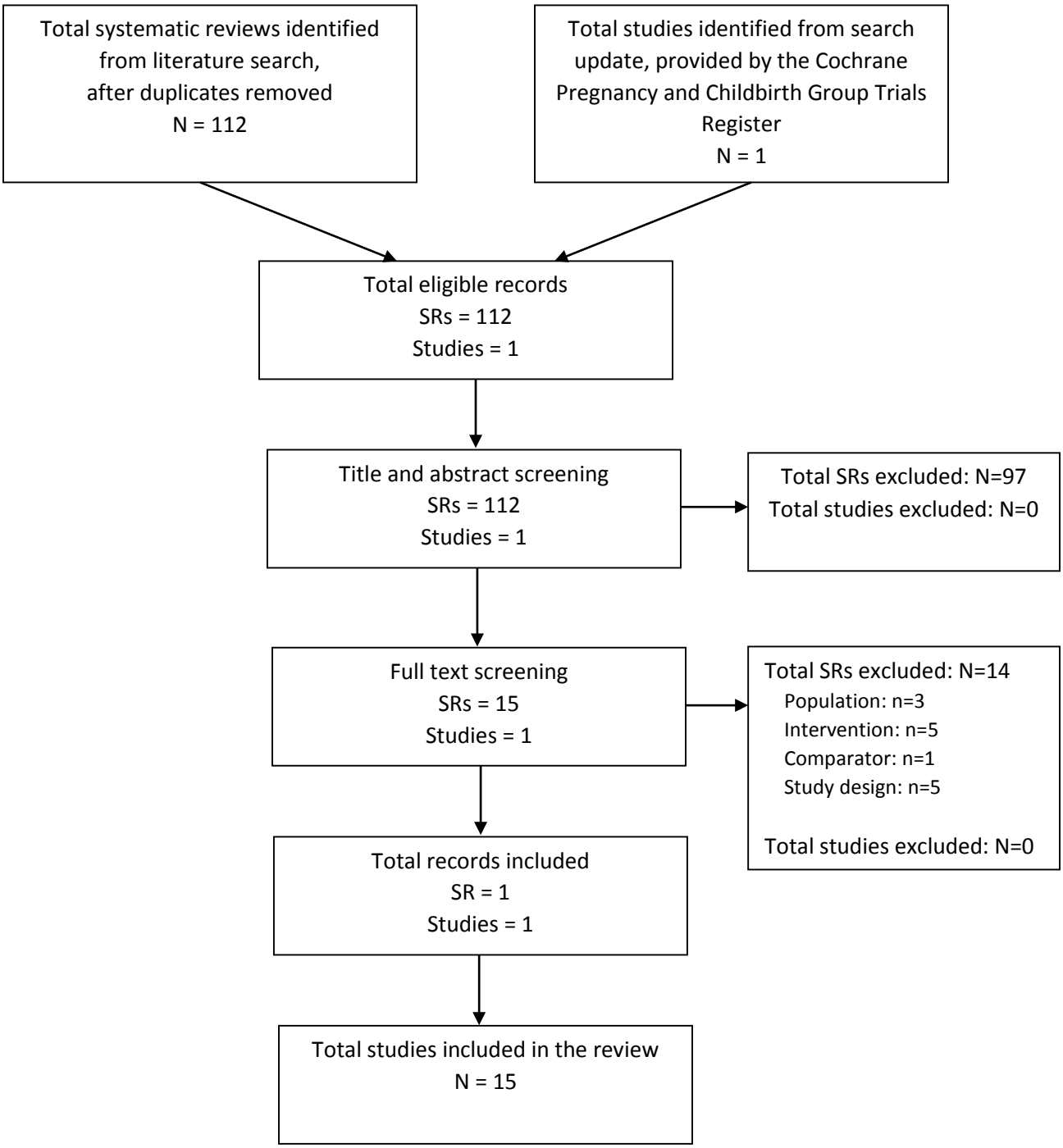
Evidence on screening effectiveness (KQs 1a and 1b) was very low quality, therefore we did not review studies on cost-effectiveness of screening programs which would have relied on similar evidence.

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 al[50]) 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[50, 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[64, 67, 68] reported this.

The outcome reported by the most number of studies (n=12[50, 55, 57-65, 67]) was pyelonephritis. Most studies[50, 55, 57, 59, 61-63, 67] 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[58, 60, 65] did not define criteria for pyelonephritis, and one study[64] used "acute symptoms of cystopyelitis".

Perinatal mortality was variably defined among the studies[50, 57, 61-63, 68] that reported this outcome. Two studies used gestation to define perinatal mortality: >20 weeks[61] and >28 weeks.[62] One study[50] defined perinatal death as stillbirth, death during labor or death within 28 days of life. One study[63] did not define "perinatal mortality". Two studies[57, 68] combined stillbirths with "neonatal death" or "death prior to hospital discharge".

Spontaneous abortion was reported by two studies[59, 68] that did not specify gestational age.

Of the four studies that reported on preterm delivery, three studies[50, 66, 68] used <37 weeks of gestation as the criteria, and the study by Furness et al[59] used <38 weeks of gestation.

Seven studies[50, 55, 57, 61-63, 68] reported low birth weight as ≤2500g or <2500g; Kazemier at al[50] 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[50] as confirmed with culture, and without criteria in another study.[66]

For harms (any serious adverse event (AE)), two studies[50, 57] reported congenital/abnormalities, one study[63] reported fetal abnormalities and one study[59] reported anencephaly. Additionally, Elder et al[57] 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[62, 63, 66] assessed as having unclear ROB, and only one study[50] 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[55, 57, 59, 62-67] reported their methodological design as "random" without adequate details, with only one study[50] using a computer-generated random assignment of participants. Many (n=9) studies[55, 56, 58, 59, 63-67] did not adequately describe concealment of allocation, with four studies[57, 60, 61, 68] describing allocation by alternation. The Netherlands study[50] used central allocation to support a judgment of low ROB for this domain. Five studies[50, 55, 56, 61, 62] that reported double-blinding were assessed at low ROB for this domain; the remaining ten studies[57-60, 63-68] were assessed as unclear ROB for blinding of participants and personnel due to lack of reporting within the context of objective outcomes. Four studies[50, 55, 56, 62] mentioned blinding of assessors or "double-blind" conditions to support a judgment of low ROB, whereas eleven studies[57-61, 63-68] 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,[55] 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.[59] Five studies[57, 58, 61, 62, 67] 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[50, 56, 60, 63-66, 68] reported on details of dropouts, if any. Six studies[55, 56, 58, 64, 65, 67] were assessed at high ROB for selective reporting due to lack of reporting on pyelonephritis and/or neonatal outcomes. Eight studies[57, 59-63, 66, 68] 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[a] - KQ4 (treatment effectiveness)

Study	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Incomplete Reporting	Selective Reporting	Other Bias*	Overall Risk of Bias**
Brumfitt 1975[55]								
Elder 1966[56]								
Elder 1971[57]								
Foley 1987[58]								
Furness 1975[59]								
Gold 1966[60]								
Kass 1960[61]								
Kazemier 2015[50]								
Kincaid-Smith 1965[62]								
Little 1966[63]								
Mulla 1960[64]								
Pathak 1969[65]								
Thomsen 1987[66]								
Williams 1969[67]								
Wren 1969[68]								

[a]Assessed using the Cochrane Risk of Bias[34] tool

*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?

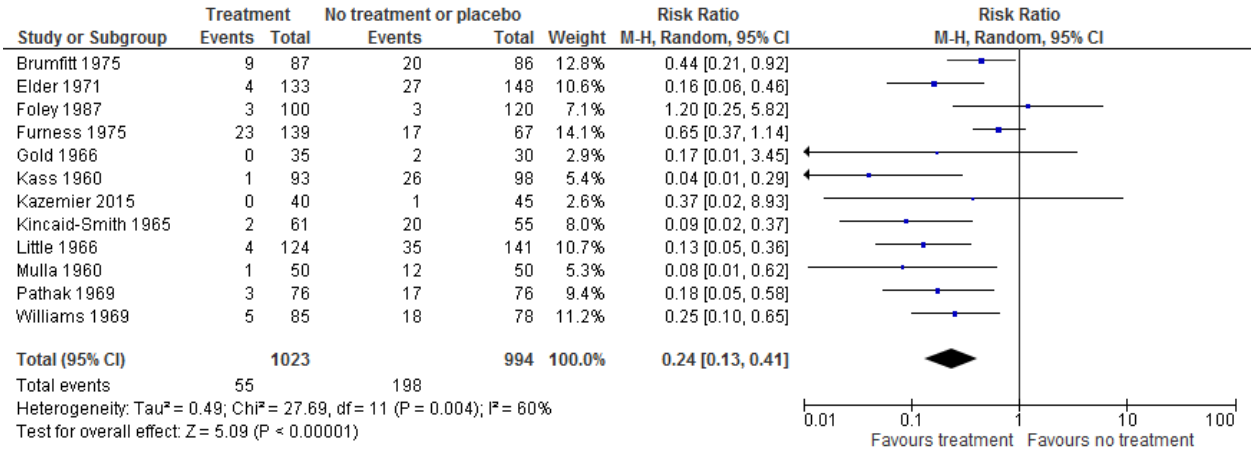
Results are summarized below by outcome. See Evidence Set 3 for GRADE EP and SOF tables and forest plots. We conducted subgroup analyses to explore possible reasons for heterogeneity among studies, whenever sufficient number of studies (e.g., 2 per subgroup if categorical) reported on the *a priori*

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

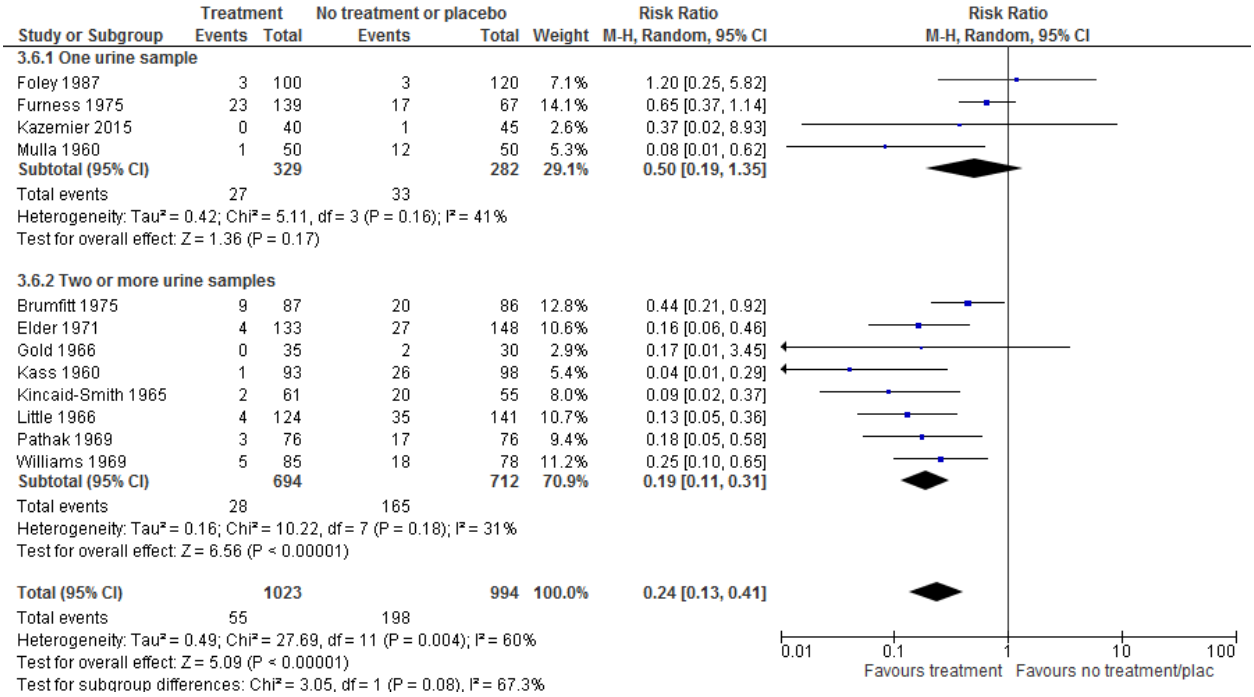
A total of 12 studies[50, 55, 57-65, 67] (2,017 women) with the majority at high ROB examined the effects of antibiotic treatment and found a significant difference in development of pyelonephritis (RR 0.24; 95% CI 0.13, 0.41; I^2=60%; ARR 17.6%; NNT 6, 95% CI 5, 7). Three of the trials clearly stated 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)



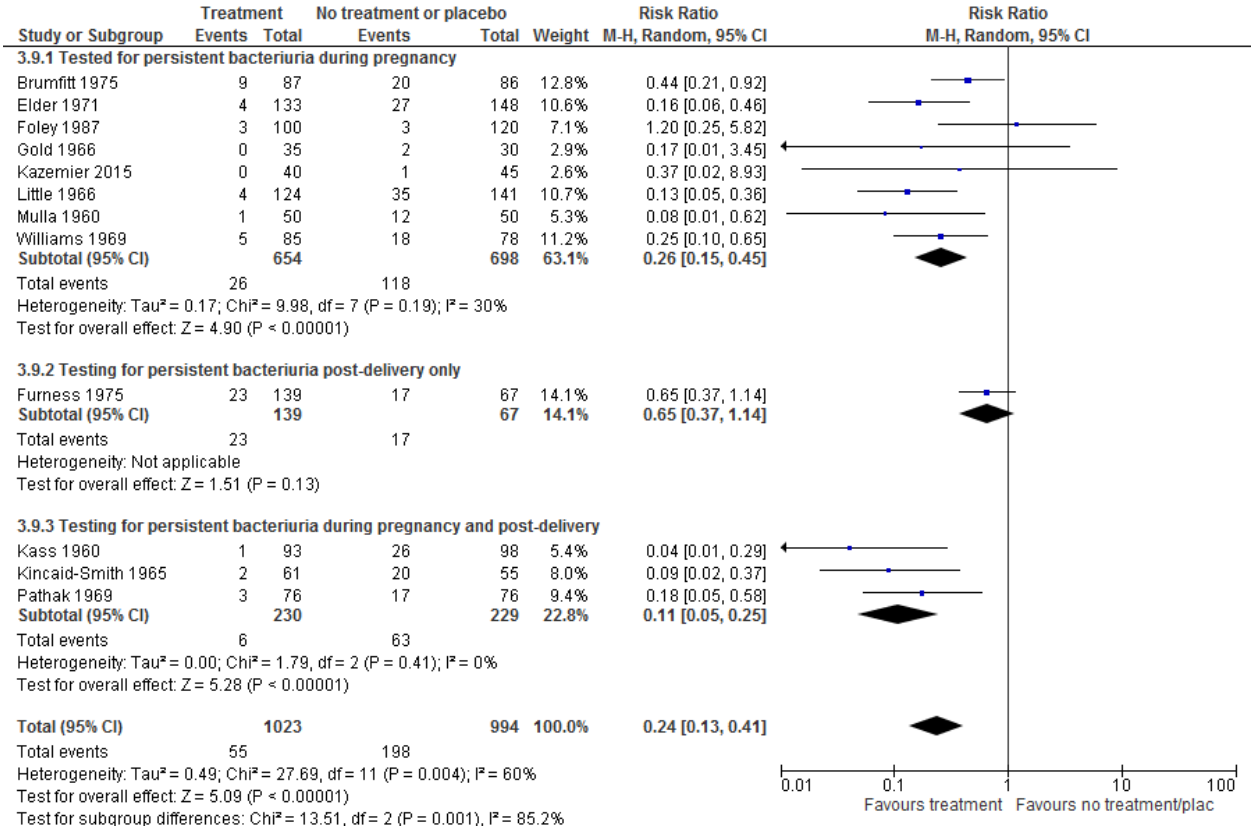
Subgroup analyses considered to have some credibility examined the number of urine samples (e.g. use of confirmatory culture), testing for persistent bacteriuria, and length of follow-up (ES Forest Plots 3.1.1-3.1.3).

3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit*

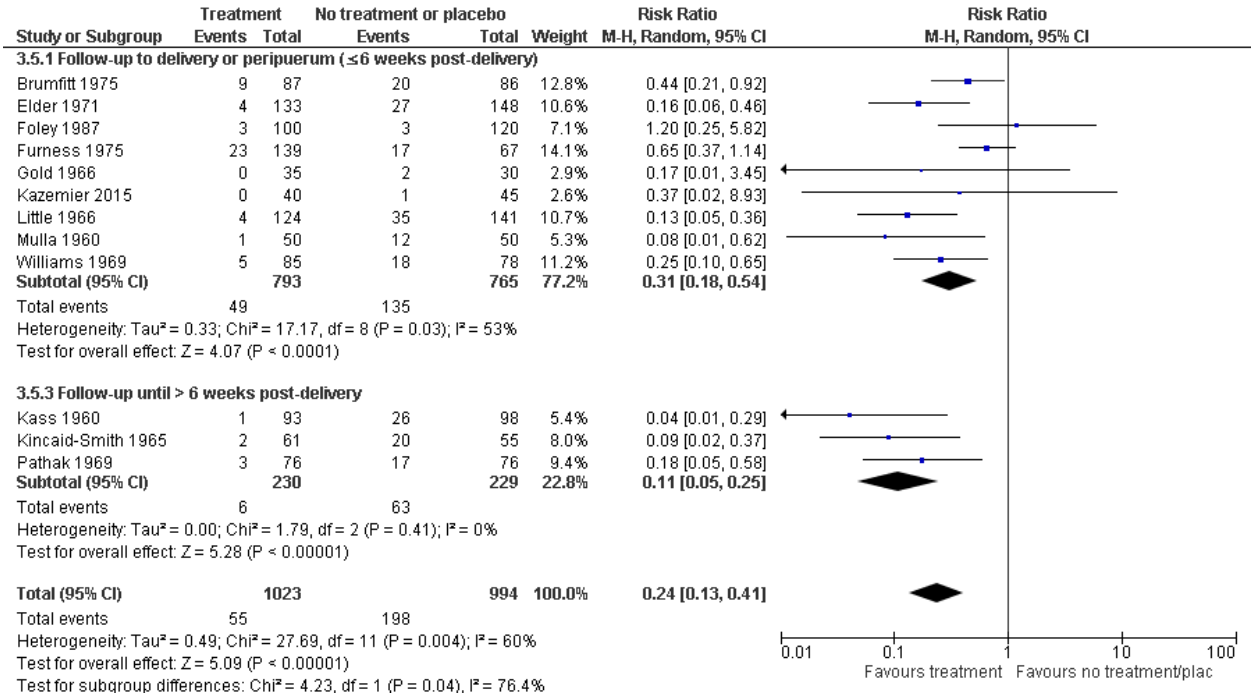


*The additional culture(s) was used to confirm levels of bacteriuria.

3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria



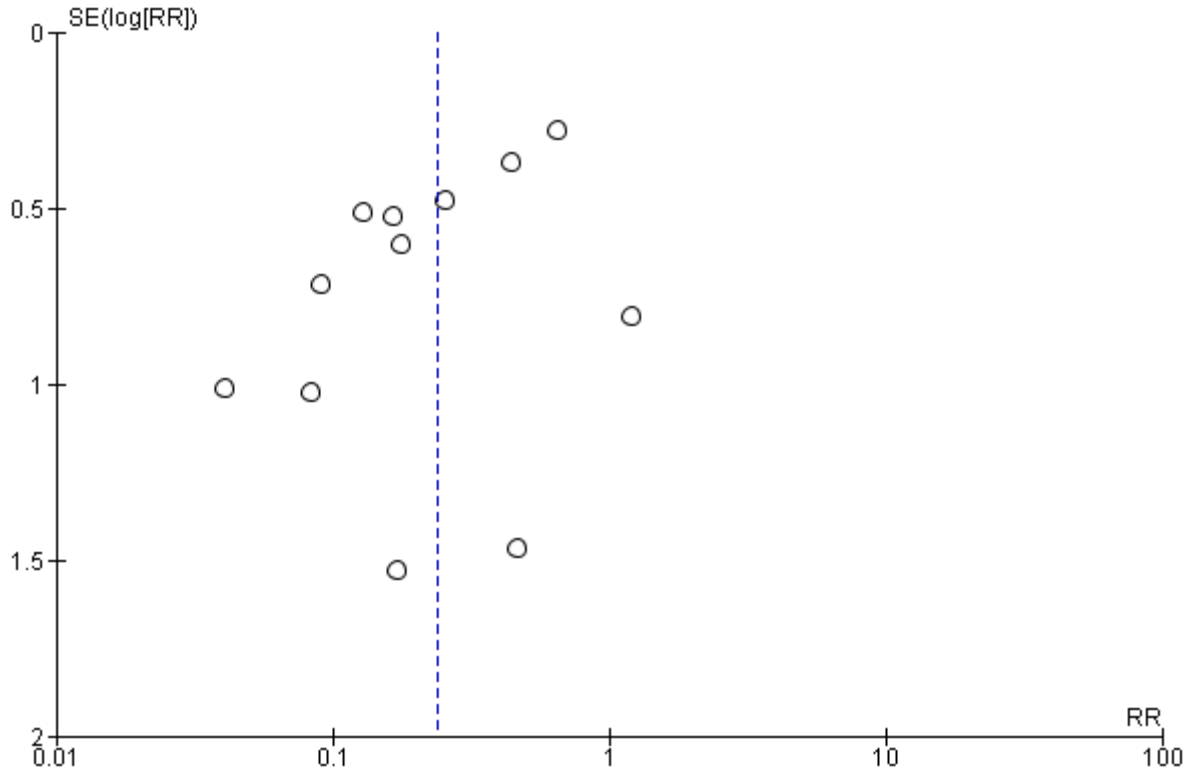
3.1.3 Pyelonephritis subgroup: duration of follow-up



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 (I^2=60%) for the outcome of pyelonephritis (RR 0.19, 95% CI 0.11, 0.31; I^2=31% versus RR 0.50, 95% CI 0.19, 1.35; I^2=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; I^2=0%) compared with testing during pregnancy (RR 0.26, 95% CI 0.15, 0.45; I^2=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; I^2=0%) compared with those that only followed women until delivery or six weeks post-delivery (RR 0.31, 95% CI 0.18, 0.54; I^2=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.

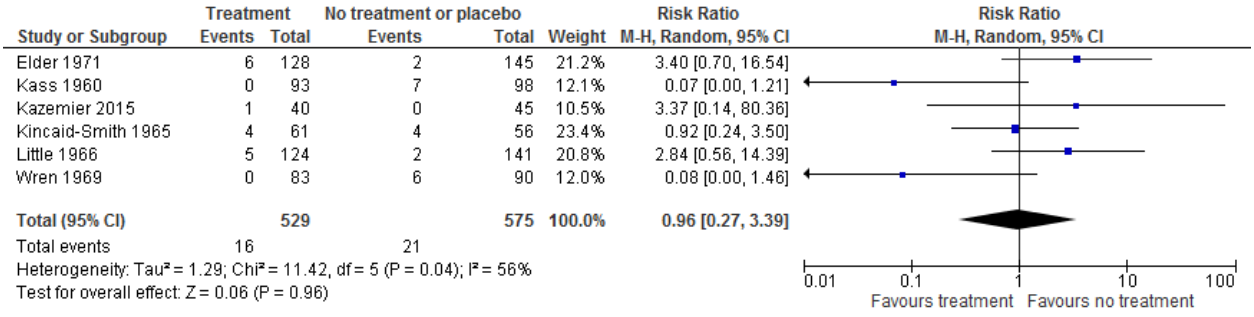
Figure 5. Funnel Plot Asymmetry Test for outcome of pyelonephritis for KQ4 (treatment)



Perinatal mortality

A total of six studies (1,104 women) examined the outcome of perinatal mortality; one study[50] was at low ROB, three studies[57, 61, 68] were at high ROB, and two studies[62, 63] 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; I^2=56%). This body of evidence was rated as very low due to downgrading for ROB, indirectness, and imprecision.

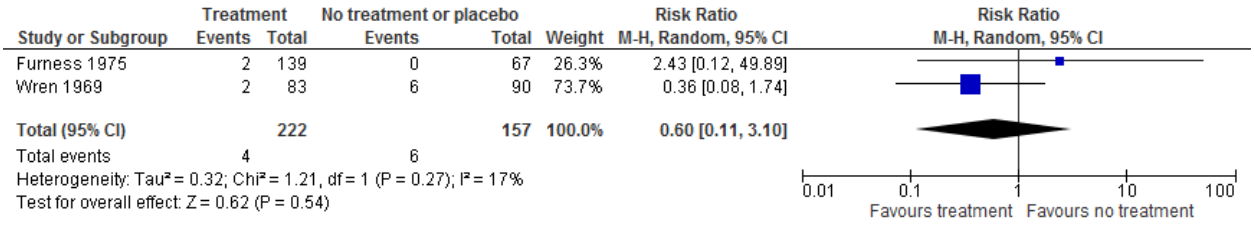
3.2 Perinatal mortality



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.

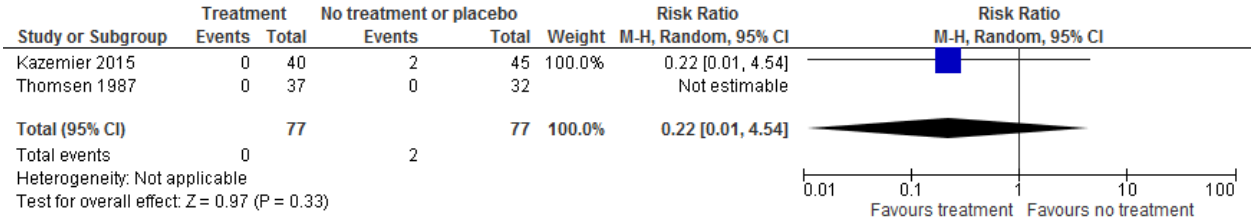
3.3 Spontaneous abortion



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.

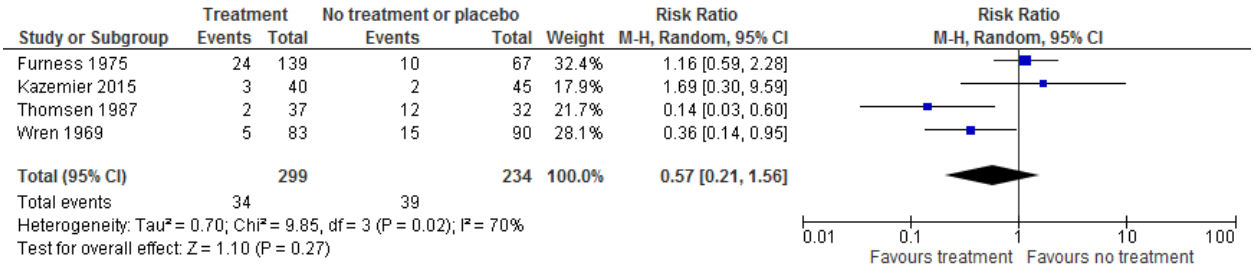
3.4 Neonatal sepsis



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.

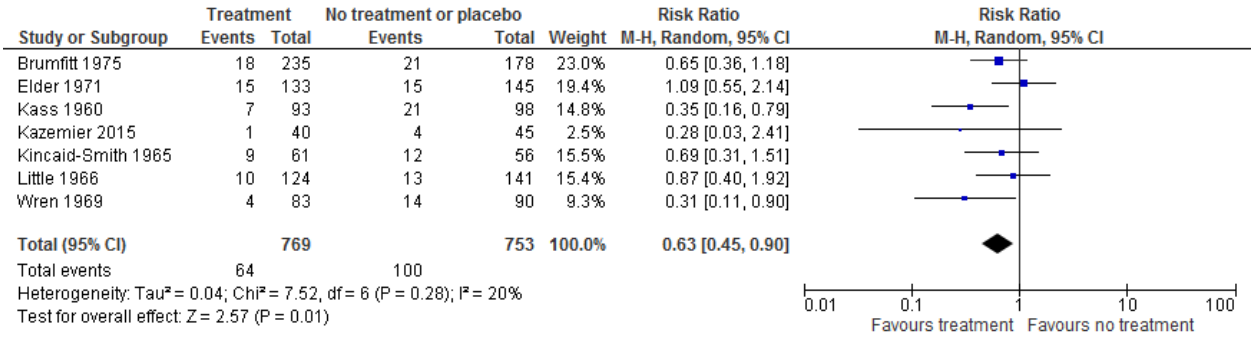
3.5 Preterm delivery



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.

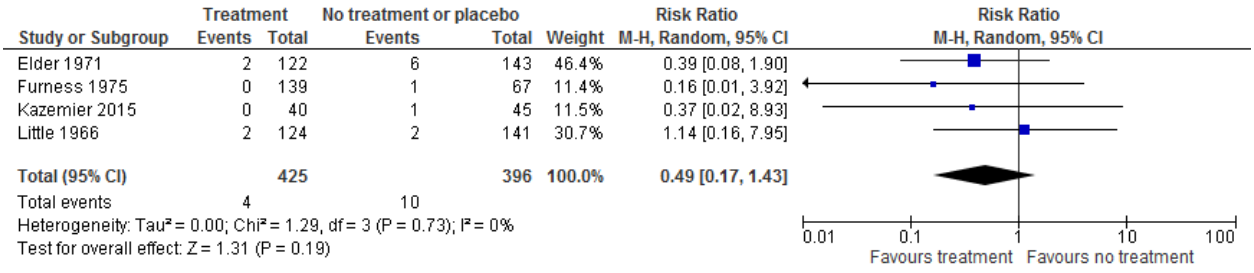
3.6 Low birthweight



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; I^2=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; I^2=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; I^2=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[69] 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[50] and three others (Elder et al[56], Mulla[64], and Williams et al[67]). 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[69] 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.[69]

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[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.[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.[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[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,[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,[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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no screening	Risk with screening				
Maternal mortality	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal mortality.
Maternal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal sepsis.
Pyelonephritis	Median		RR 0.28 (0.15 to 0.54)	5659 (3 observational studies[43, 44, 45])	⊕◯◯◯ VERY LOW [1, a]	We are very uncertain about the effects of screening on pyelonephritis.
	18 per 1,000	13 fewer per 1,000 (from 8 fewer to 16 fewer)				
Perinatal mortality	Median		RR 1.21 (0.01 to 102.93)	724 (2 observational studies[43, 45])	⊕◯◯◯ VERY LOW [1, b]	We are very uncertain about the effects of screening on perinatal mortality.
	19 per 1,000	4 more per 1,000 (from 19 fewer to 1,000 more)				
Spontaneous abortion	55 per 1,000	2 fewer per 1,000 (from 32 fewer to 70 more)	RR 0.96 (0.41 to 2.27)	370 (1 observational study[43])	⊕◯◯◯ VERY LOW [1, c]	We are very uncertain about the effects of screening on spontaneous abortion.
Neonatal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on neonatal sepsis.
Preterm delivery	Median					

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no screening	Risk with screening				
	13 per 1,000	102 more per 1,000 (from 9 fewer to 1,000 more)	RR 8.70 (0.32 to 240.07)	722 (2 observational studies[43, 45])	⨁◯◯◯ VERY LOW [1, d]	We are very uncertain about the effects of screening on preterm delivery.
Low birthweight	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on low birthweight.
Maternal serious harm(s)	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal serious harms.
Neonatal serious harm: fetal abnormalities	11 per 1,000	5 more per 1,000 (from 8 fewer to 85 more)	RR 1.50 (0.25 to 8.87)	372 (1 observational study[45])	⨁◯◯◯ VERY LOW [1, e]	We are very uncertain about the effects of screening on fetal abnormalities.

*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[42] 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

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	screening	no screening	Relative (95% CI)	Absolute (95% CI)		
Maternal mortality												
0									not estimable		-	CRITICAL
Maternal sepsis												
0									not estimable		-	CRITICAL
Pyelonephritis												
3	observational studies[43, 44, 45]	serious	not serious	not serious	serious	none	10/2008 (0.5%)	1.8%	RR 0.28 (0.15 to 0.54)	13 fewer per 1,000 (from 8 fewer to 16 fewer)	⨁◯◯◯ VERY LOW [1, a]	CRITICAL
Perinatal mortality												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	screening	no screening	Relative (95% CI)	Absolute (95% CI)		
2	observational studies[43, 45]	serious	not serious	not serious	serious	none	6/349 (1.7%)	1.9%	RR 1.21 (0.01 to 102.93)	4 more per 1,000 (from 19 fewer to 1,000 more)	⊕◯◯◯ VERY LOW [1, b]	CRITICAL
Spontaneous abortion												
1	observational studies[43]	serious	serious	not serious	serious	none	9/170 (5.3%)	11/200 (5.5%)	RR 0.96 (0.41 to 2.27)	2 fewer per 1,000 (from 32 fewer to 70 more)	⊕◯◯◯ VERY LOW [1, c]	CRITICAL
Neonatal sepsis												
0									not estimable		-	CRITICAL
Preterm delivery												
2	observational studies[43, 45]	serious	not serious	not serious	serious	none	33/347 (9.5%)	1.3%	RR 8.70 (0.32 to 240.07)	102 more per 1,000 (from 9 fewer to 1,000 more)	⊕◯◯◯ VERY LOW [1, d]	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	screening	no screening	Relative (95% CI)	Absolute (95% CI)		
Low birthweight												
0									not estimable		-	IMPORTANT
Maternal serious harm(s)												
0									not estimable		-	CRITICAL
Neonatal serious harm: fetal abnormalities												
1	observational studies[45]	serious	serious	not serious	serious	none	3/186 (1.6%)	2/186 (1.1%)	RR 1.50 (0.25 to 8.87)	5 more per 1,000 (from 8 fewer to 85 more)	⨁◯◯◯ VERY LOW [1, e]	CRITICAL

CI: Confidence interval; RR: Risk ratio

[1] The imprecision domain is assessed using GRADE guidance[42] 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.

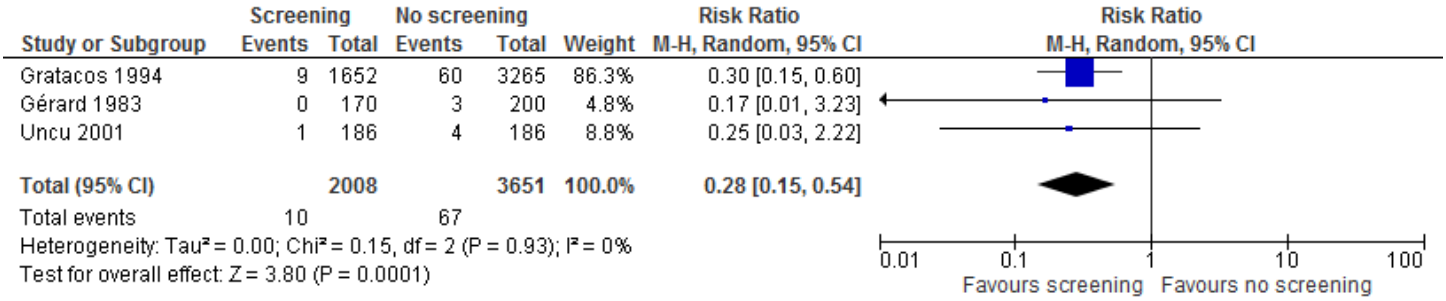
Neonatal serious harm: fetal abnormalities [e] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome (n=370; Uncu 2001). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious 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

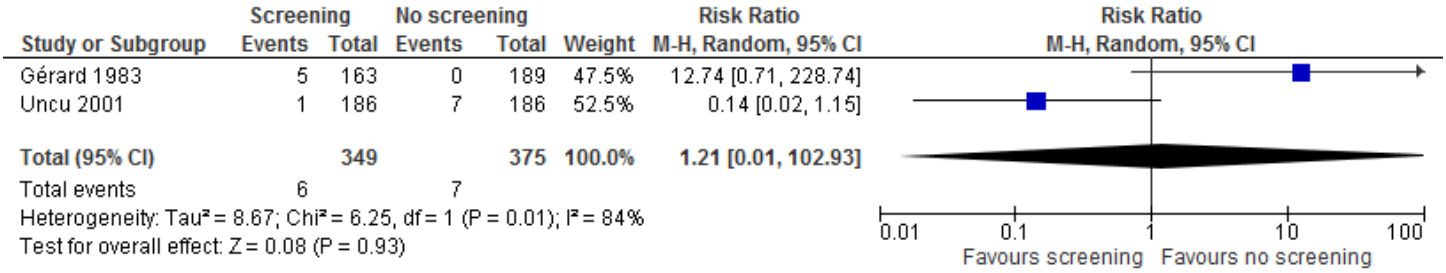
Outcome	No. of studies	No. of participants	Effect size (Risk Ratio; M-H, Random, 95%CI)
1.1 Pyelonephritis	3	5659	0.28 [0.15, 0.54]
1.2 Perinatal mortality >=20 wks GA note: Gérard >=31 wks; Uncu >20 wks	2	724	1.21 [0.01, 102.93]
1.3 Spontaneous abortion <20 wks GA note: 1 study <=28 wks (all occurred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

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

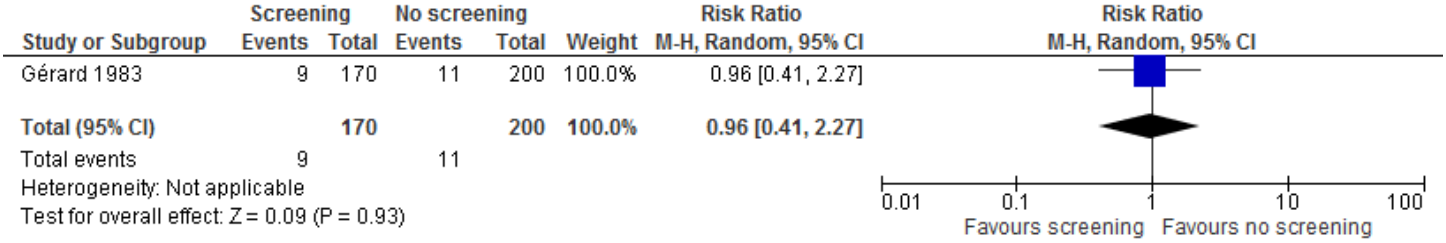
1.1 Pyelonephritis



1.2 Perinatal mortality (>=20 wks GA)



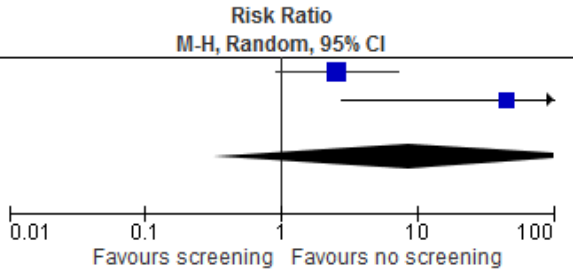
1.3 Spontaneous abortion (<20 wks GA)



1.4 Preterm delivery (<37 wks GA)

Study or Subgroup	Screening Events	Screening Total	No screening Events	No screening Total	Weight	Risk Ratio M-H, Random, 95% CI
Gérard 1983	11	161	5	189	57.5%	2.58 [0.92, 7.28]
Uncu 2001	22	186	0	186	42.5%	45.00 [2.75, 736.39]
Total (95% CI)		**347**		**375**	**100.0%**	**8.70 [0.32, 240.07]**
Total events	33		5			

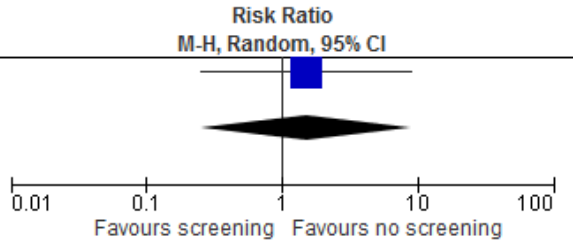
Heterogeneity: Tau² = 4.70; Chi² = 5.07, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 1.28 (P = 0.20)



1.5 Neonatal serious harm: fetal abnormalities

Study or Subgroup	Screening Events	Screening Total	No screening Events	No screening Total	Weight	Risk Ratio M-H, Random, 95% CI
Uncu 2001	3	186	2	186	100.0%	1.50 [0.25, 8.87]
Total (95% CI)		**186**		**186**	**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

Patient or population: asymptomatic bacteriuria

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

Intervention: frequent screening

Comparison: one-time screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with one-time screening	Risk difference with frequent screening				
Pyelonephritis	4 per 1,000	0 fewer per 1,000 (from 3 fewer to 13 more)	RR 1.09 (0.27 to 4.35)	1952 (1 observational study[46])	⨁◯◯◯ VERY LOW [1, a]	We are very uncertain about the effects of frequent screening compared to one-time screening on pyelonephritis.
Preterm delivery	49 per 1,000	28 more per 1,000 (from 5 more to 60 more)	RR 1.57 (1.11 to 2.23)	1952 (1 observational study[46])	⨁◯◯◯ VERY LOW [1, b]	We are very uncertain about the effects of frequent screening compared to one-time screening on preterm delivery.

*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[42] 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:

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Other considerations	frequent screening	one-time screening	Relative (95% CI)	Absolute (95% CI)		
Pyelonephritis												
1	observational studies[46]	serious	serious	serious	serious	none	4/933 (0.4%)	4/1019 (0.4%)	RR 1.09 (0.27 to 4.35)	0 fewer per 1,000 (from 3 fewer to 13 more)	⨁◯◯◯ VERY LOW [1, a]	CRITICAL
Preterm delivery												
1	observational studies[46]	serious	serious	serious	serious	none	72/933 (7.7%)	50/1019 (4.9%)	RR 1.57 (1.11 to 2.23)	28 more per 1,000 (from 5 more to 60 more)	⨁◯◯◯ VERY LOW [1, b]	CRITICAL

CI: Confidence interval; RR: Risk ratio

[1] The imprecision domain is assessed using GRADE guidance[42] 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.

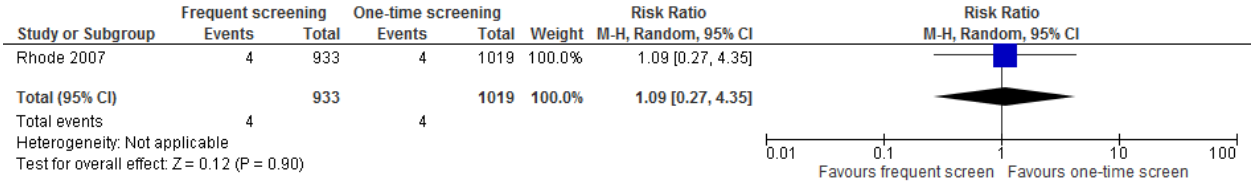
Preterm delivery [b] → Very Low Quality Evidence: One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to very serious risk of bias associated 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. Forest Plots 2.1-2.2 - KQ1b: Benefits and harms of frequent screening compared to one-time screening

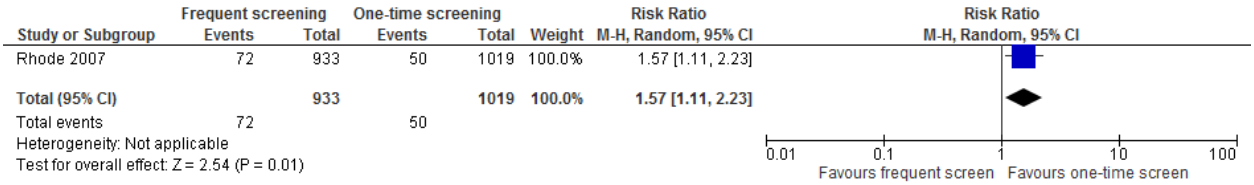
Outcome	No. of studies	No. of participants	Effect size (Risk Ratio; M-H, Random, 95%CI)
2.1 Pyelonephritis	1	1952	1.09 [0.27, 4.35]
2.2 Preterm delivery <37 wks GA	1	1952	1.57 [1.11, 2.23]

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with treatment				
Maternal mortality	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal mortality.
Maternal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal sepsis.
Pyelonephritis	Median		RR 0.24 (0.13 to 0.41)	2017 (12 RCTs[50, 55, 57-65, 67])	⨁⨁◯◯ LOW [1, a]	There may be a reduction in pyelonephritis from treatment.
	232 per 1,000	176 fewer per 1,000 (from 137 fewer to 202 fewer)				
Perinatal mortality	Median		RR 0.96 (0.27 to 3.39)	1104 (6 RCTs[50, 57, 61-63, 68])	⨁◯◯◯ VERY LOW [1, b]	We are very uncertain about the effects of treatment on perinatal mortality.
	40 per 1,000	2 fewer per 1,000 (from 29 fewer to 97 more)				
Spontaneous abortion	Median		RR 0.60 (0.11 to 3.10)	379 (2 RCTs[59, 68])	⨁◯◯◯ VERY LOW [1, c]	We are very uncertain about the effects of treatment on spontaneous abortion.
	33 per 1,000	13 fewer per 1,000 (from 30 fewer to 70 more)				
Neonatal sepsis	Median		RR 0.22 (0.01 to 4.54)	154 (2 RCTs[50, 66])	⨁◯◯◯ VERY LOW [1, d]	We are very uncertain about the effects of treatment on neonatal sepsis.
	22 per 1,000	17 fewer per 1,000 (from 22 fewer to 79 more)				

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with treatment				
Preterm delivery	Median		RR 0.57 (0.21 to 1.56)	533 (4 RCTs[50, 59, 66, 68])	⨁◯◯◯ VERY LOW [1, e]	We are very uncertain about the effects of treatment on preterm delivery.
	158 per 1,000	68 fewer per 1,000 (from 125 fewer to 88 more)				
Low birth weight	Median		RR 0.63 (0.45 to 0.90)	1522 (7 RCTs[50, 55, 57, 61, 62, 63, 68])	⨁◯◯◯ LOW [1, f]	There may be a reduction in low birth weight from treatment.
	118 per 1,000	44 fewer per 1,000 (from 12 fewer to 65 fewer)				
Maternal serious harm(s)	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal serious harms.
Neonatal serious harm: fetal abnormalities	Median		RR 0.49 (0.17 to 1.43)	821 (4 RCTs[50, 57, 59, 63])	⨁◯◯◯ VERY LOW [1, g]	We are very uncertain about the effects of treatment on harms (fetal abnormalities).
	19 per 1,000	9 fewer per 1,000 (from 15 fewer to 8 more)				
Neonatal serious harm: hemolytic anemia	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	265 (1 RCT[57])	⨁◯◯◯ VERY LOW [1, h]	We are very uncertain about the effects of treatment on harms (hemolytic anemia).

*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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	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 effect

[1] The imprecision domain is assessed using GRADE guidance[42] 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 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 (I^2=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:

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	treatment	no treatment	Relative (95% CI)	Absolute (95% CI)		
Maternal mortality												
0									not estimable		-	CRITICAL
Maternal sepsis												
0									not estimable		-	CRITICAL
Pyelonephritis												
12	randomised trials[50, 55, 57-65, 67]	serious	not serious	serious	not serious	none	55/1023 (5.4%)	23.2%	RR 0.24 (0.13 to 0.41)	176 **fewer per** 1,000 (from 137 fewer to 202 fewer)	⨁⨁◯◯ LOW [1, a]	CRITICAL
Perinatal mortality												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	treatment	no treatment	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials[50, 57, 61-63, 68]	serious	not serious	serious	serious	none	16/529 (3.0%)	4.0%	RR 0.96 (0.27 to 3.39)	2 fewer per 1,000 (from 29 fewer to 97 more)	⨁◯◯◯ VERY LOW [1, b]	CRITICAL
Spontaneous abortion												
2	randomised trials[59, 68]	serious	not serious	serious	very serious	none	4/222 (1.8%)	3.3%	RR 0.60 (0.11 to 3.10)	13 fewer per 1,000 (from 30 fewer to 70 more)	⨁◯◯◯ VERY LOW [1, c]	CRITICAL
Neonatal sepsis												
2	randomised trials[50, 66]	not serious	not serious	serious	very serious	none	0/77 (0.0%)	2.2%	RR 0.22 (0.01 to 4.54)	17 fewer per 1,000 (from 22 fewer to 79 more)	⨁◯◯◯ VERY LOW [1, d]	CRITICAL
Preterm delivery												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	treatment	no treatment	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials[50, 59, 66, 68]	serious	serious	not serious	very serious	none	34/299 (11.4%)	15.8%	RR 0.57 (0.21 to 1.56)	68 fewer per 1,000 (from 125 fewer to 88 more)	⊕◯◯◯ VERY LOW [1, e]	CRITICAL
Low birth weight												
7	randomised trials[50, 55, 57, 61, 62, 63, 68]	serious	not serious	serious	not serious	none	64/769 (8.3%)	11.8%	RR 0.63 (0.45 to 0.90)	44 fewer per 1,000 (from 12 fewer to 65 fewer)	⊕⊕◯◯ LOW [1, f]	IMPORTANT
Maternal serious harm(s)												
0									not estimable		-	CRITICAL
Neonatal serious harm: fetal abnormalities												
4	randomised trials[50, 57, 59, 63]	serious	not serious	serious	very serious	none	4/425 (0.9%)	1.9%	RR 0.49 (0.17 to 1.43)	9 fewer per 1,000 (from 15 fewer to 8 more)	⊕◯◯◯ VERY LOW [1, g]	CRITICAL
Neonatal serious harm: hemolytic anemia												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [1]	Other considerations	treatment	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[57]	serious	serious	serious	very serious	none	0/122 (0.0%)	0/143 (0.0%)	not estimable		⨁◯◯◯ VERY LOW [1, h]	CRITICAL

[1] The imprecision domain is assessed using GRADE guidance[42] 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).

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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.

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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 (I^2=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.

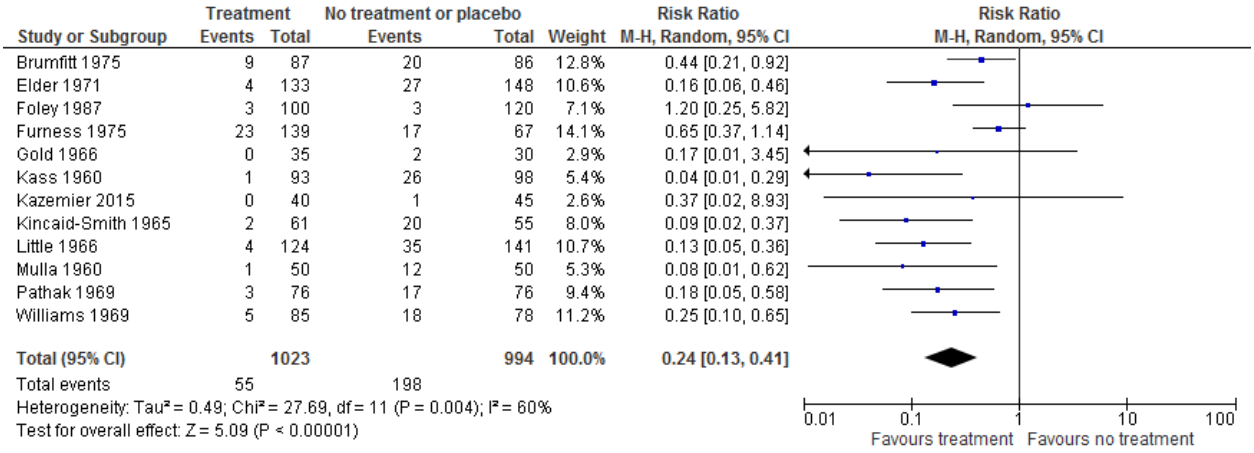
Neonatal serious harm: hemolytic anemia [h] → Very Low Quality Evidence: One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only 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: Forest Plots 3.1-3.8 - KQ4: Benefits and harms of treatment compared to no treatment

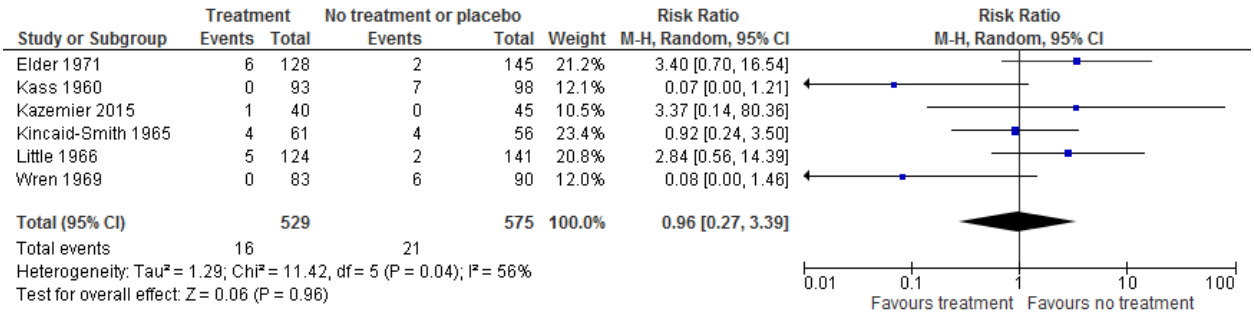
Outcome	No. of studies	No. of participants	Effect size (Risk Ratio; M-H, Random, 95%CI)
3.1 Pyelonephritis	12	2017	0.24 [0.13, 0.41]
3.2 Perinatal mortality (≥20 wks, including intrauterine demise, stillbirth, early neonatal death)	6	1104	0.96 [0.27, 3.39]
3.3 Spontaneous abortion (<20 wks)	2	379	0.60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

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

3.1 Pyelonephritis



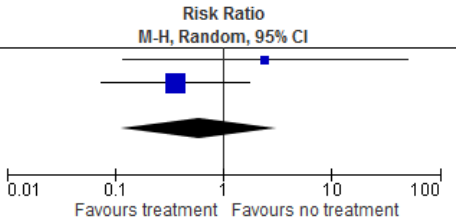
3.2 Perinatal mortality



3.3 Spontaneous abortion

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Furness 1975	2	139	0	67	26.3%	2.43 [0.12, 49.89]
Wren 1969	2	83	6	90	73.7%	0.36 [0.08, 1.74]
Total (95% CI)		**222**		**157**	**100.0%**	**0.60 [0.11, 3.10]**
Total events	4		6			

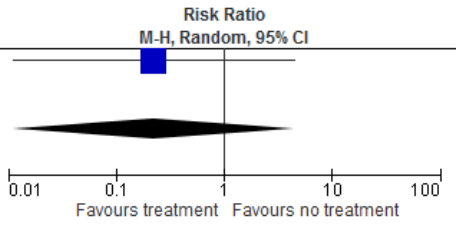
Heterogeneity: Tau² = 0.32; Chi² = 1.21, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 0.62 (P = 0.54)



3.4 Neonatal sepsis

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kazemier 2015	0	40	2	45	100.0%	0.22 [0.01, 4.54]
Thomsen 1987	0	37	0	32		Not estimable
Total (95% CI)		**77**		**77**	**100.0%**	**0.22 [0.01, 4.54]**
Total events	0		2			

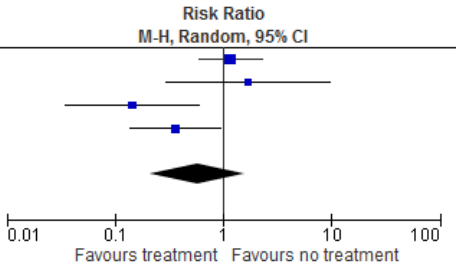
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)



3.5 Preterm delivery

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Furness 1975	24	139	10	67	32.4%	1.16 [0.59, 2.28]
Kazemier 2015	3	40	2	45	17.9%	1.69 [0.30, 9.59]
Thomsen 1987	2	37	12	32	21.7%	0.14 [0.03, 0.60]
Wren 1969	5	83	15	90	28.1%	0.36 [0.14, 0.95]
Total (95% CI)		**299**		**234**	**100.0%**	**0.57 [0.21, 1.56]**
Total events	34		39			

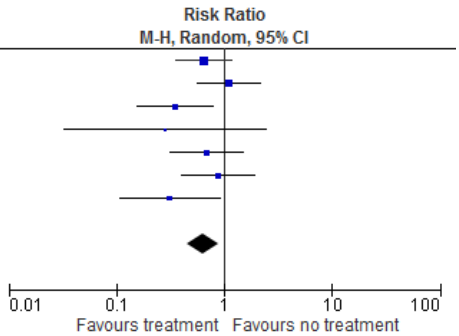
Heterogeneity: Tau² = 0.70; Chi² = 9.85, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 1.10 (P = 0.27)



3.6 Low birthweight

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brumfitt 1975	18	235	21	178	23.0%	0.65 [0.36, 1.18]
Elder 1971	15	133	15	145	19.4%	1.09 [0.55, 2.14]
Kass 1960	7	93	21	98	14.8%	0.35 [0.16, 0.79]
Kazemier 2015	1	40	4	45	2.5%	0.28 [0.03, 2.41]
Kincaid-Smith 1965	9	61	12	56	15.5%	0.69 [0.31, 1.51]
Little 1966	10	124	13	141	15.4%	0.87 [0.40, 1.92]
Wren 1969	4	83	14	90	9.3%	0.31 [0.11, 0.90]
Total (95% CI)		**769**		**753**	**100.0%**	**0.63 [0.45, 0.90]**
Total events	64		100			

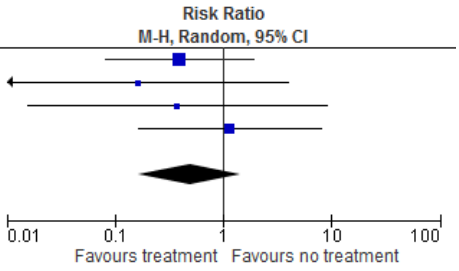
Heterogeneity: Tau² = 0.04; Chi² = 7.52, df = 6 (P = 0.28); I² = 20%
Test for overall effect: Z = 2.57 (P = 0.01)



3.7 Neonatal serious harm: fetal abnormalities

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Elder 1971	2	122	6	143	46.4%	0.39 [0.08, 1.90]
Furness 1975	0	139	1	67	11.4%	0.16 [0.01, 3.92]
Kazemier 2015	0	40	1	45	11.5%	0.37 [0.02, 8.93]
Little 1966	2	124	2	141	30.7%	1.14 [0.16, 7.95]
Total (95% CI)		**425**		**396**	**100.0%**	**0.49 [0.17, 1.43]**
Total events	4		10			

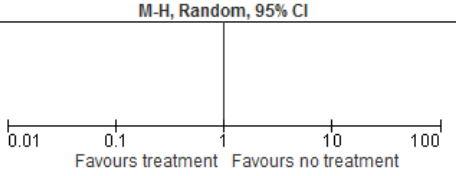
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)



3.8 Neonatal serious harm: hemolytic anemia

Study or Subgroup	Treatment Events	Total	No treatment or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Elder 1971	0	122	0	143		Not estimable
Total (95% CI)		**122**		**143**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

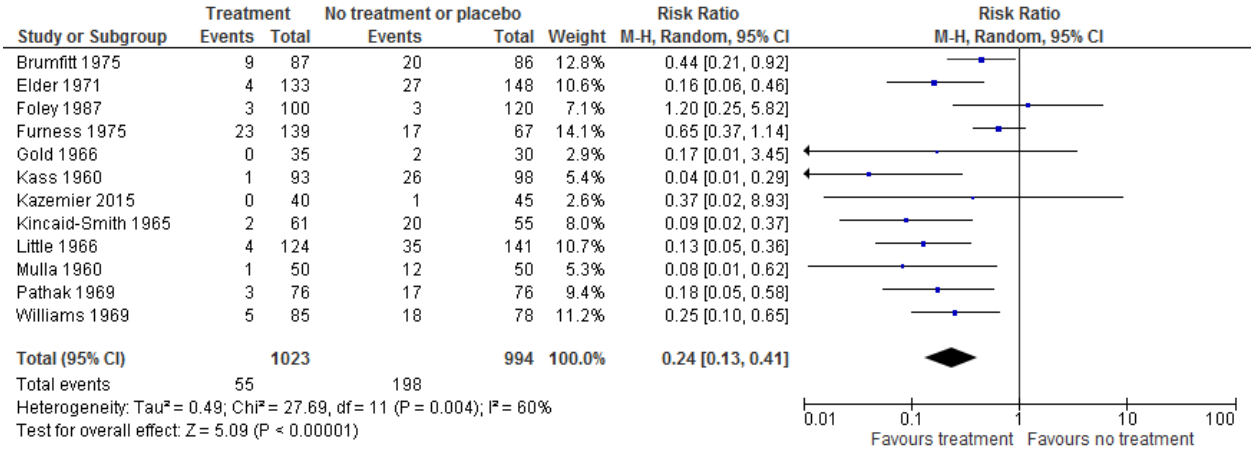


Evidence Set 3. Forest Plots for Subgroup Analyses 3.1.1-3.1.4 – KQ4: Benefits and harms of treatment compared to no treatment

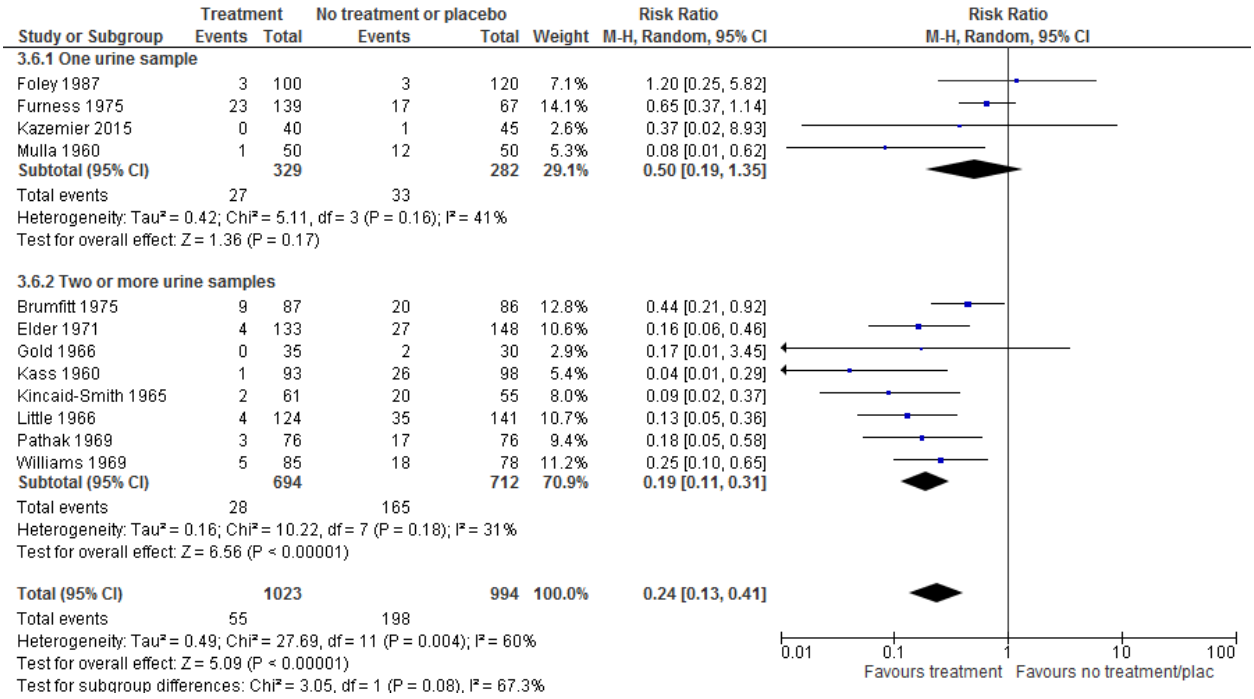
Outcome	No. of studies	No. of participants	Effect size (Risk Ratio; M-H, Random, 95%CI)
3.1 Pyelonephritis (overall)	**12**	**2017**	**0.24 [0.13, 0.41]**
3.1.1 Subgroup analysis: no. of urine samples before confirming bacteriuria and giving treatment			
One urine sample	4	611	0.50 [0.19, 1.35]
Two or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

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

3.1 Pyelonephritis (overall)

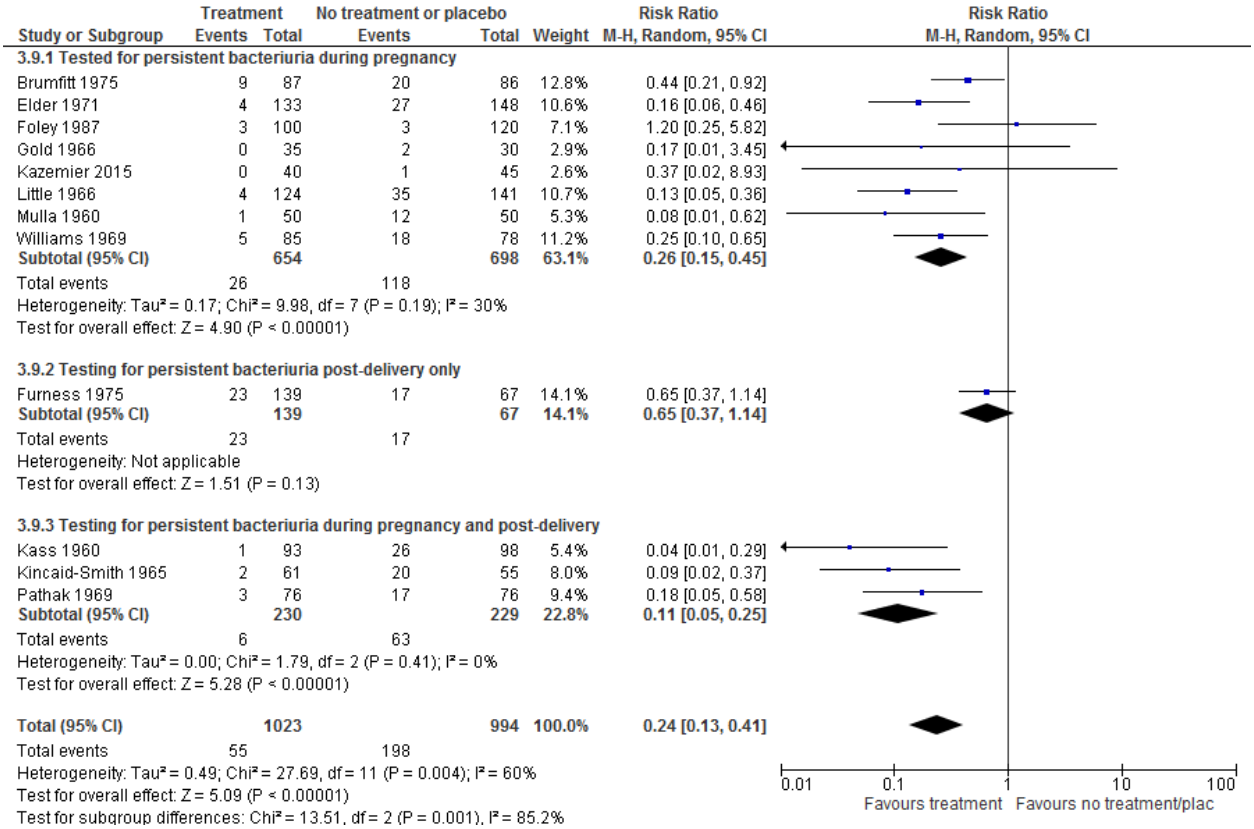


3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit*

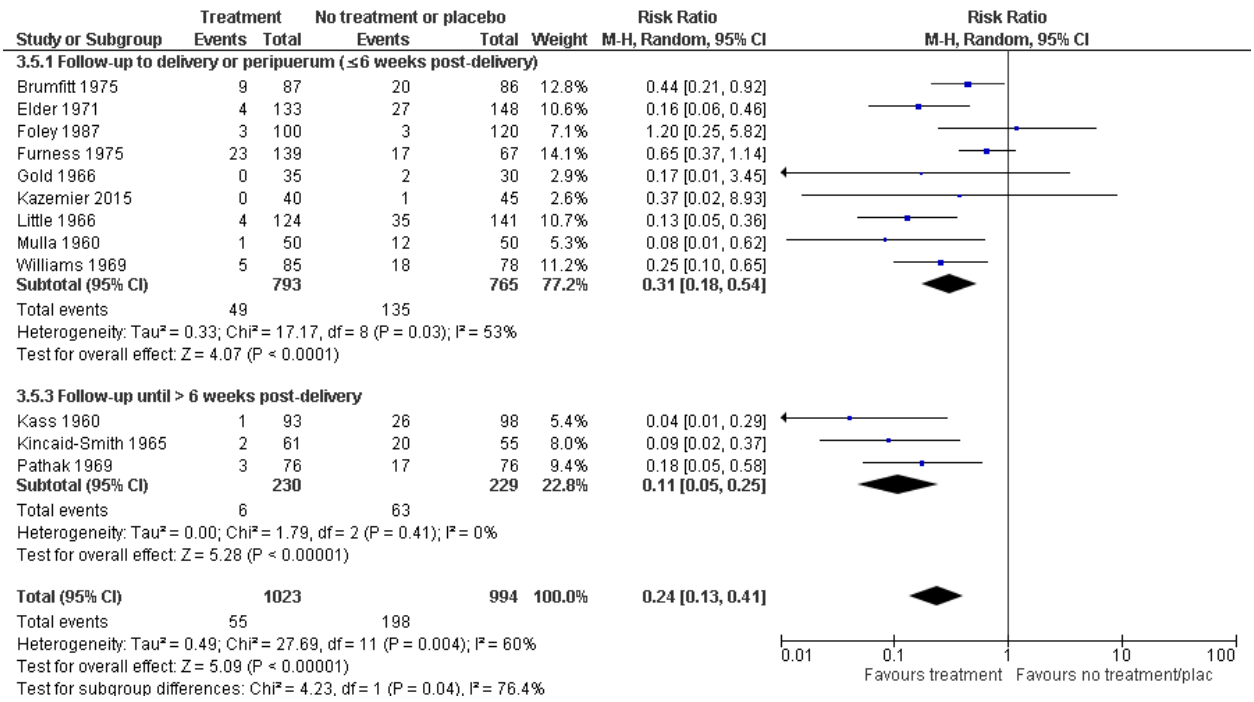


*The additional culture(s) was used to confirm levels of bacteriuria.

3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria



3.1.3 Pyelonephritis subgroup: duration of follow-up



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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External Reviewers

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List of Abbreviations

AAFP	American Academy of Family Physicians
AAP	American Academy of Physicians
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ARDS	Acute Respiratory Distress Syndrome
ARR	Absolute Risk Reduction
ASB	Asymptomatic Bacteriuria
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	Controlled Clinical Trial
CFU	Colony-Forming Units
CI	Confidence Interval
CTFPHC	Canadian Task Force on Preventive Healthcare
DARE	Database of Abstracts of Reviews of Effects
EP	Evidence Profile
ES	Evidence Set
GBS	Group B Streptococcus
GRADE	Grading of Assessment, Development and Evaluation
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Diseases Society of America
IDSOG	Infectious Diseases Society of Obstetrics and Gynecology
KQ	Key Question
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NNS	Number Needed to Screen
NNT	Number Needed to Treat
NOS	Newcastle-Ottawa Quality Assessment Scale
OIS	Optimal Information Size

OR	Odds Ratio
PHAC	Public Health Agency of Canada
PICOTS	Population, Intervention, Comparator, Timing and Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QALY	Quality-Adjusted Life-Year
RCT	Randomized Clinical Trial
ROB	Risk of Bias
RR	Risk Ratio
SGA	Small for Gestational Age
SIGN	Scottish Intercollegiate Guidelines Network
SMFM	Society for Maternal-Fetal Medicine
SOF	Summary of Findings
SOGC	Society of Obstetricians and Gynaecologists of Canada
USPSTF	US Preventive Services Task Force
UTI	Urinary Tract Infection

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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
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6. Quality Assessments for Included Studies – KQ1a & b
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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

Study; Design; Setting	Sample		Population characteristics (risk factors of interest)	Screening timing, frequency & details	Comparator	Treatment protocol	Definition of outcomes
	Screened (n)	Unscreened (n)					
Gérard 1983 Non-concurrent cohort Hospital; France Funding NR	170	200	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 $\geq 10^5$ 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 Non-concurrent cohort Obstetrics clinic, academic; Spain Funding NR	1652	3265	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 Non-concurrent cohort	933	1019	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 reagent strip only if	ND	**Pyelonephritis:** ND; however, clearly differentiated from ASB, cystitis and undetermined UTI **Preterm delivery:** <37 weeks of gestation

Hospital-based midwifery practice; USA Funding NR			• Predominantly medically underserved and Hispanic women (72%) • GDM: routine 9% vs. indicated 4%	reagent strips, culture or urinalysis as indicated[1] ASB+=8.7%	one of the criteria was present (risk factors for UTI, GDM). Follow-up of culture or lab urinalysis as indicated[1]		
Uncu 2001 Non-concurrent cohort Outpatient obstetrics clinic, academic; Turkey Funding NR	186	186	All pregnant women ≤32 weeks of gestation GDM: ~3%	First visit (<32 weeks of gestation) Urine culture (positive at > 10^5 CFU/mL of same organism) ASB+=9.3% (more positive at 25-32 weeks)	No screening with culture	• ASB+ treated 7-10 days after sensitivity testing • Follow-up cultures 1 week post-treatment- 5/23 (22%) recurrence	**Pyelonephritis:** ND **Intrauterine death:** no fetal cardiac activity by USG, after 20 weeks of gestation[2] **Preterm delivery:** <37 weeks of gestation[2] **Fetal abnormalities:** ND

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

[1] 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)

[2] criteria for outcomes were confirmed by study author

Appendix 2a. Summary of Characteristics of Systematic Review – KQ4: Benefits and harms of treatment

Systematic Review	Population; No. of studies (no. of participants)	Intervention(s)	Comparator(s)	Outcome(s)	Study Design	QA; Analysis
Smaill 2015	Pregnant women found via antenatal screening to have asymptomatic bacteriuria, as defined by the study authors, at any stage of pregnancy 7 (1932)	Any antibiotic regimen	Placebo or no treatment	Primary: 1) Development of pyelonephritis 2) Preterm birth <37 wks of gestation 3) Birthweight <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	RCTs and CCTs 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

* 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

Study; Design; Setting; Funding	Sample		Population characteristics (risk factors of interest)	Screening & Treatment details	Comparator details	Definition of outcomes	ROB (overall)
	Treated	Not treated/ placebo-treated					
Brumfitt 1975 (Partial data obtained from Condie 1968 & Williams, 1968, preliminary reports) Controlled trial (unclear if randomized) "double blind" 3 antenatal clinics in Birmingham and London, UK Non-industry funded	247	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 >10^5 CFU/mL **Prematurity*:** ≤2500g	High
Elder 1966 RCT Boston City Hospital, USA Non-industry funded	54	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; ≥10^4 CFU/mL of same organism in one sample and ≥10^5 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

				treatment and at each clinic visit until delivery			
Elder 1971 Quasi-RCT; 4 groups; some patients may have participated for >1 pregnancy Boston City Hospital, USA Non-industry funded	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:	**Screening test:** clean-voided x 3; $\geq 10^5$ CFU/mL in 2 samples (no colony counts of $<10^4$ CFU/mL), of the same organism **Treatment:** tetracycline, nitrofurantoin, other drugs (NR) **Follow-up:** until delivery, and a short period of time (NR) after delivery for complications **Persistent bacteriuria:** retested at each clinic visit until delivery (includes recurrence and excludes those who became symptomatic)	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
Foley 1987 RCT National Maternity Hospital, Dublin, Ireland Funding source NR	100	120	• First antenatal visit.	**Screening test:** MSU x 1; $>10^5$ CFU/mL **Treatment:** sulphamethizole, nitrofurantoin **Follow-up:** until delivery **Persistent bacteriuria:** retested 'at follow-up', not further defined.	No treatment	**Pyelonephritis:** ND; 'admitted with pyelonephritis'	High
Furness 1975 RCT; 3 groups	139	67	• Second antenatal visit.	**Screening test:** MSU x 1; dipslide, $>10^5$ CFU/mL or $>10^4$ CFU/mL in 2 samples	No treatment	**Pyelonephritis:** frequency and burning on micturition	High

Queen Victoria Hospital, Adelaide, Australia Industry and non-industry funded				**Treatment:** methenamine mandelate, methenamine hippurate **Follow-up:** until 6 wks post-delivery **Persistent bacteriuria:** retested for postnatal bacteriuria at 6 wks post-partum (excludes those who developed pyelonephritis)		accompanied by pyrexia or loin tenderness, with presence of a significant number of bacteria in urine **Spontaneous abortion:** ND; 'abortions' **Fetal abnormalities:** major fetal abnormality (anencephaly)	
Gold 1966 Quasi-RCT (odd and even number assignment) Prenatal clinic in New York, USA Non-industry funded	35	30	• Prenatal visit. • 85% nonwhite, 6% Puerto Rican, 9% other white Excluded those who failed to return, aborted, delivered at other hospitals, were found to not be pregnant, had an ectopic pregnancy, transferred to other care, or were delivered by a private physician.	**Screening test:** MSU x2; $>10^5$ CFU/mL **Treatment:** sulfadimethoxine, sulfadiazine **Follow-up:** until the 'post-partum period' (exact time ND) **Persistent bacteriuria:** retested at each clinic visit until delivery (either for initial diagnosis or persistent bacteriuria); persistent bacteriuria defined as at delivery	Placebo	**Pyelonephritis:** ND	High
Kass 1960 (data obtained from updated report: Savage, 1967)	93	98	• First prenatal visit (registration); <32 wks GA • Similar age distribution between	**Screening test:** first prenatal visit with 10^3-10^5 CFU/mL, followed by 10^5 CFU/mL in 2 cultures of the same organism	Placebo	**Pyelonephritis:** dysuria, frequency, and flank pain or other localizing evidence of inflammation, with either documented	High

Quasi-RCT, double-blind, some patients participated for >1 pregnancy; 4 groups Boston City Hospital, USA Non-industry funded			treated and placebo groups • 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)		temperature of 100 degrees F or above or a history of chills and fever. Not always clear that patients were febrile. **Perinatal mortality:** 'perinatal death' and loss >20 wks **Prematurity*:** <2500g	
Kazemier 2015 Cohort (screening vs. no screening), with embedded RCT	40	45 placebo; 163 untreated	• Cohort from ultrasound centres, 4412 (78%) and hospitals, 1209 (22%)	**Screening:** MSU; dipslide, with ≥10^5 CFU/mL of single organism (or at least of one organism if multiple present)	Placebo or no treatment	**Pyelonephritis:** hospital admission with ≥2 symptoms of: fever ≥38 degrees C, symptoms of pyelonephritis (nausea,	Low

(treatment vs. no treatment) 8 hospitals and 5 ultrasound centres, Netherlands Non-industry funded			• ≥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	
Kincaid-Smith 1965 RCT, "double-blind" Queen Victoria Hospital, Melbourne, Australia	61	56	• First antenatal visit at <26 wks GA • All from lowest income category in community At post-delivery testing:	**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

Industry and non-industry funded			• >50% patients had radiological renal abnormalities • 5 patients had poor or non-functioning kidneys on one side due to ureteric obstruction	**Follow-up:** until 6 months post-delivery **Persistent bacteriuria:** Retested at monthly intervals until delivery, then at 6 wks to 3 months and 6 months post-partum		babies born after the 36th wk of gestation") **Perinatal mortality:** >28 wks GA	
Little 1966 RCT Charing Cross Hospital and Culham Maternity Hospital, London, England Industry and non-industry funded	124	141	• First antenatal visit • Past history of renal-tract disease: 62 (23.4%) with bacteriuria	**Screening:** MSU x 2; $>10^5$ CFU/mL **Treatment:** sulphamethoxypyridazine, nitrofurantoin, ampicillin **Follow-up:** until 6 wks post-delivery **Persistent bacteriuria:** Treatment group retested monthly until delivery	Placebo	**Pyelonephritis:** loin pain and tenderness, a fever >100 degrees F, $>10^5$ CFU/mL, and often frequency, dysuria, rigors and hematuria **Prematurity*:** birth weight <2500g **Perinatal mortality:** ND **Fetal abnormalities:** ND	Unclear
Mulla 1960 RCT St. Elizabeth Hospital, Ohio, USA Funding not reported	50	50	• 30-32 wks GA	**Screening:** culture, microbiological criteria NR **Treatment:** sulfadimethoxine **Follow-up:** to delivery and immediately after **Persistent bacteriuria:** Followed at weekly intervals until delivery; retested at least once, after 1 wk of treatment	No treatment	**Pyelonephritis:** Clinical evidence of active infection, including acute symptoms of cystopyelitis and premature labour that subsided with treatment; urine was tested	High

Pathak 1969 RCT University College Hospital and Kingston Public Hospital, Jamaica Industry and non-industry funded	76	76	• ≤24 wks GA • 18/84 (21.4%) ASB+ positive for sickle-cell trait ("sickling"), had approx. twice rate of bacteriuria as patients without trait On postpartum intravenous pyelogram: • 9/50 (18%) patients had radiological renal abnormalities; however, no major differences between groups for developing pyelonephritis Excluded women >24 wks GA, or with blood pressure >130 mmHg, did not re-attend the clinic, early abortions (6/217), clinical pyelonephritis (9/217), 'mentally defective'	**Screening:** clean-voided x 2; $>10^5$ CFU/mL **Treatment:** nitrofurantoin **Follow-up:** until 9 months post-delivery (bacteriuria) **Persistent bacteriuria:** Retested weekly during treatment, then every 2 wks until delivery, and at 3-9 months postpartum	Placebo	**Pyelonephritis:** ND	High
Thomsen 1987 RCT, "double-blind" University Hospital, Denmark Industry-funded	37	32	• 27-31 wks GA • Screening for Group B streptococci • All patients White • All patients similar socioeconomic status	**Screening:** MSU x 1; 10^2-10^6 CFU/mL (group B streptococci) **Treatment:** penicillin **Follow-up:** until delivery (one infant found to have group-B streptococcal sepsis at 6 wks post-delivery)	Placebo	**Preterm delivery:** <37 wks GA (mean 39.6 wks GA treated vs. 36.2 wks GA placebo-treated) **Neonatal sepsis:** ND	Unclear

				Persistent bacteriuria: Retested weekly until delivery			
Williams 1969 RCT Maternity Hospital and St. David's Hospital, Wales, England Non-industry funded	85	78	• First antenatal visit • <30 wks GA	**Screening:** MSU x 2; $>10^5$ CFU/mL **Treatment:** sulphadimidine, ampicillin, nitrofurantoin **Follow-up:** until 10 days post-delivery **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	High
Wren 1969 Quasi-RCT (alternation) Royal Hospital for Women, New South Wales, Australia Industry-funded	83	90	• First antenatal visit	**Screening:** MSU x 2; microbiological criteria NR **Treatment:** nitrofurantoin, ampicillin, sulphurazole, nalidixic acid **Follow-up:** until up to 6 wks post-delivery **Persistent bacteriuria:** Retested once per month when possible until delivery	No treatment	**Prematurity*:** birth weight <2501g **Perinatal mortality:** stillbirths and neonatal deaths **Spontaneous abortion:** ND **Preterm delivery:** <37 wks GA	High

ASB: asymptomatic bacteriuria; C: celsius; CFU/mL: colony-forming units per millitre; DM: diabetes mellitus; F: Fahrenheit; g: gram(s); GA: gestational age; mmHg: millimeters of mercury; MSU: midstream urine; ND: no description; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; NR: not reported; PVL: periventricular leukomalacia; RCT: randomized controlled trial; RDS: respiratory distress syndrome; SES: socioeconomic status; UTI urinary tract infection; wks: weeks

*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

Gérard, Blazquez & Mounac, 1983	
Objective	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
Methods	Design: Non-concurrent cohort 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). Exclusion criteria: NR
Participants	Setting: Centre Hospitalier de Corbeil-Essonnes (a Hospital) Study period: January-October 1979 (and 10 previous months for the control group) Sample: n=370 pregnant women; n=170 in study group; n=200 in control group Mean age, y (SD): NR Risk factors: NR 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.
Interventions	Implementation of a routine screening and treatment program for ASB: 1) Screening of all women at 3, 5, 7 and 9 months of pregnancy, and treatment of those diagnosed with ASB 2) Controls only screened after presenting with clinical signs Urine testing characteristics: Urine collection: Midstream urine sample with cleansing of the vulva before micturition Urine testing: Microscopy, urine culture and Gram staining Criteria for positive test: $\geq 10^5$ CFU/mL Gestational age (weeks) at first prenatal visit: ~3 months for the treatment group; NR for the control group Number of prenatal visits: at least 4 (every 2 months) for the treatment group; NR for control group Treatment: Treatment based on antibiotic sensitivity and at the discretion of the prescribing physician
Outcomes	Acute pyelonephritis: Clinical signs (fever, lumbar pain, dysuria, pollakiuria (urinary frequency)) and positive urine culture of 10^5 CFU/mL Spontaneous abortion: ≤28 wks GA Preterm delivery: Delivery at <37 wks GA Birth weight: Reported means for ASB vs. non-ASB in study group; symptomatic + positive culture vs. asymptomatic in controls Perinatal mortality: “stillbirth” as either death in utero or during delivery, all ≥31 wks GA Adverse event(s): NR

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	
Objective	To determine the incidence of pyelonephritis in pregnant women before and after the introduction of a screening program for ASB
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 Study period: January 1987-December 1992 (study group: January 1991-December 1992; controls: January 1987-December 1990) 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

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)

Rhode, 2007	
Objective	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
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 indicated[1] 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 indicated[1] 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

	Gestational age (wks) at start of care (SD): Routine screening= 20.5 (9.4); Indicated screening= 20.3 (8.9) Number of prenatal visits: NR Treatment: NR
Outcomes	Pyelonephritis: ND; however, clearly differentiated from ASB, cystitis and undetermined UTI Preterm delivery: <37 wks GA[2] Adverse event(s): NR
Notes	Authors compared eligible participants to those who became ineligible during the study period. In the routine screening group, eligible and ineligible women differed in terms of marital status, race, payment source, # preterm deliveries, and # weeks gestation at start of care. In the indicated screening group, eligible and ineligible women differed in terms of race, # of abortions, and # weeks of gestation at start of care.

ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; UTI: urinary tract infection; GDM: gestational diabetes mellitus; wks: weeks; y: year(s)

[1] 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)

[2] Criteria for outcomes were confirmed by study author(s)

Uncu, 2001	
Objective	To determine the incidence of asymptomatic bacteriuria during pregnancy and its relation to pregnancy complications
Methods	Design: Non-concurrent cohort 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 Exclusion criteria: Patients who were followed-up at clinic due to prior renal disease, positive for ASB or were taking antibiotics
Participants	Setting: Antenatal outpatient clinic, Uludag University Faculty of Medicine, Department of Obstetrics and Gynecology, Turkey Study period: June 1998-January 1999 Sample: Screened= 186; Controls= 186 Mean age, y (SD): Screened= 27.7 (5.1); Controls= 27.7 (4.6) Risk factors: Gestational diabetes mellitus: Screened=7 (3.8%); Controls= 5 (2.7%) Socioeconomic status: lower SES correlated with high prevalence of ASB* Length of follow-up: NR; loss to follow-up: NR
Interventions	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.

	Urine testing characteristics: Urine collection: midstream morning urine sample, first visit Urine testing: whole blood count, total urine analysis, and urine culture Criteria for positive test: $>10^5$ CFU/mL of the same organism Gestational age (wks), at time of urine culture: beginning of pregnancy Number of prenatal visits: NR 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%)
Outcomes	Pyelonephritis: ND Intrauterine death[2]: no fetal cardiac activity by USG, after 20 weeks' gestation Prematurity[2]: <37 wks of gestation Adverse event(s): NR Fetal abnormalities: ND
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

Butters, 1990 Awareness among pregnant women of the effect on the fetus of commonly used drugs	
Objective	To determine the level of knowledge of the effects of commonly used drugs on a fetus
Methods	Design: Cross-sectional (self-completed questionnaire) Recruitment: Participants were recruited from postnatal wards of the hospitals on a weekly basis
Participants	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. 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). 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. Study period: October 1, 1987 and March 31, 1988. Sample: n=514 Age range: 15 to 40 years; 66 (13%) between 15 and 20 years, 141 (27%) between 21 and 25 years, 176 (34%) between 26 and 30 years, and 127 (25%) aged over 30 years. Gestational age: NA Parity: First pregnancy (53%) Race/ethnicity: Multiple ethnicities, mainly Scottish. Education level: NR
Interventions	Anonymous short questionnaire with mostly tick boxes.
Outcomes	-254 (49%) said they would take an antibiotic prescribed by their doctor, 246 (48%) said they would not, and 14 (3%) did not respond. -The responses were similar for all ages and social class groups. -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<0.0001.

NA: not applicable; NR: not reported

Kazemier, 2015 Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomized controlled trial	
Objective	To investigate the consequences of treated and untreated ASB in pregnancy
Methods	Design: Prospective cohort (screening vs. no screening) with embedded RCT (decision on entry into the study considered cross-sectional) Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available)
Participants	Setting: 8 hospitals and 5 ultrasound centres, the Netherlands 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 GA, warning signs of imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 weeks 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). 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 Sates 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	
Objective	To examine the awareness of pregnant women about the effects of drugs in pregnancy
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 Gravidity: 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	
Objective	To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used
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

	Education level: NR
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).

cm: centimeter(s); NR: not reported

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).

	Inclusion criteria: Women who were pregnant or within one year of giving birth. Exclusion criteria: NR Study period: November 15, 2011 to January 15, 2012 Sample: n=1120 Mean age (SD): 30.5 (5.2) years Gestational age: 442 (39.5%) were currently pregnant Parity (95% CI): No previous children – 48.0% (45.1-50.9%) Race/ethnicity: NR Education level (95% CI): 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).
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

Brumfitt, 1975	
Objective	To assess the impact of screening and treatment for ASB on maternal and fetal health
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 ≥100◦F and $>10^5$ CFU/mL (Condie, 1968) Low birth weight (reported as prematurity): ≤2500g 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.

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

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 $\geq 10^4$ CFU/mL in one and $\geq 10^5$ 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 ≥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 ≥100◦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): ≤2500g 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; ◦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).
Interventions	Screening characteristics: Timing: First antenatal visit Urine collection: Midstream urine sample Urine testing method: NR Criteria for a positive test: One urine sample with $>10^5$ CFU/mL Treatment characteristics: Type of antibiotic and length of treatment: 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 Control group: Received no treatment Follow-up testing: Retested 'at follow-up'; not further defined
Outcomes	Benefits: Pyelonephritis: ND; 'admitted with pyelonephritis' Harms: NR
Notes	Reported as a letter to the editor, not a full publication.

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

Furness, 1975	
Objective	To examine the effectiveness of urinary antiseptics in preventing pyelonephritis and adverse among pregnant women with ASB
Methods	Design: RCT Recruitment: Pregnant women attending their initial prenatal visit Inclusion criteria: Pregnant women with 'significant' bacteriuria at the second prenatal visit Exclusion criteria: NR
Participants	Setting: Queen Victoria Hospital, Adelaide, Australia; urban Study period: NR

	Sample: n=206; treated (n=139); not treated (n=67) Mean age (SD), years: NR Risk factors: NR Length of follow-up: Until 6 wks postpartum Loss to follow-up: None reported
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 $>10^5$ 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).

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

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 ≥2 of the following: fever (body temperature ≥38◦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

Methods	Design: RCT; placebo-controlled Recruitment: Pregnant women attending their first antenatal visit before 26 wks GA Inclusion criteria: Pregnant women <26 wks GA with ASB at the first antenatal visit and confirmed by a subsequent positive test Exclusion criteria: NR
Participants	Setting: Queen Victoria Hospital, Melbourne, Australia; urban Study period: 1964-1965 Sample: n=145; treated (n=61), placebo (n=56) (see notes) Mean age (SD), years: NR Risk factors: (see notes) Socioeconomic status: All from lowest income category in community, but the community has a high standard of living Urogenital anomalies: 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. Length of follow-up: Until 6 months postpartum Loss to follow-up: 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
Interventions	Screening characteristics: Timing: First antenatal visit Urine collection: Midstream urine sample; the second test was clean-voided (first was not) Urine testing method: Urine culture Criteria for a positive test: $>10^5$ CFU/mL on two occasions Treatment characteristics: Type of antibiotic and length of treatment: 0.5g sulphamexydiazine 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. Control group: Received identical placebo capsules and tablets Follow-up testing: 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.
Outcomes	Benefits:

	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 >10^5 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
Outcomes	Benefits: Pyelonephritis: Loin pain and tenderness, a fever >100◦F, >10^5 CFU/mL. Usually there was also frequency and dysuria, and sometimes rigors and hematuria Perinatal mortality: ND Low birth weight (reported as prematurity): <2500g Harms: Serious adverse events: fetal abnormalities, ND
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	
Objective	To evaluate the clinical results of treatment of bacteriuria in pregnant women with long-acting sulfonamide
Methods	Design: RCT Recruitment: Pregnant women attending the obstetrical clinic Inclusion criteria: Pregnant women with ASB at their 30-32 wks GA obstetric visit Exclusion criteria: NR
Participants	Setting: St. Elizabeth Hospital, Ohio, US; urban Study period: NR Sample: n=100; treated (n=50), not treated (n=50) Mean age (SD), years: NR Risk factors: NR Length of follow-up: Until delivery and immediately after Loss to follow-up: None reported.
Interventions	Screening characteristics: Timing: Obstetric visit at 30-32 wks GA

	Urine collection: Catheter urinalysis (antimicrobial jelly used on the catheter) Urine testing method: Urine culture Criteria for a positive test: NR 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.
Outcomes	Benefits: Pyelonephritis: Clinical evidence of active infection, including acute symptoms of cystopyelitis; urine was tested at the time of the episode Harms: NR
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

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 hydroureter 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 Length of follow-up: Until delivery (see notes) Loss to follow-up: None reported.
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

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

	Exclusion criteria: NR
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 [a]

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

Domain	Author's judgement	Support for judgement
Selection of the non-exposed cohort	1	All pregnant women who enrolled for care at the same practice and delivered before August 15, 2002.
Ascertainment of exposure	1	Used delivery records.
Outcome not present at start of study (pyelonephritis/other outcomes)	0/1	Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.
Comparability of the cohorts	1	Compared 10 demographic factors, showing that groups were similar.
Assessment of outcome	1	Used a chart review.
Adequacy of length of follow-up	1	Followed-up until delivery of the patient left the practice.
Adequacy of follow-up of cohorts	1	112 (4.6%) lost to follow-up.
Selective outcome reporting[b]	suspected	Did not report on spontaneous abortion, perinatal mortality or fetal abnormalities.
Total score (maximum 10)	8	
Uncu, 2002 (cohort)		
Representativeness of the exposed cohort	1	All pregnant women <32 wks GA seen at an antenatal outpatient clinic.
Selection of the non-exposed cohort	1	Women who visited the clinic prior to the start of the screening study.
Ascertainment of exposure	1	Used delivery records.
Outcome not present at start of study (pyelonephritis/other outcomes)	0/1	Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.
Comparability of the cohorts	0	No evidence of comparability.
Assessment of outcome	1	Used delivery records.
Adequacy of length of follow-up	1	Follow-up until post-delivery.
Adequacy of follow-up of cohorts	0	Not reported.
Selective outcome reporting[b]	not suspected	Reported on all outcomes, including fetal death >20 wks GA (eligible for perinatal mortality).
Total score (maximum 10)	6	

GA: gestational age; wks: weeks

[a]Assessed using the Newcastle-Ottawa Quality Assessment Scale

[b]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[a]

Domain	Author's judgement*	Support for judgement
Butters, 1990 (cross-sectional survey)		
Clearly focused question/issue	1	Awareness of the effects of commonly used drugs, cigarettes and alcohol on the fetus
Appropriate research method (study design)	1	Cross-sectional survey of women in postnatal wards
Selection of subjects clearly described	1	Provides inclusion and exclusion criteria, outlines selection methods
Sampling method introduces bias	2	Sampling was not random, may be consecutive
Sample of subjects representative of the population	1	Included women who were recently post-partum
Sample size based on pre-study considerations of statistical power	2	Not reported
Satisfactory response rate	1	Response rate was 87%
Questionnaires are likely to be valid and reliable	2	Validation of survey questions was not reported
Statistical significance assessed	1	Chi-square analysis
Confidence intervals for main results	3	No confidence intervals reported
Confounding factors not accounted for	1	Confounders were not addressed with study design or analysis
Applicability of the results	1	Identifies areas for further education in this population
Kazemier, 2015 (Prospective multi-centre screening cohort with embedded treatment RCT; valuation of outcomes obtained/reported in cross-sectional manner)		
Clearly focused question/issue	2	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
Appropriate research method (study design)	2	Appears to be cross-sectional for information regarding why eligible women did not consent to participate in treatment trial
Selection of subjects clearly described	1	Clear inclusion and exclusion criteria for screening cohort and treatment RCT, with study flow documented
Sampling method introduces bias	3	Various clinics, hospitals and ultrasound centres in the Netherlands
Sample of subjects representative of the population	1	Women 18 years or older with singleton pregnancy without symptoms of urinary tract infection.
Sample size based on pre-study considerations of statistical power	2	Sample size estimates reported in statistical analysis, but none specified for cross-section of women for outcome valuation
Satisfactory response rate	2	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

		authors do not report if those who participated in treatment trial were asked/provided reason(s)
Questionnaires are likely to be valid and reliable	2	Validation of reason(s) for dissenting not reported
Statistical significance assessed	3	Fisher's exact test for outcomes from screening cohort and treatment trial; no significance for outcome valuation data
Confidence intervals for main results	3	CI's reported for outcomes from screening cohort and treatment trial; no CI's for outcome valuation data
Confounding factors not accounted for	2	Assessed confounders for outcomes from screening cohort and treatment trial, but not for outcome valuation data
Applicability of the results	3	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
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

Sample of subjects representative of the population	1	Included pre and postnatal women in hospital wards
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	Chi-square, Student's t-test, Pearson correlations, ANOVA
Confidence intervals for main results	3	Not reported
Confounding factors not accounted for	1	Confounders were not addressed with study design or analysis
Applicability of the results	1	Identifies roles for pharmacists in education of this population
Nordeng, 2010 (cross-sectional survey)		
Clearly focused question/issue	1	Women's perception of risk during pregnancy
Appropriate research method (study design)	1	Cross-sectional survey of pregnant women and 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 and young mothers (child less than 5 years) 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	Linear regression, ANOVA, Student's t-test
Confidence intervals for main results	3	Confidence intervals were available in graph format only
Confounding factors not accounted for	2	Addressed in limitations
Applicability of the results	1	Indicates women overestimate risks and more education in this area is needed.
Sanz, 2000 (cross-sectional)		
Clearly focused question/issue	1	Drug utilization in pregnant women
Appropriate research method (study design)	1	Cross sectional, visual analogue scale
Selection of subjects clearly described	3	Selection methods are not reported for all populations
Sampling method introduces bias	2	Not reported for all populations
Sample of subjects representative of the population	1	Pregnant women attending out-patient clinic at a hospital
Sample size based on pre-study considerations of statistical power	2	Not reported
Satisfactory response rate	2	Small n, no response rate reported
Questionnaires are likely to be valid and reliable	2	Validation of VAS questions was not reported

Statistical significance assessed	1	Mann-Whitney U, Kruskal Wallis, Chi-squared
Confidence intervals for main results	3	Only in graph format
Confounding factors not accounted for	1	Confounders were not addressed with study design or analysis
Applicability of the results	1	Pregnant women have high perceptions of teratogenic risk
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

[a]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 [a]

Domain	Author's judgement	Support for judgement
Brumfitt, 1975		
Random sequence generation	Unclear	No description of the sequence generation process, how women were assigned to treatment or placebo, unequal numbers in treatment and placebo groups.
Allocation concealment	Unclear	No information provided to judge.
Blinding of participants and personnel	Low	"…were given placebo under double-blind conditions". Method not described in sufficient detail. Objective outcomes.
Blinding of outcome assessment	Low	"…were given placebo under double-blind conditions". Method not described in sufficient detail. Objective outcomes.
Incomplete outcome data	High	Inconsistencies in total number of women not explained (number of <2500g babies provided for 413/326 bacteriuric women); results not provided for pyelonephritis for all women in treated group (only subset).
Selective reporting	High	Results not provided for pyelonephritis for all women allocated to treatment.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Elder, 1966		
Random sequence generation	Unclear	"…a random sequence". Insufficient information to judge.
Allocation concealment	Unclear	No information provided to judge.
Blinding of participants and personnel	Low	"…double-blind trial"; no information provided to judge. Objective outcomes.
Blinding of outcome assessment	Low	"…double-blind trial"; no information provided to judge. Objective outcomes.
Incomplete outcome data	Low	Information provided on women lost to follow-up, reasonably balanced between groups.
Selective reporting	High	Result not provided for pyelonephritis for all participants; no pregnancy outcomes (GA, birthweight).
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Elder, 1971		
Random sequence generation	High	"…alternate bacteriuric…were assigned."
Allocation concealment	High	Participants were allocated by alternation.
Blinding of participants and personnel	Unclear	"identical-appearing placebo"; insufficient information to judge.
Blinding of outcome assessment	Unclear	"identical-appearing placebo"; insufficient information to judge.
Incomplete outcome data	Unclear	Insufficient information to judge.
Selective reporting	Unclear	Unable to judge; twin deliveries were excluded.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Foley, 1987		

Domain	Author's judgement	Support for judgement
Random sequence generation	Low	Allocated to treatment or no treatment by "toss of a coin".
Allocation concealment	Unclear	No information to judge.
Blinding of participants and personnel	Unclear	No description of any attempt at blinding; not placebo-controlled. Objective outcomes.
Blinding of outcome assessment	Unclear	No description of any attempt at blinding; not placebo-controlled. Objective outcomes.
Incomplete outcome data	Unclear	Loss to follow-up: 19%; no reasons provided for missing outcome data.
Selective reporting	High	No pregnancy outcomes (GA, birthweight).
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Furness, 1975		
Random sequence generation	Unclear	"by random allocation"; no additional information to judge.
Allocation concealment	Unclear	No information to judge.
Blinding of participants and personnel	Unclear	Not placebo-controlled. Objective outcomes.
Blinding of outcome assessment	Unclear	No information to judge.
Incomplete outcome data	High	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.
Selective reporting	Unclear	Unable to separate incidence of pyelonephritis during pregnancy and puerperium; results combined.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Gold, 1966		
Random sequence generation	High	Women allocated to treatment based on study number: odd number treatment, even number control.
Allocation concealment	High	Allocated to treatment based on study number.
Blinding of participants and personnel	Unclear	Placebo-controlled; no further details provided. Objective outcomes.
Blinding of outcome assessment	Unclear	No information to judge. Objective outcomes.
Incomplete outcome data	Low	Does not appear to be any loss to follow-up.
Selective reporting	Unclear	No definition provided for prematurity.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Kass, 1960		
Random sequence generation	High	"alternate women received a placebo".
Allocation concealment	High	Allocation based on alternation: "alternate women received a placebo".
Blinding of participants and personnel	Low	Placebo was used and "the nature of the treatment was not known to the patient or to the attending obstetrical staff".
Blinding of outcome assessment	Unclear	Although a placebo was used, no further details are provided on blinding of outcome assessment. Objective outcomes.

Domain	Author's judgement	Support for judgement
Incomplete outcome data	Unclear	40 (21%) women were not enrolled either because they were >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.
Selective reporting	Unclear	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.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Kazemier, 2015		
Random sequence generation	Low	Random assignment in 1:1 ratio; computer-generated list with random block sizes of 2/4/6 participants.
Allocation concealment	Low	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.
Blinding of participants and personnel	Low	Double-blinded. Women, treating physicians and researchers remained unaware of bacteriuria status and treatment allocation. Objective outcomes.
Blinding of outcome assessment	Low	Outcomes recorded by participants on questionnaires, and from data provided by hospitals and midwives up to 6 weeks post-delivery.
Incomplete outcome data	Low	ITT and dropout rate <10% (12/255 ASB-positive)
Selective reporting	Low	Cost-effectiveness was outlined in protocol but not reported in final study methods or results.
Other bias	Low	No other sources of bias identified.
Overall risk of bias	Low	
Kincaid-Smith, 1965		
Random sequence generation	Unclear	No description of sequence generation process.
Allocation concealment	Low	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen".
Blinding of participants and personnel	Low	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen".
Blinding of outcome assessment	Low	"a code of instructions to the pharmacist ensured that the trial remained double-blind despite…alterations in therapeutic regimen".
Incomplete outcome data	Unclear	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).
Selective reporting	Unclear	Insufficient information to judge.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	Unclear	

Domain	Author's judgement	Support for judgement
Little, 1966		
Random sequence generation	Unclear	No information to judge.
Allocation concealment	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.
Blinding of participants and personnel	Unclear	Participants in the control group "were given placebo"; no further details provided. Objective outcomes.
Blinding of outcome assessment	Unclear	No information to judge. Objective outcomes.
Incomplete outcome data	Low	No missing outcome data.
Selective reporting	Unclear	Insufficient information to judge.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	Unclear	
Mulla, 1960		
Random sequence generation	Unclear	No description of sequence generation process.
Allocation concealment	Unclear	Women were "randomly divided into two groups"; no other details provided
Blinding of participants and personnel	Unclear	Not placebo-controlled. Objective outcomes.
Blinding of outcome assessment	Unclear	No information to judge. Objective outcomes.
Incomplete outcome data	Low	No missing outcome data.
Selective reporting	High	No definition for outcome of cystopyelitis; no pregnancy outcomes (GA, birthweight).
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Pathak, 1969		
Random sequence generation	Unclear	"on a random basis". Insufficient information provided to permit further judgement.
Allocation concealment	Unclear	Method of concealment not described.
Blinding of participants and personnel	Unclear	No information to judge.
Blinding of outcome assessment	Unclear	No information to judge.
Incomplete outcome data	Low	Missing outcome data balanced; reasons similar and unlikely to have introduced bias.
Selective reporting	High	No pregnancy outcomes (GA, birthweight).
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Thomsen, 1987		
Random sequence generation	Unclear	Described as "randomly allocated" but no description of the sequence generation process.
Allocation concealment	Unclear	Method of concealment of allocation not described.
Blinding of participants and personnel	Unclear	Placebo-controlled, described as "double-blinded" but no additional data. Objective outcomes.

Domain	Author's judgement	Support for judgement
Blinding of outcome assessment	Unclear	Described as "double-blinded" but no specific information provided to ensure outcome assessment was blinded. Objective outcomes.
Incomplete outcome data	Low	No missing outcome data.
Selective reporting	Unclear	Insufficient information to judge.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	Unclear	
Williams, 1969		
Random sequence generation	Unclear	"allocation at random"; no additional information to judge.
Allocation concealment	Unclear	No information to judge.
Blinding of participants and personnel	Unclear	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.
Blinding of outcome assessment	Unclear	No blinding; assessment of outcome (pyelonephritis) may have been influenced by knowledge of treatment allocation. Objective outcomes.
Incomplete outcome data	Unclear	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.
Selective reporting	High	No pregnancy outcomes (GA, birthweight).
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	
Wren, 1969		
Random sequence generation	High	Women "were divided into two groups, alternate patients being treated".
Allocation concealment	High	Women "were divided into two groups, alternate patients being treated".
Blinding of participants and personnel	Unclear	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.
Blinding of outcome assessment	Unclear	No blinding; however, outcome of birthweight unlikely to be influenced by lack of blinding.
Incomplete outcome data	Low	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.
Selective reporting	Unclear	Insufficient information to judge; outcome of pyelonephritis not reported.
Other bias	Low	Insufficient information to judge.
Overall risk of bias	High	

[a]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. (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. exp Pregnancy/
44. Pregnancy Complications, Infectious/
45. Pregnant Women/
46. Prenatal Care/
47. Prenatal Diagnosis/
48. (antenatal* or pre-natal* or prenatal*).mp.
49. (expect* adj (female? or mother? or wom#n)).tw,kf.
50. pregnan*.mp.
51. or/43-50 [Combined MeSH & text words for pregnancy]
52. and/16,42,51 [Combined searches for bacteriuria, screening & pregnancy]
53. Male/ not (Female/ and Male/)
54. 52 not 53 [Male only records excluded]
55. exp Animals/ not (exp Animals/ and Humans/)
56. 54 not 55 [Animal only records excluded]
57. (comment or editorial or news or newspaper article).pt.
58. (letter not (letter and randomized controlled trial)).pt.
59. 56 not (57 or 58) [Opinion pieces excluded]
60. case reports.pt.
61. 59 not 60 [Case reports excluded]
62. limit 61 to (english or french)
63. remove duplicates from 62

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. (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. 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]

#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
#38 "strip* test*":ti,ab,kw
#39 "urine test*":ti,ab,kw
#40 (urinalys* or "urine analys*"):ti,ab,kw
#41 uriscreen:ti,ab,kw
#42 {or #17-#41}
#43 [mh Pregnancy]
#44 [mh ^"Pregnancy Complications, Infectious"]
#45 [mh ^"Pregnant Women"]
#46 [mh ^"Prenatal Care"]
#47 [mh ^"Prenatal Diagnosis"]
#48 (antenatal* or pre-natal* or prenatal*):ti,ab,kw
#49 (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw
#50 pregnan*:ti,ab,kw
#51 {or #43-#50}
#52 {and #16, #42, #51}

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. 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. (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

(((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR "utis"[All Fields]))) OR "bacteriuria"[MeSH Terms:noexp] OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control"[Majr] OR "Pyelonephritis/microbiology"[Majr] OR "Pyelonephritis/urine"[Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human

experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])
> 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.
62. ceftri?xone*.mp.
63. cefuroxime*.mp.
64. cephalexin*.mp.
65. cephalosporin*.mp.
66. cephradine*.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 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,kf.
117. ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf.
118. (choice? adj2 (behavio?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.

124. health utilit*.tw,kf.
125. HUI.tw,kf.
126. (multi?attribute or multi?criteria).tw,kf.
127. (preference? adj1 (elicit* or scor* or state*)).tw,kf.
128. prospect theor*.tw,kf.
129. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.
130. (trade off? or tradeoff?).tw,kf.
131. (willing* adj2 pay*).tw,kf.
132. or/99-131 [Combined MeSH & text words for patient preferences & values]
133. and/43,132 [Combined searches for patient preferences & ASB screening]
134. and/98,132 [Combined searches for patient preferences & antibiotic treatment and pregnancy]
135. or/133-134 [Combined sets of patient preferences for ASB screening & patient preferences for antibiotic treatment in pregnancy]
136. Male/ not Female/
137. 135 not 136 [Male only records excluded]
138. exp Animals/ not (exp Animals/ and Humans/)
139. 137 not 138 [Animal only records excluded]
140. (comment or editorial or news or newspaper article).pt.
141. (letter not (letter and randomized controlled trial)).pt.
142. 139 not (140 or 141) [Opinion pieces excluded]
143. case reports.pt.
144. 142 not 143 [Case reports excluded]
145. limit 144 to (english or french)
146. remove duplicates from 145

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. ceftri?xone*.mp.
75. cefuroxime*.mp.
76. cephalexin*.mp.
77. cephalosporin*.mp.
78. cephradine*.mp.
79. clindamycin*.mp.
80. (co-trimoxazole* or cotrimoxazole*).mp.
81. cycloserine*.mp.
82. fosfomycin*.mp.
83. gentam#cin*.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 (behavio?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. gambl*.tw,kw.
131. health utilit*.tw,kw.
132. HUI.tw,kw.
133. (multi?attribute or multi?criteria).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 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]
#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

#38 "strip* test*":ti,ab,kw
#39 "urine test*":ti,ab,kw
#40 (urinalys* or "urine analys*"):ti,ab,kw
#41 uriscreen:ti,ab,kw
#42 {or #17-#41}
#43 #16 and #42
#44 [mh ^"Anti-Bacterial Agents"]
#45 [mh ^"Antibiotic Prophylaxis"]
#46 [mh ^"Anti-Infective Agents, Urinary"]
#47 [mh ^"Asymptomatic Infections"/DT,TH]
#48 [mh ^Bacteriuria [mj]/DT,TH]
#49 [mh ^"Drug Therapy, Combination"]
#50 [mh ^Norfloxacin]
#51 [mh Penicillins]
#52 [mh Sulfonamides]
#53 [mh ^"Urinary Tract Infections" [mj]/DT,TH]
#54 amoxicillin*:ti,ab,kw
#55 ampicillin*:ti,ab,kw
#56 ("anti-bacteria*" or antibacteria*):ti,ab,kw
#57 ("anti-biotic*" or antibiotic*):ti,ab,kw
#58 aztreonam*:ti,ab,kw
#59 cefadroxil*:ti,ab,kw
#60 cefepime*:ti,ab,kw
#61 ceftibuten*:ti,ab,kw
#62 ceftri?xone*:ti,ab,kw
#63 cefuroxime*:ti,ab,kw
#64 cephalexin*:ti,ab,kw
#65 cephalosporin*:ti,ab,kw
#66 cephradine*:ti,ab,kw
#67 clindamycin*:ti,ab,kw
#68 ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw
#69 cycloserine*:ti,ab,kw
#70 fosfomycin*:ti,ab,kw
#71 gentam?cin*:ti,ab,kw
#72 "nalidixic acid*":ti,ab,kw
#73 nitrofurantoin*:ti,ab,kw
#74 penicillin*:ti,ab,kw
#75 piperacillin*:ti,ab,kw
#76 pivampicillin*:ti,ab,kw
#77 pivmecillinam*:ti,ab,kw
#78 sulfadimethoxine*:ti,ab,kw
#79 sulfadiazine*:ti,ab,kw
#80 sulfamethizole*:ti,ab,kw
#81 sulfamethoxazole*:ti,ab,kw
#82 sulfamethoxypyridazine*:ti,ab,kw
#83 sulfonamide*:ti,ab,kw
#84 sulphadimidine*:ti,ab,kw
#85 sulphonamide*:ti,ab,kw

#86 tetracycline*:ti,ab,kw
#87 vancomycin*:ti,ab,kw
#88 {or #44-#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
#99 [mh ^"Choice Behavior"]
#100 [mh ^"Consumer Behavior" [mj]]
#101 [mh "Consumer Participation"]
#102 [mh ^"Cooperative Behavior"]
#103 [mh "Decision Making"]
#104 [mh ^"Focus Groups"]
#105 [mh ^"Health Care Surveys"]
#106 [mh "Informed Consent"]
#107 [mh ^"Interviews as Topic"]
#108 [mh ^"Patient Acceptance of Health Care"]
#109 [mh "Patient Education as Topic"]
#110 [mh ^"Patient Participation"]
#111 [mh ^"Patient Preference"]
#112 [mh ^"Social Values"]
#113 [mh ^"Surveys and Questionnaires"]
#114 [mh ^"Treatment Refusal"]
#115 (15D* and (HRQoL or QoL or "quality of life")):ti,ab,kw
#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 percepti* or perspective? or prefer* or refus* or respons* or valuation or value? or valuing or view*) near/3 (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,kw
#117 ((analys?s or valuation? or value? or valuing) near/3 (conjoint or contingent)):ti,ab,kw
#118 (choice? near/2 (behavio?r* or discrete or experiment*)):ti,ab,kw
#119 ((choice? or choos* or consent* or decision*) near/1 informed):ti,ab,kw
#120 ((choice? or choos* or decision*) near/2 (made or make or makes or making or shar* or support*)):ti,ab,kw
#121 ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D):ti,ab,kw
#122 ("focus group?" or interview* or questionnaire? or survey*):ti,ab,kw
#123 gambl*:ti,ab,kw
#124 "health utilit*":ti,ab,kw
#125 HUI:ti,ab,kw
#126 ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria):ti,ab,kw
#127 (preference? near/1 (elicit* or scor* or state*)):ti,ab,kw
#128 "prospect theor*":ti,ab,kw
#129 ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D):ti,ab,kw

#130 ("trade off?" or tradeoff?):ti,ab,kw
#131 (willing* near/2 pay*):ti,ab,kw
#132 {or #99-#131}
#133 #43 and #132
#134 #98 and #132
#135 #133 or #134

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. cystiti*.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. ceftri?xone*.mp.
46. cefuroxime*.mp.
47. cephalexin*.mp.
48. cephalosporin*.mp.
49. cephradine*.mp.
50. clindamycin*.mp.
51. (co-trimoxazole* or cotrimoxazole*).mp.
52. cycloserine*.mp.
53. fosfomycin*.mp.
54. gentam#cin*.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. pregnan*.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 (behavio?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. gambl*.ti,ab.
104. health utilit*.ti,ab.
105. HUI.mp.
106. (multi?attribute or multi?criteria).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 "Antiinfective 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. ceftri?xone*
S59. cefuroxime*
S60. cephalexin*
S61. cephalosporin*
S62. cephradine*
S63. clindamycin*
S64. ("co-trimoxazole*" or cotrimoxazole*)
S65. cycloserine*
S66. fosfomycin*
S67. gentam?cin*
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

S134. ((MH "Vertebrates+") NOT MH Human)
S135. S133 NOT S134
S136. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter
S137. S135 NOT S136
S138. S135 NOT S136 Narrow by Language: - english [RF: No French records in results to include]

KQ2: Women's Outcome Valuation
Database: PubMed via NCBI Entrez (1946 to Present)
Date Searched: 5 July 2016
Records Retrieved: 65

(((((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR "utis"[All Fields]))) OR "bacteriuria"[MeSH Terms:noexp] OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control"[Majr] OR "Pyelonephritis/microbiology"[Majr] OR "Pyelonephritis/urine"[Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent

test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer Behavior"[majr:noexp] OR "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR "Decision Making"[mh] OR "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR "Informed Consent"[mh] OR "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health Care"[mh:noexp] OR "Patient Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient Preference"[mh:noexp] OR "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] OR "Treatment Refusal"[mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "quality of life"[tiab])) OR ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] OR consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR chooses[tiab] OR choosing[tiab] OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab] OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to pay"[tiab])) OR ((("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract Infections/drug therapy"[Majr] OR "Urinary Tract Infections/therapy"[Majr] OR amoxicillin[tiab] OR

amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "anti-bacterial"[tiab] OR "anti-bacterials"[tiab] AND "anti-biotic"[tiab] OR "anti-biotics"[tiab] OR antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR "nalidixic acid"[tiab] OR nitrofurantoin[tiab] OR penicillin[tiab] OR penicillins[tiab] OR piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer Behavior"[majr:noexp] OR "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR "Decision Making"[mh] OR "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR "Informed Consent"[mh] OR "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health Care"[mh:noexp] OR "Patient Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient Preference"[mh:noexp] OR "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] OR "Treatment Refusal"[mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "quality of life"[tiab])) OR ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] OR consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR chooses[tiab] OR choosing[tiab] OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab]

OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to pay"[tiab]))) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti])))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])) AND ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))
> limit to English or French

KQs4,5: Systematic Review & HTA Search
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Records Retrieved: 104

(((((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR "utis"[All Fields]))) OR "bacteriuria"[MeSH Terms:noexp] OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND (("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR

"Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control"[Majr] OR "Pyelonephritis/microbiology"[Majr] OR "Pyelonephritis/urine"[Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) OR ("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract Infections/drug therapy"[Majr] OR "Urinary Tract Infections/therapy"[Majr] OR amoxicillin[tiab] OR amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "anti-bacterial"[tiab] OR "anti-bacterials"[tiab] AND "anti-biotic"[tiab] OR "anti-biotics"[tiab] OR antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR "nalidixic acid"[tiab] OR nitrofurantoin[tiab] OR penicillin[tiab] OR penicillins[tiab] OR piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]))) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab])

AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal])) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])

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}

#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
#38 "strip* test*":ti,ab,kw
#39 "urine test*":ti,ab,kw
#40 (urinalys* or "urine analys*"):ti,ab,kw
#41 uriscreen:ti,ab,kw
#42 {or #17-#41}
#43 [mh ^"Anti-Bacterial Agents"]
#44 [mh ^"Antibiotic Prophylaxis"]
#45 [mh ^"Anti-Infective Agents, Urinary"]
#46 [mh ^"Asymptomatic Infections"/DT,TH]
#47 [mh ^Bacteriuria [mj]/DT,TH]
#48 [mh ^"Drug Therapy, Combination"]
#49 [mh ^Norfloxacin]
#50 [mh Penicillins]
#51 [mh Sulfonamides]
#52 [mh ^"Urinary Tract Infections" [mj]/DT,TH]
#53 amoxicillin*:ti,ab,kw
#54 ampicillin*:ti,ab,kw
#55 ("anti-bacteria*" or antibacteria*):ti,ab,kw
#56 ("anti-biotic*" or antibiotic*):ti,ab,kw
#57 aztreonam*:ti,ab,kw
#58 cefadroxil*:ti,ab,kw
#59 cefepime*:ti,ab,kw
#60 ceftibuten*:ti,ab,kw
#61 ceftri?xone*:ti,ab,kw
#62 cefuroxime*:ti,ab,kw
#63 cephalexin*:ti,ab,kw
#64 cephalosporin*:ti,ab,kw

#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 sulfonamide*: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)

Studies Excluded Due to Study Design (189)

1. Abbasi IA, Hess LW, Johnson TR, McFadden E, Chernow B. Leukocyte esterase activity in the rapid detection of urinary tract and lower genital tract infections in obstetric patients. Am J Perinatol. 1985;2(4):311-3.
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Note: no studies were excluded due to outcome

Appendix 11. Excluded Studies – KQ2 (women's outcome valuation)

Studies Excluded Due to Study Design (20)

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Studies Excluded Due to Population (31)

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Studies Excluded as Full Text was Unavailable (1)

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Appendix 12. Excluded Studies – KQ4 (treatment effectiveness)

Studies Excluded Due to Study Design (5)
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Studies Excluded Due to Population (3)
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Studies Excluded due to Comparator (1)
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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

1. Robinson KA, Chou R, Berkman ND, et al. Integrating bodies of evidence: existing systematic reviews and primary studies. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Feb.

2. Robinson KA, Chou R, Berkman ND, et al. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. J Clin Epidemiol. 2016 Feb;70:38-44. PMID: 26261004.

3. Foisy M, Hartling L. Challenges and considerations involved in using AMSTAR in overviews of reviews. 22nd Cochrane Colloquium. Hyderabad (India); 2014 Sept 21-26.