UK National Screening Committee

Antenatal screening for asymptomatic bacteriuria

External review against programme appraisal criteria for the UK National Screening Committee

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Author: Kleijnen Systematic Reviews Ltd.

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UK NSC, Floor 5, Wellington House, 133-155 Waterloo Road, London, SE1 8UG
www.gov.uk/uknsc
Twitter: @PHE_Screening Blog: phescreening.blog.gov.uk

For queries relating to this document, please contact: phe.screeninghelpdesk@nhs.net

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Plain English summary

Asymptomatic bacteriuria (ASB) is a phrase used to describe a situation in which there are bacteria in the kidneys, bladder or the tubes that connect them, but they are not causing any symptoms. If these bacteria grow and do cause symptoms and are not treated with antibiotics, then pregnant women are more likely to develop a kidney infection. Though very rare this can be very serious for the mother and can also cause her baby to be born too early or even die before birth.

This document describes the new evidence about screening women for ASB while they are pregnant. It looks at scientific evidence published between 1990 and December 2019. As ASB, fortunately, causes very few early births or other problems for the baby we looked to see whether a screening programme would work to stop kidney infections as we believe that this will prevent harm to the mother and baby.

The UK National Screening Committee (UK NSC) published its last review in 2017. The committee did not recommend starting a screening programme for ASB in the UK because:

- it is not known how many women and babies are affected
- there is not enough knowledge about the best way to screen pregnant women, such as when in the pregnancy and how often
- it is not known if antibiotics would have a negative effect on the pregnancy or when in the pregnancy, they should be used
- the benefits of screening over the current testing process is not known

This review picks up where the last one left off and looked to see there was new evidnce good enough to support the consideration of a screening programme:

1. How many pregnant women have ASB; and how many get a kidney infection and symptoms and how many women get ASB more than once?
2. What would be the best way of screening for ASB in pregnancy?
3. How effective is screening for ASB in pregnancy in preventing kidney infections?
4. How effective are treatments such as antibiotics for ASB in pregnant women at preventing kidney infections?
5. How do women feel about screening for ASB and antibiotic treatment for ASB in pregnancy?

This review of the evidence found that the UK NSC still cannot recommend screening because there is not enough information available from research studies. The studies did not help to decide which screening test was best. There was not good information to help understand how women might feel about ASB screening and treatment in pregnancy. The limited evidence suggested that some women do not want to take

antibiotics during pregnancy and fear that it might harm their unborn baby, but there is no information about how women feel about screening for ASB and how this influences their decision to undergo screening and/or treatment.

Finally, the studies we found did not say how many pregnant women have ASB; how many get a kidney infection and symptoms and how many women have ASB more than once.

Answers to the questions are vital to an effective and acceptable programme to stop kidney infections and harm to mothere etr and baby. So, the fact that these questions could not be answered means that the review concludes a population screening programme should not be introduced in the UK.

Executive summary

Purpose of the review

To carry out a series of rapid reviews to synthesise evidence published between 1990 and December 2019 on screening the whole antenatal population for asymptomatic bacteriuria (ASB).

Background

Asymptomatic bacteriuria (ASB) is defined as a positive culture (≥10^5CFU/ml of urine) of the same uropathogen on two occasions in a patient without urinary symptoms. Pregnant women with untreated ASB are at risk of developing pyelonephritis. There are excess risks of maternal and fetal mortality in women who have pyelonephtritis. There is also excess morbidity: including maternal fever, acute respiratory distress, acute renal failure, stillbirth, and preterm birth.

National Institute of Health and Care Excellence (NICE) have published a clinical guideline for routine uncomplicated pregnancy which addresses the issue of detecting asymptomatic bacteriuria in early pregnancy. It recommends that:

'*Women should be offered routine screening for asymptomatic bacteriuria by midstream urine culture early in pregnancy. Identification and treatment of asymptomatic bacteriuria reduces the risk of pyelonephritis*.'

However, the guideline does not provide guidance on screening methodology, timing or practicalities and is currently under review; future updates of the guideline will not consider the issue of routine screening for ASB.

Focus of the review

The current review explores the volume, quality and direction of the literature published since the last (2017) UK National Screening Committee (UK NSC) review of this topic and focuses on key questions coming out of the conclusions of the previous review. The review also addresses a new question on how the women regard screening and antibiotic tearement in pregnancy and whether that affect their decision to undergo screening and treatment for ASB.

The aim of the review is to inform discussion on whether the recent evidence provides a sufficient basis on which to reconsider the current UK NSC recommendation that a systematic population screening programme is not recommended in the uk, and clinical

practice guidelines are covered by NICE (antenatal care for uncomplicated pregnancies guideline (clinical guideline 62)).[5]

NICE is currently undertaking an update of the 2008 guidance on antenatal care for uncomplicated pregnancies but is not planning to undertake a review of the evidence for ASB screening as part of this. Therefore, the recommendation of offering routine screening for ASB in early pregnancy will be deleted and no recommendation on this subject will be made in this guideline. Consequently, the UK NSC recommendation will be the only national recommendation on screening for ASB in the UK. Therefore, the aim of this evidence summary is to provide an evaluation of the volume and direction of the literature on this topic, the aim being to assess whether a formal population screening programme for ASB in pregnancy should be introduced in the UK.

For a screening programme to be recommended in the UK, the criteria specified by the UK NSC must be fulfilled.[1] In order to do this the following key questions were considered in this review:

1. What is the disease burden associated with ASB? – addresses UK NSC criterion 1
2. What is the performance of screening tests for detecting ASB infection in pregnancy? – addresses criteria 4 and 7
3. What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? – addresses criterion 11
4. What are the benefits and harms of antibiotic treatment compared with no treatment for asymptomatic bacteriuria in pregnancy? – addresses criterion 9
5. How benefits and harms of screening and treatment inform womens' decisions to undergo screening for bacterial infections during pregnancy? – addresses criterion 12

The evidence reviewed (published between 1990 and December 2019) relates to pregnant women in the UK (or healthcare settings deemed similar to the UK) without symptoms of a urinary tract infection, who are eligible for ASB screening and subsequent treatment with antibiotics if evidence of ASB is found.

Recommendation under review

The current UK NSC policy is based on an evidence summary published in May 2017. The key questions addressed by this review were based on the key areas where asymptomatic bacteriuria did not meet the UK NSC's criteria for a screening programme in the previous 2011 UK NSC review. These included:

a. No new evidence available on how many pregnant women have asymptomatic bacteriuria in the UK.
b. No new evidence on testing for ASB during pregnancy. Therefore, the most effective way of screening pregnant women for asymptomatic bacteriuria was uncertain.
c. There was evidence from a study in the Netherlands that there is no difference between treated and untreated women for a range of maternal and neonatal outcomes.
d. A systematic review suggested no difference in cure rates, recurrence of ASB, pyelonephritis or preterm birth rates between a short course or single dose of antibiotics.

Findings and gaps in the evidence of this review

Twelve research reports were included in this review: eight systematic reviews and four primary studies. A summary of results per UK NSC criterion and review question is presented below. Some systematic reviews and primary studies were relevant to more than one question.

Criterion 1: 'The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.'

Question 1: What is the disease burden associated with ASB in the UK?

Three primary studies were identified, two prospective cohort studies and one retrospective cohort study. No systematic reviews were found. None of the studies were conducted in the UK. Data from countries which could be considered similar to the UK were included to explore the association between ASB and adverse maternal and neonatal outcomes. Most data came from one good-quality prospective cohort study. This study reported that presence of ASB may be associated with increased incidence of pyelonephritis: adjusted odds ratio (OR) 3.9 (95% confidence interval [CI] 1.4 to 11.4). The same study reported that presence of ASB may be associated with incidence of symptomatic UTI requiring treatment with antibiotics antenally: adjusted OR 2.9 (95% CI 2.0 to 4.2). Other data from the included studies suggested that the presence of ASB was not associated with neonatal mortality (2 studies); neonatal sepsis (1 study); or pre-term delivery (3 studies). Data were not reported in any included study for recurrence of ASB, maternal sepsis, maternal mortality, or low birth weight. The applicability of the evidence to the UK is uncertain considering the low volume of available evidence and methodological issues within some studies. Therefore, criterion 1 is not met.

Criterion 4: 'There should be a simple, safe, precise and validated screening test.'

Criterion 7. 'There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.'

Question 2: What is the performance of screening strategies for detecting ASB infection in pregnancy?

One systematic review and one primary study (a prospective cohort, not included in the systematic review) were identified. All primary studies within the review and also the independent primary study assessed the performance of onsite tests (index tests) against urine culture as the reference standard. Urine culture is commonly used as a reference standard in studies, though consensus is lacking on the appropriate thesholds or organisms considered as

positive for ASB, which contributes to the difficulties when assessing index tests. A range of different index tests were assessed including urine dipstick tests (to detect nitrites only or both nitrites and leucocytes), dipslides (gram staining, Uricult and Microstix-3), chlorhexidine reaction, Uriscreen catalase test, Griess test for nitrites, different types of urinalysis and microscopy. Within the systematic review, all included studies that were conducted in the UK or in countries similar to the UK were published earlier than 2003. The primary study (published in 2005) was conducted in Canada. Most of the index tests achieved acceptable specificity (92% or above) but sensitivity varied considerably (range 15% to 100%). Current evidence does not support single use of onsite tests to detect ASB in pregnancy. The optimum alternatives to urine culture (e.g. onsite or point-of-care tests) remain uncertain. Neither the systematic review nor the primary study provided evidence to inform a policy on further investigation of women with an initial positive test result. Therefore, neither criteria 4 nor criteria 7 are met.

Criterion 11: 'There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as in Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.'

Question 3: What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy?

Three systematic reviews were identified that included four unique cohort studies between them. All four studies were of low quality, involving non-concurrent control groups. Three studies comparing screening with no screening had limited relevance to current practice in the UK. A more recent study conducted in the USA compared screening at the first antenatal clinical only with screening at every antenatal visit. Screening may reduce the risk of pyelonephritis when compared with no screening: risk ratio 0.28 (95% CI 0.15 to 0.54), absolute risk reduction 1.3%, number needed to screen 77 (95% CI 65 to 121). However, no between-group difference was seen for perinatal mortality, spontaneous abortion earlier than 28 weeks or preterm birth. There was no difference between one-time screening and frequent screening for incidence of pyelonephritis. More women in the frequently screened group experienced preterm birth compared with one-time screening; this may have been explained by differential risk profiles between groups. Maternal mortality, maternal sepsis, neonatal sepsis and low birth weight were not reported in any study. The effectiveness of a one-time screening strategy would need to be confirmed by means of a good-quality RCT conducted in the UK. Criterion 11 is not met.

Criterion 9: 'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be

taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.'

Question 4: What are the benefits and harms of antibiotic treatment compared with no treatment for ASB in pregnancy?

Seven systematic reviews were identified that included 15 unique RCTs between them. Whilst the majority of RCTs (14/15) were conducted in the UK or countries similar to the UK, all were published during the 1980s or earlier with one exception published in 2015. Older studies generally suggested that antibiotics reduced the incidence of pyelonephritis, preterm birth, and low birth weight whilst the most recent RCT did not detect between-group differences for any outcome. However, the older studies have serious methodological problems and there are concerns about the applicability of their findings to current health care settings. The more recent evidence from the RCT comprised one very small, statistically underpowered RCT. Criterion 9 is not met.

Criterion 12: 'There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.'

Question 5: How do benefits and harms of screening and treatment inform women's decisions to undergo screening for bacterial infections during pregnancy?

One systematic review including six studies including five surveys and one cross-sectional study (which was also identified as a primary study) were included. No evidence was found on the benefits and harms of screening and treatment to inform women's decisions to undergo screening for bacterial infections during pregnancy; or how women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy. Low-level evidence (from surveys) was available from the systematic review and some cohort data which appeared to suggest that women may be reluctant to undergo antibiotic treatment for ASB during pregnancy. These findings should be treated with caution because of the low quality of the studies and unclear quality of the systematic review. In addition, there are difficulties in applying most findings to current practice in the UK because of locations and timings of most of the available evidence. Therefore criterion 12 is not met.

Recommendations on screening

This 2020 review concluded that, at present, the evidence base remains insufficient to recommend a UK systematic population antenatal screening programme for asymptomatic bacteriuria. The main reasons for this were the low volume and poor quality of most of the available research evidence. In addition, most studies were conducted in countries of limited relevance to the UK or did not reflect current practice in antenatal care. Research is needed to explore the value of screening in preventing negative pregnancy outcomes.

Limitations

Study selection was limited to research reports published in English language. This may have introduced a language bias, but as this series of rapid reviews sought to prioritise data relevant to UK practice this may not have impacted on the findings of the reviews. This said, data from some European countries which could be considered sufficiently similar to the UK may have been missed using this strategy. Study selection was also restricted by date. Research reports published from 1990 were selected for questions 1 and 5 as these questions had not been covered in the previous UK NSC reviews; it was deemed that research published prior to 1990 would have limited relevance to current practice. Research published from 2003 was selected for questions 2, 3 and 4 because this threshold coincided with a change in relevant clinical guidance. Interpretation of evidence was hampered by high risk of bias in some reviews and primary studies and also by the limited applicability of the evidence base to current antenatal care in the UK.

Evidence uncertainties

Further research is needed in relation to all criteria and questions outlined above. Replication of good quality studies with direct relevance to current practice in the UK would be required before the implementation of a population-based screening programme for ASB in pregnancy could be considered for implementation. However, because most women *are* currently tested for ASB this might not be feasible in the UK. Therefore, potential options in the UK could be a quasi-experimental study comparing settings that provide ASB testing and treatment in pregnancy with settings that do not offer tests. Alternatively, an RCT comparing single test to multiple tests screening protocols. that also considers the cost effectiveness of these options would be an option. However, good-quality estimates on prevalence, test accuracy, treatment effectiveness and screening uptake in relation to ASB in pregnancy in the UK would be required before any cost-effectiveness analysis could be undertaken.

Expert advice

This review was conducted with expert advice from:

Dr Annie Joseph, Consultant Microbiologist, Joint Head of Service for Clinical Microbiology, Nottingham University Hospitals NHS Trust.

Introduction and approach

Background

In a healthy individual the urinary tract is sterile apart from the area around the external urinary meatus. Asymptomatic bacteriuria (ASB) develops when bacteria colonising the gut, vagina, or perineum ascend from the urinary meatus into the urethra, bladder and in some cases, the ureters, and kidneys. ASB is defined as the presence of bacteria at a threshold of $\geq 10^5$ colony-forming units (CFUs) per millilitre (ml) or $\geq 10^8$ CFU per litre in the urine without symptoms of urinary tract infection (UTI). It is a normal physiological state in some people with increasing prevalence with age.[2] The definition of ASB was restated in 2019 by the Infectious Diseases Society of America (IDSA) as being $\geq 10^5$ CFU per ml or $\geq 10^8$ CFU per litre of a voided urine sample in people without indwelling catheters or signs or symptoms of UTI. The IDSA recommended that in women, two consecutive samples should be collected within a two-week interval in order to confirm the presence of ASB, noting that between 10% and 60% of women (varying with population characteristics) have confirmed ASB on repeat testing following a first positive result.[3] The Scottish Intercollegiate Guidelines Network (SIGN) also recommends that ASB should be confirmed with a second urine culture[4] however, this is not current practice in England.[5]

It is thought that hormonal and physiological changes in pregnancy (e.g. compression of bladder, ureters and kidneys by the expanding uterus) can increase urinary stasis, making pregnant women susceptible to developing ASB.[6, 7] Women with untreated ASB are thought to be at greater risk of developing pyelonephritis (a kidney infection). Pregnant women with pyelonephritis are at increased risk of maternal and foetal mortality and morbidity, including maternal fever, acute respiratory distress, acute renal failure, stillbirth, and preterm birth. Acute pyelonephritis is also associated with anaemia and pre-eclampsia.[8]

The most consistently reported causative micro-organism for ASB in pregnancy is *Escherichia coli (E. coli)*[6, 7, 9-13] with individual microbiological surveys reporting frequencies of 40% (from 60 positive urine cultures)[12] and 71% (of 182 pregnant women with positive dipslide results).[13]. A wide range of other colonising bacteria have also been reported including group B Streptococcus (GBS), *Klebsiella* species (spp), *Staphylococcus* spp*, Proteus* spp, *Enterobacter* spp and *Enterococcus* spp.[6, 7, 9-13]

There are no recent estimates on the prevalence of ASB in pregnancy in the UK. Up to date estimates of ASB within the general UK population are also lacking. Between 1965 and 1997, the prevalence of ASB in pregnancy in the UK was estimated between 2.0% and 6.3%. This was within the range reported in other developed countries during the same period: 1.9% to 9.5% overall and 2.0% to 7.0% during the first trimester (the latter range being similar to non-

pregnant women of the same age).[6, 14] More recent studies report prevalence rates of 4.7% (from Canada)[12] and 2.8% and 5.0% (both from the Netherlands)[13, 15] for ASB in pregnant women receiving routine antenatal care.

The role of antibiotics in treating screen-identified ASB is unclear given the potential for adverse effects of treatment and antimicrobial resistance. In light of this, the IDSA does not recommend screening and treatment for ASB other than for selected patients e.g. those undergoing endoscopic urological procedures and pregnant women.[14] Authors of a recent Canadian guideline observed that some women may opt not to be screened or treated because of concerns about potential adverse effects of antibiotics for the fetus and suggested that the decision to screen should be jointly made between clinicians and patients.[16]. In light of the poor quality of available evidence and the lack of current data, both the IDSA and the Canadian guidelines noted the persisting uncertainty about which groups of pregnant women may benefit the most from screening for and treating ASB within the current context of health care.[14, 16]

Current and relevant cost effectiveness data should underpin the implementation of any new screening programme.[17] There are no models or recent evidence from UK sources on the cost effectiveness of ASB screening in pregnant women. However, a study from the Netherlands assessed the cost effectiveness of single dipslide screening for ASB among low risk women at 16 to 22 weeks of pregnancy and subsequent nitrofurantoin treatment. Although the study was prematurely halted the authors implied that the cessation of screen and treat strategies would result in lower costs, but no other data were reported.[13] The only other study assessing cost effectiveness was conducted in Bangladesh[18] and therefore not relevant to the UK setting. This study from 2007 assessing the validity and cost effectiveness of rapid screening tests in Bangladesh calculated the incremental cost effectiveness ratio between the different screening test methods (bacterial count, leukocyte and/or nitrite dipsticks) based on a single screen and the least costly method (microscopic urine analysis). The incremental costs per additional positive case of bacterial count, were US $3, US $25 and US $23 for microscopic ASB bacterial count, leukocyte esterase dipstick and combined leukocyte esterase and nitrite dipstick, respectively.[18]

Current policy context and previous reviews

Clinical practice guidelines for routine pregnancy clinics in the UK are currently informed by guidance from the National Institute of Health and Care Excellence (NICE, clinical guideline 62).[5] This recommends that women should be offered routine screening for ASB by midstream urine culture early in pregnancy with the aim of reducing the risk of pyelonephritis.[5] However, the guideline is currently under review and will no longer consider screening for ASB in pregnancy. There is no evidence regarding the implementation of NICE guidelines on ASB screening in pregnancy in the UK setting.

The UK NSC have published summaries of evidence relating to screening for ASB in 2011 and 2017.[19, 20] Both reviews concluded that whilst there appeared to be no reason to discontinue existing antenatal services relating to testing for ASB, there was insufficient evidence to recommend a population-based screening programme. In particular, evidence was lacking in four key areas: prevalence of ASB in the UK; outcomes for ASB if untreated; effectiveness of screening methods; and effectiveness of antibiotic treatment for ASB.[19, 20] It was notable that neither review retrieved sufficient evidence to inform the choice of screening method or the timing, frequency or number of repetitions of any test.[19, 20] Therefore, the UK NSC recommended that a systematic population screening programme for ASB should not be introduced in the UK and that clinical practice should be directed by the NICE antenatal care for uncomplicated pregnancies guideline (clinical guideline 62).[5]

NICE is currently undertaking an update of the 2008 guidance on antenatal care for uncomplicated pregnancies but is not planning to undertake a review of the evidence for ASB screening as part of this. Therefore, the recommendation of offering routine screening for ASB in early pregnancy will be deleted and no recommendation on this subject will be made in this guideline. Consequently, the UK NSC recommendation will be the only national recommendation on screening for ASB in the UK. Therefore, the aim of this review was to provide an up to date evaluation of the volume and direction of the literature on screening for ASB in pregnancy in the UK, with the intention of resolving the persisting uncertainties described by the previous UK NSC evidence reviews.[19, 20] A further aim was to assess whether a formal population screening programme for ASB in pregnancy should be introduced in the UK.[21]

Objectives

The aim of this project is to review the available evidence relating to antenatal screening for ASB by means of a series of rapid reviews of the literature. The work involved rapid review methods proposed by the UK NSC[1] and was also informed by guidance on systematic review methods published by the Cochrane Collaboration[22] and the Centre for Reviews and Dissemination (CRD).[23] The project has been reported in accordance with the UK NSC Reporting Checklist for Evidence Summaries (ReCESs).[24] Several research questions were addressed, as follows.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence	What is the prevalence and incidence of ASB in pregnancy in the UK?	Review question 1: 0 systematic reviews, and 3 primary studies

	Criterion	Key questions	Studies Included
	and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	What is the prevalence and incidence of recurrent ASB in pregnancy in the UK? What is the incidence of pyelonephritis in pregnant women with or without screen-detected ASB in the UK or in countries similar to the UK? What are the other outcomes (maternal and neonatal) of untreated ASB in pregnancy in the UK or in countries similar to the UK?	
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	What is the performance of screening strategies for detecting ASB infection in pregnancy?	Review question 2: 1 systematic review and 1 primary study
7	There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.		
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.	What are the benefits and harms of antibiotic treatment compared with no treatment for ASB in pregnancy?	Review question 4: 7 systematic reviews and 1 primary study
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The	What are the benefits and harms of screening compared with no screening for ASB in pregnancy?	Review question 3: 3 systematic reviews and 0 primary studies

	Criterion	Key questions	Studies Included
	information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.		
12	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	How does information about the benefits and harms of screening and treatment inform women's decisions to undergo screening for ASB during pregnancy?	Review question 5: 1 systematic review and 1 primary study

Methods

The current review was conducted by Kleijnen Systematic Reviews Ltd., in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 11 December 2019 to identify studies relevant to the questions detailed in Table 1. Full details of the search strategy are shown in Appendix 1.

Eligibility for inclusion in the review

The following review process was applied:

6. Each title and abstract identified through electronic database and web searching was screened for relevance to any of the review questions by two reviewers working independently. Where relevance was unclear, the article was marked for full text retrieval in order to ensure that all potentially relevant studies were captured. Disagreements were resolved by discussion until a consensus was achieved; failing this, a third reviewer was consulted.
7. Full-text articles were retrieved for all records deemed to be potentially relevant at the title and abstract screening stage.
8. Each full-text article was assessed against the study selection criteria for each review question by two reviewers working independently. As before, all disagreements were resolved by discussion or if necessary, by consulting a third reviewer.

A PRISMA flow diagram summarising the study selection process is shown in Appendix 2 along with lists of records included and excluded per question at the full text screening stage. The lists also indicate reasons for exclusion.

Eligibility criteria for each review question are presented in Tables 2 to 6 below. In each table, the column entitled 'Study designs' shows a list of types of studies ranked according to the quality of evidence provided. In each instance, the top of the list shows the source of highest quality evidence, working down to the lowest quality evidence at the end of the list.

Table 2. Inclusion and exclusion criteria for question 1 – disease burden associated with antenatal ASB

Type of criteria	Population	Exposure	Comparator	Outcomes	Study designs	Other criteria
Inclusion criteria	Pregnant women	Untreated ASB*	Pregnant women without ASB	Prevalence or incidence of ASB in pregnancy Maternal: • Mortality • Sepsis • Pyelonephritis • Symptomatic cystitis • Recurrent ASB Neonatal: • Perinatal mortality (≥20 weeks gestation) • Spontaneous abortion or pregnancy loss <20 weeks gestation • Neonatal sepsis • Preterm birth (<37 weeks gestation) • Low birth weight (<2500g)	Systematic reviews Comparative observational studies (cohorts, case controls) Observational studies Non-intervention arms of RCTs	UK data for prevalence and incidence of ASB; data relevant to UK for association between ASB and adverse maternal and neonatal outcomes; reports published in English from 1990
Exclusion criteria	Populations other than pregnant women	Exposure other than untreated ASB	Alternative exposure	Outcomes in relation to treatment of ASB or UTI	RCTs, qualitative studies	Not relevant to UK setting, non-English language, earlier than 1990

*It was planned to give priority to studies reporting ASB defined according to the IDSA definition: ≥10^5 CFU per ml or ≥10^8 CFU per litre in a voided urine specimen without signs or symptoms attributable to a UTI.[25]

Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; RCT randomised controlled trial; UTI urinary tract infection

Table 3. Inclusion and exclusion criteria for question 2 – performance of screening tests for detecting ASB in pregnancy

Type of criteria	Population	Index test	Reference test	Target condition	Outcomes	Study designs	Other criteria
Inclusion criteria	Pregnant women without: • history of kidney infection • urogenital anomalies • polycystic kidneys • symptoms of UTI • recurrent UTI • diabetes • sickle cell disease	Any screening test or algorithm for ASB including: • urine culture • repeat urine culture • urine dipstick analysis for nitrites or leucocytes • dipslide test	Urine culture	ASB	Sensitivity Specificity Positive predictive value Negative predictive value Positive likelihood ratio Negative likelihood ratio	Systematic reviews Prospective or retrospective studies with consecutive random sample Cross-sectional studies RCTs using an independent blinded comparison and a valid reference test	Data relevant to UK; reports published in English from 2003
Exclusion criteria	Women at high risk of bacterial infection in the urogenital tract	Urine screening for other conditions; non-urine screening test	Reference tests other than urine culture	Conditions other than ASB	Outcomes in relation to treatment of ASB or UTI	Case-control studies; studies with longitudinal assessment of the reference standard	Not relevant to UK setting, non-English language, earlier than 2003

Table 4. Inclusion and exclusion criteria for question 3 – benefits and harms of antibiotic treatment

Type of criteria	Population	Intervention	Comparator	Outcomes	Study designs	Other criteria
Inclusion criteria	Pregnant women with ASB*	Antibiotic therapies with UK marketing authorisation for use in pregnancy	No treatment or placebo	Clinical maternal outcomes: • mortality • sepsis • pyelonephritis • symptomatic cystitis Clinical neonatal outcomes: • perinatal mortality (≥20 weeks gestation (e.g. intrauterine demise, stillbirth, early neonatal death) • spontaneous abortion/pregnancy loss <20 weeks gestation • neonatal sepsis (includes surrogate outcomes of acute respiratory distress syndrome or admission to neonatal intensive care unit) • preterm birth (<37 weeks gestation) • low birth weight (<2500g) Maternal adverse effects: • anaphylaxis • thrombocytopenia • haemolytic anaemia • alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis) • antibiotic-induced diarrhoea (including Clostridium difficile disease) • vomiting • rash	Systematic reviews RCTs Comparative cohort studies	Reports in English language available from 2003 onwards

				Neonatal adverse effects: a) foetal abnormalities b) alterations in foetal microbiome and its implications (e.g. increased risk of infections, atopy) c) candidiasis d) gastrointestinal upset e) rash f) antibiotic-sensitisation (e.g. increased risk of allergy in later life) Antimicrobial resistance (maternal or neonatal)	
Exclusion criteria	Populations other than pregnant women with ASB	Antibiotic therapies lacking UK marketing authorisation for use in pregnancy; non-antibiotic therapies	Alternative antibiotics or other active treatment	Non-comparative studies, qualitative studies	Non-English language, earlier than 2003

*In the event of no information being found in pregnant women with ASB, it was planned to seek evidence for harms associated with antibiotic treatment in pregnant women in general (i.e. for conditions other than ASB)

Table 5. Inclusion and exclusion criteria for question 4 – benefits and harms of screening for antenatal ASB

Type of criteria	Population	Intervention	Comparator	Outcomes	Study designs	Other criteria
Inclusion criteria	Pregnant women without: • history of kidney infection • urogenital anomalies • polycystic kidneys • symptoms of UTI • recurrent UTI • diabetes • sickle cell disease Subgroups of interest (where available) include eligible women grouped according to socioeconomic status, ethnicity or maternal characteristics	Any screening test or algorithm for ASB including: • urine culture • repeat urine culture • urine dipstick analysis for nitrites or leucocytes • dipslide	No screening or other screening test or algorithm	Number of patients with confirmed ASB Number of patients treated with antibiotics for ASB Maternal and neonatal clinical outcomes and adverse effects as for question 3 Antimicrobial resistance (maternal or neonatal)	Systematic reviews RCTs Comparative cohort studies	Reports in English language available from 2003 onwards
Exclusion criteria	Women at high risk of bacterial infection in the urogenital tract	Urine screening for other conditions; non-urine screening test			Non-comparative studies, qualitative studies	Non-English language, earlier than 2003

Table 6. Inclusion and exclusion criteria for question 5 – how benefits and harms of screening and treatment inform women's decisions to undergo screening for antenatal ASB

Type of criteria	Population	Intervention	Comparator	Outcomes	Study designs	Other criteria
Inclusion criteria	Pregnant women	Any screening programme for ASB during pregnancy*	Not applicable	Relative weight/utilities of benefit and harms of screening or treatment Willingness to be screened based on relative values placed on benefits and harms of screening or treatment or both Qualitative information e.g. themes arising from interviews with pregnant women who have been screened or treated for ASB or who have considered screening or treatment for ASB	Systematic reviews Qualitative studies Mixed methods studies Surveys Cross-sectional studies	Reports in English language available from 1990 onwards
Exclusion criteria	Non-pregnant women				RCTs	Non-English language, earlier than 2003

Quality (risk of bias) assessment

Risk of bias (ROB) assessment tools were selected based on the study design as indicated in Table 7 (below). Detailed information about each ROB tool is provided in Appendix 3. A topic-specific ROB criterion relating to the number of consecutive samples examined was added for studies involving voided urine specimen collection from participants. The reviewers planned to rate studies reporting acquisition of at least two consecutive voided urine samples (the second sample taken to confirm presence of ASB following an initial positive result) as being at low ROB for that criterion. Studies reporting one sample were classified as being at high ROB. An unclear classification was assigned when the number of samples was not reported, or not clearly reported. One reviewer assessed the ROB for each included study and a second reviewer performed an independent check of data for accuracy. Discrepancies were resolved by referring to the source material or by consulting a third reviewer if necessary.

Table 7: Risk of bias assessment tools for different study designs

Study design	Risk of bias assessment tool
Systematic reviews	Risk Of Bias In Systematic reviews (ROBIS)[26]
Randomised controlled trials	Cochrane ROB tool for randomised controlled trials[27]
Cohort studies	Joanna Briggs Institute (JBI) Checklist for Cohort Studies[28]
Diagnostic accuracy studies	QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2)[29]

Databases/sources searched

Literature searches were conducted in accordance with the UK NSC: Evidence Review Process Guidance [1]. The searches were designed to provide an evaluation of the volume of literature on antenatal screening for asymptomatic bacteriuria (ASB) in order to assess whether a formal screening programme for ASB in pregnancy should be introduced to the UK. Searches were undertaken, firstly, to identify systematic reviews on ASB in pregnancy. Secondly, targeted strategies were designed to identify evidence for each question. Searches for systematic reviews and targeted searches for questions 1 and 5 and for interventions were limited by date range to 1990-2019. Searches developed to identify evidence for questions 2, 3 and 4 were limited by date to 2003-2019. Date limits were set at the request of the commissioner. All searches were limited to English language. Search strategies (indexed keywords and text terms) were developed specifically for each database and, where applicable, validated search filters were applied.

To identify systematic reviews and guidelines the following databases were searched:

- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid): 1946 – 30/12/2019
- Embase (Ovid): 1974 – 27/12/2019
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to Issue 12, December 2019
- KSR Evidence (https://ksrevidence.com): up to 31/12/2019
- NHS Evidence (www.evidence.nhs.uk): up to 31/12/2019
- Guidelines International Network (G-I-N) (https://g-i-n.net/): up to 31/12/2019
- ECRI Institute (https://guidelines.ecri.org/): up to 31/12/2019

Targeted searches to identify evidence for specific questions were undertaken in the following databases:

- MEDLINE and In-Process & Other Non-Indexed Citations (Ovid): 1946 - 31/12/2019
- MEDLINE Epub Ahead of Print, Daily Update (Ovid): up to 31/12/2019
- Embase (Ovid): 1974 – 30/12/2019

Finally, a search was undertaken in the following database to provide additional evidence on interventions to support the treatment of asymptomatic bacteriuria in pregnancy:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to Issue 12, December 2019

All strategies are provided in Appendix 1.

Identified references from the bibliographic database searches were downloaded into Endnote bibliographic management software for further assessment and handling.

For all searches undertaken by the Kleijnen Systematic Reviews Information team, the main Embase search strategies were independently peer reviewed by a second KSR Information Specialist. Search strategy peer review was informed by items based on the CADTH PRESS checklist.[30, 31]

Overall results

Database searches generated 3,292 records. After removing 1,761 duplicates, a total of 1,531 records were screened as titles and abstracts, of which 90 were retrieved as full

reports. Of these 90, 12 records were included in the review. Appendix 2 shows a PRISMA flow diagram which summarises the study selection process.[32]

As outlined above in Tables 2 to 6 (inclusive), systematic reviews and primary studies were eligible study designs for all questions. For questions where one or more relevant systematic review was identified, eligible primary studies were also included if they were not described within any identified systematic review. The 12 included records comprised eight systematic reviews and four primary studies.

Relative and absolute measures of effect have been presented in this review when these were provided within reports of the included systematic reviews and primary studies. The authors of this review have not undertaken additional calculations.

Question level synthesis

Criterion 1 — The disease burden associated with asymptomatic bacteriuria in pregnancy

1: 'The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.'

Overarching question 1 – What is the disease burden (both maternal and neonatal) associated with ASB in pregnancy?

Specific questions:

- *What is the prevalence and incidence of ASB in pregnancy in the UK?*
- *What is the prevalence and incidence of recurrent ASB in pregnancy in the UK?*
- *What is the incidence of pyelonephritis in pregnant women with or without screen detected ASB in the UK?*
- *What are the other outcomes (maternal and neonatal) of untreated ASB in pregnancy in the UK?*

The previous UK NSC reviews identified limited up to date evidence on the prevalence or incidence of ASB in pregnancy in the UK as well as few data on adverse maternal or neonatal outcomes associated with the infection.[19, 20] Therefore, this question aimed to identify new evidence in order to investigate the prevalence and incidence of ASB in pregnancy in the UK and to explore the association between ASB in pregnancy and adverse maternal and neonatal outcomes. Specific maternal outcomes include mortality, sepsis, pyelonephritis, recurrent ASB and symptomatic urinary tract infection (UTI). Neonatal outcomes comprise perinatal mortality (at 20 weeks gestation or later), spontaneous pregnancy loss before 20 weeks gestation, sepsis, preterm birth (before 37 weeks gestation) and low birth weight (less than 2500g).

Eligibility for inclusion in the review

Comparative and non-comparative observational studies recruiting pregnant women with untreated ASB (the exposure variable) were eligible for inclusion. The intention was to prioritise evidence from studies defining ASB according to the IDSA definition: at least 10^5

CFU per ml or at least 10^8 CFU per litre of a voided urine specimen from a woman without signs or symptoms of UTI.[3] Non-comparative studies could include the control arms of relevant RCTs. For comparative studies, the unexposed group comprised pregnant women without untreated ASB. Studies had to report at least one of the following outcomes in order to be included: prevalence or incidence of ASB in pregnancy; maternal mortality, sepsis, pyelonephritis, symptomatic cystitis or recurrent ASB; neonatal perinatal mortality or sepsis; pregnancy loss; preterm birth, or low birth weight. Systematic reviews of the types of studies detailed above were also eligible for inclusion and were regarded as the highest level of evidence. Selection of studies was limited to those with settings which were sufficiently similar to the UK in terms of economic development, those reported in English language and publications from 1990 onwards. It was planned to include estimates of prevalence or incidence of ASB only from studies conducted in the UK. Full details of the study eligibility criteria are provided in Table 2, including specific outcome definitions.

Description of the evidence

In the current review, 17 papers were identified through title and abstract screening as potentially relevant to question 1. After further full text review, only three were included, all of which were primary studies.[13, 15, 33] No relevant systematic reviews were identified. Full details of study selection can be found in Appendix 2.

None of the three primary studies reported on the incidence or prevalence of ASB or the burden of disease in the UK population. However, all reported data on burden of disease from countries which could be considered analogous to the UK, namely the Netherlands[13, 15] and the USA.[33]

All three evaluations were cohort studies, two of a prospective design[13, 15] and one retrospective.[33] The retrospective study had unclear eligibility because it reported adverse maternal and neonatal outcomes associated with polymicrobial growth in the urine rather than ASB and did not explicitly state that participants were asymptomatic. However, contextual information suggested that this study may have related to ASB in pregnancy and therefore it was included.[33] Table 8 presents information about recruitment details, participant characteristics and urine sampling methods. The ensuing text outlines the results of the studies. Full details of data extracted from the studies can be found in Appendix 3.

Table 8: Question 1 – summary of included studies

Study identifier	Kazemier 2015[13, 34]	Naresh 2011[33]	Schneeberger 2018[15]
Study design and country	Prospective cohort; the Netherlands	Retrospective cohort; USA	Prospective cohort; the Netherlands
Recruitment setting	Antenatal hospital clinics and ultrasound centres	Hospital antenatal clinic	Antenatal care settings at university medical centres, non-university hospitals and midwifery practices
Number of participants recruited	5,132	755	528
Participant selection criteria	Singleton pregnancy; no signs or symptoms of UTI; no other risk factors for adverse pregnancy outcomes or complicated UTI	Pregnancy <20 weeks gestation, receiving hospital-based antenatal care 2002 to 2007. Allowed inclusion of women with risk factors e.g. current smoker, history of preeclampsia or preterm birth	Recruited women with and without diabetes mellitus (both gestational and pre-gestational)
Type of urine sample and planned timing and frequency of sample collection	One MSU sample taken from 16 to 22 weeks	One clean catch sample taken before 20 weeks (mean 12 weeks)	MSU samples taken at two time points (around 12 and 32 weeks)
Definition of positive test result for ASB	At least 10^5 CFU/ml urine of a single microorganism or same in the presence of a second isolate	No definition of ASB but defined polymicrobial growth as mixed flora in excess of 10^5 CFU/ml	At least 10^5 CFU/ml urine of a single microorganism or same in the presence of a second isolate
Prevalence of ASB	250/5132 (5%)	NR	9/322 (2.8%) at 12 weeks and 13/422 (3.1%) at 32 weeks
Recurrence of ASB	NR	NR	NR
Findings	Findings below are for comparison between ASB+^{ive} women who were untreated or received placebo within a linked RCT (n=208) versus ASB-^{ive} women (n=4035). All OR estimates are as reported by the study authors and were adjusted for smoking, educational	Findings below are for comparison between women with positive polymicrobial growth culture (n= 380) versus women with negative growth culture (n=378)	Findings below are for comparison between ASB-+^{ive} (n=20) versus ASB-^{ive} women (n=454) No between group difference observed for preterm birth for ASB+^{ive}

	status, conception through in-vitro fertilisation or intracytoplasmic sperm injection and pre-existent hypertension. More ASB-positive women developed pyelonephritis compared with ASB-negative women: 5/208 (2.4%) versus 24/4035 (0.6%), OR 3.9 (95% CI 1.4 to 11.4) Median duration of hospital stay for women with pyelonephritis was 3 days (range 2–10 days). The course of disease in these women was mild, and none needed admission to an intensive care unit. No between-group difference observed for delivery <34 wks: 2/208 (1.0%) versus 54/4035 (1.3%) for ASB+ive and ASB-ive respectively, OR 0.7 (95% CI 0.2 to 2.8) No between-group difference observed for the composite primary outcome, defined as pyelonephritis or delivery <34 wks or both: 6/208 (2.9%) versus 77/4035 (1.9%) for ASB+ive and ASB-ive respectively, OR 1.5 (95% CI 0.6 to 3.5^) More ASB+ive women had a UTI treated with antibiotics antenatally compared with ASB-ive women: 42/208 (20.2%) versus 317/4035 (7.9%), respectively (OR 2.9, 95% CI 2.0 to 4.2). There was a similar result for the outcome of recurrent UTI treated with antibiotics antenatally: 18/208 (8.7%) versus 105/4035 (2.6%), OR 3.5 (95% CI 1.8 to 6.7). No between-group difference was observed for UTI treated with antibiotics postpartum, within 6 wks of delivery: 12/208 (5.8%)	No between-group differences were observed between women with polymicrobial growth and those with negative urine cultures for the following outcomes: incidence of pyelonephritis (1/380 [0.3%] versus 0/375 [0%] respectively; p=0.32); preterm delivery (64/380 [16.8%] versus 60/375 [16%] respectively; p=0.76); preterm delivery <34 wks (21/380 [5.5%] versus 17/375 [4.5%] respectively; p=0.53); and stillbirth (1/380 [0.3%] versus 1/375 [0.3%] respectively; p=0.98)	and ASB-ive women respectively: 10.0% versus 7.7%, RR 1.30 (95% CI 0.34 to 5.02)

	versus 164/4035 (4.1%), OR 1.4 (95% CI 0.8 to 2.7) Between-group differences were not observed for the following: preterm birth at <37 wks (11/208 [5.3%] versus 207/4035 [5.1%], OR 1.0, 95% CI 0.6 to 1.9); neonatal sepsis (2/208 [1.0%] versus 25/4035 [0.6%], OR 1.6, 95% CI 0.4 to 7.1); perinatal death (2/208 [1.0%] versus 22/4035 [0.5%], OR 1.8, 95% CI 0.4 to 7.7)		

Key:
+ive positive (test result); -ive negative (test result); ^ Two women had pyelonephritis and a preterm delivery before 34 wks; ASB asymptomatic bacteriuria; CFU/ml colony forming units per millilitre; CI confidence interval; MSU mid-stream urine; n number of participants/samples; NR not reported; OR odds ratio; RR risk ratio; UTI urinary tract infection; wk week

One prospective study reported on the association between ASB and pyelonephritis[13] and the retrospective study reported on the association between polymicrobial growth in the urine and pyelonephritis.[33] The prospective study reported that more ASB-positive women developed pyelonephritis compared with ASB-negative women: 5/208 (2.4%) versus 24/4035 (0.6%), adjusted odds ratio (OR) 3.9 (95% confidence interval [CI] 1.4 to 11.4). The median duration of hospital stay for women with pyelonephritis was 3 days (range 2–10 days) and the course of disease was described as 'mild' in all cases, none necessitating admission to an intensive care unit.[13] By contrast, the retrospective study reported similar incidence of pyelonephritis for women with polymicrobial growth in the urine (this is a poor definition of ASB because it might be caused by different type of infection, or contamination etc) when compared with those with a negative urine culture: 1/380 (0.3%) versus 0/375 (0%) respectively, author reported p-value for between-group difference 0.32.[33]

The prospective study described above also reported on the association between ASB and incidence of UTI during pregnancy.[13] More ASB-positive women had a UTI treated with antibiotics antenatally compared with ASB negative women: 42/208 (20.2%) versus 317/4035 (7.9%), adjusted OR 2.9 (95% CI 2.0 to 4.2). There was a similar result for the outcome of recurrent UTI treated with antibiotics antenatally: 18/208 (8.7%) versus 105/4035 (2.6%), OR 3.5 (95% CI 1.8 to 6.7). However, no clear between-group difference was seen for UTI treated with antibiotics postpartum, within 6 weeks of delivery: 12/208 (5.8%) versus 164/4035 (4.1%), adjusted OR 1.4 (95% CI 0.8 to 2.7).[13]

Discussion of findings

Assessment of risk of bias

The risk of bias of studies was assessed using the JBI Critical Appraisal Checklist for Cohort Studies.[28] A narrative outline of the assessment is provided below together with summary tabulation (Table 9). Full details of the risk of bias assessment are provided in Appendix 3.

Table 9: Question 1 – summary of risk of bias assessment in primary studies (JBI checklist for cohort studies)[28]

JBI checklist item (cohort studies)	Kazemier 2015[13, 34]	Naresh 2011[33]	Schneeberger 2018[15]
1. Were the 2 groups similar & recruited from the same population?	Yes	Yes	Yes
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	Yes	No	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	No	Yes
4. Were confounding factors identified?	Yes	Yes	Unclear
5. Were strategies to deal with confounding factors stated?	Yes	Yes	No
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Unclear	Yes
7. Were the outcomes measured in a valid and reliable way?	Yes	No	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Unclear	Yes
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes	Yes	No
10. Were strategies to address incomplete follow up utilised?	Yes	Not applicable	Unclear
11. Was appropriate statistical analysis used?	Yes	Yes	No
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias)	No (high risk of bias)	No (high risk of bias)

Each checklist item was judged for each study and one of the following responses assigned: Yes, No, Unclear or Not applicable. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review. Full details of the risk of bias assessment are presented in Appendix 3.

The risk of bias for the three studies overall was variable. One of the prospective studies achieved a low risk of bias for all 11 individual JBI checklist items (Table 9); this study was therefore considered as being at low risk of bias overall.[13]. There were risk of bias concerns with the other two studies with both achieving favourable responses for six out of the 11 JBI checklist items.[15, 33] The nature of the methodological weaknesses varied between the two studies and are briefly outlined in the following paragraphs.

The second prospective study provided a report of potential confounding factors at baseline stratified according to diagnosis or no diagnosis of diabetes mellitus and there was no such presentation for women with positive and negative test results for ASB.[15] This study used cross-tabulation to examine relationships between variables but did not include analysis for covariate adjustment (e.g. multiple regression) which would have been preferable. The study authors planned to collect urine samples at two time points (12 and 32 weeks). Whilst it was apparent that some data were missing at both time points, this was not explained further and there was no mention of using statistical methods to handle missing data.[15]

Information in the report of the retrospective study suggested that presence of the exposure (polymicrobial growth in the urine) was assessed slightly earlier on average in the group which proved to have a negative test result when compared to those with a positive result (11.6 versus 12.2 weeks gestation).[33] It was unclear from the information provided whether participants could have already experienced the outcome of pyelonephritis before assessment of presence of the exposure. In addition, ASB was measured using non-standard definitions which may have lacked validity, and this may be a major source of bias in this study. The follow up period was not clear.[33]

All three included studies were at high risk of bias in relation to the additional, topic-specific criterion (item 12 on Table 9) as none reported undertaking collection and analysis of a second, voided urine sample to confirm a diagnosis of ASB identified from a first voided sample.[13, 15, 33] Two studies obtained a single sample per participant[13, 33] and whilst the other included a protocol to acquire two samples per participant, these were not consecutive, having been collected at different stages of gestation.[15] However, the natural history of ASB in pregnancy is too unclear to specify what interval should be used between samples.

Conclusions

Limited evidence was available from three cohort studies: two of prospective design and one retrospective. For the latter, the exposure was described as polymicrobial growth in the urine rather than ASB. Most data came from one, good-quality prospective study, the

other two studies showing some issues with risk of bias. None of the studies reported on the incidence or prevalence of ASB or the burden of disease in the UK population. In the absence of UK data, reported data from countries similar to the UK (the Netherlands and the USA) were included.

Results from the good-quality prospective cohort suggested that presence of ASB may be associated with incidence of pyelonephritis in pregnant women but the retrospective study did not find an association between polymicrobial growth in the urine and pyelonephritis. The good-quality prospective study found that the presence of ASB may be associated with symptomatic UTI requiring treatment with antibiotics antenatally; however, no association between ASB and requirement to treat UTI with antibiotics post-partum was seen. There was no evidence to suggest that presence of ASB was associated with neonatal mortality or morbidity including sepsis or pre-term delivery. Maternal mortality, maternal sepsis, and recurrence of ASB and low birth weight were not reported in any study.

Although the included studies were conducted in countries deemed similar to the UK, the applicability of the evidence to the UK setting is uncertain.

Summary of Findings Relevant to Criterion 1: criterion not met

Quantity: No relevant systematic reviews were identified for this question. Three primary studies recruiting 6,361 pregnant women overall were identified, two of which were prospective cohort studies and one a retrospective cohort. Most of the outcome data came from one prospective study reporting a comprehensive range of outcomes in relation to the disease burden associated with ASB in pregnancy.

Quality: One prospective study had a low risk of bias overall whereas the other two studies had methodological weaknesses. These included lack of adjustment for confounding variables, incomplete follow-up data and differential measurement of the exposure variable for exposed and non-exposed groups. None of the three studies undertook consecutive repeat sampling to confirm initial ASB-positive urine cultures to ensure that only women with ASB were included.

Applicability: None of the primary studies reported on the incidence or prevalence of ASB or the burden of disease in the UK population. However, all reported data from countries which could be considered similar to the UK including the Netherlands and the USA. Despite this, the applicability of the evidence to the UK setting remains uncertain considering the low volume of available evidence and methodological issues. Data were not available for some relevant outcomes including recurrence of ASB, maternal sepsis, maternal mortality, and low birth weight.

Consistency: All participants were recruited from routine antenatal care services. One study recruited women with low risk profiles whilst the other two included participants with risk factors for pregnancy complications e.g. gestational diabetes mellitus and prior preterm birth. Definition of ASB varied, with some studies not using the standard IDSA definition. One study described the prevalence of polymicrobial growth in the urine rather than ASB and the significance of polymicrobial growth in urine cultures in pregnancy is uncertain; in non-pregnant women it is usually interpreted to equate to contamination with perineal flora. Two studies collected a single urine sample for culture from each participant whereas the other collected two samples. Findings from one, good quality, prospective cohort study suggested an association between presence of ASB and both incidence of pyelonephritis and symptomatic UTI requiring treatment with antibiotics antenatally. A lower quality retrospective study reported similar incidence of pyelonephritis for pregnant women exposed and unexposed to polymicrobial growth in the urine. Findings of this study should be viewed with caution considering methodological weaknesses and lack of clarity about the exact nature of the exposure variable.

Conclusions: Findings from one good quality study suggested that presence of ASB may be associated with increased incidence of pyelonephritis and symptomatic UTI requiring treatment with antibiotics antenatally. A second, lower quality study found no evidence of an association between presence of polymicrobial growth in the urine and incidence of pyelonephritis. There

was no evidence to suggest that presence of ASB was associated with neonatal mortality or morbidity including sepsis or pre-term delivery.

Criteria 4 & 7 — the performance of screening strategies for detecting ASB in pregnancy

4: 'There should be a simple, safe, precise and validated screening test.'

7. 'There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.'

Question 2 – What is the performance of screening strategies for detecting ASB infection in pregnancy?

The 2017 UK NSC review[20] identified seven new evaluations of screening test performance published since the 2011 review.[19] All seven included studies employed a single midstream urine specimen as the sampling strategy and specified urine culture as the reference standard. Overall, these evaluations provided limited data because of the considerable variation across studies in estimates of test performance, high risk of bias in relation to how the index test was conducted and interpreted[29] and potentially low external validity due to study locations having marginal relevance to the UK context (India, Bangladesh, Ethiopia and Nigeria). In addition, there was no new evidence on the timing of testing in relation to gestational stage or the frequency or number of repetitions of the test. In light of these observations, the review authors concluded that, there was insufficient evidence to recommend a specific screening strategy.[20]

Although a national screening programme is not recommended in the UK the current NICE antenatal care guidance states that pregnant women should be offered routine screening for ASB using culture of a mid-stream urine specimen during early gestation. However, the NICE guidance does not provide any information about the methods, timing or frequency of testing.[5]

The aim of this question was to assess the performance of screening tests for detecting ASB infections in pregnant women. Additional aims included the evaluation of optimum timing and frequency of testing during gestation.

Eligibility for inclusion in the review

Studies recruiting pregnant women at low risk of bacterial infection in the urogenital tract comparing any index test (e.g. dipstick or dipslide tests) with urine culture as the reference standard and reporting suitable data for populating a 2x2 diagnostic data table were included. Eligible study designs included RCTs and prospective, retrospective, or cross-sectional studies. Case control studies and those with longitudinal assessment of the reference standard were excluded. Systematic reviews of the types of studies detailed

above were also eligible for inclusion and were regarded as the highest level of evidence. Selection of studies was limited to those with settings which were sufficiently similar to the UK in terms of economic development, those reported in English language and publications from 2003 onwards. Full details of the study eligibility criteria are provided in Table 3.

Description of the evidence

In the current review, 35 papers were identified through title and abstract screening as potentially relevant to question 2. After further full text review, one systematic review[35] and one primary study (not included in the identified systematic review)[12] were included. Full details of study selection are presented in Appendix 2. Key characteristics of the systematic review and primary study are shown below in Table 10 whilst full details of data extraction are presented in Appendix 3.

Table 10: Question 2 – summary of included studies

Study identifier	**Rogozinska 2016[35]**	**McIsaac 2005[12]**
Study design and sample size details	Systematic review of diagnostic accuracy studies; last search date June 2015; 27 articles (13,641 women) with test accuracy data and reporting on nine tests	Primary study – prospective cohort recruiting 1,050 women
Population	Pregnant women with ASB	Women attending routine antenatal care with varying pregnancy risk profiles, assessed using the Ontario Antenatal Record[36, 37]
Setting	Antenatal care settings	Outpatient antenatal clinics provided by obstetricians and family doctors affiliated to a large teaching hospital
Screening test(s)	Dipsticks including: Dipstick (marker: nitrites); Dipstick (marker: leucocytes or nitrites). Dip slides including: Uricult & Uricult Trio (Orion Diagnostica); Microstix-3. Microscopic techniques: Microscopic analysis of urine (marker & threshold: >20 bacteria per High Power Field); Dip slide with gram staining. Other tests not usually used to detect bacteriuria: Uriscreen catalase tests (Savyon Diagnostics); Chlorhexidine reaction; Griess test (test to detect nitrites).	Four screening strategies were compared: 1. Urine dipstick testing at each prenatal visit using the LEN dipstick (Uristix 4, Bayer Pharmaceuticals) followed by a urine culture if positive 2. A single urine culture < 20 wks gestation 3. Two urine cultures, one < 20 wks and the other at 28 wks gestation 4. Three urine cultures, one < 20 wks, one at 28 wks and the third at 36 wks gestation
Outcomes	Sensitivity, specificity, likelihood ratios, or receiver operating characteristic; reference standard was urine culture	Sensitivity of each screening strategy; reference standard was a single positive urine culture

ASB definition	≥10^5 CFU of a single causative organism per ml of urine	Growth of a single organism at ≥10^6 CFU/mL or two organisms at ≥10^8 CFU/mL in a woman without symptoms
Study locations	USA (7 studies); India (7 studies); Nigeria (3 studies); and 1 study in each of the following: UK, Germany, Spain, Turkey, Argentina, Venezuela, South Africa, Ethiopia, Pakistan and Thailand.	Canada
Findings	Sensitivity and specificity estimates were combined using a bivariate, hierarchical random effects model. The pooled sensitivity and specificity of nitrites when detected by urine dipstick test were 0.55 (95% CI 0.42 to 0.67) and 0.99 (95% CI 0.98 to 0.99) respectively (generated from analysis of 21 studies recruiting 9,491 women). The pooled sensitivity of detected nitrites or leukocytes was 0.73 (95% CI 0.59 to 0.83) and the specificity was 0.89 (95% CI 0.79 to 0.94) (based on eight studies recruiting 5,940 women). Respective values for the Griess test to detect nitrites were 0.65 (95% CI 0.50 to 0.78) and 0.99 (95% CI 0.98 to 1.00) (data were from two studies recruiting 728 women) and for dipslide with gram staining 0.86 (95% CI 0.80 to 0.91) and 0.97 (95% CI 0.93 to 0.99) (six studies recruiting 3,201 women).	Sensitivity estimates: 1. 7/49 (14.3%) 2. 20/49 (40.8%) 3. 31/49 (63.3%) 4. 43/49 (87.8%) No further information was reported in the paper.
Key: ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval		

The systematic review included 27 studies (recruiting 13,641 women) that evaluated nine different onsite tests, using urine culture as the reference standard with a positive culture defined as growth of a single organism with a colony count of ≥ 10^5 CFU/litre; further details of the reference standards used in the individual studies were not reported.[35] The overall results suggested high specificity estimates for most onsite tests (mostly 92% or above) whilst sensitivity values were variable (15% to 100%), the highest being for dipslide with gram staining (Table 10). This suggests the potential for such tests to fail to identify many women with ASB. The included studies were conducted in a variety of countries worldwide and there were no sub-group analyses according to the income level of national settings. All research conducted in the UK or in countries similar to the UK was published earlier than 2003, which is the date threshold for inclusion in this review.[35]

The primary study was conducted in Canada and compared four strategies for screening for ABU in pregnancy:[12]

- Urine dipstick testing at each prenatal visit using the leukocyte-esterase-nitrite (LEN) dipstick (Uristix 4, Bayer Pharmaceuticals) followed by a urine culture if positive
- A single urine culture before 20 weeks gestation
- Two urine cultures, one before 20 weeks and the other at 28 weeks gestation
- Three urine cultures, one before 20 weeks, one at 28 weeks and the third at 36 weeks gestation

The reference standard was a defined as a single positive urine culture derived from any strategy at any stage. A positive culture was defined as growth of a single organism with a colony count of ≥ 10^6 CFU/litre or two organisms at ≥ 10^8 CFU/litre. The proportion of positive LEN tests at each prenatal visit ranged from 3.5% to 13.9% (mean 6.4%). In terms of sensitivity, of 49/1050 (4.7%) ASB-positive cases confirmed by urine culture, 7/49 (14.3%) were identified with LEN. The values for a single culture, two cultures and three cultures were 20/49 (40.8%), 31/49 (63.3%) and 43/49 (87.8%) respectively. The study authors concluded that of the four testing strategies, LEN dipstick testing was the least sensitive. In addition, a single urine culture undertaken before 20 weeks gestation may miss more than half of positive ABU cases. A strategy of three urine cultures proved to be the most sensitive however, the cost-effectiveness of this approach would need to be determined.[12]

Discussion of findings

Assessment of risk of bias

The systematic review[35] was assessed using the ROBIS checklist[26] and the primary study[12] was appraised with QUADAS-2.[29] A narrative outline of the assessment is provided below together with summary tabulation for the systematic review (Table 11) and the primary study (Table 12). Full details of the risk of bias assessment are provided in Appendix 3.

Table 11: Question 1 – summary of risk of bias assessment in systematic reviews (ROBIS)[26]
Each domain was judged as at low, high, or unclear risk of bias

Assessment domain	**Rogozinska 2016[35]**
Domain 1: Study eligibility criteria	Low risk
Domain 2: Identification & selection of studies	High risk
Domain 3: Data collection & study appraisal	Low risk
Domain 4: Synthesis & findings	Low risk
Overall rating of bias	**High risk of bias**

The systematic review was judged to have an overall high risk of bias, due to a high risk of bias within Domain 2 (Identification and selection of studies).[35] The search strategy included a filter for diagnostic test evaluations which is not a recommended approach in light of evidence to suggest that the use of such filters comes with the risk of missing relevant records.[26] This aside, the search methods were appropriate and comprehensive and reported in enough detail. Other aspects of review methods were satisfactory as evidenced by the low risk of bias attributed to the other domains.[35]

Table 12: Question 1 – summary of risk of bias assessment in primary study (QUADAS-2)[29]
Each domain was judged as at low, high, or unclear risk of bias

Study: McIsaac 2005[12] McIsaac W, Carroll JC, Biringer A, Bernstein P, Lyons E, Low DE and Permaul JA. *Screening for asymptomatic bacteriuria in pregnancy. JOGC* 2005;27(1):20-4.	
DOMAIN 1: PATIENT SELECTION	RISK: Low
DOMAIN 2: INDEX TEST(S)	RISK: High
DOMAIN 3: REFERENCE STANDARD	RISK: High
DOMAIN 4: FLOW AND TIMING	RISK: High

The primary study[12] assessed with QUADAS-2[29] was also allocated a high risk of bias overall in light of a high risk of bias rating for three of the four individual domains (Table 12).

Although the LEN tests were interpreted without knowledge of the reference standard test (urine culture), the same could not be said for the other testing strategies which involved different numbers of urine culture tests (Domain 2 – Index tests). The index test was not always independent of the reference standard and it was not clear whether the reference standard would always identify the presence or absence of ASB correctly because the number of urine cultures undertaken differed across participants (and could have been zero in some instances) (Domain 3 – Reference standard). The information relating to flow and timing was very unclear (Domain 4 – Flow and timing). It was unclear whether all participants had received at least one urine culture test. Assuming this to be the case, the number of urine culture tests per participant at each gestational stage was not clearly explained. The only component to achieve a low risk of bias was Domain 1 (Patient selection) because an appropriate source population was accessed, and participants were recruited consecutively.

Conclusions

One systematic review[35] and one primary study[12] were included for question 2. The systematic review did not include any recent studies from the UK or countries similar to the UK. The review findings suggested that onsite tests generally have favourable specificity but variable sensitivity therefore some true positives could be missed by such strategies. The review was deemed to be at high risk of bias overall because of applying a potentially restrictive methodological filter to the list of search terms that risked failure to retrieve relevant studies.[35] The primary study in a Canadian population suggested that the LEN test had low sensitivity and may miss most true positives.[12] However, results should be viewed with caution as this study was judged to be at high risk of bias in the index test, reference standard and flow and timing domains. [29, 38] No evidence was found on the performance of urine culture in the context of screening for ASB. These studies tend to be older and so likely not picked up by our literature searches (from 2003 onwards); the relevance of such older studies to current clinical practice is questionable. Overall, taking into the account the poor quality and limited applicability of the evidence base to UK practice for this question, the above evidence cannot underpin any strategy for testing for ASB in pregnancy.

Summary of Findings Relevant to Criteria 4 & 7: neither criteria met

Quantity: One systematic review and one primary study were identified. The review included 27 studies (N=13,641 women). The primary study was a prospective cohort that recruited 1,050 women and was not included in the systematic review.

Quality: The systematic review reported that the overall methodological quality of included studies was moderate. The review was judged to be at high risk of bias overall because of limitations of the search methods. The primary study was also judged to have an overall high risk of bias because of lack of independence between the index and reference tests and an unclear account of the number of participants undergoing urine culture testing at different gestational stages.

Applicability: The systematic review assessed data from multiple countries worldwide but did not include recent (published in 2003 or later) studies conducted in the UK or countries similar to the UK. The primary study reported on the performance of four testing strategies in a Canadian population, which has uncertain relevance to the UK setting.

Consistency: There was considerable variation in national settings and test characteristics within the studies included in the systematic review. A range of different onsite index tests were assessed, the most frequently evaluated being urine dipstick and dipslide tests. Urine culture was the reference standard in all studies, but the specific details of the reference standard in each study were not reported. Despite different settings and tests, most studies estimated acceptable specificity values of 92% or above (range 54% to 100%) whereas sensitivity estimates were much more varied, ranging from 15% to 100%. The primary study compared the performance of four testing strategies (leukocyte-esterase-nitrite (LEN) dipstick testing followed by urine culture in the event of a positive dipstick result, a single urine culture, two cultures, and three cultures) and considered any positive result from urine culture as the reference standard. The LEN test was estimated as having very low sensitivity (14.3%). Although sensitivity improved with increasing numbers of urine cultures, all estimates were below 90%: single culture 40.8%; two cultures 63.3%; and three cultures 87.8%. Specificity estimates were not reported.

Conclusions: Most of the index tests achieved acceptable specificity but sensitivity was variable and low in many cases, meaning that a large proportion of true positive cases of ASB could be missed. Taking into the account the methodological limitations of the research and limited applicability to UK practice, the potential for the available evidence to underpin a strategy for testing for ASB in pregnancy in the UK is uncertain.

Criterion 11 — the benefits and harms of screening for asymptomatic bacteriuria in pregnancy

11: 'There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality of morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as in Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.'

Question 3: What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy?

The early UK NSC review (published in 2011) found insufficient evidence to underpin the implementation of a programme to screen pregnant women for ASB in the UK. In particular, there was uncertainty in relation to prevalence of the condition in the UK, the impact of screening on incidence of pyelonephritis and the optimal test and treatment strategies.[19] The subsequent UK NSC review (2017) did not identify sufficient new evidence to resolve the persisting uncertainties, therefore, a screening programme still could not be recommended.[20] Current NICE guidance states that pregnant women should be offered a test to detect ASB during early pregnancy but does not refer to a population based screening programme.[5] However, NICE recommends an RCT to confirm the beneficial effects of screening for ASB.

The aim of this question was to evaluate the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy.

Eligibility for inclusion in the review

RCTs and comparative cohort studies recruiting pregnant women without history of kidney infection, polycystic kidneys, urogenital anomalies, symptoms of UTI, recurrent UTI, diabetes or sickle cell disease that compared screening for ASB with no screening or an alternative screening strategy were eligible for inclusion. In addition, at least one of the following outcomes had to be reported: number of participants with confirmed ASB; number of participants treated with antibiotics for ASB; maternal mortality; maternal sepsis; pyelonephritis; symptomatic UTI; perinatal mortality; spontaneous pregnancy loss; neonatal sepsis; preterm birth, or low birth weight. In addition, outcomes relating to potential adverse effects of antibiotic therapy included any maternal or neonatal harms such as anaphylaxis, thrombocytopenia, haemolytic anaemia, alterations in vaginal/perineal microbiome (e.g.,

candidiasis or vaginitis), antibiotic-induced diarrhoea (including *Clostridioides difficile* disease), rash, vomiting, foetal abnormalities, alterations in foetal microbiome, candidiasis, rash, gastrointestinal upset and antibiotic-sensitisation and antimicrobial resistance. Systematic reviews meeting the same criteria for participant, screening programme comparison and outcome characteristics were also eligible for inclusion. Both primary studies and systematic reviews had to be published in English from 2003. Full details of the study eligibility criteria including definitions are provided in Table 4.

Description of the evidence

In the current review, 35 papers were identified through title and abstract screening as potentially relevant to question 3. After further full text review, three systematic reviews were included.[39-41] No additional primary studies which were not already included in the identified systematic reviews were retrieved. This may be explained by the recent publication of two of the systematic reviews (both published in 2019); it is possible that between them, they included all available, relevant evidence.[39, 40]. Full details of study selection are presented in Appendix 2. Key characteristics of the systematic review and primary study are shown below in Table 13 whilst full details of data extraction are presented in Appendix 3.

Two systematic reviews provided the underpinning evidence for practice guidelines.[39, 40] All three reviews were also included in the treatment review (question 4).[39-41] The included systematic reviews assessed data from multiple countries worldwide.

Table 13: Question 3 – summary of systematic reviews

Study identifier	Angelescu 2016[41]	Henderson 2019[39]	Wingert 2019[40]
Population	Pregnant women taking part in routine maternal care without symptoms of UTI and with an unknown ASB status	All adults, but separate subgroup data for pregnant women with ASB	Pregnant women with ASB. A proportion (not specified) of women in some studies had symptomatic UTI
Setting	Any care setting	Prenatal or primary care settings	Hospital- or university-based outpatient antenatal clinics
Screening test(s)	Any ASB screening strategy followed by treatment, if necessary, versus any treatment for ASB	Screening with urine testing (e.g., urine culture, urinalysis with microscopy, dipstick, dipslide, screening with reflex urine culture) versus no screening.	Any screening test for ASB. Comparators could be no screening or an alternative screening programme. Screening was based on testing urine cultures for all studies.
Outcomes	Pyelonephritis; UTI; Symptoms linked directly or indirectly to UTI (e. g. headache or visual impairment as symptoms of pre-eclampsia, fever); Infant morbidity (e. g. respiratory distress syndrome, sepsis, cerebral haemorrhage, necrotising enterocolitis); Perinatal mortality; Early preterm birth (< 32 wks of gestation); Very low birth weight (< 1500 g); Health-related quality of life and psychosocial functioning; Any adverse event	Low birthweight; pyelonephritis; AEs.	Pyelonephritis; perinatal mortality; spontaneous abortion; preterm delivery; foetal abnormalities; low birth weight; neonatal sepsis; feasibility; acceptability; cost; equity; patient values and preferences.
Study designs	RCTs and prospective non-randomised studies	RCTs, observational cohort studies with a comparator of no screening or no treatment	RCTs and if necessary, cohort studies and controlled observational studies.
ASB definition	≥10^5 CFU of a single causative organism per ml of urine	≥10^5 CFU of a single causative organism per ml of urine, but studies using lower screening thresholds (e.g.,10^4 CFU) or requiring specific bacterial species or numbers of species, were not excluded	Not limited to one definition, studies comparing different definitions were compared.
Last search date	February 2016	September 7, 2018	October 2017
Included studies	No eligible studies were found that investigated the benefits and harms of screening for ASB versus no screening or that compared different screening strategies.	2 cohort studies on the effectiveness and/or harms of screening (n=5,289)	4 non-concurrent cohort studies (before and after the introduction of a screening programme); 7,611 women. 3 studies assessed screening versus no screening; 1 compared one-time screening (only at the first antenatal clinic visit) with frequent

			screening (at all antenatal visits).
Study locations (year of publication)	No studies	Spain (1 study; 1994) and Turkey (1 study; 2002)	1 study from each of the following: USA (2007), France (1983), Spain (1994), and Turkey (2002)
Findings	No studies were found on screening and so it was only possible to assess the effects of treatment (see summary presented in Q4).	Of the two cohort studies on screening in pregnant women, one conducted in Spain (N=4,917) identified a three-fold reduction in risk in unadjusted comparisons on a retrospective unscreened and screened cohort. The other cohort study of screening in pregnant women was conducted in Turkey (N=372) and had low statistical power for comparisons of health outcomes in a screened and unscreened cohort due to rarity of outcome events.	Findings suggested that screening may reduce the incidence of pyelonephritis when compared with no screening: RR 0.28 (95% CI 0.15 to 0.54); ARR 1.3%; NNS 77 (95% CI 65 to 121). However, no between-group difference was apparent for one-time versus frequent screening for the same outcome: RR 1.09 (95% CI 0.27 to 4.35). No between-group differences were observed between screening and no screening for the outcomes of perinatal mortality, spontaneous abortion before 28 weeks gestation and preterm delivery. In the study comparing one-time versus frequent screening, more women experienced preterm delivery in the group receiving frequent screening: RR 1.57 (95% CI 1.11 to 2.23). Potential explanations for this finding were not explored by the original investigators or the review authors. None of the studies reported on maternal mortality, maternal sepsis, neonatal sepsis or low birth weight.
Key: ARR absolute risk reduction; ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; NNS number needed to screen; RCT randomised controlled trial; RR relative risk; UTI urinary tract infection.			

One systematic review conducted in Canada included four non-concurrent cohort studies (recruiting 7,611 women overall) comparing outcomes before and after the introduction of a screening programme.[2, 40] Three studies assessed screening versus no screening and one compared one-time screening (only at the first antenatal clinic visit) with frequent screening (at all antenatal visits). Screening was based on testing urine cultures for all studies. Findings suggested that screening may reduce the incidence of pyelonephritis when compared with no screening: RR 0.28 (95% CI 0.15 to 0.54) and absolute risk reduction (ARR) 1.3% with number needed to screen (NNS) of 77 (95% CI 65 to 121). However, no

between-group difference was apparent for one-time versus frequent screening for the same outcome: RR 1.09 (95% CI 0.27 to 4.35). No between-group differences were observed between screening and no screening for the outcomes of perinatal mortality, spontaneous abortion before 28 weeks gestation and preterm delivery. In the study comparing one-time versus frequent screening, more women experienced preterm delivery in the group receiving frequent screening: RR 1.57 (95% CI 1.11 to 2.23). Potential explanations for this finding were not mentioned by the original investigators or the review authors. However, scrutiny of a more detailed review report suggested the possibility of a difference in risk profiles between the two groups, specifically that more women in the frequent screening group had gestational diabetes compared with those in the one-time screening group (9% versus 4%).[2] None of the studies reported on maternal mortality, maternal sepsis, neonatal sepsis or low birth weight. The quality of evidence was rated as very low (using GRADE assessment) for all estimates.[42, 43] The four studies were conducted in the USA (published in 2007), France (published in 1983), Spain (published in 1994) and Turkey (published in 2002). The study from the USA was the only one to be published after 2003 (cut off date for inclusion in our review); this was the study comparing one-time with frequent screening.[40]

Another systematic review was conducted in the USA and included two cohort studies comparing screening with no screening;[39] both studies were also included in the review described above.[40] The third systematic review aimed to assess the benefits and harms of screening and treatment for ASB in pregnant women but did not retrieve any relevant studies in relation to screening.[41] The difference in study retrieval across the three reviews is likely to be explained by differences in the list of search terms used for database searching. The coverage of search terms was the most extensive in the review that retrieved four eligible studies.[2, 40]

Discussion of findings

Assessment of risk of bias

The systematic reviews were assessed using the ROBIS tool.[26] A narrative outline of the assessment is provided below together with summary tabulation (Table 14). Full details of the risk of bias assessment are provided in Appendix 3.

Table 14: Question 3 – summary of risk of bias assessment in systematic reviews (ROBIS)[26]
Each domain was judged as at low, high, or unclear risk of bias

Assessment domain	Angelescu 2016[41]	Henderson 2019[39]	Wingert 2019[40]
Domain 1: Study eligibility criteria	Unclear risk	High risk	High risk

Assessment domain	Angelescu 2016[41]	Henderson 2019[39]	Wingert 2019[40]
Domain 2: Identification & selection of studies	High risk	Low risk	Unclear risk
Domain 3: Data collection & study appraisal	Low risk	Low risk	Low risk
Domain 4: Synthesis & findings	Low risk	Low risk	Low risk
Overall rating of bias	**High risk of bias**	**High risk of bias**	**High risk of bias**

All three systematic reviews were classified as being at high risk of bias overall.[39-41] Two applied language restrictions during study selection therefore the possibility of language bias could not be discounted.[39, 40] One of the reviews also included only full text reports and not abstracts.[40] The third systematic review (which did not retrieve any screening studies) did not use a fully developed list of search terms resulting in non-retrieval of relevant evidence.[41]

Conclusions

There is a lack of available data to inform population screening strategies for ASB in pregnancy. Three systematic reviews were identified focusing on screening and treatment of ASB. One review did not retrieve any screening studies whilst the other two included four unique primary studies between them. The four primary evaluations were cohort studies with non-current comparison groups which assessed outcomes before and after the implementation of a screening programme. Three studies compared screening with no screening and were conducted in countries with limited relevance to the UK setting; in addition, these sources of evidence were not current. The fourth study, conducted in the USA and published during 2007, compared screening only at the first antenatal visit with screening at each antenatal visit. Screening may reduce the risk of pyelonephritis when compared with no screening but there was no difference between one-time screening and frequent screening for this outcome. There was no difference between screening and no screening for perinatal mortality, spontaneous abortion earlier than 28 weeks and preterm birth. More women in the frequently screened group experienced preterm birth compared with one-time screening, possibly because of a more adverse risk profile in the frequently screened group. Some relevant outcomes were not reported in any study, including maternal mortality, maternal sepsis, neonatal sepsis, and low birth weight. The review authors rated all four primary studies as having low quality. The three reviews were at high risk of bias overall because of limitations of study selection or search methods. This means that relevant evidence may have been missed from all three reviews.

Summary of findings relevant to criterion 11: criterion not met

Quantity: Three systematic reviews were identified that assessed the evidence on screening and treatment of ASB in pregnancy. One review did not retrieve any screening studies whilst the other two included four unique primary studies between them (recruiting 7,611 women overall).

Quality: All four primary studies were cohort studies with non-concurrent comparison groups. The systematic review authors rated all four primary studies as being very low-quality sources of evidence according to GRADE assessment. All three reviews were classified as being at high risk of bias overall because of restricting inclusion according to language and publication format or having insufficient coverage of search terms. This means that language bias and omission of relevant material could not be discounted.

Applicability: Three studies compared screening with no screening. Each study was conducted in a different country (France, Spain, and Turkey) and all were published before 2003 (publication dates ranged from 1983 to 2002). The fourth study was conducted in the USA and was published in 2007. This study compared screening only at the first antenatal visit (one-time screening) with screening at each antenatal visit (frequent screening). A screening strategy involving testing at each antenatal clinic visit may have uncertain relevance to the UK because of resource implications.

Consistency: Comparisons differed with three studies comparing screening with no screening whilst the fourth compared one-time screening with frequent screening. Screening when compared with no screening may reduce the incidence of pyelonephritis but no between group difference was apparent for this outcome for one-time versus frequent screening. No between-group differences were observed for screening versus no screening for perinatal mortality, spontaneous abortion before 28 weeks gestation and preterm delivery. In the study comparing one-time versus frequent screening, more women experienced preterm delivery in the group receiving frequent screening.

Conclusions: There is currently a lack of available data to inform population screening strategies for ASB in pregnancy in the UK. Four very low-quality cohort studies were identified from two systematic reviews. Screening may reduce the risk of pyelonephritis by 72% on average when compared with no screening. The ARR for incidence of pyelonephritis for screening when compared with no screening was 1.3% and the NNS 77 (95% CI 65 to 121). There was no difference between one-time screening and frequent screening for this outcome. There was no difference between screening and no screening for perinatal mortality, spontaneous abortion earlier than 28 weeks and preterm birth. The risk of experiencing preterm birth was increased by 57% on average for women in the frequently screened group compared with one-time screening.

Some relevant outcomes were not reported in any study, including maternal mortality, maternal sepsis, neonatal sepsis, and low birth weight. Findings should be treated with caution because of the poor quality of the evidence base and its limited applicability to the UK setting.

Criterion 9 — the benefits and harms of antibiotic treatment for asymptomatic bacteriuria in pregnancy

9: 'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.'

Question 4 – What are the benefits and harms of antibiotic treatment compared with no treatment for ASB in pregnancy?

The most recent UK NSC review considered evidence from three systematic reviews plus an additional primary study and concluded that the effects of antibiotic treatment for ASB in pregnancy is uncertain. This conclusion was in light of conflicting findings and methodological weaknesses within the research.[20]. Current NICE guidance on antenatal care suggests that pregnant women who test positive for ASB should be treated but does not include further guidance in relation to antibiotic therapy, for example, in terms of specific drugs or duration or treatment.[5] The current review searched for studies published from 2003 that evaluated the effects of antibiotic therapy in pregnant women with ASB.

This question aimed to evaluate the benefits and harms of antibiotics for the treatment of ASB in pregnant women when compared with placebo or no treatment.

Eligibility for inclusion in the review

Randomised controlled trials and comparative cohort studies recruiting pregnant women with ASB and comparing antibiotics (with UK marketing authorisation for use in pregnancy) with no treatment or placebo were eligible for inclusion. Studies had to report at least one relevant outcome to be included; these comprised clinical outcomes and those relating to adverse effects of treatment. Clinical outcomes included maternal mortality, maternal sepsis, pyelonephritis, symptomatic UTI, perinatal mortality, pregnancy loss, neonatal sepsis, preterm birth, and low birth weight. Outcomes relating to potential adverse effects of antibiotic therapy included any maternal or neonatal harms such as anaphylaxis, thrombocytopenia, haemolytic anaemia, alterations in vaginal/perineal microbiome (e.g., candidiasis or vaginitis), antibiotic-induced diarrhoea (including *Clostridioides difficile* disease), rash, vomiting, foetal abnormalities, alterations in foetal microbiome, candidiasis, rash, gastrointestinal upset and antibiotic-sensitisation and antimicrobial resistance.

Systematic reviews meeting the same criteria for participant, treatment comparison and outcome characteristics were also eligible for inclusion. Both primary studies and systematic reviews had to be published in English from 2003. Full details of the study eligibility criteria including definitions are provided in Table 5.

Description of the evidence

In the current review, 29 papers were identified through title and abstract screening as potentially relevant to question 4. After further full text review, seven systematic reviews were included[10, 11, 14, 39-41, 44] and one primary study.[13] No additional relevant primary studies were identified outside of the systematic reviews.

The included systematic reviews assessed data from multiple countries worldwide. Full details of study selection are presented in Appendix 2. A summary of key review characteristics is provided in Table 15 below. Full details of data extraction can be found in Appendix 3.

Table 15: Question 4 – summary of included studies

Study identifier	Allen 2018[10]	Angelescu 2016[41]	Henderson 2019[39]	Koves 2017[44]
Study type	'Systematic review	Systematic review	Systematic review	Systematic review
Population	Pregnant women with group B streptococcal (GBS) bacteriuria	Pregnant women taking part in routine maternal care without symptoms of UTI and with an unknown ASB status	All adults, but separate subgroup data for pregnant women with ASB	All adults, but separate subgroup data for pregnant women with ASB
Setting	Not described	Any care setting	Prenatal or primary care settings	Not described
Treatment(s)	Antibiotics	Antibiotic vs. no treatment or placebo	Antibiotic vs. no treatment or placebo	Antibiotic treatment vs. no antibiotics; single vs. short course antibiotic treatments
Outcomes	Neonatal GBS disease, preterm birth, pyelonephritis, chorioamnionitis, and recurrence of GBS colonisation.	Pyelonephritis; UTI; symptoms linked directly or indirectly to UTI (eg. headache or visual impairment as symptoms of pre-eclampsia, fever); infant morbidity (eg. respiratory distress syndrome, sepsis, cerebral haemorrhage, necrotising enterocolitis); perinatal mortality; early preterm birth (< 2wks of gestation); very low birth weight (< 500 g); HRQoL and psychosocial functioning; and AE	Low birthweight; pyelonephritis; AEs.	Symptomatic UTI, resolution of ASB, low birthweight, pre-term delivery, side effects
Study designs	Systematic reviews, RCTs and observational studies	RCTs and prospective non-randomised studies	RCTs, observational cohort studies with a comparator of no screening or no treatment	RCTs, prospective non-RCTs and prospective or retrospective observational studies with a comparator arm.
ASB definition	GBS bacteria in urine, regardless of the number of CFU/ml	≥10^5 CFU/ml of a single causative organism per ml of urine	Not defined.	≥10^5 CFU/ml
Last search date	December 2010	February 2016	September 7, 2018	December 2010
Included studies	1 systematic review (Smaill 2019[11])	4 RCTs (n=454) comparing antibiotics vs. no treatment or placebo	12 RCTs comparing antibiotics vs. control (n=2377)	50 studies (n=7088) of which 13 RCTs in pregnant women compared antibiotics vs.

Study identifier	Allen 2018[10]	Angelescu 2016[41]	Henderson 2019[39]	Koves 2017[44]
				control (no treatment or placebo)
Study locations	Not described	USA (2 studies); Netherlands (1 study); UK (1 study)	Australia (3 studies); Ireland (1 study); Jamaica (1 study); Netherlands (1 study)[13]; UK (3 studies), USA (3 studies).	Not described.
Findings	Antibiotic treatment for ASB reduces the risk of pyelonephritis (RR 0.23; 95% CI 0.13 to 0.41) and low birth weight (RR 0.66; 95% CI 0.49 to 0.89), but with no apparent significant reduction in rates of preterm birth. Antibiotic allergies, including anaphylaxis associated with GBS prophylaxis are rare, and antibiotic morbidity is balanced by the reduction in adverse outcomes associated with GBS colonisation. Penicillin is the agent of choice for GBS prophylaxis	2 RCTs (published 1960s) showed a statistically significant reduction in pyelonephritis (OR 0.21, 95% CI: 0.07 to 0.59 and lower UTI (OR 0.10, 95% CI: 0.03 to 0.35) in women treated with antibiotics. 1 recent RCT found no statistically significant differences in pyelonephritis (0% vs. 2.2%; OR 0.37, 95% CI: 0.01 to 9.25, p = 0.515) or UTI during pregnancy (10 % vs. 18 %; Peto OR 0.53, 95% CI: 0.16 to 1.79). Data were insufficient to determine the risk of harms. Overall, 3 of 4 studies were >50 years old and had serious methodological shortcomings, therefore applicability to current health care settings is likely to be low. The recent high-quality RCT was stopped early due to low number of primary outcome events (composite of preterm delivery and pyelonephritis). Therefore, the results did not show a benefit of treating ASB.	Treatments varied widely with respect to timing, dosage, duration, and medication. Sulphonamides were most common treatment, but many specific antibiotic formulations are no longer used (e.g. sulfamethizole, and sulfadimethoxine). Pooled data suggested that in comparison with control (placebo/no treatment) antibiotics were associated with reduced rates of pyelonephritis (RR 0.24 95% CI: 0.14 to 0.40, 12 RCTs) and low birth weight (RR, 0.64, 95% CI: 0.46 to 0.90, 7 RCTs), but there was no clear difference in infant mortality (RR 0.98, 95% CI: 0.29 to 3.26, 6 RCTs).	Pooled analyses suggested a benefit for antibiotic treatment in resolving ASB (RR 2.99, 95% CI: 1.65 to 5.39; 6 RCTs, n=716; very low–quality evidence); a reduction in risk of low birthweight (RR 0.58, 95% CI: 0.36 to 0.94; 8 RCTs, n=1689; very low– quality evidence) and a reduced risk of preterm delivery (RR 0.34, 95% CI 0.18–0.66; 44 RCTs; n=854; low-quality evidence).

Study identifier	Nicolle 2019[14]	Smaill 2019[11]	Wingert 2019[40]	Kazemier 2015[13]
Study type	Systematic review	Systematic review	Systematic review	RCT
Population	All adults, but separate subgroup data for pregnant women with ASB	Pregnant women found, on antenatal screening, to have ASB by any definition	Pregnant women with ASB. A proportion (not specified) of women in some studies had symptomatic UTI	Women (≥18 yrs) with a singleton pregnancy and without symptoms of UTI.
Setting	Not described.	Hospital- or university-based outpatient antenatal clinics	Hospital-based clinics	8 hospitals and 5 ultrasound centres in the Netherlands
Treatment(s)	Antibiotic vs. no treatment	Any antibiotic regimen vs. placebo or no treatment	Any antibiotic regimen vs. placebo or no treatment	Ntrofurantoin (100mg twice daily) vs. placebo
Outcomes	Pyelonephritis; low birth weight; pre-term birth; serious AE	Pyelonephritis; preterm birth < 37 wks; birthweight < 2500g; persistent bacteriuria; neonatal mortality or other serious adverse neonatal outcome; maternal side effects; costs; birthweight; gestational age; women's satisfaction, as measured by trial authors	Pyelonephritis; perinatal mortality; spontaneous abortion; preterm delivery; foetal abnormalities; low birth weight; neonatal sepsis; feasibility; acceptability; cost; equity; patient values and preferences.	Primary outcome: Incidence of pyelonephritis, delivery <34 wks' gestation or a composite of both. Secondary maternal outcomes: Incidence of UTI requiring antibiotic treatment. Neonatal outcomes: Perinatal death, neonatal sepsis, severe neonatal morbidity, admission to neonatal intensive care unit, gestational age at delivery, small for gestational age and preterm birth.
Study designs	RCTs	RCTs, quasi-RCTs and cluster-RCTs	RCTs	No relevant (primary study)
ASB definition	≥1 species of bacteria in the urine ≥10^5 CFU]/ml or ≥10^8 CFU/l, irrespective of pyuria and in the absence of signs/symptoms of UTI	Usually defined as at least one clean-catch, midstream, or catheterised urine specimen with >100,000 bacteria/ml	Not defined.	≥1 × 10^5 CFU/ml of a single microorganism or if two different colony types were present - one with ≥ 1 × 10^5 CFU/ml
Last search date	July 2017	4 November 2018	October 2017	Not applicable
Included studies	20 RCTs (n=not reported)	15 RCTs (n=>5000)	11 RCTs and 4 controlled clinical trials (n=2869 in total)	RCT (n=85).
Study locations	Not described.	North America (5 RCTs); UK & Ireland (4 RCTs), Australia (3 RCTs); Netherlands (1 RCT); Denmark (1 RCT); Jamaica (1 RCT)	USA (5 studies); Australia (3 studies); UK (3 studies); and 1 study from each of following countries: Denmark, Ireland; Jamaica, Netherlands (1)	Netherlands

Study identifier	Nicolle 2019[14]	Smaill 2019[11]	Wingert 2019[40]	Kazemier 2015[13]
Findings	Antimicrobials may reduce the risk of pyelonephritis (RR 0.23, 95% CI: 0.13 to 0.41; 11 studies; n=1932) and may reduce the risk of low birth weight (RR 0.27, 95% CI: 0.11 to 0.62; 2 studies; n=242). Antimicrobials may also reduce the risk of preterm labour (RR 0.64, 95% CI: 0.45 to 0.93; 6 studies; n=1437). The included RCTs are generally old and limited by lack of allocation concealment and blinding, but all showed a consistently large effect on important outcomes. Serious adverse effects from antimicrobials almost certainly occur much less frequently than the expected reduction in pyelonephritis and preterm birth.	14/15 included trials (93%) were published between 1960 and 1987 (inclusive) and a more recent trial was published in 2015.[13] Antibiotic vs. placebo/no treatment may reduce risk of pyelonephritis (RR 0.24, 95% CI: 0.13 to 0.41; 12 studies, n=2017; low-certainty evidence); preterm birth (RR 0.34, 95% CI: 0.13 to 0.88; 3 studies, n=327; low-certainty evidence); low birthweight babies (RR 0.64, 95% CI: 0.45 to 0.93; 6 studies, n=1437 babies; low-certainty evidence). May reduce persistent bacteriuria at delivery (RR 0.30, 95% CI: 0.18 to 0.53; 4 studies; n=596). Evidence on serious adverse neonatal outcomes was inconclusive (RR 0.64, 95% CI: 0.23 to 1.79, 3 studies; n=549 babies). There were very limited data on the effect of antibiotics on other infant outcomes, and maternal adverse effects were rarely described	12 RCTs (n=2017) found a significant difference in development of pyelonephritis (RR 0.24; 95% CI: 0.13 to 0.41; I^2=60%; ARR 17.6%; NNT 6, 95% CI :5 to 7; low quality). Sensitivity analysis of 3 trials that explicitly included women without symptoms at baseline (other trials may have included some symptomatic women) did not affect the results (RR 0.22; 95% CI 0.10 to 0.49; I^2=0%). No significant difference was found between groups on perinatal mortality (RR 0.96, 95% CI: 0.27 to 3.39; I^2=56%; 6 studies n=1104; very low quality); spontaneous abortion (RR 0.60, 95% CI 0.11 to 3.10; I^2=17%; 2 studies; n=379; very low quality), neonatal sepsis (RR 0.22, 95% CI: 0.01 to 4.54; 2 studies; n=154; very low quality), preterm delivery (RR 0.22, 95%: 0.21 to 1.56, I^2=70%; 4 studies; n=533; very low quality), foetal abnormalities (RR 0.49, 95% CI 0.17 to 1.43; I^2=0%;4 studies, n=821; very low quality). There was a statistically significant difference favouring antibiotics on low birth weight (RR 0.63; 95% CI 0.45 to 0.90; I^2=20%; ARR 4.4%; NNT 23, 95% CI 15 to 85; 7 studies, n=1522; low quality). There were no reported cases of haemolytic anaemia in	Incidence of pyelonephritis was 0% versus 2.4% for the women receiving antibiotics compared with placebo, respectively (Risk difference -2.4, 95% CI: -19.2 to 14.5). Respective values for delivery before 34 wks were 2.5% and 1.0% (Risk difference-1.5, 95% CI: -15.3 to 18.5) and for the composite of both outcomes 2.5% versus 2.9% (RD -0.4, 95% CI: -3.6 to 9.4). Since the incidence estimates for all primary outcomes were lower than anticipated the trial was terminated early.

Study identifier	Nicolle 2019[14]	Smaill 2019[11]	Wingert 2019[40]	Kazemier 2015[13]
			infants (1 study, n=265; very low quality) and no study reported on maternal mortality, maternal, sepsis or maternal harms.	

Key:
AE adverse event; ARR absolute risk reduction; ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; GBS Group B Streptococcus; HRQoL health related quality of life; OR odds ratio; RCT randomised controlled trial; RR relative risk; UTI urinary tract infection; wk week

A recent Cochrane review included 15 trials recruiting over 5,000 women.[11] The majority (14/15, 93%) of the included trials were published between 1960 and 1987;the other was published during 2015.[13] Data synthesis was based on sub-groups according to treatment duration. Estimates from overall analyses suggested that antibiotics may reduce the incidence of pyelonephritis, preterm birth, low birth weight and persistent bacteriuria at the time of delivery compared with placebo or no treatment. However, this finding was not robust across all subgroups, namely those based on shorter duration of treatment for the outcomes of preterm birth and low birth weight, where between-group differences were not detected. In addition, no between-group differences were seen for the outcomes of serious neonatal adverse outcomes, birthweight, or gestational age at delivery. Data were not reported for other secondary outcomes. Most trials were judged to be at high or unclear risk of bias. There was no consideration of the distinction between older and more recent sources of evidence in relation to this being a potential source of clinical heterogeneity or having issues around applicability of findings to current practice.

Two other systematic reviews had broadly similar aims and approaches to the above.[41, 44] One included four RCTs (454 women)[41] whilst the other, considering a variety of populations with ASB, included 13 studies relevant to pregnant women (n=2,282).[44] It is unclear why only four RCTs were included in the former but this may have been explained by differences in search and study selection methods (e.g. inclusion limited to full text reports).[41] With one exception, all studies included in these two reviews were also included in the Cochrane review described above,[11] and the most recent trial highlighted above[13] was also included in these two reviews. Despite the overlap in study selection, the interpretation of results differed between the Cochrane review[11] and these two reviews in that the latter both highlighted the difference in findings between older and more recent evidence. Older primary studies tended to favour antibiotic treatment for several outcomes (including incidence of pyelonephritis) whereas the more recent evidence[13] found no difference between antibiotics and placebo for any outcome. Both reviews highlighted the low quality of evidence overall.[41, 44]

Four further systematic reviews were used to inform clinical practice guidelines,[10, 14, 39, 40] one of which focused on the treatment of group B streptococcal bacteriuria in pregnancy.[10]

The treatment trials included in three of the systematic reviews that informed guidelines[14, 39, 40] were the same as those retrieved by the systematic reviews with a small number of exceptions. One review found some evidence to suggest that antibiotic treatment of ASB detected by urine culture results in neonatal and maternal benefits (including reduced incidence of pyelonephritis) but noted that most data were dated and did not reflect current practice. In addition, it was noted that data on adverse effects were sparse and trials were underpowered to detect between-group differences in rarely occurring outcomes.[39]

A marked feature of all of the above systematic reviews is that with one exception, included evidence dates back to the 1960s, 1970s and 1980s, with the most recent paper published in 1987; also, many studies are performed in countries dissimilar to the UK in terms of environment, culture and economic development. Several of the above reviews included the one recent study conducted in the Netherlands and published in 2015.[13] As this setting has potential, current relevance to the UK, this study is now considered in further detail.

Kazemier et al. conducted a prospective cohort study with an embedded RCT.[13] Pregnant women with a positive screen result from a single dipslide test for ASB were invited to participate in an RCT comparing nitrofurantoin (100mg twice daily for five days) (n=40 women) with identical placebo (n=45 women). The women were tested again with the dipslide test one week after the end of treatment. Participants with a second positive test result were given another round of active treatment or placebo to match their first round. The primary outcome was defined as incidence of pyelonephritis, delivery before 34 weeks' gestation or a composite of both. Secondary maternal outcomes included incidence of UTI requiring antibiotic treatment and the following neonatal outcomes: perinatal death, neonatal sepsis, severe neonatal morbidity, admission to neonatal intensive care unit, gestational age at delivery, being small for gestational age and preterm birth. Results reported in terms of risk difference with 95% confidence interval for each outcome suggested no between-group difference for any outcome. Incidence of pyelonephritis was 0% versus 2.4% for the women receiving antibiotics compared with placebo, respectively. Respective values for delivery before 34 weeks were 2.5% and 1.0% and for the composite of both outcomes 2.5% versus 2.9%. Since the incidence estimates for all primary outcomes were lower than anticipated the trial was terminated early.

Discussion of findings

Assessment of risk of bias

The systematic reviews were assessed using ROBIS[26] A narrative outline of the assessment is provided below together with summary tabulation (Table 16). Full details of the risk of bias assessment are provided in Appendix 3.

Table 16: Question 4 – summary of risk of bias assessment in systematic reviews (ROBIS)[26]

Each domain was judged as at low, high or unclear risk of bias

Assessment domain	**Allen 2018[10]**	**Angelescu 2016[41]**	**Henderson 2019[39]**	**Koves 2017[44]**	**Nicolle 2019[14]**	**Smaill 2019[11]**	**Wingert 2019[40]**
Domain 1: Study eligibility criteria	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Low risk	High risk
Domain 2: Identification & selection of studies	Unclear risk	High risk	Low risk	High risk	Unclear risk	Low risk	Unclear risk
Domain 3: Data collection & study appraisal	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Domain 4: Synthesis & findings	Unclear risk	Low risk	Low risk	High risk	Unclear risk	Unclear risk	Low risk
Overall rating of bias	**Unclear risk of bias**	**High risk of bias**	**High risk of bias**	**High risk of bias**	**Unclear risk of bias**	**Unclear risk of bias**	**High risk of bias**

Four reviews had an overall high risk of bias[39-41, 44] and three were unclear.[10, 11, 14]

Of those deemed to be at high risk of bias, one restricted inclusion to full text reports without explaining the rationale for this or the potential impact on retrieval of relevant evidence. The search strategy did not include all relevant search terms and an unexplained date restriction was applied. Statistical heterogeneity was apparent in some meta-analyses and was not explored.[44] Another review failed to use a fully expanded list of search terms meaning that relevant material may have been missed (and this was evidenced in the low retrieval of eligible studies relative to other reviews conducted during a similar period).[41] The two other reviews applied language restrictions therefore the possibility of language bias could not be discounted,[39, 40] and one of these also limited selection to full text reports.[40]

One of the reviews judged to be at unclear risk of bias overall was a Cochrane review which was generally well conducted however, details of exploring the robustness of findings were not clear. The planned sensitivity analysis (based on the primary studies' overall risk of bias) was not carried out and this omission was not explained. Most results were stratified according to subgroups based on small numbers of participants which made interpretation of findings difficult.[11] The remaining two reviews were assigned an unclear risk of risk overall as they included insufficient detail of review methods in relation to three[14] and all[10] of the four domains.

The primary study was assessed using the Cochrane risk of bias tool for RCTs.[27] A narrative outline of the assessment is provided below together with summary tabulation (Table 17). Full details of the risk of bias assessment are provided in Appendix 3.

Table 17: Question 4 – summary of risk of bias assessment in primary study (Cochrane Risk of Bias Tool)[27]

Each domain was assessed as low, unclear or high risk of bias

Kazemier 2015[13]		
Bias	**Domain**	**Decision**
Selection bias	**Random sequence generation**	Low risk
	Allocation concealment	Low risk
Performance bias	**Blinding of participants**	Low risk
	Blinding of caregivers	Low risk
Detection bias	**Blinding of outcome assessment**	Low risk
Attrition bias	**Incomplete outcome data**	Low risk
Reporting bias	**Selective reporting**	Low risk
Other bias	**Other sources of bias**	Unclear risk
Summary of risk of bias		**Unclear risk of bias**

The primary study was judged to have a low risk of selection bias (computer-generated randomisation list administered by an independent trial manager), performance bias (identical placebo used), detection bias and attrition bias (data from all randomised participants were included in the analysis).[13] Data were reported for all specified outcomes. However, this RCT terminated earlier than planned because of lower than anticipated incidence of some outcomes. Overall, this risk of bias in this RCT was unclear due to the early termination.

Conclusions

Seven systematic reviews[10, 11, 14, 39-41, 44] and a small RCT[13] were identified for this question. The reviews were of high or unclear overall risk of bias and the RCT had an overall unclear risk of bias.

One recent Cochrane review concluded that antibiotics were effective in reducing the incidence of pyelonephritis (relative risk reduction [RRR] 76%, ARR 17.6% and NNT 6, 95% CI 5 to 7), preterm birth (RRR 66%, ARR and NNT not reported) and low birth weight (RRR 36%, ARR 4.4% and NNT 23, 95% CI 15 to 85) however it failed to distinguish between older and more recent sources of evidence. The other reviews observed that older evidence (of questionable relevance to current practice) was more likely to report results in favour of antibiotics whereas the more recent studies did not observe any between-group differences.

Most of the evidence included in the systematic reviews dated back to the 1960s, 1970s and 1980s and have serious methodological problems and there are concerns about the applicability of their findings to current health care settings. The included RCT (published in 2015) was conducted in the Netherlands and did not detect any differences in maternal or neonatal outcomes between participants receiving antibiotics or placebo. This RCT terminated early because of low incidence of the primary outcomes as well as low uptake of antibiotics in pregnant women; it therefore provided limited information to inform current practice in the UK.

Summary of findings relevant to criterion 9: criterion not met

Quantity: Seven systematic reviews including 15 unique RCTs (recruiting around 2,000 women) between them that compared antibiotics with placebo or no intervention for the treatment of confirmed ASB in pregnant women were identified.

Quality: The reviews were of high or unclear overall risk of bias. Within the reviews, the primary studies were rated as low quality according to GRADE assessment.

Applicability: Most of the studies included in the systematic reviews were published during the 1960s, 1970s and 1980s. In addition, many studies were performed in countries dissimilar to the UK. One recent RCT (published in 2015) was conducted in the Netherlands and did not detect any differences in maternal or neonatal outcomes between participants receiving antibiotics or placebo. This RCT terminated early because of low incidence of the primary outcomes and therefore provided limited information to inform current practice in the UK.

Consistency: Several different antibiotic drugs and regimens were considered in the reviews and so this is a clinically heterogeneous body of evidence overall. In addition, duration of antibiotic therapy varied. In a Cochrane review, some meta-analyses were based on sub-groups of trials according to treatment duration. Whilst this makes sense clinically, it made for small numbers of participants in some analyses, rendering the estimates difficult to interpret. Authors of some reviews noted differential findings in older and more recent sources of evidence, with older studies tending to favour antibiotics in relation to various outcomes (including incidence of pyelonephritis) whilst the most recent RCT (which assessed a comprehensive range of outcomes) did not detect between-group differences for any outcome.

Conclusions: One recent Cochrane review concluded that antibiotics were effective in reducing the incidence of pyelonephritis (RRR 76%, ARR 17.6% and NNT 6, 95% CI 5 to 7), preterm birth (RRR 66%, ARR and NNT not reported) and low birth weight (RRR 36%, ARR 4.4% and NNT 23, 95% CI 15 to 85), however it failed to distinguish between older and more recent sources of evidence. Six other reviews observed that older evidence was more likely to report results in favour of antibiotics whereas the more recent evidence did not observe any between-group differences. Findings should be treated with caution because of the low quality of the primary studies and variable quality of the systematic reviews. It is doubtful that that most of these findings are applicable to current practice in the UK because of locations and timings of much of the available evidence.

Criterion 12 — The complete screening programme (test, diagnostic procedures, treatment/intervention) is acceptable to pregnant women

12: 'There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.'

Overarching question 5 – How benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy?

Specific questions:

How benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy?

How do women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy?

The most recent relevant NICE guidance (published in 2008)[5] recommends that women with uncomplicated pregnancies should be offered routine screening for ASB early in pregnancy. The rationale for this is that early identification and treatment of the condition with antibiotics may reduce the risk of pyelonephritis.[5] The UK NSC review protocol states that of interest in this question is how women weigh the benefits and harms of screening and any subsequent antibiotic treatment, when making the decision to go for ASB screening. This question was not considered in the previous 2017 UKNSC review.[20]

This question aimed to examine how acceptable the complete ASB screening programme (including testing and treatment with antibiotic) is to women who are pregnant in the UK. A further aim was to explore the acceptability of antibiotic treatment in general in pregnancy. More specific aspects of acceptability included how women perceive the benefits and harms of screening or treatment; and their willingness to take part.

Eligibility for inclusion in the review

Systematic reviews and qualitative studies, including those using mixed methods, surveys and cross-sectional designs, to assess any screening programme were eligible for inclusion. The intention was to prioritise evidence from studies published from 1990 onwards assessing ASB screening programmes, but other screening and treatment programmes in pregnant women may also be considered. Studies had to report at least one of the following outcomes in order to be included: relative weight/utilities of benefit and harms of screening or treatment; willingness to be screened and/or treated; and any

qualitative information. Selection of studies was limited to those reported in English language and publications from 1990 onwards to ensure the relevance of the evidence to current UK settings. Full details of the study eligibility criteria are provided in Table 6, including specific outcome definitions.

Description of the evidence

In the current review, nine papers were identified through title and abstract screening as potentially relevant to question 5. After further full text review, only two were included, including one systematic review[40] and one primary study.[13]

The systematic review did not focus solely on the UK population, but considered evidence from any country. Similarly, the primary study did not report on a UK population, but instead reported on pregnant women from the Netherlands, which could be considered similar to the UK. Further details of the included studies are outlined below and detailed data extraction tables can be found in Appendix 3.

The systematic review[40] assessed the effectiveness of the screening and treatment of ASB, and patient preferences. Multiple databases (including Medline, CINAHL and PsycINFO) were searched from inception to September 2017. Any study that examined screening or antibiotic treatment during pregnancy where women were asked to balance the benefits and harms of screening and treatment for ASB, or to state/choose their willingness to be screened and treated was included. Studies had to report outcomes related to the weighing of benefits and harms of screening and treatment and how this may affect womens' 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). Other outcomes included anxiety.

The primary study[13] was a multicentre prospective cohort with an embedded randomised trial. The study included pregnant women (aged ≥18 years) with a singleton pregnancy (16- and 22-weeks' gestation) recruited at eight hospitals and five ultrasound centres in the Netherlands. The women (n=5,621) were offered screening for ASB which was not routinely available in the Netherlands. All women who tested positive for ASB (n=255) were eligible to enter a randomised controlled trial to compare treatment with nitrofurantoin or placebo for five days.

The systematic review identified no studies that examined how women weigh the benefits and harms of screening and/or treatment of ASB in pregnancy or how their valuation of benefits and harms informs their decision to undergo screening and treatment. However, six surveys and one propospective cohort study provided information on women's opinions

on either drug utilisation or perceptions of teratogenic risk (none considered complete screening programmes, i.e. testing and treatment). Two were in UK populations.[45, 46] and four were from UK relevant countries including one multinational survey,[47] one prospective cohort study from the Netherlands,[13] and surveys from Spain[48] and Norway.[#3380} These studies are summarised in Table 18.

Table 18: Question 5 – summary of studies included in systematic review of the effectiveness of the screening and treatment of ASB, and patient preferences (Wingert 2019)[40]

Study name, citation and study design	Aim	Population and location	Findings
UK studies			
Butters 1990[45] Butters L, Howie CA. Awareness among pregnant women of the effect on the fetus of commonly used drugs. Midwifery 1990;6(3):146-54. Cross-sectional face-to-face survey	To assess women's knowledge of the effects of commonly used drugs on the foetus.	Postnatal women (n=514) in wards of two maternity units (Glasgow, UK) between October 1987 and April 1988 *[NOTE: data collection is before 1990]*	48% (246/514) of women would not take an antibiotic prescribed by their doctor and 49% (254/514) said they would. Responses were similar for all ages and social classes; strong relationship ($p < 0.0001$) between avoiding analgesic and avoiding antibiotic.
Twigg 2016[46] Twigg MJ, Lupattelli A, Nordeng H. Women's beliefs about medication use during their pregnancy: a UK perspective. Int J Clin Pharm 2016;38(4):968-76. Cross-sectional internet-based survey	To describe beliefs and risk perception associated with medicines use for the treatment of common acute conditions among UK women.	Women who were pregnant or within 1 year of giving birth (n=856) responding to a questionnaire though two UK support websites for pregnant women and new mothers from 15th November 2011 to 15th January 2012	17.1% (n=191) of women experienced a UTI and of which 65.4% (125/191) received unspecified antibiotic. Of these 60.8% (76/125) reported prescribed or OTC use. 6.3% (n=70) said they would avoid taking any medication (not limited to antibiotics) during pregnancy/ endure as long as possible before taking medication.
Studies from other UK relevant countries			
Kazemier 2015[13] Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de	To assess the maternal and neonatal consequences of treated and untreated	Pregnant women ≥18 years (n=5,621) with a singleton pregnancy (16- and 22-weeks' gestation) recruited at eight	94% (155/163) of women who tested positive for ASB did not want to participate in a subsequent linked RCT of antibiotic treatment

Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis 2015;15(11):1324-33. Multicentre prospective cohort	asymptomatic bacteriuria in pregnancy.	hospitals and five ultrasound centres in the Netherlands between 11 October 2011 and 10 June 2013	(nitrofurantoin), because they did not want to receive antibiotics during pregnancy for an asymptomatic condition
Lupattelli 2014[47] Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health behavior during pregnancy. Patient Educ Couns 2014;96(2):171-8. Cross-sectional internet-based survey	To investigate the association between health literacy and perception of medication risk (teratogenic), beliefs about medications, use and non-adherence to prescribed pharmacotherapy during pregnancy	Pregnant woman (n=4999) between 1 October 2011 and 29 February 2012 across 18 countries: Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, UK, USA	Women (low/medium health literacy) more likely non-adherent to prescribed antibiotics - penicillin (low: 3.5%, medium: 3.7%, high: 2.2%, p-value < 0.01); perceived risk of penicillin had highest correlation with health literacy (Rho=-0.216) in model.*
Nordeng 2010[49] Nordeng H, Ystrøm E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol 2010;66(2):207-14. Cross-sectional internet-based survey	To evaluate the perception of risk of 17 commonly used drugs and other substances by pregnant women and which sources of information on exposures during pregnancy were most used	Pregnant women or mothers (children ≤ 5yrs) 1,793 between mid-September 2008 to October 2008, University of Oslo's (Norway) website.	16.6% (297/1793) reported using penicillin during pregnancy. Mean perception risk score in those using penicillin = 3.0 and 4.6 in those not using penicillin**
Sanz 2001[48] Sanz E, Gómez-López T, Martínez-Quintas MJ. Perception of teratogenic risk of common medicines. European Journal of Obstetrics and Gynecology and	To assess the perception of the teratogenic risk of common medications (includes amoxycillin and erythromycin) by professionals and lay people.	Medics (15 GPs; 10 gynaecologists) and 81 pregnant women attending regular obstetric clinic and 63 non-pregnant women from obstetric/ gynaecological clinic	Mean value of 'perceived teratogenic risk' of erythromycin was 55.6% in non-pregnant women and 38.7% in pregnant women (true risk was <5%); and of amoxycillin was 49.3% in non-pregnant women and

Reproductive Biology 2001;95(1):127-31. Cross-sectional face-to-face survey		in Tenerife, Spain. Dates NR.	40.4% in pregnant women (true risk was <5%).^
Key: GP general practitioner: NR not reported; OTC over the counter; RCT randomised controlled trial; yr year			
* Using numerical risk scoring system to measure the perceived risk of medications to the foetus; measured on a scale of 0 ('not harmful to the foetus') to 10 ('very harmful to the foetus'). Mean scores for antibiotics (penicillin) were 6.55 (low health literacy); 5.97 (medium health literacy); 4.25 (high health literacy). ** Using a numeric rating scale ranging from 0 (no risk to the foetus) to 10 (foetal malformation after every exposure ^ Using a Visual Analogue Scale (VAS) using 10 cm horizontal line with a short vertical line at each end, one marked 0% and the other 100%. Participants were asked to mark on the scale what they thought the potential risk for major malformations was (between 0% - lowest and 100% - highest).			

Two small UK studies reported on antibiotic use as part of much broader surveys about womens' use of commonly used drugs during pregnancy.[45, 46] One older survey (n=514) from 1990 reported that 48% (246/514)[45] of women attending a postnatal clinic would not take antibiotics prescribed by their doctor (for any reason), compared with 49% (254/514) who said they would. In the second larger (n=856) more recent survey,[46] 17.1% (n=191) of pregnant women/new mothers reported experiencing a UTI for which only 65.4% (125/191) received antibiotic treatment (type of antibiotic not reported). Neither survey reported on the specific reasons behind any decision not to take antibiotics.

Of the four non-UK studies, two surveys (n=81[48] and n=1793[49]) suggested that women thought penicillin posed a risk to their unborn child and a further study suggested this may be linked to low/medium health literacy.[47] The final non-UK study[40] was a multicentre prospective cohort study that provided specific information on antibiotic use in ASB. This study from the Netherlands, was also identified as an included primary study for this rapid review.[13] The study reported that 94% (155/163) of women who tested positive for ASB did not want to participate in the randomised controlled trial of antibiotic treatment (nitrofurantoin) because they did not want to receive antibiotics during pregnancy for an asymptomatic condition.[13]

None of the studies from the UK or the other relevant non-UK countries reported on how womens' attitudes may inform their decisions about screening for ASB and there was no information on the accuracy or understanding of information about the potential risks and benefits of ASB screening and treatment.

Discussion of findings

Assessment of risk of bias

The risk of bias of the systematic review[40] as assessed using the ROBIS tool for the assessment of the risk of bias within systematic reviews. A narrative outline of the assessment is provided below together with summary tabulation (Table 19). Full details of the risk of bias assessment are provided in Appendix 3.

Table 19 Question 5 – summary of risk of bias assessment in systematic reviews (ROBIS tool for assessing the risk of bias in systematic reviews)
Each checklist item was judged for each study and one of the following responses assigned: Probably Yes, Yes, Probably No, No, or Not enough information. The risk of bias was assigned one of the following responses: Low risk; High risk; Unclear risk. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Wingert 2019[40]	
Domain	**Overall domain rating**
Domain 1: Study eligibility criteria	High risk
Domain 2: Identification and selection of studies	Unclear risk
Domain 3: Data collection and study appraisal	Low risk
Domain 4: Synthesis and findings	Low risk
OVERALL RATING OF RISK OF BIAS	
Question	**Rating**
Did the interpretation of findings address all the concerns identified in domains 1 to 4?	Unclear risk
Was the relevance of identified studies to the review's research question appropriately considered?	Low risk
Did the reviewers avoid emphasising results on the basis of their statistical significance?	Low risk
UNCLEAR RISK OF BIAS	

Across the four domains assessed by the ROBIS tool, the systematic review was judged as at low risk of bias in two (Domain 3 and 4), high risk in one (Domain 1) and unclear risk in another (Domain 2). The review was judged at a high risk of bias for domain 1 (study eligibility criteria) as it may have missed relevant data by limiting inclusion to only studies published in English or French; and conference abstracts were not sought leading to an unclear risk of bias for domain 2 (identification and selection of studies). However, the review was judged as at an unclear risk of bias overall for the purposes of this rapid review.

Using the Oxford Hierarchy of Evidence (levels the level of evidence[38] was rated as level 2a (systematic review of level 2b studies and lower).[15] Full details of the risk of bias assessment are presented in Appendix 3

The risk of bias of the primary study from the Netherlands[13] was assessed using the JBI checklist for cohort studies. A narrative outline of the assessment is provided below together with summary tabulation (Table 20). Full details of the risk of bias assessment are provided in Appendix 3.

Table 20: Question 5 – summary of risk of bias assessment in primary studies (JBI checklist for cohort studies)

Each checklist item was judged for each study and one of the following responses assigned: Yes, No, Unclear or Not applicable. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review. Full details of the risk of bias assessment are presented in Appendix 3

JBI checklist item (cohort studies)	**Kazemier 2015[13]**
1. Were the 2 groups similar & recruited from the same population?	Yes
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	Yes
5. Were strategies to deal with confounding factors stated?	Yes
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes
10. Were strategies to address incomplete follow up utilised?	Yes
11. Was appropriate statistical analysis used?	Yes
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias)
Abbreviations: ASB asymptomatic bacteriuria; JBI Joanna Briggs Institute	

The study was judged as at ‘low risk of bias’ for the all of the checklist items with the exception of the topic specific criterion relating to the number of consecutive voided urine samples obtained, as only one urine sample was gathered for each participant.

Overall, the level of evidence[38] was rated as Level 1b (prospective cohort study with good follow-up).[13]

Conclusions

The studies (one systematic review and one primary study from the Netherlands) do not provide sufficiently robust evidence to recommend a screening programme for ASB in pregnant women in the UK. The 2017 UKNSC review did not assess evidence for this criterion. This update review found no strong evidence of the acceptability of screening (including subsequent antibiotic treatment) to pregnant women. No evidence was found on how the benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy; or how women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy. The only available information was from a systematic review of cross-sectional data from surveys (only two surveys were performed in the UK) and one study in the Netherlands assessing women's opinions on drug utilisation and their perceptions of teratogenic risk associated with various drugs including antibiotics. None of the studies considered screening programmes (i.e. testing and treatment). Given the lack of evidence, this criterion is therefore not met.

Summary of Findings Relevant to Criterion 12: criterion not met

Quantity: One systematic review reporting on six studies including five surveys and one prospective cohort study were included; the cohort study was also identified as an included primary study. None of the studies reported on how the benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy; or how women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy. The only available information reported on women's opinions on drug utilisation and their perceptions of teratogenic risk associated with antibiotics.

Quality: The risk of bias in the systematic review was unclear but the included studies concerning women's opinions on antibiotic use and teratogenic risk were likely at high risk of bias and were lower level evidence. The cohort study was also considered lower level evidence.

Applicability: Only two of the six studies included in the systematic review were based in the UK and one used data pre-1990; the remaining four were in UK relevant countries. This presents challenges for generalising to current practice in the UK. The cohort data came from a study (published in 2015) conducted in the Netherlands, where testing and treatment of ASB is not usually available.

Consistency: The only data available was on women's opinions of antibiotic treatment and their perceptions on the teratogenic risk posed by antibiotics. Though there was little information available beyond the numbers of women expressing an opinion (i.e. no further investigation of reasons behind the opinions), the findings appeared to all suggest that women were reluctant to take antibiotics during pregnancy and the risks posed to the foetus appeared to be potentially one reason for this decision.

Conclusions: No evidence was found on the benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy; or how women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy. There was some low-level evidence (from surveys) available from one previous systematic review and some data from a cohort study which appeared to suggest that women may be reluctant to undergo antibiotic treatment for ASB during pregnancy. However, these findings should be treated with caution because of the low quality of the studies and unclear quality of the systematic review. In addition, there are difficulties in applying most findings to current practice in the UK because of locations and timings of most of the available evidence.

Review summary

Conclusions and implications for policy

Based on the review of evidence against the UK NSC criteria, the evidence base remains insufficient to recommend a UK systematic population antenatal screening programme for asymptomatic bacteriuria. The main reasons for this are the sparse volume of current and relevant data to inform each key review question within the UK context and the generally poor methodological quality of the available evidence. Research is needed to explore the value of screening in preventing negative pregnancy outcomes.

Three non-UK primary studies were identified to address question 1 (burden of disease associated with ASB in pregnancy).[13, 15, 33] There was inconsistent evidence across two studies that ASB was associated with an increase in the incidence of pyelonephritis.[13, 33] Evidence from one study suggested an association between ASB and incidence of symptomatic UTI requiring antibiotic treatment during pregnancy.[13] When considering data from all three studies, there was no evidence of an association between ASB and increased risk of perinatal mortality, neonatal sepsis, preterm birth, mean gestational age at delivery, frequency of neonates being small for gestational age, neonatal morbidity or admission to the neonatal intensive care unit. These studies were at high risk of bias and had limited applicability to the UK. No data were available for the following outcomes: maternal mortality, maternal sepsis, recurrence of ASB and low birth weight and this makes for an important gap in the evidence base.

Question 2 addressed the performance of different screening tests to detect ASB in pregnancy. One systematic review[35] (including 27 studies) and one primary study not included in the review[12] were identified. All the primary studies included in the systematic review and the independent evaluation evaluated onsite (or 'rapid') tests compared against urine culture as the reference standard. A wide range of index tests was evaluated in the primary studies, urine dipstick being the most frequently evaluated. None of the studies assessed urine culture as an index test although current NICE antenatal care guidance states that pregnant women should be offered routine screening for ASB using culture of a mid-stream urine specimen during early gestation. The timing and national settings of studies varied considerably, and most were not relevant to current practice in the UK. The results overall suggested that whilst the index tests often had acceptable specificity (92% or above in most studies), sensitivity was much more variable (15% to 100%) meaning that a substantial proportion of true positive cases could be missed. The systematic review[35] and the primary study[12] were at high risk of bias. There is currently no evidence to support the use of onsite tests within a screening programme for ASB in pregnancy in the UK. Further

research is required of adequate methodological quality and of clear relevance to the UK setting.

There is a lack of available data to inform population screening strategies for ASB in pregnancy in the UK (question 3). Findings from three systematic reviews (including four unique cohort studies between them) focusing on screening and treatment of ASB suggested that screening reduced the risk of pyelonephritis by 72% (RR 0.28 [95% CI 0.15 to 0.54], ARR 1.3% and NNS 77 [95% CI 65 to 121]) when compared with no screening but there was no difference between one-time screening and frequent screening for this outcome.[39-41] There was no difference between screening and no screening for perinatal mortality, spontaneous abortion earlier than 28 weeks and preterm birth. The risk of experiencing preterm birth was increased by 57% (RR 1.57 [95% CI 1.11 to 2.23]) for women in the frequently screened group experienced compared with one-time screening. This may have been explained by more women in the frequent screening group having gestational diabetes compared with those in the one-time screening group (9% versus 4%).[2] Some relevant outcomes were not reported in any of the four studies, including maternal mortality, maternal sepsis, neonatal sepsis and low birth weight. Omission of these key outcomes represents a gap in the evidence base. The review authors rated all four primary studies as having very low quality. All three reviews were at high risk of bias overall. Given the paucity of data the benefits and harms of implementing an antenatal ASB screening programme in the UK remain uncertain. Current and relevant cost effectiveness data are also required. However, good-quality estimates on prevalence, test accuracy, treatment effectiveness and screening uptake in relation to ASB in pregnancy in the UK would be required before any cost-effectiveness analysis could be undertaken.

Seven systematic reviews[10, 11, 14, 39-41, 44] and an RCT[13] were identified for question 4 (benefits and harms of antibiotic treatment for ASB in pregnancy). Evidence emerging from the systematic reviews revealed the disparity between older and more recent sources of evidence with older studies indicating a benefit of antibiotics for some outcomes (incidence of pyelonephritis, preterm birth and low birth weight) and the recent evidence suggesting no difference between antibiotics and placebo. Most of the studies included in the systematic reviews were of low quality, performed in countries dissimilar to the UK and dated back to the 1960s, 1970s and 1980s. In particular, the lack of current research impedes the potential to apply the main body of evidence to current practice. The standard of antenatal care in developed countries has changed considerably during the last 40 to 50 years and it is likely that outcomes observed during the 1960s and 1970s will not apply currently. Furthermore, there is much more awareness and concern now about the potential for adverse effects of antibiotic treatment both for the mother and infant, including antimicrobial resistance arising from inappropriate use of these drugs.[39] It should be noted that the more recent evidence only amounts to the above-noted Dutch RCT published in 2015.[13] This

RCT did not detect any differences in any maternal or neonatal outcome between participants receiving antibiotics versus placebo or no treatment, however it was likely to be statistically underpowered. This RCT terminated early because of low incidence of the primary outcomes, which may in itself be of importance to the understanding of ASB and pyelonephritis in a modern antenatal setting but means that the findings provide limited information to inform current practice in the UK. Four reviews were at high risk of bias overall and three were unclear. The application of the evidence to inform a treatment protocol within a screening programme for antenatal ASB in the UK remains uncertain given the very sparse recent evidence relevant to the UK.

Finally, very few data were identified to address question 5 on how information about the benefits and harms of screening and treatment inform women's decisions to undergo screening for ASB in pregnancy. One systematic review and one primary study were identified. Only two of the six studies included in the systematic review were based in the UK, one of which included data gathered prior to 1990. The remaining four were conducted in UK relevant countries. including one prospective cohort study from the Netherlands with an embedded RCT which has been described earlier (for questions 1 and 4).[13] This study reported that 94% (155/163) of women who tested positive for ASB did not want to participate in the RCT of antibiotic treatment (nitrofurantoin) versus placebo as they did not want to receive antibiotics during pregnancy for an asymptomatic condition.[13] Therefore, there are currently no studies reporting on how the benefits and harms of screening and treatment inform women's decisions to undergo screening for ASB infections during pregnancy; or how women might weigh up the benefits and harms of a screening and treatment for ASB during pregnancy. The only available information reported on women's opinions on antibiotic utilisation and their perceptions of teratogenic risk associated with antibiotics. These data came from low quality studies only two of which used a UK population (one pre-1990). This is an evidence gap that warrants further investigation in future well-designed, UK based studies, which also seek to identify the reasoning and motivation behind women's views on ASB screening and treatment.

Limitations

Study selection was limited to research reports published in English language. This may have introduced a language bias for some of the research questions (Q3, Q4, Q5) which were not limited to UK relevant data. However throughout, this series of rapid reviews has sought to prioritise data relevant to UK practice so this may not have a significant impact on the findings of the rapid reviews. This said data from some European countries which could be considered sufficiently similar to the UK may have been missed using this strategy.

Study selection was also restricted by date: 1990 and later for questions 1 and 5; and 2003 and later for questions 2, 3 and 4. Whilst these thresholds can be considered as arbitrary, they were applied to ensure that evidence of most relevance to current practice was identified.

Appendix 1 — Search strategy

Systematic reviews/Guidelines

MEDLINE and In-Process & Other Non-Indexed Citations (Ovid): 1946 to December 30, 2019 Searched: 31.12.19

1 Bacteriuria/ (7596)
2 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (5931)
3 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (1551)
4 or/1-3 (11069)
5 exp Guideline/ or exp Guidelines as Topic/ or Guideline Adherence/ or Health Planning Guidelines/ (207118)
6 Critical Pathways/ or Clinical Protocols/ or Consensus/ (45358)
7 Consensus Development Conferences as Topic/ or Consensus Development Conferences, NIH as Topic/ (2776)
8 guideline$.ti. (72801)
9 guidance.ti,ab. (103318)
10 (clinical adj3 (pathway or pathways)).ti,ab. (5711)
11 (practice adj3 (parameter or parameters)).ti,ab. (1505)
12 (care pathway or care pathways).ti,ab. (3854)
13 consensus development conference$.pt. (11717)
14 or/5-13 (375363)
15 4 and 14 (223)
16 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ (196579)
17 (Systematic Review or Meta-Analysis).pt. (178844)
18 ((systematic$ or methodologic$) adj3 (review$ or overview$ or synthes$)).ti,ab. (167589)
19 ((quantitative or integrative) adj3 (review$ or overview$ or synthes$)).ti,ab. (8456)
20 (pool$ adj3 (data or analy$)).ti,ab. (33359)
21 (evidence based review$ or structured analysis or evidence synthesis or evidence syntheses).ti,ab. (6137)
22 (mantel haenszel or peto or der simonian or dersimonian or fixed effect$ or latin square$).ti,ab. (24415)
23 (met analy$ or metanaly$ or metaanaly$ or meta regression$ or metaregression$ or meta synthes$ or metasynthes$ or technology assessment$ or HTA or HTAs or technology appraisal$).ti,ab. (18827)
24 (comparative adj3 (efficacy or effectiveness)).ti,ab. (11793)
25 (selection criteria or inclusion criteria or exclusion criteria).ab. (121425)
26 search strategy.ti,ab. (16400)
27 (systematic literature adj (search$ or synthesis or syntheses)).ti,ab. (7606)
28 (systematic$ adj2 search$).ab. (31155)
29 (medline or pubmed or cochrane or embase or cinahl or psyc?lit or psyc?info or science citation index or electronic databases or online databases or literature databases or bibliographic databases).ab. (220664)

30 (handsearch$ or hand search$).ti,ab. (8769)
31 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. (1910)
32 or/16-31 (466684)
33 4 and 32 (290)
34 15 or 33 (477)
35 limit 34 to english language (418)
36 limit 35 to yr="1990 -Current" (409)

Pragmatic guidelines filter based on:
Search Filters for Various Databases: Ovid Medline. Guidelines/Recommendations (revised 12/3/2015). Available from:
http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters

Pragmatic systematic reviews filter based on:
Strings attached: CADTH database search filters: Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO [Internet]. Ottawa: CADTH; 2016. [cited 2019 Oct 18]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst

Embase (Ovid): 1974 to 2019 December 27
Searched: 31.12.19

1 bacteriuria/ (6799)
2 asymptomatic bacteriuria/ (1827)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (6885)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (2083)
5 or/1-4 (11821)
6 (clinical adj3 pathway).ti,ab,kw. (5642)
7 (clinical adj3 pathways).ti,ab,kw. (4999)
8 (practice adj3 parameter).ti,ab,kw. (742)
9 (practice adj3 parameters).ti,ab,kw. (1581)
10 care pathway.ti,ab,kw. (4641)
11 care pathways.ti,ab,kw. (3705)
12 guidance.ti,ab. (154761)
13 guideline*.ti. (98658)
14 practice guideline/ or clinical pathway/ or clinical protocol/ or consensus development/ or nursing protocol/ (512942)
15 or/6-14 (690871)
16 5 and 15 (562)
17 exp meta-analysis/ (177970)
18 "systematic review"/ (228500)
19 "meta analysis (topic)"/ (41000)
20 "systematic review"/ (228500)
21 "systematic review (topic)"/ (24274)
22 biomedical technology assessment/ (14010)
23 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kw. (12341)
24 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw. (221521)

25 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw. (35998)
26 (data synthes* or data extraction* or data abstraction*).ti,ab,kw. (31558)
27 (handsearch* or hand search*).ti,ab,kw. (10830)
28 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw. (32916)
29 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw. (14459)
30 (meta regression* or metaregression*).ti,ab,kw. (10319)
31 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (460445)
32 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (274217)
33 (cochrane or (health adj2 technology assessment) or evidence report).jw. (25980)
34 (comparative adj3 (efficacy or effectiveness)).ti,ab,kw. (18820)
35 (outcomes research or relative effectiveness).ti,ab,kw. (13047)
36 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw. (3902)
37 or/17-36 (649591)
38 5 and 37 (431)
39 16 or 38 (916)
40 animal/ (1443094)
41 animal experiment/ (2459357)
42 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6606345)
43 or/40-42 (6606345)
44 exp human/ (20354003)
45 human experiment/ (477213)
46 or/44-45 (20355426)
47 43 not (43 and 46) (5095701)
48 39 not 47 (906)
49 limit 48 to (english language and yr="1990 -Current") (820)

Pragmatic guidelines filter based on:
Search Filters for Various Databases: Ovid MEDLINE. Guidelines/Recommendations (revised 12/3/2015). Available from:
http://libguides.sph.uth.tmc.edu/search_filters/ovid_medline_filters

Pragmatic systematic reviews filter based on:
Strings attached: CADTH database search filters: Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO [Internet]. Ottawa: CADTH; 2016. [cited 2019 Oct 18]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 12 of 12, December 2019 Searched: 31.12.19
#1 MeSH descriptor: [Bacteriuria] explode all trees 487
#2 MeSH descriptor: [Asymptomatic Infections] explode all trees 21
#3 bacteri*:ti,ab,kw 39837

#4 #2 and #3 12
#5 (bacteriuria* or bacilluria* or bacteruria*):ti,ab,kw 1130
#6 (bacteria* NEAR/2 (urin* or bladder* or kidney* or genitourin* or urogenita*)):ti,ab,kw 186
#7 #1 or #4 or #5 or #6 1280

CDSR = 27
CDSR Protocols = 1

KSR Evidence (Internet): database last updated 31 December 2019
www.ksrevidence.com
Searched: 31.12.19

1	(bacteriuria* or bacilluria* or bacteruria*) in All text	67
2	bacteria* AND (urin* OR bladder* OR kidney* OR genitourin* OR urogenital*) in All text	185
3	#1 or #2	229
4	pregnan* OR antenatal* OR "ante natal" OR ante-natal OR prenatal* OR "pre natal" OR pre-natal in All text	5507
5	expect* AND (women OR woman OR female* OR mother* OR mum OR mums or mom or moms or lady or ladies) in All text	766
6	#4 or #5	6055
7	#3 and #6	22

Database last updated 31 Dec 2019, 11:18 a.m.

NICE Evidence (Internet) 2015 – 31 December 2019
https://www.evidence.nhs.uk/
Searched: 31.12.19

Search terms filtered to Guidance and Policy / Secondary Evidence 01/01/2015-31/12/2019	**Results**
“Bacteriuria”	117
“bacilluria”	0
“bacteruria”	6
Total (duplicate removed)	122/123

Guidelines International Network (GIN) Library (Internet): up to 31 December 2019
http://www.g-i-n.net
Searched: 31.12.19

Search terms	**Results**
bacteriuria* OR bacilluria* OR bacteruria*	2
pyelonephrit*	2
Total	4

ECRI Institute Guidelines Trust (Internet): up to 31 December 2019
https://guidelines.ecri.org/
Searched: 31.12.19
bacteriuria OR bacilluria OR bacteruria OR pyelonephritis
10 records retrieved

Q1: What is the disease burden associated with ASB?

Medline and In-Process & Other Non-Indexed Citations (Ovid): 1946 - 31 December 2019
Searched: 2.1.20

1 Bacteriuria/ (7596)
2 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (5932)
3 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (1551)
4 or/1-3 (11070)
5 exp Pyelonephritis/ (14522)
6 (pyelonephriti$ or (pyelo adj2 nephriti$)).ti,ab. (12671)
7 or/5-6 (19005)
8 exp Pregnancy/ (877598)
9 exp Pregnancy Complications/ (417380)
10 Prenatal Care/ (26628)
11 Pregnant Women/ (7826)
12 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (552690)
13 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums)).ti,ab. (4034)
14 or/8-13 (1041495)
15 absenteeism/ (8905)
16 caregivers/ (34675)
17 ((human$ or Social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (Burden$ or Consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,ot,hw. (113346)
18 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$ or diseas$)).ti,ab,ot,hw. (18704)
19 (llsi or ((emergenc$ or domestic$ or famil$ or carer$ or caregiver$) adj3 leave$)).ti,ab,ot,hw. (1046)
20 (burden adj2 (illness$ or disease$ or sickness$)).ti,ab,ot,hw. (23421)
21 ((allowance or status or long-term or pension$ or benefit$) adj2 (disab$ or incapacit$)).ti,ab,ot,hw. (12062)
22 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,ot,hw. (1773)
23 ((resource$ or fund$) adj2 (use$ or utilis?ation)).ti,ab,ot,hw. (21097)
24 ("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ti,ab,ot,hw. (113872)
25 ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention$ or trip or trips or visit$ or stay$ or admission$ or admitted or transport$)).ti,ab,ot,hw. (153980)
26 ((GP or general practitioner$ or doctor$ or clinician$ or specialist$ or physician$ or p?ediatrician$) adj2 (appointment$ or attention or trip or trips or visit$)).ti,ab,ot,hw. (12615)
27 (in-patient stay$ or inpatient stay$).ti,ab,ot,hw. (2587)
28 or/15-27 (454921)
29 Incidence/ (252957)
30 exp Morbidity/ (536395)
31 Mortality/ or Fatal Outcome/ or Hospital Mortality/ or Survival Rate/ (304119)
32 prevalence/ (280343)
33 Demography/ (60193)
34 Epidemiology/ (12271)
35 disease progression/ (156301)

36 (occurrence$ or incidence$ or prevalence$ or episode$ or mortalit$ or morbidit$ or epidemiolog$ or demograph$).ti,ab,ot. (2785000)
37 or/29-36 (3235383)
38 4 and 28 (197)
39 (4 or 7) and 14 and 37 (763)
40 38 or 39 (946)
41 exp animals/ not humans/ (4657106)
42 40 not 41 (925)
43 limit 42 to english language (757)
44 limit 43 to yr="1990 -Current" (582)
45 exp United Kingdom/ (359336)
46 (national health service* or nhs*).ti,ab,in. (178208)
47 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (92307)
48 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in. (1966726)
49 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (1320673)
50 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (51478)
51 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (197111)
52 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (24278)
53 or/45-52 (2531944)

54 (exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/) (2790583)
55 53 not 54 (2390186)
56 44 and 55 (42)

UK geographic filter:
NICE UK geographic filter. [Changed MeSH: Great Britain to United Kingdom]. Ayiku L, Levay P, Hudson T, Craven J, Barrett E, Finnegan A, Adams R. The medline UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID medline. Health Info Libr J 2017;34(3):200-16

Medline Epub Ahead of Print, Daily Update (Ovid): up to 31 December 2019
Searched: 2.1.20
1 Bacteriuria/ (4)
2 Asymptomatic Infections/ and exp Bacteria/ (0)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (60)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (19)
5 or/1-4 (77)
6 exp Pyelonephritis/ (5)
7 (pyelonephriti$ or (pyelo adj2 nephriti$)).ti,ab. (97)
8 or/6-7 (97)
9 exp Pregnancy/ (660)
10 exp Pregnancy Complications/ (354)
11 exp Prenatal Care/ (46)
12 Pregnant Women/ (26)
13 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (8756)
14 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (90)
15 or/9-14 (9057)
16 absenteeism/ (1)
17 caregivers/ (68)
18 ((human$ or Social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (Burden$ or Consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,ot,hw. (3007)
19 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$ or diseas$)).ti,ab,ot,hw. (401)
20 (llsi or ((emergenc$ or domestic$ or famil$ or carer$ or caregiver$) adj3 leave$)).ti,ab,ot,hw. (26)
21 (burden adj2 (illness$ or disease$ or sickness$)).ti,ab,ot,hw. (777)
22 ((allowance or status or long-term or pension$ or benefit$) adj2 (disab$ or incapacit$)).ti,ab,ot,hw. (351)
23 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,ot,hw. (17)
24 ((resource$ or fund$) adj2 (use$ or utilis?ation)).ti,ab,ot,hw. (499)
25 ("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ti,ab,ot,hw. (1992)
26 ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention$ or trip or trips or visit$ or stay$ or admission$ or admitted or transport$)).ti,ab,ot,hw. (3720)

27 ((GP or general practitioner$ or doctor$ or clinician$ or specialist$ or physician$ or p?ediatrician$) adj2 (appointment$ or attention or trip or trips or visit$)).ti,ab,ot,hw. (227)
28 (in-patient stay$ or inpatient stay$).ti,ab,ot,hw. (127)
29 or/16-28 (10281)
30 incidence/ or prevalence/ or mortality/ or "cause of death"/ or fatal outcome/ or hospital mortality/ or survival rate/ (1289)
31 Demography/ (17)
32 Epidemiology/ (4)
33 Disease Progression/ (276)
34 Morbidity/ (32)
35 (occurrence$ or incidence$ or prevalence$ or episode$ or mortalit$ or morbidit$ or epidemiolog$ or demograph$).ti,ab,ot. (53219)
36 or/30-35 (53785)
37 5 and 29 (6)
38 (5 or 8) and 15 and 36 (10)
39 or/37-38 (16)
40 exp animals/ not (exp animals/ and humans/) (2666)
41 39 not 40 (16)
42 limit 41 to (english language and yr="1990 -Current") (16)

Embase: 1974 – 30 December 2019
Searched: 31.12.19
1 bacteriuria/ (6799)
2 asymptomatic bacteriuria/ (1830)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (6887)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (2085)
5 or/1-4 (11825)
6 exp pyelonephritis/ (20536)
7 (pyelonephriti$ or (pyelo adj2 nephriti$)).ti,ab. (14524)
8 or/6-7 (23384)
9 exp pregnancy/ (646363)
10 exp pregnancy complication/ (118393)
11 exp prenatal care/ (145758)
12 pregnant woman/ (74144)
13 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (699620)
14 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (5198)
15 or/9-14 (991731)
16 Productivity/ (38044)
17 Absenteeism/ (16814)
18 Caregiver Burden/ (7299)
19 Caregiver/ (76522)
20 Work Disability/ (5091)
21 ((human$ or social$ or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,ot,hw. (161807)

22 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,ot,hw. (14319)
23 (llsi or ((emergenc$ or domestic$ or famil$ or carer$ or caregiver$) adj3 leave$)).ti,ab,ot. (1040)
24 (burden adj2 (illness$ or disease$ or sickness$)).ti,ab,ot,hw. (47240)
25 ((allowance or status or long-term or pension$ or benefit$) adj2 (disab$ or incapacit$)).ti,ab,ot,hw. (25494)
26 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,ot,hw. (2605)
27 ((resource$ or fund$) adj2 (use$ or utili?ation)).ti,ab,ot,hw. (46589)
28 ((health or healthcare) adj2 (resource$ or fund$)).ti,ab,ot,hw. (40740)
29 ("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ti,ab,ot,hw. (194533)
30 ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention$ or trip or trips or visit$ or stay$ or admission$ or admitted or transport$)).ti,ab,ot,hw. (391894)
31 ((GP or general practitioner$ or doctor$ or clinician$ or specialist$ or physician$) adj2 (appointment$ or attention$ or trip or trips or visit$)).ti,ab,ot,hw. (19441)
32 (in-patient stay$ or inpatient stay$).ti,ab,ot,hw. (5358)
33 or/16-32 (932353)
34 incidence/ (383199)
35 standardized incidence ratio/ (2751)
36 Prevalence/ (682224)
37 standardized mortality ratio/ (2764)
38 demography/ (207469)
39 epidemiological data/ (31902)
40 mortality/ (728824)
41 disease progression/ (76527)
42 disease activity/ (75193)
43 morbidity/ (332443)
44 (occurrence$ or incidence$ or prevalence$ or episode$ or mortalit$ or morbidit$ or epidemiolog$ or demograph$).ti,ab,ot. (3975370)
45 or/34-44 (4564594)
46 5 and 33 (469)
47 (5 or 8) and 15 and 45 (1182)
48 46 or 47 (1616)
49 animal/ (1443098)
50 animal experiment/ (2462255)
51 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6609608)
52 or/49-51 (6609608)
53 exp human/ (20368111)
54 human experiment/ (477798)
55 or/53-54 (20369534)
56 52 not (52 and 55) (5098704)
57 48 not 56 (1592)
58 conference$.pt,st,so. (4458597)
59 57 not 58 (1263)

60 limit 59 to (english language and yr="1990 -Current") (939)
61 United Kingdom/ (380748)
62 (national health service* or nhs*).ti,ab,in,ad. (332765)
63 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (41046)
64 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jx,in,ad. (3079349)
65 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad. (2364124)
66 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad. (96424)
67 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad. (326834)
68 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad. (43709)
69 or/61-68 (3748881)
70 (exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (exp united kingdom/ or europe/) (2993237)
71 69 not 70 (3542106)
72 60 and 71 (122)

UK geographic filter:
Ayiku L, Levay P, Hudson T, Craven J, Finnegan A, Adams R, Barrett E. The Embase UK filter: validation of a geographic search filter to retrieve research about the UK from OVID Embase. Health Info Libr J 2019;36(2):121-33

Q2: What is the performance of screening tests for detecting ASB infections in pregnancy?

Q3: What are the benefits and harms of screening compared with no screening for ASB in pregnancy?

Medline and In-Process & Other Non-Indexed Citations (Ovid): 1946 to December 31. 2019
Searched: 2.1.20

1 Bacteriuria/ (7596)
2 Asymptomatic Infections/ and exp Bacteria/ (293)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (5932)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (1551)
5 or/1-4 (11336)
6 exp Pregnancy/ (877598)
7 exp Pregnancy Complications/ (417380)
8 exp Prenatal Care/ (26628)
9 Pregnant Women/ (7826)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (552690)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (4062)
12 or/6-11 (1041496)
13 exp Mass Screening/ (124658)
14 exp Prenatal Diagnosis/ (72709)
15 "Diagnostic Techniques and Procedures"/ (3216)
16 exp Urogenital system/ and Physical Examination/ (1534)
17 exp Urinalysis/ (7838)
18 Antibody-Coated Bacteria Test, Urinary/ (148)
19 Microbial Sensitivity Tests/ (124380)
20 Predictive Value of Tests/ (197050)
21 Diagnostic Equipment/ (557)
22 Reagent Strips/ (3334)
23 "Sensitivity and Specificity"/ (341625)
24 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (10259892)
25 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (15989)
26 (urinalys$ or uriscreen$).ti,ab. (7890)
27 (microscopy or micro scopy).ti,ab. (436999)
28 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (2522)
29 "point of care testing"/ (1487)
30 (point of care or bedside).ti,ab. (43304)
31 or/13-30 (10687355)
32 5 and 12 and 31 (864)
33 limit 32 to (english language and yr="2003 -Current") (330)

Medline Epub Ahead of Print, Daily Update (Ovid): up to December 31, 2019
Searched: 2.1.20

1 Bacteriuria/ (4)

2 Asymptomatic Infections/ and exp Bacteria/ (0)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (60)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (19)
5 or/1-4 (77)
6 exp Pregnancy/ (660)
7 exp Pregnancy Complications/ (354)
8 exp Prenatal Care/ (46)
9 Pregnant Women/ (26)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (8756)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (90)
12 or/6-11 (9057)
13 exp Mass Screening/ (138)
14 exp Prenatal Diagnosis/ (68)
15 "Diagnostic Techniques and Procedures"/ (2)
16 exp Urogenital system/ and Physical Examination/ (1)
17 exp Urinalysis/ (3)
18 Antibody-Coated Bacteria Test, Urinary/ (0)
19 Microbial Sensitivity Tests/ (165)
20 Predictive Value of Tests/ (261)
21 Diagnostic Equipment/ (0)
22 Reagent Strips/ (1)
23 "Sensitivity and Specificity"/ (237)
24 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (182526)
25 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (255)
26 (urinalys$ or uriscreen$).ti,ab. (170)
27 (microscopy or micro scopy).ti,ab. (5532)
28 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (22)
29 "point of care testing"/ (23)
30 (point of care or bedside).ti,ab. (1160)
31 or/13-30 (185641)
32 5 and 12 and 31 (5)
33 limit 32 to (english language and yr="2003 -Current") (3)

Embase: 1974 – 30 December 2019
Searched: 31.12.19

1 bacteriuria/ (6799)
2 asymptomatic bacteriuria/ (1830)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (6887)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (2085)
5 or/1-4 (11825)
6 exp pregnancy/ (646363)
7 exp pregnancy complication/ (118393)
8 exp prenatal care/ (145758)
9 pregnant woman/ (74144)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (699620)

11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (5198)
12 or/6-11 (991731)
13 exp screening/ (671496)
14 diagnostic procedure/ (84745)
15 exp urogenital system examination/ (357487)
16 exp urinalysis/ (103018)
17 antibody-coated bacteria test/ (5)
18 microbial sensitivity test/ (9195)
19 predictive value/ (161092)
20 diagnostic kit/ (5930)
21 test strip/ (3973)
22 "sensitivity and specificity"/ (344247)
23 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (13437360)
24 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (23568)
25 (urinalys$ or uriscreen$).ti,ab. (13266)
26 (microscopy or micro scopy).ti,ab. (497839)
27 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (3462)
28 "point of care testing"/ (12553)
29 (point of care or bedside).ti,ab. (65337)
30 exp prenatal diagnosis/ (105356)
31 or/13-30 (14087482)
32 5 and 12 and 31 (1121)
33 conference$.pt,st,so. (4458597)
34 32 not 33 (948)
35 limit 34 to (english language and yr="2003 -Current") (490)

Q4: What are the benefits and harms of antibiotic treatment compared with no treatment for ASB in pregnancy?
Medline and In-Process & Other Non-Indexed Citations: 1974 – 31 December 2019
Searched: 2.1.20

1 Bacteriuria/ (7596)
2 Asymptomatic Infections/ and exp Bacteria/ (293)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (5932)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (1551)
5 or/1-4 (11336)
6 exp Pregnancy/ (877598)
7 exp Pregnancy Complications/ (417380)
8 exp Prenatal Care/ (26628)
9 Pregnant Women/ (7826)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (552690)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (4062)
12 or/6-11 (1041496)
13 exp Anti-Bacterial Agents/ (713345)

14 exp Antibiotic Prophylaxis/ (13492)
15 Anti-Infective Agents, Urinary/ (2662)
16 (antibiotic$ or anti biotic$ or antimicrobial$ or anti microbial$ or antimycobacterial$ or anti mycobacterial$ or antiviral$ or anti viral$ or antivirus$ or anti virus$ or antibacteria$ or anti bacteria$ or bacterium or bacteriocidal$ or microbial$).ti,ab. (755581)
17 Amoxicillin/ (9332)
18 (Amoxicot or Amoxicillin or actimoxi or amoclen or amolin or amopen or amopenixin or amoxibiotic or amoxil or AMPC or apo-amoxi or clamyoxyl or dispermox or efpenix or flemoxin or hiconcil or ibiamox or imacilin or larotid or moxacin or moxal or moxatag or moxilin or moxtag or ospamox or pamoxicillin or penamox or polymox or trimox or wymox).ti,ab,rn. (22223)
19 Nitrofurantoin/ (2620)
20 (Berkfurin or Furadantin or furadoine or furadonine or Furalan or furantoin or Macrobid or Macrodantin or Nitrofurantoin or Nitro Macro or Urantoin).ti,ab,rn. (4534)
21 Trimethoprim/ (6464)
22 (Abacin or Abaprim or Alprim or Apo-Sulfatrim or Bactin or Bactramin or Bactrim or Baktar or Chemotrim or Co-Trim$ or Comox or Cotrim$ or Drylin or Eusaprim or Fectrim or Gantaprim or Gantrim or Idotrim or Imexim or Instalac or Ipral or Kepinol or Laratrim or Lidaprim or Linaris or Methoprim or Microtrim or Monoprim or Monotrim$ or Nopil or Oraprim or Priloprim or Primosept or Primsol or Proloprim or Septra or Septrin or Sigaprim or Sulfameth$ or Sulfatrim or Sulfotrim or Sulmeprim or Sulprim or Sumetrolim or Supracombin or Suprim or Syraprim or Teleprim or Thiocuran or Tiempe or Tmp-Ratiopharm or tmp smx or Trigonyl or Trimanyl or Trimesulf or Trimeth-Sulfa or Trimethioprim or Trimethopriom or Trimetoprim or Trimexazole or trimezole or Trimogal or Trimopan or Trimpex or Triprim or Unitrim or Uretrim or Uro-Septra or Uroplus or Wellcoprim).ti,ab,rn. (23494)
23 Cephalexin/ (2049)
24 (Alcephin or Alexin or Alsporin or Biocef or Carnosporin or Cefa-iskia or Cefablan or Cefadal or Cefadin or Cefadina or Cefaleksin or cefalexin or Cefalin or Cefaloto or Cefaseptin or Cefax or Ceforal or Cefovit or Celexin or Cepastar or Cepexin or Cephacillin or cephalexin or Cephanasten or Cephaxin or Cephin or Cepol or Ceporex$ or Check or Cophalexin or Durantel or Ed A-Ceph or Erocetin or Factagard or Felexin or Fexin or Ibilex or Ibrexin or Inphalex or Kefalospes or Keflet or Keflex or Kefolan or Keforal or Keftab or Kekrinal or Kidolex or L-Keflex or Lafarine or Larixin or Lenocef or Lexibiotico or Lonflex or Lopilexin or Madlexin or Mamalexin or Mamlexin or Medoxine or Neokef or Neolexina or Novolexin or Nufex or Oracef or Oriphex or Oroxin or Ortisporina or Ospexin or Palitrex or Panixine Disperdose or Pectril or Pyassan or Roceph or Sanaxin or Sartosona or Sencephalin or Sepexin or Servispor or Sialexin or Sinthecillin or Sporicef or Sporidex or Syncl or Syncle or Synecl or Tepaxin or Tokiolexin or Uphalexin or Voxxim or Winlex or Zozarine).ti,ab,rn. (53306)
25 Fosfomycin/ (1956)
26 (fosfomycin$ or 883A or BRN 1680831 or fosfocina or fosfomicin or fosfomicina or fosfomicina or fosfonomycin$ or infectophos or Levo-phosphonomycin or MK-955 or phosphomycin or phosphonomycin or 23155-02-4 or 78964-85-9 or monurol or veramina).ti,ab,rn. (3346)
27 Amdinocillin Pivoxil/ (220)
28 (pivmecillinam$ or Amdinocillin pivoxil or coactabs or penomax or fl 1039 or fl1039 or Ro 10-9071 or selexid or 32886-97-8).ti,ab,rn. (326)
29 Amoxicillin-Potassium Clavulanate Combination/ (2521)
30 (co amoxiclav or coamoxiclav or (amox$ adj2 clav$) or augmentin or brl 25000 or brl25000 or clavulin or spektramox or synulox).ti,ab,rn. (6990)

31 (Abactrim or Acuco or Agoprim or Alfatrim or Aposulfatrim or Bacteral or Bacterial forte or bactifor or Bactilen or Bactiver or Bacton or Bactoreduct or Bactrim or Bactrizol or Bactromin or Bactropin or Baktrisid-DS or Berlocid or Bibacrim or Biseptol or Centrim or Chemitrim or Ciplin or Cotribene or cotrimoxazole or Cotriver or Dibaprim or Diseptyl or Duon or Duratrimet or Eltrianyl or Escoprim or Esteprim or Gantaprin or Groprim or Helveprim or Jenamoxazol or Kemoprim or Maxtrim or Mikrosid or Momentol or Omsat or Oriprim or Oxaprim or Pantoprim or Primazole or Septrim or Servitrim or Sigaprin or Strepto-Plus or trimoxazole$).ti,ab,rn. (6137)
32 (Acilin or adobacillin or alpen or amblosin or Amcill or amfipen or Aminobenzylpenicillin or amipenix or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil$ or ampicin or ampifarm or ampikel or Ampimed or Ampipenin or Ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or aztreonam$ or binotal or bonapicillin or britacil or campicillin or cefadroxil$ or cefepime$ or ceftibuten$ or ceftri?xone$ or cefuroxime$ or cephalosporin$ or cephradine$ or cimex or clindamycin$ or copharcilin or cycloserine$ or delcillin or deripen or divercillin or doktacillin or duphacillin or gentam?cin$ or grampenil or guicitrina or lifeampil or morepen or norobrittin or olin kid or omnipen or orbicilina or nalidixic acid$ or pen ampil or penbrisol or penbritin or penbrock or penicillin$ or penbritin or penicline or penimic or pensyn or pentrex$ or pfizerpen or piperacillin$ pivampicillin$ or polycillin or ponecil or princillin or principen or qidamp or sulfadimethoxine$ or sulfadiazine$ or sulfamethizole$ or sulfamethoxazole$ or sulfamethoxypyridazine$ or sulfonamide$ or sulphadimidine$ or sulphonamide$ or tetracycline$ or vancomycin$).ti,ab,rn,hw. (288679)
33 or/13-32 (1344463)
34 5 and 12 and 33 (672)
35 exp animals/ not (exp animals/ and humans/) (4657106)
36 34 not 35 (670)
37 limit 36 to (english language and yr="2003 -Current") (242)

Medline and In-Process & Other Non-Indexed Citations: 1974 – 31 December 2019
Searched: 2.1.20

1 Bacteriuria/ (4)
2 Asymptomatic Infections/ and exp Bacteria/ (0)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (60)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (19)
5 or/1-4 (77)
6 exp Pregnancy/ (660)
7 exp Pregnancy Complications/ (354)
8 exp Prenatal Care/ (46)
9 Pregnant Women/ (26)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (8756)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (90)
12 or/6-11 (9057)
13 exp Anti-Bacterial Agents/ (584)
14 exp Antibiotic Prophylaxis/ (14)
15 Anti-Infective Agents, Urinary/ (0)
16 (antibiotic$ or anti biotic$ or antimicrobial$ or anti microbial$ or antimycobacterial$ or anti mycobacterial$ or antiviral$ or anti viral$ or antivirus$ or anti virus$ or antibacteria$ or anti bacteria$ or bacterium or bacteriocidal$ or microbial$).ti,ab. (11880)

17 Amoxicillin/ (8)
18 (Amoxicot or Amoxicillin or actimoxi or amoclen or amolin or amopen or amopenixin or amoxibiotic or amoxil or AMPC or apo-amoxi or clamyoxyl or dispermox or efpenix or flemoxin or hiconcil or ibiamox or imacilin or larotid or moxacin or moxal or moxatag or moxilin or moxtag or ospamox or pamoxicillin or penamox or polymox or trimox or wymox).ti,ab,rn. (276)
19 Nitrofurantoin/ (1)
20 (Berkfurin or Furadantin or furadoine or furadonine or Furalan or furantoin or Macrobid or Macrodantin or Nitrofurantoin or Nitro Macro or Urantoin).ti,ab,rn. (59)
21 Trimethoprim/ (1)
22 (Abacin or Abaprim or Alprim or Apo-Sulfatrim or Bactin or Bactramin or Bactrim or Baktar or Chemotrim or Co-Trim$ or Comox or Cotrim$ or Drylin or Eusaprim or Fectrim or Gantaprim or Gantrim or Idotrim or Imexim or Instalac or Ipral or Kepinol or Laratrim or Lidaprim or Linaris or Methoprim or Microtrim or Monoprim or Monotrim$ or Nopil or Oraprim or Priloprim or Primosept or Primsol or Proloprim or Septra or Septrin or Sigaprim or Sulfameth$ or Sulfatrim or Sulfotrim or Sulmeprim or Sulprim or Sumetrolim or Supracombin or Suprim or Syraprim or Teleprim or Thiocuran or Tiempe or Tmp-Ratiopharm or tmp smx or Trigonyl or Trimanyl or Trimesulf or Trimeth-Sulfa or Trimethioprim or Trimethopriom or Trimetoprim or Trimexazole or trimezole or Trimogal or Trimopan or Trimpex or Triprim or Unitrim or Uretrim or Uro-Septra or Uroplus or Wellcoprim).ti,ab,rn. (252)
23 Cephalexin/ (0)
24 (Alcephin or Alexin or Alsporin or Biocef or Carnosporin or Cefa-iskia or Cefablan or Cefadal or Cefadin or Cefadina or Cefaleksin or cefalexin or Cefalin or Cefaloto or Cefaseptin or Cefax or Ceforal or Cefovit or Celexin or Cepastar or Cepexin or Cephacillin or cephalexin or Cephanasten or Cephaxin or Cephin or Cepol or Ceporex$ or Check or Cophalexin or Durantel or Ed A-Ceph or Erocetin or Factagard or Felexin or Fexin or Ibilex or Ibrexin or Inphalex or Kefalospes or Keflet or Keflex or Kefolan or Keforal or Keftab or Kekrinal or Kidolex or L-Keflex or Lafarine or Larixin or Lenocef or Lexibiotico or Lonflex or Lopilexin or Madlexin or Mamalexin or Mamlexin or Medoxine or Neokef or Neolexina or Novolexin or Nufex or Oracef or Oriphex or Oroxin or Ortisporina or Ospexin or Palitrex or Panixine Disperdose or Pectril or Pyassan or Roceph or Sanaxin or Sartosona or Sencephalin or Sepexin or Servispor or Sialexin or Sinthecillin or Sporicef or Sporidex or Syncl or Syncle or Synecl or Tepaxin or Tokiolexin or Uphalexin or Voxxim or Winlex or Zozarine).ti,ab,rn. (876)
25 Fosfomycin/ (4)
26 (fosfomycin$ or 883A or BRN 1680831 or fosfocina or fosfomicin or fosfomicina or fosfomicina or fosfonomycin$ or infectophos or Levo-phosphonomycin or MK-955 or phosphomycin or phosphonomycin or 23155-02-4 or 78964-85-9 or monurol or veramina).ti,ab,rn. (58)
27 Amdinocillin Pivoxil/ (0)
28 (pivmecillinam$ or Amdinocillin pivoxil or coactabs or penomax or fl 1039 or fl1039 or Ro 10-9071 or selexid or 32886-97-8).ti,ab,rn. (12)
29 Amoxicillin-Potassium Clavulanate Combination/ (2)
30 (co amoxiclav or coamoxiclav or (amox$ adj2 clav$) or augmentin or brl 25000 or brl25000 or clavulin or spektramox or synulox).ti,ab,rn. (88)
31 (Abactrim or Acuco or Agoprim or Alfatrim or Aposulfatrim or Bacteral or Bacterial forte or bactifor or Bactilen or Bactiver or Bacton or Bactoreduct or Bactrim or Bactrizol or Bactromin or Bactropin or Baktrisid-DS or Berlocid or Bibacrim or Biseptol or Centrim or Chemitrim or Ciplin or Cotribene or cotrimoxazole or Cotriver or Dibaprim or Diseptyl or Duon or Duratrimet or Eltrianyl or Escoprim or Esteprim or Gantaprin or Groprim or Helveprim or Jenamoxazol or Kemoprim or

Maxtrim or Mikrosid or Momentol or Omsat or Oriprim or Oxaprim or Pantoprim or Primazole or Septrim or Servitrim or Sigaprin or Strepto-Plus or trimoxazole$).ti,ab,rn. (52)
32 (Acilin or adobacillin or alpen or amblosin or Amcill or amfipen or Aminobenzylpenicillin or amipenix or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil$ or ampicin or ampifarm or ampikel or Ampimed or Ampipenin or Ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or aztreonam$ or binotal or bonapicillin or britacil or campicillin or cefadroxil$ or cefepime$ or ceftibuten$ or ceftri?xone$ or cefuroxime$ or cephalosporin$ or cephradine$ or cimex or clindamycin$ or copharcilin or cycloserine$ or delcillin or deripen or divercillin or doktacillin or duphacillin or gentam?cin$ or grampenil or guicitrina or lifeampil or morepen or norobrittin or olin kid or omnipen or orbicilina or nalidixic acid$ or pen ampil or penbrisol or penbritin or penbrock or penicillin$ or penbritin or penicline or penimic or pensyn or pentrex$ or pfizerpen or piperacillin$ pivampicillin$ or polycillin or ponecil or princillin or principen or qidamp or sulfadimethoxine$ or sulfadiazine$ or sulfamethizole$ or sulfamethoxazole$ or sulfamethoxypyridazine$ or sulfonamide$ or sulphadimidine$ or sulphonamide$ or tetracycline$ or vancomycin$).ti,ab,rn,hw. (2021)
33 or/13-32 (13841)
34 5 and 12 and 33 (8)
35 exp animals/ not (exp animals/ and humans/) (2666)
36 34 not 35 (8)
37 limit 36 to (english language and yr="2003 -Current") (6)

Embase: 1974 – 30 December 2019
Searched: 31.12.19
1 bacteriuria/ (6799)
2 asymptomatic bacteriuria/ (1830)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (6887)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (2085)
5 or/1-4 (11825)
6 exp pregnancy/ (646363)
7 exp pregnancy complication/ (118393)
8 exp prenatal care/ (145758)
9 pregnant woman/ (74144)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (699620)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (5198)
12 or/6-11 (991731)
13 exp antibiotic agent/ (1406369)
14 exp antibiotic prophylaxis/ (30493)
15 exp urinary tract antiinfective agent/ or exp urinary tract agent/ (634688)
16 (antibiotic$ or anti biotic$ or antimicrobial$ or anti microbial$ or antimycobacterial$ or anti mycobacterial$ or antiviral$ or anti viral$ or antivirus$ or anti virus$ or antibacteria$ or anti bacteria$ or bacterium or bacteriocidal$ or microbial$).ti,ab. (960129)
17 amoxicillin/ (61014)
18 (Amoxicot or Amoxicillin or actimoxi or amoclen or amolin or amopen or amopenixin or amoxibiotic or amoxil or AMPC or apo-amoxi or clamyoxyl or dispermox or efpenix or flemoxin or hiconcil or ibiamox or imacilin or larotid or moxacin or moxal or moxatag or moxilin or moxtag or ospamox or pamoxicillin or penamox or polymox or trimox or wymox).ti,ab,rn. (69098)

19 nitrofurantoin/ (14911)
20 (Berkfurin or Furadantin or furadoine or furadonine or Furalan or furantoin or Macrobid or Macrodantin or Nitrofurantoin or Nitro Macro or Urantoin).ti,ab,rn. (15210)
21 trimethoprim/ (25940)
22 (Abacin or Abaprim or Alprim or Apo-Sulfatrim or Bactin or Bactramin or Bactrim or Baktar or Chemotrim or Co-Trim$ or Comox or Cotrim$ or Drylin or Eusaprim or Fectrim or Gantaprim or Gantrim or Idotrim or Imexim or Instalac or Ipral or Kepinol or Laratrim or Lidaprim or Linaris or Methoprim or Microtrim or Monoprim or Monotrim$ or Nopil or Oraprim or Priloprim or Primosept or Primsol or Proloprim or Septra or Septrin or Sigaprim or Sulfameth$ or Sulfatrim or Sulfotrim or Sulmeprim or Sulprim or Sumetrolim or Supracombin or Suprim or Syraprim or Teleprim or Thiocuran or Tiempe or Tmp-Ratiopharm or tmp smx or Trigonyl or Trimanyl or Trimesulf or Trimeth-Sulfa or Trimethioprim or Trimethopriom or Trimetoprim or Trimexazole or trimezole or Trimogal or Trimopan or Trimpex or Triprim or Unitrim or Uretrim or Uro-Septra or Uroplus or Wellcoprim).ti,ab,rn. (96207)
23 cefalexin/ (16473)
24 (Alcephin or Alexin or Alsporin or Biocef or Carnosporin or Cefa-iskia or Cefablan or Cefadal or Cefadin or Cefadina or Cefaleksin or cefalexin or Cefalin or Cefaloto or Cefaseptin or Cefax or Ceforal or Cefovit or Celexin or Cepastar or Cepexin or Cephacillin or cephalexin or Cephanasten or Cephaxin or Cephin or Cepol or Ceporex$ or Check or Cophalexin or Durantel or Ed A-Ceph or Erocetin or Factagard or Felexin or Fexin or Ibilex or Ibrexin or Inphalex or Kefalospes or Keflet or Keflex or Kefolan or Keforal or Keftab or Kekrinal or Kidolex or L-Keflex or Lafarine or Larixin or Lenocef or Lexibiotico or Lonflex or Lopilexin or Madlexin or Mamalexin or Mamlexin or Medoxine or Neokef or Neolexina or Novolexin or Nufex or Oracef or Oriphex or Oroxin or Ortisporina or Ospexin or Palitrex or Panixine Disperdose or Pectril or Pyassan or Roceph or Sanaxin or Sartosona or Sencephalin or Sepexin or Servispor or Sialexin or Sinthecillin or Sporicef or Sporidex or Syncl or Syncle or Synecl or Tepaxin or Tokiolexin or Uphalexin or Voxxim or Winlex or Zozarine).ti,ab,rn. (98201)
25 fosfomycin/ (9444)
26 (fosfomycin$ or 883A or BRN 1680831 or fosfocina or fosfomicin or fosfomicina or fosfomicina or fosfonomycin$ or infectophos or Levo-phosphonomycin or MK-955 or phosphomycin or phosphonomycin or 23155-02-4 or 78964-85-9 or monurol or veramina).ti,ab,rn. (10314)
27 pivmecillinam/ (987)
28 (pivmecillinam$ or Amdinocillin pivoxil or coactabs or penomax or fl 1039 or fl1039 or Ro 10-9071 or selexid or 32886-97-8).ti,ab,rn. (1016)
29 amoxicillin plus clavulanic acid/ (37207)
30 (co amoxiclav or coamoxiclav or (amox$ adj2 clav$) or augmentin or brl 25000 or brl25000 or clavulin or spektramox or synulox).ti,ab,rn. (16656)
31 cotrimoxazole/ (77925)
32 (Abactrim or Acuco or Agoprim or Alfatrim or Aposulfatrim or Bacteral or Bacterial forte or bactifor or Bactilen or Bactiver or Bacton or Bactoreduct or Bactrim or Bactrizol or Bactromin or Bactropin or Baktrisid-DS or Berlocid or Bibacrim or Biseptol or Centrim or Chemitrim or Ciplin or Cotribene or cotrimoxazole or Cotriver or Dibaprim or Diseptyl or Duon or Duratrimet or Eltrianyl or Escoprim or Esteprim or Gantaprin or Groprim or Helveprim or Jenamoxazol or Kemoprim or Maxtrim or Mikrosid or Momentol or Omsat or Oriprim or Oxaprim or Pantoprim or Primazole or Septrim or Servitrim or Sigaprin or Strepto-Plus or trimoxazole$).ti,ab,rn. (77926)
33 (Acilin or adobacillin or alpen or amblosin or Amcill or amfipen or Aminobenzylpenicillin or amipenix or ampi-bol or ampi-co or ampi-tab or ampichel or ampicil$ or ampicin or ampifarm or

ampikel or Ampimed or Ampipenin or Ampiscel or ampisyn or ampivax or ampivet or amplacilina or amplin or amplipenyl or amplisom or amplital or ampy-penyl or austrapen or aztreonam$ or binotal or bonapicillin or britacil or campicillin or cefadroxil$ or cefepime$ or ceftibuten$ or ceftri?xone$ or cefuroxime$ or cephalosporin$ or cephradine$ or cimex or clindamycin$ or copharcilin or cycloserine$ or delcillin or deripen or divercillin or doktacillin or duphacillin or gentam?cin$ or grampenil or guicitrina or lifeampil or morepen or norobrittin or olin kid or omnipen or orbicilina or nalidixic acid$ or pen ampil or penbrisol or penbritin or penbrock or penicillin$ or penbritin or penicline or penimic or pensyn or pentrex$ or pfizerpen or piperacillin$ pivampicillin$ or polycillin or ponecil or princillin or principen or qidamp or sulfadimethoxine$ or sulfadiazine$ or sulfamethizole$ or sulfamethoxazole$ or sulfamethoxypyridazine$ or sulfonamide$ or sulphadimidine$ or sulphonamide$ or tetracycline$ or vancomycin$).ti,ab,rn,hw. (490720)
34 or/13-33 (2554831)
35 5 and 12 and 34 (915)
36 animal/ (1443098)
37 animal experiment/ (2462255)
38 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6609608)
39 or/36-38 (6609608)
40 exp human/ (20368111)
41 human experiment/ (477798)
42 or/40-41 (20369534)
43 39 not (39 and 42) (5098704)
44 35 not 43 (911)
45 conference$.pt,st,so. (4458597)
46 44 not 45 (786)
47 limit 46 to (english language and yr="2003 -Current") (407)

Q5: How do benefits and harms of screening and treatment inform womens' decisions to undergo screening for ASB in pregnancy?

Medline and In-Process & Other Non-Indexed Citations (Ovid): 1946– 31 December 2019 Searched: 2.1.20

1 Bacteriuria/ (7596)
2 Asymptomatic Infections/ and exp Bacteria/ (293)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (5932)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (1551)
5 or/1-4 (11336)
6 exp Pregnancy/ (877598)
7 exp Pregnancy Complications/ (417380)
8 exp Prenatal Care/ (26628)
9 Pregnant Women/ (7826)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (552690)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (4062)
12 or/6-11 (1041496)
13 exp Mass Screening/ (124658)

14 exp Prenatal Diagnosis/ (72709)
15 "Diagnostic Techniques and Procedures"/ (3216)
16 exp Urogenital system/ and Physical Examination/ (1534)
17 exp Urinalysis/ (7838)
18 Antibody-Coated Bacteria Test, Urinary/ (148)
19 Microbial Sensitivity Tests/ (124380)
20 Predictive Value of Tests/ (197050)
21 Diagnostic Equipment/ (557)
22 Reagent Strips/ (3334)
23 "Sensitivity and Specificity"/ (341625)
24 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (10259892)
25 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (15989)
26 (urinalys$ or uriscreen$).ti,ab. (7890)
27 (microscopy or micro scopy).ti,ab. (436999)
28 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (2522)
29 "point of care testing"/ (1487)
30 (point of care or bedside).ti,ab. (43304)
31 or/13-30 (10687355)
32 exp Decision Making/ or exp Patient Preference/ or exp "Patient Acceptance of Health Care"/ (337169)
33 (decision$ or decide or deciding or choice$ or choos$ or prefer$).ti,ab,kw. (1092951)
34 ((patient$ or women or woman or mum$ or mom$ or mother$ or maternal) adj3 (value$ or concern$ or perspective$ or perception$ or perceive$ or reason$ or view$ or worry$ or worries)).ti,ab,kw. (146464)
35 or/32-34 (1439105)
36 5 and 12 and 31 and 35 (67)
37 limit 36 to (english language and yr="1990 -Current") (45)

Medline Epub Ahead of Print and Daily Update (Ovid): up to 31 December 2020
Searched: 2.1.20

1 Bacteriuria/ (4)
2 Asymptomatic Infections/ and exp Bacteria/ (0)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (60)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (19)
5 or/1-4 (77)
6 exp Pregnancy/ (660)
7 exp Pregnancy Complications/ (354)
8 exp Prenatal Care/ (46)
9 Pregnant Women/ (26)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (8756)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or mom or moms or lady or ladies)).ti,ab. (90)
12 or/6-11 (9057)
13 exp Mass Screening/ (138)
14 exp Prenatal Diagnosis/ (68)

15 "Diagnostic Techniques and Procedures"/ (2)
16 exp Urogenital system/ and Physical Examination/ (1)
17 exp Urinalysis/ (3)
18 Antibody-Coated Bacteria Test, Urinary/ (0)
19 Microbial Sensitivity Tests/ (165)
20 Predictive Value of Tests/ (261)
21 Diagnostic Equipment/ (0)
22 Reagent Strips/ (1)
23 "Sensitivity and Specificity"/ (237)
24 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (182526)
25 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (255)
26 (urinalys$ or uriscreen$).ti,ab. (170)
27 (microscopy or micro scopy).ti,ab. (5532)
28 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (22)
29 "point of care testing"/ (23)
30 (point of care or bedside).ti,ab. (1160)
31 or/13-30 (185641)
32 exp Decision Making/ or exp Patient Preference/ or exp "Patient Acceptance of Health Care"/ (448)
33 (decision$ or decide or deciding or choice$ or choos$ or prefer$).ti,ab,kw. (23829)
34 ((patient$ or women or woman or mum$ or mom$ or mother$ or maternal) adj3 (value$ or concern$ or perspective$ or perception$ or perceive$ or reason$ or view$ or worry$ or worries)).ti,ab,kw. (3310)
35 or/32-34 (26750)
36 5 and 12 and 31 and 35 (0)
37 limit 36 to (english language and yr="1990 -Current") (0)

Embase: 1974 – 30 December 2019
Searched: 31.12.19
1 bacteriuria/ (6799)
2 asymptomatic bacteriuria/ (1830)
3 (bacteriuria$ or bacilluria$ or bacteruria$).ti,ab. (6887)
4 (bacteria$ adj2 (urin$ or bladder$ or kidney$ or genitourin$ or urogenita$)).ti,ab. (2085)
5 or/1-4 (11825)
6 exp pregnancy/ (646363)
7 exp pregnancy complication/ (118393)
8 exp prenatal care/ (145758)
9 pregnant woman/ (74144)
10 (pregnan$ or antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab. (699620)
11 (expect$ adj2 (women or woman or female$ or mother$ or mum or mums or lady or ladies)).ti,ab. (5155)
12 or/6-11 (991723)
13 exp screening/ (671496)
14 diagnostic procedure/ (84745)
15 exp urogenital system examination/ (357487)
16 exp urinalysis/ (103018)

17 antibody-coated bacteria test/ (5)
18 microbial sensitivity test/ (9195)
19 predictive value/ (161092)
20 diagnostic kit/ (5930)
21 test strip/ (3973)
22 "sensitivity and specificity"/ (344247)
23 (screen$ or test$ or analys$ or algorithm$ or detect$ or predict$ or diagno$).ti,ab. (13437360)
24 ((urin$ or bacteria$) adj3 (culture or dipstick$ or dip stick$ or dipslide$ or dip slide$ or strip$)).ti,ab. (23568)
25 (urinalys$ or uriscreen$).ti,ab. (13266)
26 (microscopy or micro scopy).ti,ab. (497839)
27 (reagent$ adj3 (strip$ or stick$ or test$)).ti,ab. (3462)
28 "point of care testing"/ (12553)
29 (point of care or bedside).ti,ab. (65337)
30 exp prenatal diagnosis/ (105356)
31 or/13-30 (14087482)
32 exp decision making/ or exp patient decision making/ or exp patient preference/ (371283)
33 (decision$ or decide or deciding or choice$ or choos$ or prefer$).ti,ab,kw. (1465959)
34 ((patient$ or women or woman or mum$ or mom$ or mother$ or maternal) adj3 (value$ or concern$ or perspective$ or perception$ or perceive$ or reason$ or view$ or worry$ or worries)).ti,ab,kw. (234246)
35 or/32-34 (1821249)
36 5 and 12 and 31 and 35 (124)
37 limit 36 to (english language and yr="1990 -Current") (87)
38 conference$.pt,st,so. (4458597)
39 37 not 38 (67)

Targeted search to identify interventions for ASB in pregnancy

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 12, December 2019 Searched: 31.12.19

#1 MeSH descriptor: [Bacteriuria] explode all trees 487
#2 MeSH descriptor: [Asymptomatic Infections] explode all trees 21
#3 bacteri*:ti,ab,kw 39837
#4 #2 and #3 12
#5 (bacteriuria* or bacilluria* or bacteruria*):ti,ab,kw 1130
#6 (bacteria* NEAR/2 (urin* or bladder* or kidney* or genitourin* or urogenita*)):ti,ab,kw 186
#7 #1 or #4 or #5 or #6 1280
#8 MeSH descriptor: [Pregnancy] explode all trees 7524
#9 MeSH descriptor: [Pregnancy Complications] explode all trees 10810
#10 MeSH descriptor: [Prenatal Care] this term only 1390
#11 MeSH descriptor: [Pregnant Women] this term only 236
#12 (pregnan* or antenatal* or ante-natal* or prenatal* or pre-natal*):ti,ab,kw 62173
#13 (expect* NEAR/2 (women or woman or female* or mother* or mum or mums or mom or moms or lady or ladies)):ti,ab,kw 1266
#14 #8 or #9 or #10 or #11 or #12 or #13 64722

#15	#7 and #14 with Publication Year from 1990 to 2019, in Trials	96

Appendix 2 — Included and excluded studies

PRISMA flowchart

Error! Reference source not found. summarises the volume of publications included and excluded at each stage of the review. Fourteen publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 2. Summary of publications included and excluded at each stage of the review

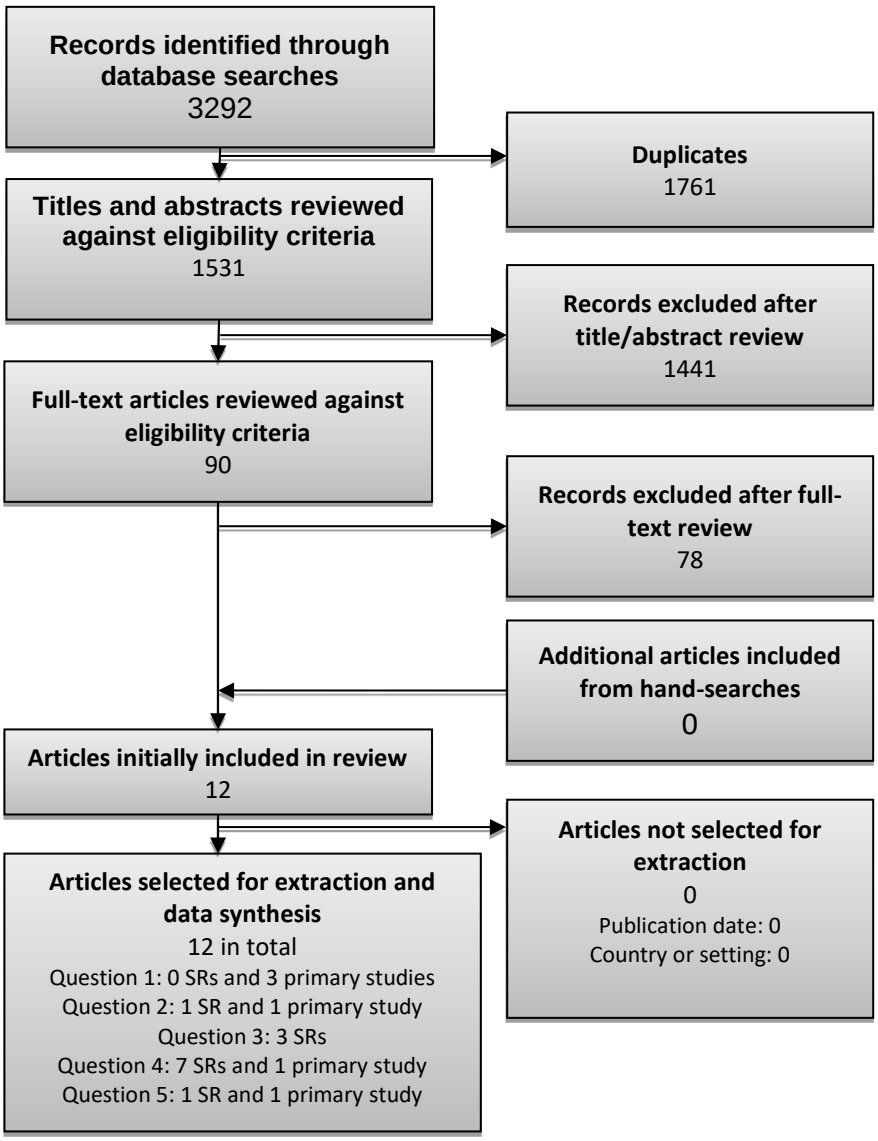

Table 21. Summary of inclusion assessment of primary studies selected for Q1: disease burden

Q1: Summary of selection criteria

Question 1	**What is the disease burden associated with ASB?**	
Item	**Included**	**Excluded**
Population	Pregnant women	
Exposure	Untreated ASB*	
Comparator	Pregnant women without ASB	
Outcomes	*Maternal:* • Mortality • Sepsis • Pyelonephritis • Symptomatic cystitis *Neonatal:* • Perinatal mortality (≥20wks gestation) • Spontaneous abortion/pregnancy loss <20wks gestation • Neonatal sepsis • Preterm birth (<37wks gestation) • Low birth weight (<2500g)	
Study designs	Study designs will be included using the following hierarchy of evidence (from high to low quality evidence): • Systematic reviews • Comparative observational studies (cohorts, case controls) • Observational studies • Non-intervention arms of RCTs UK data in English language available from 1990 onwards	

*It was planned to give priority to studies reporting ASB defined according to the IDSA definition: ≥10^5 CFU per ml or ≥10^8 CFU per litre in a voided urine specimen without signs or symptoms attributable to a UTI.[3]

Table 22. Summary of full paper screening of studies for Q1

Citation	Country	Outcomes	Included/excluded	Notes
Systematic reviews				
UK National Screening Committee 2017[20]	UK	No relevant outcomes	Excluded – not relevant design; no relevant outcome data	Previous NSC ASB screening review (to be included in the introduction and discussion sections). Not a full systematic review.
National Institute for Health and Care Excellence (NICE) 2008[5]	UK	No relevant outcomes	Excluded – not relevant design; no relevant outcome data	Guidelines GC62 on 'Antenatal care for uncomplicated pregnancies'
Scottish Intercollegiate Guidelines Network (SIGN)[4]	UK	No relevant outcomes	Excluded – not relevant design; no relevant outcome data	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Wingert 2017[2]	Canada	No relevant outcomes	Excluded- not relevant outcome	Systematic review and meta-analysis on screening for asymptomatic bacteriuria in pregnancy
Nicolle 2019[3]	USA	No relevant outcomes	Excluded – not relevant design; not relevant outcome	Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America
Wingert 2019[40]	Canada	No relevant outcomes	Excluded- not relevant outcome	Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences
Bianchi-Jassir 2017[50]	USA	Pre-term birth	Excluded – no relevant outcome data	Systematic review and meta-analysis of preterm birth and the association with Group B Streptococcus colonisation
Canadian Task Force on Preventive Health Care 2018[51]	Canada	No relevant outcomes	Excluded – no relevant outcome data	Guidelines informed by systematic review in Henderson 2019[52]
Primary studies				
Kazemier 2015[13]	Netherlands	% positive for ASB Maternal and neonatal outcomes after ASB	Included (2nd level – not UK but similar country)	Full paper - link to methods paper - Kazemier 2012[34] and conference abstract – Kazemier 2014[53] – ASB Study
Versi 1997[54]	UK (comparison	% bacteriuria Birth weight	Excluded – not relevant population	No comparison between positive and negative – reports rates of bacteriuria and

Citation	Country	Outcomes	Included/excluded	Notes
	between Bangladeshi and Caucasian women)	Pre-term birth	(combined asymptomatic and symptomatic)	no distinction between symptoms and no symptoms. 'overall prevalence of bacteriuria was 6.3% among Caucasian women but only 2.0% in the group of Bangladeshi women. After adjustment for year of delivery, parity and maternal age, we estimated the risk among Caucasian women to be 3.5 times that observed among Bangladeshi women (95% CI 2.8-4.3).'
Meis 1995[55]	Wales	Pre-term birth	Excluded – not relevant population	Cardiff Births Survey in Wales (date from 1970 to 1979). Definition of bacteriuria suggests that the women don't have UTI symptoms though the population appears to include those with and without symptoms.
Nazareth 1993[56]	UK	No relevant outcomes	Excluded – not relevant population (all had symptoms, and none were pregnant)	Population has UTI symptoms and pregnant women were excluded.
McIsaac 2005[12]	Canada	ASB	Excluded (reported prevalence of ASB for Canada, not UK; did not report disease burden outcomes)	Included for question 2
Schneeberger 2018[15]	Netherlands	ASB UTI Preterm birth Babies small for age	Included (2nd level – not UK but similar country)	
Kazemier 2012[34]	Netherlands	No outcome data	Excluded – no outcome data reported	Methods paper only – no results – link to full paper - Kazemier 2015[13] and conference abstract – Kazemier 2014[53] – ASB Study

Citation	Country	Outcomes	Included/excluded	Notes
Naresh 2011[33]	USA	Pyelonephritis Preterm delivery Stillbirth Mean gestational age at delivery	Included (2nd level – not UK but similar country)	
Kazemier 2012[53]	Netherlands	No outcome data	Excluded – no outcome data reported	Conference abstract only –link to results paper - Kazemier 2015[13] and methods paper Kazemier 2012[34] – ASB Study

Table 23. Summary of inclusion assessment of primary studies selected for Q2: performance of screening tests

Q2: Summary of selection criteria

Question 2	**What is the performance of screening tests for detecting ASB infections in pregnancy?**	
Item	**Included**	**Excluded**
Population	Pregnant women from the UK without: history of kidney infection; urogenital anomalies; polycystic kidneys; symptoms of UTI; recurrent UTI; diabetes, or; sickle-cell disease If a lack of UK populations, populations from countries similar to the UK will be included.	Women at high risk of bacterial infection in the urogenital tract Non-UK populations from countries dissimilar to the UK
Index test	Any screening test/algorithm for ASB including: • Urine culture • Repeat urine culture • Point-of-care tests (urine dipstick analysis for nitrites/leucocytes, dipslide)	Urine screening for other conditions; non-urine screening test
Reference test	Urine culture	
Target condition	ASB	
Outcomes	• Sensitivity • Specificity • Positive predictive values • Negative predictive values • Positive likelihood ratio • Negative likelihood ratio	

Study designs	Study designs will be included using the following hierarchy of evidence (from high to low quality evidence): • Systematic reviews • Prospective/retrospective studies with consecutive random sample; cross-sectional studies; or RCTs using an independent blinded comparison and a valid reference test • Any other studies English language available from 2003 onwards	Case-control studies; studies with longitudinal assessment of the reference standard

Table 24. Summary of full paper screening of studies for Q2

Citation	Country	Included/excluded	Notes
Systematic reviews			
UK National Screening Committee 2017[20]	UK	Excluded – not relevant design; no relevant outcome data	Previous NSC ASB screening review (to be included in the introduction and discussion sections). Not a full systematic review.
National Institute for Health and Care Excellence (NICE) 2008[5]	UK	Excluded – not relevant design; no relevant outcome data	Guidelines GC62 on 'Antenatal care for uncomplicated pregnancies'
Scottish Intercollegiate Guidelines Network (SIGN)[4]	UK	Excluded – not relevant design; no relevant outcome data	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Wingert 2017[2]	Canada	Excluded- not relevant outcome	Systematic review and meta-analysis on screening for asymptomatic bacteriuria in pregnancy
Nicolle 2019[3]	USA	Excluded – not relevant design	Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America

Citation	Country	Included/excluded	Notes
Gehani 2019[57]	India	Excluded – studies included in the review are set in multiple countries but none are similar to the UK	Systematic review of multiple types of screening tests for ASB in pregnant women.
Wingert 2019[40]	Canada	Excluded- not relevant outcome	Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. Does not report screening performance outcomes.
Rogozinska2016[35]	UK	Included	Systematic review and meta-analysis of onsite tests in detecting the presence of bacteria in the urine using urine culture as a reference standard. Includes data from multiple countries.
Deville 2004[58]	Netherlands	Excluded – not relevant population	Broad population including separate data for pregnant women, but considers UTI and ASB as this same condition
Canadian Task Force on Preventive Health Care 2018[51]	Canada	Excluded – no relevant outcome data	Guidelines informed by systematic review in Henderson 2019[52]
Primary studies			
Aigere 2013[59]	Nigeria	Excluded – population (non-UK relevant)	
Ajayi 2010[60]	Africa	Excluded – population (non-UK relevant)	
Awonuga 2011[61]	Africa	Excluded – population (non-UK relevant)	
Azhari 2012[62]	Iran	Excluded – population (non-UK relevant)	
Balamurugan 2012[63]	India	Excluded – population (non-UK relevant)	
Demilie 2014[64]	Ethiopia	Excluded – population (non-UK relevant)	
Dhanalakshmi 2012[65]	India	Excluded – population (non-UK relevant)	

Citation	Country	Included/excluded	Notes
Eigbefoh 2008[66]	Nigeria	Excluded – population (non-UK relevant)	
Gutierrez-Fernandez 2012[67]	Spain	Excluded – not relevant population	
Jayalakshmi 2008[68]	India	Excluded – population (non-UK relevant)	
Kacmaz 2006[69]	Japan	Excluded – not relevant reference test (i.e. not culture)	
Karabulut 2007[70]	Turkey	Excluded – population (non-UK relevant)	
Kodikara 2009[71]	Sri Lanka	Excluded – population (non-UK relevant)	
Kovavisarach 2008[72]	Thailand	Excluded – population (non-UK relevant)	
Kovavisarach 2017[73]	Thailand	Excluded – population (non-UK relevant)	
Mangalgi 2018[74]	India	Excluded – population (non-UK relevant)	
McIsaac 2005[12]	Canada	Included (2nd level – not UK but similar country)	
Mignini 2009[75]	Argentina, Philippines, Thailand, and Vietnam	Excluded – population (non-UK relevant)	
NCT03274960 2017[76]	Zimbabwe	Excluded – population (non-UK relevant) - ongoing study – no data	
Okusanya 2014[77]	Lagos	Excluded – population (non-UK relevant)	
Onakoya 2008[78]	Nigeria	Excluded – population (non-UK relevant)	
Tamayo 2004[79]	Spain	Excluded – not relevant comparison – compares two types of culture – limited to Group B Step only	

Citation	Country	Included/excluded	Notes
Teppa 2005[80]	Venezuela	Excluded – population (non-UK relevant)	
Thakre 2012[81]	India	Excluded – population (non-UK relevant)	
Ullah 2012[18]	Bangladesh	Excluded – population (non-UK relevant)	

Table 25. Summary of inclusion assessment of primary studies selected for Q3: benefits and harms of screening compared to no screening

Q3: Summary of selection criteria

Question 3	**What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy?**	
Item	**Included**	**Excluded**
Population	Pregnant women from the UK without: history of kidney infection; urogenital anomalies; polycystic kidneys; symptoms of UTI; recurrent UTI; diabetes, or; sickle-cell disease. Subgroups of interest (where available) include eligible women grouped according to socioeconomic status, ethnicity or maternal characteristics. If a lack of UK populations, populations from countries similar to the UK will be included.	Women at high risk of bacterial infection in the urogenital tract Non-UK populations
Intervention	Any screening test/algorithm for ASB	Urine screening for other conditions; non-urine screening test
Comparator	No screening/other screening algorithm	
Outcomes	• Clinical outcomes, including maternal mortality, maternal sepsis, pyelonephritis, symptomatic cystitis, perinatal mortality (≥20 weeks of gestation (e.g. intrauterine demise, stillbirth, early neonatal death), spontaneous abortion/pregnancy loss before 20 weeks of gestation, neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome or admission to neonatal intensive care unit), preterm birth (<37 weeks of gestation), low birth weight (< 2500g). • Any maternal or neonatal harms such as anaphylaxis, thrombocytopenia, haemolytic anaemia, alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis), antibiotic-induced diarrhoea (including Clostridioides difficile disease), rash and vomiting, foetal abnormalities alterations in foetal microbiome and its implications (e.g. increased risk of infections, atopy), candidiasis, rash, gastrointestinal upset and antibiotic-sensitisation (e.g. increased risk of allergy in later life), and antimicrobial resistance	

Study designs	Study designs will be included using the following hierarchy of evidence (from high to low quality evidence): • Systematic reviews • RCTs, comparative cohort studies English language available from 2003 onwards	

Table 26. Summary of full paper screening of studies for Q3

Citation/country	Country	Included/excluded	Notes
Systematic reviews			
UK National Screening Committee 2017[20]	UK	Excluded – not relevant design	Previous NSC ASB screening review (to be included in the introduction and discussion sections). Not a full systematic review.
National Institute for Health and Care Excellence (NICE) 2008[5]	UK	Excluded – not relevant design	Guidelines GC62 on 'Antenatal care for uncomplicated Pregnancies'.
Scottish Intercollegiate Guidelines Network (SIGN)[4]	UK	Excluded – not relevant design	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Wingert 2017[2]	Canada	Excluded- not relevant outcome	Systematic review and meta-analysis on screening for asymptomatic bacteriuria in pregnancy
Henderson 2019[52]	USA	Excluded – same data as main publication Henderson 2019[39]	Systematic review to update the USPSTF's previous recommendation statement on Screening for Asymptomatic Bacteriuria in Adults. Includes some separate data on pregnant women. Same data as reported in Henderson 2019[39]
Nicolle 2019[3]	USA	Excluded – not relevant design	Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America
Wingert 2019[40]	Canada	Included	Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences.
Allen 2018[10]	Canada	Excluded – not relevant population	Group B streptococcus in pregnancy

Citation/country	Country	Included/excluded	Notes
Angelescu 2016[41]	Austria, Germany, UK	Included	Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. Includes data from multiple countries
Henderson 2019[39]	USA	Included	Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. Includes data from multiple countries
Canadian Task Force on Preventive Health Care 2018[51]	Canada	Excluded – not relevant design	Guidelines informed by systematic review.
Primary studies			
Aigere 2013[59]	Nigeria	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Ajayi 2010[60]	Africa	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Awonuga 2011[61]	Africa	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Azhari 2012[62]	Iran	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Balamurugan 2012[63]	India	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Demilie 2014[64]	Ethiopia	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Dhanalakshmi 2012[65]	India	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Eigbefoh 2008[66]	Nigeria	Excluded – population (non-UK relevant) – outcomes - test accuracy only	

Citation/country	Country	Included/excluded	Notes
Gutierrez-Fernandez 2012[67]	Spain	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Jayalakshmi 2008[68]	India	Excluded – population (non-UK relevant)	
Kacmaz 2006[69]	Japan	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Karabulut 2007[70]	Turkey	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Kazemier 2014[53]	Netherlands	Excluded – no relevant comparison - compares antibiotic vs. no antibiotic – no data comparing screened vs. no screening	
Kazemier 2015[13]	Netherlands	Excluded – no relevant comparison - compares antibiotic vs. no antibiotic – no data comparing screened vs. no screening	
Kodikara 2009[71]	Sri Lanka	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Kovavisarach 2008[72]	Thailand	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Kovavisarach 2017[73]	Thailand	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Mangalgi 2018[74]	India	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
McIsaac 2005[12]	Canada	Excluded – no relevant outcomes	
Mignini 2009[75]	Argentina, Philippines, Thailand, and Vietnam	Excluded – population (non-UK relevant) – outcomes - test accuracy only	

Citation/country	Country	Included/excluded	Notes
NCT03274960 2017[76]	Zimbabwe	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Okusanya 2014[77]	Lagos	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Onakoya 2008[78]	Nigeria	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Tamayo 2004[79]	Spain	Excluded – no relevant outcomes - test accuracy only	
Teppa 2005[80]	Venezuela	Excluded – population (non-UK relevant) – outcomes - test accuracy only	
Thakre 2012[81]	India	Excluded – population (non-UK relevant)	
Ullah 2012[18]	Bangladesh	Excluded – population (non-UK relevant) – outcomes - test accuracy only	

Table 27. Summary of inclusion assessment of studies selected for Q4: benefits and harms of antibiotic treatment compared with no treatment

Q4: Summary of selection criteria

Question 4	What are the benefits and harms of antibiotic treatment compared with no treatment for ASB in pregnancy?	
Item	**Included**	**Excluded**
Population	Pregnant women with ASB*	
Intervention	Antibiotic therapies with UK marketing authorisation for use in pregnancy	
Comparator	No treatment or placebo	
Outcomes	• Number of patients with confirmed ASB • Number of patients treated with antibiotics for ASB • Clinical outcomes, including maternal mortality, maternal sepsis, pyelonephritis, symptomatic cystitis, perinatal mortality (>=20 weeks of gestation (e.g. intrauterine demise, stillbirth, early neonatal death), spontaneous abortion/pregnancy loss before 20 weeks of gestation, neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome or admission to neonatal intensive care unit), preterm birth (<37 weeks of gestation), low birth weight (< 2500g). • Any maternal or neonatal harms such as anaphylaxis, thrombocytopenia, haemolytic anaemia, alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis), antibiotic-induced diarrhoea (including Clostridioides difficile disease), rash and vomiting, foetal abnormalities alterations in foetal microbiome and its implications (e.g. increased risk of infections, atopy), candidiasis, rash, gastrointestinal upset and antibiotic-sensitisation (e.g. increased risk of allergy in later life), and antimicrobial resistance	

Study designs	Study designs will be included using the following hierarchy of evidence (from high to low quality evidence): • Systematic reviews • RCTs, comparative cohort studies English language available from 2003 onwards	

*If no information is found in pregnant women with ASB, evidence will be sought for harms associated with antibiotic treatment in pregnant women in general (i.e. for conditions other than ASB)

Table 28: Summary of full paper screening of studies for Q4

Citation	Country	Included/excluded	Notes
Systematic reviews			
UK National Screening Committee 2017[20]	UK	Excluded – not relevant design	Previous NSC ASB screening review (to be included in the introduction and discussion sections). Not a full systematic review.
National Institute for Health and Care Excellence (NICE) 2008[5]	UK	Excluded – not relevant design	Guidelines GC62 on 'Antenatal care for uncomplicated pregnancies'
Scottish Intercollegiate Guidelines Network (SIGN)[4]	UK	Excluded – not relevant design	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Wingert 2017[2]	Canada	Excluded – not relevant design	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Henderson 2019[52]	USA	Excluded – reports same data as Henderson 2019[39]	Systematic review to update the USPSTF's previous recommendation statement on Screening for Asymptomatic Bacteriuria in Adults. Includes some separate data on pregnant women. Linked to Henderson 2019[39]
Nicolle 2019[14]	USA	Included	Systematic review underpinning Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America
Wingert 2019[40]	Canada	Included	Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and

Citation	Country	Included/excluded	Notes
			treatment effectiveness and patient preferences.
Allen 2018[10]	Canada	Included	Guideline informed by a systematic review to help clinicians identify pregnancies in which it is appropriate to treat GBS bacteriuria to optimise maternal and perinatal outcomes, reduce the occurrences of antibiotic anaphylaxis, and antibiotic resistance.
Koves 2017[44]	Europe	Included	Systematic review and meta-analysis by the European Association of Urology to inform guidelines on the benefits and harms of treatments for ASB. Includes separate data for pregnant women.
Angelescu 2016[41]	Austria, Germany, UK	Included	Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. Includes data from multiple countries
Iarikov 2017[82]	USA	Excluded – not relevant design	A review of fosfomycin safety using the Food and Drug Administration Adverse Event (AE) Reporting System (FAERS) and published literature. Review is not systematic but a literature review.
Guinto 2010[7]	Philippines and UK	Excluded – not relevant comparison	Cochrane review but compares different antibiotic regimens and does not compare antibiotic treatment to no antibiotic treatment.
Widmer 2015[9]	Switzerland	Excluded – not relevant comparison	Cochrane review but compares different durations of the same antibiotic and does not compare antibiotic treatment to no antibiotic treatment.
Henderson 2019[39]	USA	Included	Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. Includes data from multiple countries. Linked to Henderson 2019[52]

Citation	Country	Included/excluded	Notes
Smaill 2019[11]	Canada	Included	Cochrane review. Includes data from multiple countries. Compares antibiotic versus no antibiotic treatment.
Canadian Task Force on Preventive Health Care 2018[51]	Canada	Excluded – not relevant design	Guidelines informed by systematic review.
Primary studies			
Khawaja 2015[83]	India	Excluded – comparison of dosing regimen – no relevant comparator	
Kazemier 2015[13]	Netherlands	Included	
Lumbiganon 2009[84]	Thailand, Philippines, Vietnam and Argentina	Excluded – comparison of dosing regimen – no relevant comparator	
Estebanez 2009[85]	Spain	Excluded – comparison of dosing regimen – no relevant comparator	
Bayrak 2007[86]	Turkey	Excluded – comparison of two antibiotics – no relevant comparator	
Vousden 2009[87]	Thailand, Philippines, Vietnam and Argentina	Excluded – comparison of dosing regimen – no relevant comparator	
Lumbiganon 2009[88]	Thailand, Philippines, Vietnam and Argentina	Excluded – comparison of dosing regimen – no relevant comparator	
Rafal'skiĭ 2013[89]	Russia	Excluded – Russian language – no relevant comparator	
NCT03275623[90]	USA	Excluded – no data – ongoing trial of relevance	
NCT02911662[91]	USA	Excluded – terminated early – no results	
NCT03548129[92]	Egypt	Excluded – no results	
Kazemier 2014[53]	Netherlands	Excluded – not relevant population	
NICE Prescribing Guide NG109 2018[93]	UK	Excluded – not relevant study design	

Table 29. Summary of inclusion assessment of studies selected for Q5: benefits and harms of screening and treatment women's decision making

Q5: Summary of selection criteria

Question 5	**How do the benefits and harms of screening and treatment inform women's decisions to undergo screening for ASB in pregnancy?**	
Item	**Included**	**Excluded**
Population	Pregnant women	
Intervention	Any screening programme for ASB during pregnancy*	
Comparator	Not applicable	
Outcomes	• Relative weight/utilities of benefit and harms of screening or treatment • Willingness to be screened based on relative values placed on benefits and harms of screening or treatment or both • Qualitative information e.g. themes arising from interviews with pregnant women who have been screened or treated for ASB or who have considered screening or treatment for ASB	
Study designs	Study designs will be included using the following hierarchy of evidence (from high to low quality evidence): • Systematic reviews • Qualitative, mixed methods, surveys/cross-sectional English language available from 1990 onwards	

Table 30: Summary of full paper screening of studies for Q5

Citation	**Country**	**Outcomes**	**Notes**
Systematic reviews			
UK National Screening Committee 2017[20]	UK	Excluded – not relevant design	Previous NSC ASB screening review (to be included in the introduction and discussion sections). Not a full systematic review.

Citation	Country	Outcomes	Notes
National Institute for Health and Care Excellence (NICE) 2008[5]	UK	Excluded – not relevant design	Guidelines GC62 on antenatal care for uncomplicated pregnancies.
Scottish Intercollegiate Guidelines Network (SIGN)[4]	UK	Excluded – not relevant design	Guidelines on the 'Management of suspected bacterial urinary tract infection in adults'
Nicolle 2019[3]	USA	Excluded – not relevant design	Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America
Wingert 2019[40]	Canada	Included	Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences.
Smaill 2019[11]	Canada	Excluded – no relevant outcome	Cochrane review. Includes data from multiple countries. Compares antibiotic versus no antibiotic treatment.
Canadian Task Force on Preventive Health Care 2018[51]	Canada	Excluded – not relevant design	Guidelines informed by systematic review.
Primary studies			
Nazareth 1993[56]	UK	Excluded – not relevant population (all had symptoms, and none were pregnant)	
Kazemier 2015[13]	Netherlands	Included (2nd level – not UK but similar country)	Very little data but reports on acceptability of antibiotic treatment.

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 31. Studies relevant to criterion 1

Question 1: What is the disease burden associated with ASB?

g) What is the prevalence of ASB in pregnancy in the UK?

h) What is the incidence of pyelonephritis in the UK in pregnancy in women with or without screen detected ASB?

i) What is the incidence of recurrent ASB in pregnancy in the UK?

j) What is the incidence of other adverse maternal and neonatal outcomes associated with ASB?

Study ID	Study design	Population	Test for ASB
Kazemier 2015[13] Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised	**Study design:** Prospective cohort study **Level of evidence**: Level 1b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** Netherlands **Study aim:** To assess the maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy in a national prospective cohort study **Study conclusions:** In women with an uncomplicated singleton pregnancy, ASB is not associated with preterm birth. ASB showed a	**No. of participants:** 5132 eligible, 4283 analysed **Inclusion criteria:** Women aged ≥18 years with singleton pregnancy without symptoms of UTI at 16–22 wks of gestation **Exclusion criteria:** History of spontaneous preterm delivery <34 wks; signs of threatening preterm delivery; foetal congenital malformations; use of antibiotics within 2 wks of screening; known G6PD deficiency or allergy to nitrofurantoin or risk factors for	**Timing:** 16–22 wks gestation **Setting:** 8 hospitals and 5 ultrasound centres **Sample collection method:** Mid-stream urine sample **Number of samples per patient:** Single **Test description:** Single dipslide (UricultW, Orion Diagnostica, Espoo, Finland) consisting of two different culture media (cysteine lactose electrolyte deficient medium and MacConkey medium) – reported to have 98.0% sensitivity and 99.6% specificity to detect ASB in pregnancy. Inoculated with urine at hospital,

controlled trial. *Lancet Infect Dis* 2015;15(11):1324-33. Additional information taken from methods paper[34] and abstract[53]	significant association with pyelonephritis, but the absolute risk of pyelonephritis in untreated asymptomatic bacteriuria is low. These findings question a routine screen-treat policy for ASB in pregnancy. **Outcomes assessed:** • Composite of pyelonephritis,* delivery before 34 wks gestation, or both (primary outcome) • Adverse neonatal outcome (death or severe morbidity) • Neonatal death before discharge from the neonatal ward • Severe neonatal morbidity** • Neonatal birthweight • Congenital abnormalities • Time to delivery • Spontaneous preterm birth rate 32 to 37 wks • Admission to neonatal ICU • Maternal morbidity (including UTI; gestational diabetes; pregnancy induced hypertension; pre-eclampsia; HELLP syndrome; kidney stones; cholestasis; thromboembolic events; non-spontaneous labour onset; epidural/spinal analgesia during labour; endometritis within 6wk of delivery; mastitis within 6wks of delivery) • Costs • Chorioamnionitis (only mentioned in protocol) • No. of days maternal admission for (threatened) preterm labour and/or pyelonephritis (only mentioned in protocol) • Number of women willing to take part in subsequent RCT comparing antibiotic treatment versus no treatment	complicated UTI (pre-gestational diabetes mellitus, immunosuppressive medication, functional or structural abnormalities of the urinary tract). **Stage of pregnancy:** 16–22 wks of gestation **Antenatal risk factors for ASB**: NR.	ultrasound centre or midwifery practices. Dipslides were sent by mail to laboratory for infectious diseases in Groningen, the Netherlands the same day. Laboratory technicians read the dipslide directly when incubated for 2-3 days at RT. If no colonies formed, the dipslide was incubated for another 24 hrs at 35°C. **Confirmatory methodology:** None - Urinary culture was not feasible in the Dutch antenatal care system since 70% of Dutch women attend antenatal care at a midwifery practice where there is no direct access to a microbiology laboratory to perform the cultures. **Contamination:** Defined as >2 species present – excluded from the study **Definition of ASB:** Positive diplslide (≥1 × 10^5CFU/ml urine for single microorganism or ≥ 1 × 10^5 CFU/ ml for at least one microorganism when two are present) without any symptoms of UTI.
Summary of results:			
5132 eligible women were screened for ASB of which 250 (5%) testing positive			

Comparison
ASB-positive women who were untreated or given placebo during the linked RCT (n=208) versus ASB-negative women (n=4035)

Primary outcomes
More ASB-positive women developed pyelonephritis compared with ASB-negative women: 5/208 (2.4%) versus 24/4035 (0.6%), odds ratio (OR) 3.9 (95% confidence interval [CI] 1.4 to 11.4). Of the 29 women with acute pyelonephritis, five (17%) had ASB between 16 and 22 wks. The median duration of hospital stay for women with pyelonephritis was 3 days (range 2–10 days). The course of disease in these women was mild, and none needed admission to an intensive care unit.

No clear differences between ASB-positive and ASB-negative women were observed for delivery <34 wks (2/208 [1.0%] versus 54/4035 [1.3%] respectively, OR 0.7, 95% CI 0.2 to 2.8) or the composite primary outcome, defined as pyelonephritis or delivery <34 wks or both (6/208 [2.9%] versus 77/4035 [1.9%] respectively, OR 1.5, 95% CI 0.6 to 3.5^).

Secondary outcomes - maternal
More ASB-positive women had a UTI treated with antibiotics antenatally compared with ASB negative women (42/208 [20.2%] versus 317/4035 [7.9%], OR 2.9, 95% CI 2.0 to 4.2) and there was a similar result for the outcome of recurrent UTI treated with antibiotics antenatally (18/208 [8.7%] versus 105/4035 [2.6%], OR 3.5, 95% CI 1.8 to 6.7). No clear between-group differences were seen for other maternal outcomes: UTI treated with antibiotics postpartum, within 6 wks of delivery; treatment with antibiotics antenatally for reason other than UTI; incidence of gestational diabetes; pregnancy-induced hypertension; pre-eclampsia; kidney stones; cholestasis; non-spontaneous onset of labour; epidural or spinal analgesia during labour, and; mastitis within 6 wks of delivery. The following maternal outcomes could not be estimated because of zero events in the ASB-positive group: haemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome; thromboembolic events, and; endometritis within 6 wks of delivery.

Secondary outcomes - neonatal
More ASB-positive women delivered a female foetus compared with ASB-negative women: 129/208 (62.0%) versus 1978/4035 (49.0%), OR 1.7, 95% CI 1.3 to 2.2. Mean (standard error) birthweights per group were 3495 (40)g versus 3454 (9)g respectively. Between-group differences were not detected for other neonatal outcomes: median gestational age at delivery; preterm birth at <37 wks, <32 wks or 28 wks; small for gestational age according to 10th or 5th percentiles; perinatal death; composite severe neonatal morbidity outcome;** admission to neonatal intensive care unit; neonatal sepsis confirmed with culture, and; congenital abnormalities.

All OR estimates were as reported by the study authors and were adjusted for smoking, educational status, conception through in-vitro fertilisation or intracytoplasmic sperm injection and pre-existent hypertension.

Key:
***** Defined as hospital admission with at least two of the following features: fever (body temperature ≥ 8·0°C), symptoms of pyelonephritis (nausea, vomiting, chills, and costovertebral tenderness), and a positive urine culture indicating the presence of bacteria in the urine.
****** Defined as presence of at least one of following: severe RDS, BPD, periventricular leukomalacia > grade 1, intracerebral haemorrhage> grade 2, NEC > stage 1 or proven sepsis (including GBS sepsis), death before discharge from nursery
*** Defined as a clinical report of a UTI that was treated with antibiotics
^ Two women had pyelonephritis and a preterm delivery before 34 wks

Abbreviations:

ASB asymptomatic bacteriuria; BPD bronchopulmonary dysplasia; CFU colony forming units; CI confidence interval; DM diabetes mellitus; GDM gestational diabetes mellitus; G6PD deficiency glucose-6-phosphate dehydrogenase deficiency; GBS group B streptococcus; HELLP haemolysis, elevated liver enzymes, and low platelet count; hr hour; min minute; n number of participants/samples; N total number of participants/samples; NEC necrotising enterocolitis; NR not reported; OR odds ratio; RDS respiratory distress syndrome; rpm revolutions per minute; UTI urinary tract infection; wk week

Study ID	Study design	Population	Test for ASB
Naresh 2011[33] Naresh A, Simhan HN. Association of polymicrobial growth from urine culture with adverse pregnancy outcomes. *Am J Perinatol* 2011;28(7):537-42.	**Study design:** Retrospective cohort study **Level of evidence**: Level 2b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** USA **Study aim:** To determine whether polymicrobial growth from screening urine cultures in pregnant patients is associated with adverse pregnancy outcomes **Study conclusions:** There is no association between polymicrobial growth from screening urine culture and pyelonephritis or preterm delivery **Outcomes assessed:** • Incidence of polymicrobial growth in urine • Incidence of pyelonephritis • Frequency of pre-term delivery <37 wks • Frequency of pre-term delivery <34 wks • Mean gestational age at delivery • Frequency of stillbirths	**No. of participants:** 755 **Inclusion criteria:** Pregnancy <20 wks gestation; receipt of antenatal care in the hospital clinic between 2002 & 2007; urine culture reported by the microbiology laboratory as growing only mixed flora > 100,000 CFU/mL or negative urine culture. For both groups, only the 1st urine culture collected during an individual pregnancy was included. **Exclusion criteria:** NR **Stage of pregnancy:** < 20 wks gestation **Antenatal risk factors for ASB**: Around 32% patients in both groups were group B Beta-haemolytic *Streptococcus* carriers and around 2% patients in both groups had chronic renal disease. Pre-gestational diabetes was present in 1.9% of positive (polymicrobial growth) and 1.4% of negative urine culture patients.	**Timing:** Mean gestational age at time of urine culture collection was around 12 wks in both groups **Setting:** Hospital clinic **Sample collection method:** Clean catch method mentioned but not clear if this is what was done as no explicit details provided **Number of samples per patient:** 75% patients with positive test result for polymicrobial growth and 55% patient with negative test result had at least one repeat urine culture **Test description:** Urine culture performed by microbiology laboratory but no further details provided **Confirmatory methodology:** Confirmation protocol not mentioned, but some patients had repeat cultures (see above) **Contamination:** NR **Definition of ASB:** NR
Summary of results:			
Comparison Women including 380 pregnancies/urine cultures in 378 women (2 women had 2 pregnancies during the study period) **Primary outcomes**			

There were no clear differences between women with polymicrobial growth and those with negative urine cultures in terms of the occurrence of pyelonephritis (1/380 [0.3%] versus 0/375 [0%] respectively; p=0.32); preterm delivery (64/380 [16.8%] versus 60/375 [16%] respectively; p=0.76); preterm delivery <34 wks (21/380 [5.5%] versus 17/375 [4.5%] respectively; p=0.53); mean gestational age at delivery in wks (38.1 versus 38.2 respectively; p=0.55); and stillbirth (1/380 [0.3%] versus 1/375 [0.3%] respectively; p=0.98) **Secondary outcomes** NR
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; n number of participants/samples; NR not reported; UTI urinary tract infection; wk week

Study ID	Study design	Population	Test for ASB
Schneeberger 2018[15] Schneeberger C, Erwich J, van den Heuvel ER, Mol BWJ, Ott A, Geerlings SE. Asymptomatic bacteriuria and urinary tract infection in pregnant women with and without diabetes: Cohort study. Eur J Obstet Gynecol Reprod Biol 2018;222:176-181.	**Study design:** Prospective cohort study **Level of evidence**: Level 1b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** Netherlands **Study aim:** To investigate the prevalence of ASB and incidence of UTI in pregnant women with and without DM or GDM. Also, to assess the association between ASB/UTI and maternal/ neonatal outcomes. **Study conclusions:** The prevalence of ASB was low in pregnant women with and without DM or GDM. Neither ASB nor UTI differed significantly between the two groups. The data do not support a routine screen and treat policy in pregnant women with DM or GDM. **Outcomes assessed:** • Prevalence of ASB at 12 and 32 wks gestation • Incidence of UTI (defined as being diagnosed by physician and treated with antibiotics)	**No. of participants:** 474 **Inclusion criteria:** Pregnant women with and without DM or GDM, receiving regular antenatal care. **Exclusion criteria:** Women who did not submit at least one urine sample for culture; positive urine culture in combination with UTI symptoms at study inclusion; multiple pregnancy; pre-existing medical condition with known association with UTI (except for pregnancy and DM); anatomical abnormalities of the urinary tract. **Stage of pregnancy:** 12 wks gestation for first urine sample (range 9 to 20 wks) and 32 wks gestation for second urine sample (range 27 to 38 wks) **Antenatal risk factors for ASB**: Sample was split between those with DM or GDM (n=202) and those	**Timing:** 12 wks gestation for first urine sample (range 9 to 20 wks) and 32 wks gestation for second urine sample (range 27 to 38 wks) **Setting:** 2 university medical centres, 3 non-university hospital clinics and two midwife clinics. Most of the women with DM or GDM received care at specialist hospital-based diabetes outpatient clinics **Sample collection method:** MSU sample taken during routine antenatal visits. Those experiencing symptoms of UTI were asked to send urine samples by mail using a dipslide. **Number of samples per patient:** Each patient provided 1 or 2 urine samples for ASB screening, detail as follows: At 12 wks 64/202 (31.7%) women with DM or GDM provided a sample versus 258/272 (94.9%) women without DM or GDM At 32 wks 189/202 (93.6%) women with DM or GDM provided a sample versus 233/272 (85.7%) women without DM or GDM

	• Causative uropathogens • Association between ASB/UTI and preterm birth • Association between presence/absence of DM/GDM and neonatal outcomes • Maternal use of antibiotics 2 to 4 wks before collection of study urine samples • Perinatal mortality (> 22 wks) • Pregnancy duration (gestational age at delivery) • Preterm birth (<37 wks) • Gender of neonate • Small for gestational age (defined as birth weight below the 10th percentile) • Large for gestational age (defined as birth weight above the 90th percentile) • Appropriate for gestational age (defined as birth weight between the 10th and 90th percentiles) • Admission to neonatal intensive care unit • Five-minute Apgar score <7 • Neonatal antibiotic use within first 6 wks of life	without DM or GDM (n=272). Breakdown by type of DM: type 1 44/201 (21.9%); type 2 22/201 (10.9%); GDM 135/201 (67.2%) Number of UTIs in a lifetime for women with/without DM or GDM were: None 76/196 (38.8%); 101/266 (38.0%) 1 or 2 times 68/196 (34.7%); 96/266 (36.1%) 3, 4 or 5 times 24/196 (12.2%); 42/266 (15.8%) > 6 times 28/196 (14.3%); 27/266 (10.2%)	Multiple samples were not consecutive for the purposes of confirmation of ASB. **Test description:** Urine samples were refrigerated at 4 to 7 °C and transported to one of three participating laboratories for medical microbiology. Culture plates were examined daily for growth. Negative was defined as no growth, growth $<10^5$ CFU/mL, growth of non-uropathogens including skin flora or growth of mixed bacterial flora (>2 organisms). Positive was defined as the presence of one of two different uropathogens with a growth of ≥ 10^5 CFU/mL. **Confirmatory methodology:** None. **Contamination:** The following organisms (normally found in and around external genitalia and only rarely associated with infections) were considered as non-uropathogens and contaminants when identified from urine cultures: lactobacilli, corynebacteria and coagulase negative staphylococci) **Definition of ASB:** Positive urine culture (≥ 10^5 CFU/mL of one or two uropathogens) from a woman without UTI symptoms

Summary of results:

Comparisons
ASB-positive (n=20) versus ASB-negative women (n=454)
Women with DM or GDM (n=202) versus women without DM or GDM (n=272)

Primary outcomes
The overall prevalence of ASB was 9/322 (2.8%) and 13/422 (3.1%) at 12 and 32 weeks gestation respectively. There was no difference in the prevalence of ASB between women with and without DM or GDM: risk ratio (RR) 2.02 (95% CI 0.52 to 7.84) and RR 1.06 (95% CI 0.36 to 3.09) for weeks 12 and 32 respectively. E. *coli* was the most common causative organism of ASB at 12 (66.7%) and 32 weeks' gestation (38.5%).

Secondary outcomes The overall incidence of UTI was 69/474 (14.6%). The denominator (n=474) is the number of women providing a urine sample at week 12 and/or week 32. There was no difference in the incidence of UTI for women with and without DM or GDM: RR 1.31 (95% CI 0.85 to 2.02). A lower prevalence of ASB at 12 and/or 32 weeks gestation and a higher incidence of UTI were observed in women with a lifetime history of at least one UTI (n=285) versus those without such history (n=177): RR 0.29 (95% CI 0.11 to 0.74) and RR 2.09 (95% CI 1.60 to 5.25) per outcome respectively. No differences were found between those with the without ASB at any point during the study in preterm birth (10.0% and 7.7%, respectively; RR 1.30, 95% CI 0.34 to 5.02) or being small for gestational age (5.0% and 5.3%, respectively; RR 0.91, 95% CI 0.13 to 6.36). Similarly, there were no clear differences between women with and without at least one UTI during pregnancy.
Key: ***** Defined as presence of at least one of following: severe RDS, BPD, periventricular leukomalacia >grade 1, intracerebral haemorrhage> grade 2, NEC > stage 1 or proven sepsis (including GBS sepsis), death before discharge from nursery
Abbreviations: ASB asymptomatic bacteriuria; BPD bronchopulmonary dysplasia; CFU colony forming units; CI confidence interval; n number of participants/samples; DM diabetes mellitus; G6PD deficiency glucose-6-phosphate dehydrogenase deficiency; GBS group B streptococcus; hr hour; min minute; GDM gestational diabetes mellitus; MSU midstream urine sample; N total number of participants/samples; NEC necrotising enterocolitis; NR not reported; PPV positive predictive value; RDS respiratory distress syndrome; rpm revolutions per minute; RR relative risk; UTI urinary tract infection; wk week

Question 2: What is the performance of screening tests for detecting ASB infections in pregnancy?

a) What is the performance of screening tests for detecting ASB infections in pregnancy?

Table 32. Studies relevant to criterion 4 and 7

Study ID	Study design	Population	Test for ASB
McIsaac 2005[12] McIsaac W, Carroll JC, Biringer A, Bernstein P, Lyons E, Low DE, Permaul JA. Screening for asymptomatic bacteriuria in pregnancy. *Journal of Obstetrics & Gynaecology Canada: JOGC* 2005;27(1):20-4.	**Study design:** Prospective cohort study **Level of evidence**: Level 1b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** Toronto, Canada **Study aim:** To compare four strategies for screening for ABU in pregnancy: • Urine dipstick testing at each prenatal visit using the LEN dipstick (Uristix 4, Bayer Pharmaceuticals) followed by a urine culture if positive • A single urine culture < 20 wks gestation • Two urine cultures, one < 20 wks and the other at 28 wks gestation • Three urine cultures, one < 20 wks, one at 28 wks and the third at 36 wks gestation **Study conclusions:** A single urine culture before 20 wks gestation will miss more than half of antenatal ABU cases. LEN dipstick testing detected the fewest ABU cases. Although the most sensitive strategy was three urine cultures, the cost-effectiveness of this approach needs to be determined. **Outcomes assessed:**	**No. of participants:** 1050 women (providing 2945 urine cultures in total) **Inclusion criteria:** Women presenting for antenatal care to 2 obstetricians and 6 family doctors affiliated to a large teaching hospital in Toronto, Canada between July 1996 and April 1998 **Exclusion criteria:** Urine cultures were excluded if the woman had symptoms of dysuria or had been on antibiotics within 1 wk of the antenatal visit **Stage of pregnancy:** Urine samples collected for cultures at different points of gestation: before 20 wks, 28 wks and 36 wks **Antenatal risk factors for ASB**: 445/1050 (42.4%) healthy pregnancy; 197/1050 (18.8%) pregnancy at risk; 18/1050 (1.7%); pregnancy at high risk; 390/1050 (37.1%) NR. No further information provided about these risk classifications.	**Timing:** All antenatal visits for the LEN dipstick test; 1st urine culture before 20 wks, 2nd between 20 and 32 wks and 3rd after 32 wks gestation **Setting:** Outpatient family medicine clinics and obstetric clinics in a large urban teaching hospital **Sample collection method:** Midstream urine sample. No further details. **Number of samples per patient:** LEN dipstick test performed at each antenatal visit; up to 3 samples for urine culture **Test description:** A positive LEN test strip (Uristix 4, Bayer Pharmaceuticals) was defined as either greater than a trace of leukocyte or positive for nitrite. A standardised method was used to perform urine cultures in the same laboratory. **Confirmatory methodology:** Total number of ASB cases in the study population, determined from all positive urine cultures from an asymptomatic woman, identified from any of the three urine culture strategies or by a culture prompted by a positive LEN test. **Contamination:** no information provided

	• Proportion of positive LEN tests • Prevalence of ASB in the study sample overall (i.e. across all time points) • Prevalence of ASB in the study sample at different time points: before 20 wks, between 20 and 32 wks and after 32 wks gestation • Proportion of all cases of ASB correctly identified by the 4 different screening strategies (sensitivity)		**Definition of ASB:** The study authors planned to collect a 2nd urine sample for all positive urine cultures but < 50% of women provided this. In light of this, ASB was defined as a single positive urine culture (positive = growth of a single organism at ≥10^3 CFU/mL or two organisms at ≥10^5 CFU/mL) in a woman without symptoms

Summary of results

Comparison
Comparison between four different testing strategies for ASB (as detailed above)

Primary outcome
Prevalence of ASB across all time points: 49/1050 (4.7%)
Prevalence of ASB before 20 wks gestation: 21/1050 (2.0%)
Prevalence of ASB between 20 and 32 wks gestation: 12/1050 (1.1%)
Prevalence of ASB after 32 wks gestation: 16/1050 (1.6%)

Organisms detected in positive urine cultures
Escherichia coli: 24/60 (40.0%)
Group B *steptococcus*: 17/60 (28.3%)
Enterococcus faecalis: 6/60 (10.0%)
Coagulase negative *staphylococcus*: 6/60 (10.0%)
Klebsiella pneumoniae: 84/60 (6.8%)
Staphylococcus aureus: 1/60 (1.7%)
Streptococcus bovis: 1/60 (1.7%)
Citrobacter koseri: 1/60 (1.7%)

Abbreviations:
ASB asymptomatic bacteriuria; CFU colony forming units; LEN leukocyte-esterase-nitrite; NR not reported; wk week

Rogozinska 2016[35]	
Citation	**Rogozinska E, Formina S, Zamora J, Mignini L, Khan KS. Accuracy of Onsite Tests to Detect Asymptomatic Bacteriuria in Pregnancy: A Systematic Review and Meta-analysis. *Obstet Gynecol* 2016;128(3):495-503.**

Aim	To estimate the accuracy of onsite tests to detect asymptomatic bacteriuria among pregnant women.
Last search date	June 2015
Population	Pregnant women with ASB
Intervention/ comparators	Dipsticks including: Dipstick (marker: nitrites); Dipstick (marker: leucocytes or nitrites). Dip slides including: Uricult & Uricult Trio (Orion Diagnostica); Microstix-3. Microscopic techniques: Microscopic analysis of urine (marker & threshold: >20 bacteria per High Power Field); Dip slide with gram staining. Other tests not usually used to detect bacteriuria: Uriscreen catalase tests (Savyon Diagnostics); Chlorhexidine reaction; Griess test (test to detect nitrites).
Outcomes	Sensitivity, specificity, likelihood ratios, or receiver operating characteristic
Results	27 articles (13,641 women) with test accuracy data and reporting on nine tests met the inclusion criteria. The most commonly evaluated test was urine dipstick. The pooled sensitivity and specificity of nitrites detected by dipstick to detect asymptomatic bacteriuria were 0.55 (95% confidence interval [CI] 0.42–0.67) and 0.99 (95% CI 0.98– 0.99), respectively. The Griess test to detect nitrites had a sensitivity of 0.65 (95% CI 0.50–0.78) and specificity of 0.99 (95% CI 0.98–1.00). Dipslide with Gram staining had a pooled sensitivity of 0.86 (95% CI 0.80–0.91) and specificity of 0.97 (95% CI 0.93–0.99). The specificity of onsite tests is high; however, the sensitivity is not with the result that they will fail to detect a substantial number of cases of asymptomatic bacteriuria.
Comments	The main limitation of this review was poor reporting in individual studies and paucity of data. The quality assessment was hindered by insufficient reporting. The estimates of test accuracy for four included tests were based on data from single studies with small sample sizes This makes the parameters less reliable (wide CIs) and more prone to chance findings. To compare the accuracy of all identified tests, a univariate model was used to pool sensitivity and specificity estimates when less than four studies were available. This approach does not account for correlation between two parameters like in the bivariate model.
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; wk week	

Question 3: What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy?

a) What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy?

b) What are the comparative benefits and harms of screening with different screening pathways for asymptomatic bacteriuria in pregnancy?

Table 33. Studies relevant to criterion 11

Angelescu 2016[41]	
Citation	**Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. *BMC Pregnancy Childbirth* 2016;16(1):336.**
Aim	The systematic review had three objectives: firstly, to assess the patient-relevant benefits and harms of screening for ASB versus no screening; secondly, to compare the benefits and harms of different screening strategies; and thirdly, in case no reliable evidence on the overarching screening question was identified, to determine the benefits and harms of treatment of ASB.
Last search date	February 2016
Population	Pregnant women with ASB
Intervention/ comparators	Any ASB screening strategy followed by treatment, if necessary, vs. any treatment for ASB
Outcomes	Pyelonephritis; UTI; Symptoms linked directly or indirectly to UTI (e. g. headache or visual impairment as symptoms of pre-eclampsia, fever); Infant morbidity (e. g. respiratory distress syndrome, sepsis, cerebral haemorrhage, necrotising enterocolitis); Perinatal mortality; Early preterm birth (< 32 weeks of gestation); Very low birth weight (< 1500 g); Health-related quality of life and psychosocial functioning; Any adverse event
Results	No eligible studies were found that investigated the benefits and harms of screening for ASB versus no screening or that compared different screening strategies. Four RCTs comparing antibiotics with no treatment or placebo in 454 pregnant women with ASB. The results of 2 studies published in the 1960s showed a statistically significant reduction in rates of pyelonephritis (odds ratio [OR] = 0.21, 95 % confidence interval [CI] 0.07–0.59) and lower UTI (OR = 0.10, 95 % CI 0.03–0.35) in women treated with antibiotics. By contrast, event rates reported by a recent study were not statistically significantly different, neither regarding pyelonephritis (0 % vs. 2.2 %; OR = 0.37, CI 0.01–9.25, p = 0.515) nor regarding lower UTI during pregnancy (10 % vs. 18 %; Peto odds ratio [POR] = 0.53, CI 0.16–1.79, p = 0.357). Data were insufficient to determine the risk of harms. As three of the four studies were conducted several decades ago and have serious methodological shortcomings, the applicability of their findings to current health care settings is likely to be low. The recent high-quality RCT was stopped early due to a very low number of primary outcome events, a composite of preterm delivery and pyelonephritis. Therefore, the results did not show a benefit of treating ASB. To date, no reliable evidence supports routine screening for ASB in pregnant women. No RCTs are available that assess the benefits and harms of screening for ASB. The available evidence is limited to four treatment trials: three with serious methodological shortcomings and questionable applicability to current medical practice and one low-risk-of bias trial that was stopped due to a very low number of pyelonephritis events in both the treatment and control group. Consequently, no conclusions can be

	drawn on whether the benefits of screening for ASB outweigh the potential harms. However, no reliable evidence supports routine screening for ASB in pregnant women.
Comments	Update of HTA report of the benefits and harms of screening for ASB in pregnancy conducted by the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG).
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; HTA health technology assessment; OR odds ratio; RCT randomised controlled trial; UTI urinary tract infection; wk week	

Henderson 2019[52]	
Citation	**Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: an updated systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 183 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US), 2019 [accessed 17.10.19] Available from: https://www.ncbi.nlm.nih.gov/books/NBK547176/** Also linked to: Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2019;322(12):1195-205.
Aim	To systematically reviewed evidence on the benefits and harms of screening for asymptomatic bacteriuria (ASB) and treatment for pregnant women, non-pregnant women, and men.
Last search date	September 7, 2018
Population	All adults, but separate subgroup data for pregnant women with ASB
Intervention/ comparators	Screening vs. no screening Treatment vs. no treatment
Outcomes	Low birthweight; pyelonephritis; AEs.
Results	Fourteen included studies in pregnant women; n=2 effectiveness and/or harms of screening (N=5,289) and n=12 effectiveness and harms of treatment (N=2,377). *Screening*: Of the two cohort studies on screening in pregnant women, one conducted in Spain (N=4,917) identified a three-fold reduction in risk for in unadjusted comparisons on a retrospective unscreened and screened cohort. The other cohort study of screening in pregnant women was conducted in Turkey (N=372) and had low statistical power for comparisons of health outcomes in a screened and unscreened cohort due to rarity of outcome events. *Treatment*: Data from 12 trials provided evidence that treatment of ASB in pregnancy reduces the risk of pyelonephritis (pooled relative risk [RR], 0.24 [95% CI, 0.14 to 0.40], k=12, n=2,068, I^2 =56.9%). Seven treatment studies reported infant outcomes, demonstrating a reduction in low birthweight (<2500g or SGA <10th percentile) (pooled RR, 0.64 [95% CI, 0.46 to 0.90], k=7, n=1,522, I^2 =15.8.6%). Data on potential harms and adverse effects of antibiotic treatment of ASB in pregnancy were sparsely reported in the trials, and power was low for observing rare outcomes. A pooled analysis from five studies reporting congenital malformations was null (pooled RR, 0.44 [95% CI, 0.16 to 1.22], k=5, n=961, I^2 =0%). Adverse reactions to medications were reported, including vaginitis, diarrhoea, rashes, and nausea.

	In pregnancy, there is some evidence that treatment of urine culture screen detected ASB confers a benefit to maternal and infant health, but most of the evidence is from an earlier era. Information on harms was limited in the included studies, but established and emerging evidence highlights the importance of antibiotic stewardship to limit the development of antibiotic resistance and rising awareness of potential harms associated with antibiotic exposure, including changes to the microbiome that increasingly are found to have consequences for health.
Comments	US Preventive Services Task Force (USPSTF report)
Abbreviations: AE adverse event; ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; HTA health technology assessment; n number of participants; N total number in population; RCT randomised controlled trial; RR relative risk; SGA small for gestational age	

Wingert 2019[40]	
Citation	**Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347**. Also linked to: Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018. Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf
Aim	To provide recommendations on screening for ASB in pregnancy
Last search date	October 2017
Population	Pregnant women with ASB (women who are not at increased risk for asymptomatic bacteriuria)
Intervention/ comparators	Before vs. after ASB screening ASB screening vs. no screening Antibiotic treatment vs. no antibiotic treatment
Outcomes	Pyelonephritis; perinatal mortality; spontaneous abortion; preterm delivery; foetal abnormalities; low birth weight; neonatal sepsis; feasibility; acceptability; cost; equity; patient values and preferences.
Results	Systematic reviews on screening and treating asymptomatic bacteriuria in pregnancy found very low-quality evidence for a modest reduction in pyelonephritis among pregnant women and the number of low-birth-weight infants. Only scant and very low-quality evidence was available to infer harms associated with screening and treatment of asymptomatic bacteriuria in pregnancy. Patient values and preferences regarding screening for asymptomatic bacteriuria are variable and influenced by individual perspectives regarding the small potential benefit of antibiotic use, as well as potential harms associated with antibiotic use in pregnancy.

	A weak recommendation in favour of screening is warranted given the small but uncertain benefit of screening for asymptomatic bacteriuria, variation in women's values and preferences, and the judgment that harms associated with this long-standing practice in Canada are likely minimal. Some women who are not at increased risk of urinary tract infections in pregnancy and are more concerned with potential harms of antibiotics may choose not to be screened for asymptomatic bacteriuria; women at increased risk of urinary tract infections in pregnancy should follow guidance for higher risk populations. Guideline recommendation was: *We recommend screening pregnant women once during the first trimester with urine culture for asymptomatic bacteriuria (weak recommendation; very low-quality evidence).*
Comments	Systematic review and accompanying guidelines.
Abbreviations: ASB asymptomatic bacteriuria; wk week	

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

a) What are the benefits and harms of antibiotic treatment compared with no treatment for asymptomatic bacteriuria in pregnancy?

Table 34. Studies relevant to criterion 9

Allen 2018[10]	
Citation	**Allen VM, Yudin MH. No. 276-Management of Group B Streptococcal Bacteriuria in Pregnancy. *J Obstet Gynaecol Can* 2018;40(2):e181-e186.**
Aim	To provide information regarding the management of group B streptococcal (GBS) bacteriuria to midwives, nurses, and physicians who are providing obstetrical care
Last search date	December 2010
Population	Pregnant women with group B streptococcal (GBS) bacteriuria
Intervention/ comparators	Screening and treatments
Outcomes	Neonatal GBS disease, preterm birth, pyelonephritis, chorioamnionitis, and recurrence of GBS colonisation.
Results	*Treatment*: Treatment of any bacteriuria with colony counts ≥100 000 CFU/mL in pregnancy is an accepted and recommended strategy and includes treatment with appropriate antibiotics (II-2A). Women with documented group B streptococcal bacteriuria (regardless of level of colony-forming units per mL) in the current pregnancy should be treated at the time of labour or rupture of membranes with appropriate intravenous antibiotics for the prevention of earlyonset neonatal group B streptococcal disease (II-2A). Asymptomatic women with urinary group B streptococcal colony counts <100 000 CFU/mL in pregnancy should not be treated with antibiotics for the prevention of adverse maternal and perinatal outcomes such as pyelonephritis, chorioamnionitis, or preterm birth (II-2E). *Screening*: Women with documented group B streptococcal bacteriuria should not be re-screened by genital tract culture or urinary culture in the third trimester, as they are presumed to be group B streptococcal colonised (II-2D).
Comments	The Society of Obstetricians and Gynaecologists (SOGC) of Canada guideline II-2= Evidence from well–designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group A = There is good evidence to recommend the clinical preventive action D = There is fair evidence to recommend against the clinical preventive action E = There is good evidence to recommend against the clinical preventive action
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; wk week	

Angelescu 2016[41]	
Citation	**Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. *BMC Pregnancy Childbirth* 2016;16(1):336.**
Aim	The systematic review had three objectives: firstly, to assess the patient-relevant benefits and harms of screening for ASB versus no screening; secondly, to compare the benefits and harms of different screening strategies; and thirdly, in case no reliable evidence on the overarching screening question was identified, to determine the benefits and harms of treatment of ASB.
Last search date	February 2016
Population	Pregnant women with ASB
Intervention/ comparators	Any ASB screening strategy followed by treatment, if necessary, vs. any treatment for ASB
Outcomes	Pyelonephritis; UTI; Symptoms linked directly or indirectly to UTI (e. g. headache or visual impairment as symptoms of pre-eclampsia, fever); Infant morbidity (e. g. respiratory distress syndrome, sepsis, cerebral haemorrhage, necrotising enterocolitis); Perinatal mortality; Early preterm birth (< 32 weeks of gestation); Very low birth weight (< 1500 g); Health-related quality of life and psychosocial functioning; Any adverse event
Results	No eligible studies were found that investigated the benefits and harms of screening for ASB versus no screening or that compared different screening strategies. Four RCTs comparing antibiotics with no treatment or placebo in 454 pregnant women with ASB. The results of 2 studies published in the 1960s showed a statistically significant reduction in rates of pyelonephritis (odds ratio [OR] = 0.21, 95 % confidence interval [CI] 0.07–0.59) and lower UTI (OR = 0.10, 95 % CI 0.03–0.35) in women treated with antibiotics. By contrast, event rates reported by a recent study were not statistically significantly different, neither regarding pyelonephritis (0 % vs. 2.2 %; OR = 0.37, CI 0.01–9.25, p = 0.515) nor regarding lower UTI during pregnancy (10 % vs. 18 %; Peto odds ratio [POR] = 0.53, CI 0.16–1.79, p = 0.357). Data were insufficient to determine the risk of harms. As three of the four studies were conducted several decades ago and have serious methodological shortcomings, the applicability of their findings to current health care settings is likely to be low. The recent high-quality RCT was stopped early due to a very low number of primary outcome events, a composite of preterm delivery and pyelonephritis. Therefore, the results did not show a benefit of treating ASB. To date, no reliable evidence supports routine screening for ASB in pregnant women. No RCTs are available that assess the benefits and harms of screening for ASB. The available evidence is limited to four treatment trials: three with serious methodological shortcomings and questionable applicability to current medical practice and one low-risk-ofbias trial that was stopped due to a very low number of pyelonephritis events in both the treatment and control group. Consequently, no conclusions can be drawn on whether the benefits of screening for ASB outweigh the potential harms. However, no reliable evidence supports routine screening for ASB in pregnant women.
Comments	Update of HTA report of the benefits and harms of screening for ASB in pregnancy conducted by the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG).
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; HTA health technology assessment; OR odds ratio; RCT randomised controlled trial; UTI urinary tract infection; wk week	

Henderson 2019[52]	
Citation	**Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: an updated systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 183 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US), 2019 [accessed 17.10.19] Available from: https://www.ncbi.nlm.nih.gov/books/NBK547176/** Also linked to: Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2019;322(12):1195-205.
Aim	To systematically reviewed evidence on the benefits and harms of screening for asymptomatic bacteriuria (ASB) and treatment for pregnant women, non-pregnant women, and men.
Last search date	September 7, 2018
Population	All adults, but separate subgroup data for pregnant women with ASB
Intervention/ comparators	Screening vs. no screening Treatment vs. no treatment
Outcomes	Low birthweight; pyelonephritis; AEs.
Results	Fourteen included studies in pregnant women; n=2 effectiveness and/or harms of screening (N=5,289) and n=12 effectiveness and harms of treatment (N=2,377). *Screening*: Of the two cohort studies on screening in pregnant women, one conducted in Spain (N=4,917) identified a three-fold reduction in risk for in unadjusted comparisons on a retrospective unscreened and screened cohort. The other cohort study of screening in pregnant women was conducted in Turkey (N=372) and had low statistical power for comparisons of health outcomes in a screened and unscreened cohort due to rarity of outcome events. *Treatment*: Data from 12 trials provided evidence that treatment of ASB in pregnancy reduces the risk of pyelonephritis (pooled relative risk [RR], 0.24 [95% CI, 0.14 to 0.40], k=12, n=2,068, I^2 =56.9%). Seven treatment studies reported infant outcomes, demonstrating a reduction in low birthweight (<2500g or SGA <10th percentile) (pooled RR, 0.64 [95% CI, 0.46 to 0.90], k=7, n=1,522, I^2 =15.8.6%). Data on potential harms and adverse effects of antibiotic treatment of ASB in pregnancy were sparsely reported in the trials, and power was low for observing rare outcomes. A pooled analysis from five studies reporting congenital malformations was null (pooled RR, 0.44 [95% CI, 0.16 to 1.22], k=5, n=961, I^2 =0%). Adverse reactions to medications were reported, including vaginitis, diarrhoea, rashes, and nausea. In pregnancy, there is some evidence that treatment of urine culture screen detected ASB confers a benefit to maternal and infant health, but most of the evidence is from an earlier era. Information on harms was limited in the included studies, but established and emerging evidence highlights the importance of antibiotic stewardship to limit the development of antibiotic resistance and rising awareness of potential harms associated with antibiotic exposure, including changes to the microbiome that increasingly are found to have consequences for health.
Comments	US Preventive Services Task Force (USPSTF report)

Abbreviations:
AE adverse event; ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; HTA health technology assessment; n number of participants; N total number in population; RCT randomised controlled trial; RR relative risk; SGA small for gestational age

Koves 2017[44]	
Citation	**Koves B, Cai T, Veeratterapillay R, Pickard R, Seisen T, Lam TB, et al. Benefits and Harms of Treatment of Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. *Eur Urol* 2017;72(6):865-868.**
Aim	To determine any benefits and harms of treating ABU in particular patient groups (including pregnant women)
Last search date	December 2010
Population	Adults but subgroup data specific to pregnant women with ASB
Intervention/ comparators	Antibiotic treatment vs. no antibiotics; single vs. short course antibiotic treatments
Outcomes	Symptomatic UTI, resolution of ABU, low birthweight, pre-term delivery, side effects
Results	A meta-analysis of 11 RCTs involving 2002 pregnant women with ABU found that antibiotic treatment significantly reduced the number of symptomatic UTIs (RR = 0.22, 95% CI 0.12–0.40; very low–quality evidence) compared with placebo or no treatment. Data from six RCTs involving 716 pregnant women showed benefit for antibiotic treatment in resolving ABU (RR = 2.99, 95% CI 1.65–5.39; very low–quality evidence). Data from eight RCTs with 1689 women showed reduction in risk of low birthweight (RR = 0.58, 95% CI 0.36–0.94; very low–quality evidence) and data from 44 RCTs with 854 women showed reduced risk of preterm delivery (RR = 0.34, 95% CI 0.18–0.66; low-quality evidence). A single recent trial of higher methodological quality did not find benefit for antibiotic treatment. Nine RCTs compared a single dose with the standard short-course (2–7 d) treatment of ABU in pregnant women. Data from nine RCTs with 1268 women showed no difference in the rate of ABU resolution (RR = 0.97, 95% CI 0.89–1.07; very low–quality evidence). A meta-analysis of three RCTs with 891 women found no difference in the rate of symptomatic UTI Overall, antibiotic treatment did appear to benefit women in pregnancy. (RR = 1.07, 95% CI 0.47–2.47; low-quality evidence) and data from three RCTs with 814women showed no difference in the rate of preterm delivery (RR = 1.16, 95% CI 0.75–1.78; low-quality evidence). One RCT with 714 women showed a higher rate of low birthweights using a single dose compared with short-course treatment (RR = 1.65, 95% CI 1.06–2.57; moderate-quality evidence). Single-dose treatment was associated with significantly fewer side effects compared with short-course treatment, based on the meta-analysis of data from six RCTs including 458 women (RR = 0.40, 95% CI 0.22–0.72; low-quality evidence). Overall, in pregnant women, evidence suggested that treatment of ABU decreased risk of symptomatic UTI, low birthweight, and preterm delivery. In addition, current evidence also suggests that ABU treatment is required in pregnant women, although the results of a recent trial have challenged this view.
Comments	European Association of Urology (EAU) Urological Infection Guidelines
Abbreviations: AE adverse event; ASB asymptomatic bacteriuria; CFU colony forming units; CI confidence interval; HTA health technology assessment; n number of participants; N total number in population; RCT randomised controlled trial; RR relative risk; SGA small for gestational age	

Study ID	**Study design**	**Population**	**Test for ASB**
Kazemier 2015[13]	**Study design:** Prospective cohort study	**No. of participants:** 5132 eligible, 4283 analysed	**Timing:** 16–22 wks gestation **Setting:** 8 hospitals and 5 ultrasound centres

Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis* 2015;15(11):1324-33. Additional information taken from methods paper[34] and abstract[53]	**Level of evidence**: Level 1b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** Netherlands **Study aim:** To assess the maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy in a national prospective cohort study **Study conclusions:** In women with an uncomplicated singleton pregnancy, ASB is not associated with preterm birth. ASB showed a significant association with pyelonephritis, but the absolute risk of pyelonephritis in untreated asymptomatic bacteriuria is low. These findings question a routine screen-treat policy for ASB in pregnancy. **Outcomes assessed:** • Composite of pyelonephritis,* delivery before 34 wks gestation, or both (primary outcome) • Adverse neonatal outcome (death or severe morbidity) • Neonatal death before discharge from the neonatal ward • Severe neonatal morbidity** • Neonatal birthweight • Congenital abnormalities • Time to delivery • Spontaneous preterm birth rate 32 to 37 wks • Admission to neonatal ICU • Maternal morbidity (including UTI; gestational diabetes; pregnancy induced	**Inclusion criteria:** Women aged ≥18 years with singleton pregnancy without symptoms of UTI at 16–22 wks of gestation **Exclusion criteria:** History of spontaneous preterm delivery <34 wks; signs of threatening preterm delivery; foetal congenital malformations; use of antibiotics within 2 wks of screening; known G6PD deficiency or allergy to nitrofurantoin or risk factors for complicated UTI (pre-gestational diabetes mellitus, immunosuppressive medication, functional or structural abnormalities of the urinary tract). **Stage of pregnancy:** 16–22 wks of gestation **Antenatal risk factors for ASB**: NR.	**Sample collection method:** Mid-stream urine sample **Number of samples per patient:** Single **Test description:** Single dipslide (UricultW, Orion Diagnostica, Espoo, Finland) consisting of two different culture media (cysteine lactose electrolyte deficient medium and MacConkey medium) – reported to have 98.0% sensitivity and 99.6% specificity to detect ASB in pregnancy. Inoculated with urine at hospital, ultrasound centre or midwifery practices. Dipslides were sent by mail to laboratory for infectious diseases in Groningen, the Netherlands the same day. Laboratory technicians read the dipslide directly when incubated for 2-3 days at RT. If no colonies formed, the dipslide was incubated for another 24 hrs at 35^{o}C. **Confirmatory methodology:** None - Urinary culture was not feasible in the Dutch antenatal care system since 70% of Dutch women attend antenatal care at a midwifery practice where there is no direct access to a microbiology laboratory to perform the cultures. **Contamination:** Defined as >2 species present – excluded from the study **Definition of ASB:** Positive diplslide (≥1 × 10^5CFU/ml urine for single microorganism or ≥ 1 × 10^5 CFU/ ml for at least one microorganism when two are present) without any symptoms of UTI.

	hypertension; pre-eclampsia; HELLP syndrome; kidney stones; cholestasis; thromboembolic events; non-spontaneous labour onset; epidural/spinal analgesia during labour; endometritis within 6wk of delivery; mastitis within 6wks of delivery) • Costs • Chorioamnionitis (only mentioned in protocol) • No. of days maternal admission for (threatened) preterm labour and/or pyelonephritis (only mentioned in protocol) • Number of women willing to take part in subsequent RCT comparing antibiotic treatment versus no treatment		

Summary of results:

5132 eligible women were screened for ASB of which 250 (5%) testing positive

Comparison

ASB-positive women who were untreated or given placebo during the linked RCT (n=208) versus ASB-negative women (n=4035)

Primary outcomes

More ASB-positive women developed pyelonephritis compared with ASB-negative women: 5/208 (2.4%) versus 24/4035 (0.6%), odds ratio (OR) 3.9 (95% confidence interval [CI] 1.4 to 11.4). Of the 29 women with acute pyelonephritis, five (17%) had ASB between 16 and 22 wks. The median duration of hospital stay for women with pyelonephritis was 3 days (range 2–10 days). The course of disease in these women was mild, and none needed admission to an intensive care unit.

No clear differences between ASB-positive and ASB-negative women were observed for delivery <34 wks (2/208 [1.0%] versus 54/4035 [1.3%] respectively, OR 0.7, 95% CI 0.2 to 2.8) or the composite primary outcome, defined as pyelonephritis or delivery <34 wks or both (6/208 [2.9%] versus 77/4035 [1.9%] respectively, OR 1.5, 95% CI 0.6 to 3.5^).

Secondary outcomes - maternal

More ASB-positive women had a UTI treated with antibiotics antenatally compared with ASB negative women (42/208 [20.2%] versus 317/4035 [7.9%], OR 2.9, 95% CI 2.0 to 4.2) and there was a similar result for the outcome of recurrent UTI treated with antibiotics antenatally (18/208 [8.7%] versus 105/4035 [2.6%], OR 3.5, 95% CI 1.8 to 6.7). No clear between-group differences were seen for other maternal outcomes: UTI treated with antibiotics postpartum, within 6 wks of delivery; treatment with antibiotics antenatally for reason other than UTI; incidence of gestational diabetes; pregnancy-induced hypertension; pre-eclampsia; kidney stones; cholestasis; non-spontaneous onset of labour; epidural or spinal analgesia during labour, and; mastitis within 6 wks of delivery. The following maternal outcomes could not be estimated because of zero events in the ASB-positive group: haemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome; thromboembolic events, and; endometritis within 6 wks of delivery.

Secondary outcomes - neonatal More ASB-positive women delivered a female foetus compared with ASB-negative women: 129/208 (62.0%) versus 1978/4035 (49.0%), OR 1.7, 95% CI 1.3 to 2.2. Mean (standard error) birthweights per group were 3495 (40)g versus 3454 (9)g respectively. Between-group differences were not detected for other neonatal outcomes: median gestational age at delivery; preterm birth at <37 wks, <32 wks or 28 wks; small for gestational age according to 10th or 5th percentiles; perinatal death; composite severe neonatal morbidity outcome;** admission to neonatal intensive care unit; neonatal sepsis confirmed with culture, and; congenital abnormalities. **All OR estimates were as reported by the study authors and were adjusted for smoking, educational status, conception through in-vitro fertilisation or intracytoplasmic sperm injection and pre-existent hypertension.**
Key: ***** Defined as hospital admission with at least two of the following features: fever (body temperature ≥ 8·0°C), symptoms of pyelonephritis (nausea, vomiting, chills, and costovertebral tenderness), and a positive urine culture indicating the presence of bacteria in the urine. ****** Defined as presence of at least one of following: severe RDS, BPD, periventricular leukomalacia > grade 1, intracerebral haemorrhage> grade 2, NEC > stage 1 or proven sepsis (including GBS sepsis), death before discharge from nursery *** Defined as a clinical report of a UTI that was treated with antibiotics ^ Two women had pyelonephritis and a preterm delivery before 34 wks
Abbreviations: ASB asymptomatic bacteriuria; BPD bronchopulmonary dysplasia; CFU colony forming units; CI confidence interval; DM diabetes mellitus; GDM gestational diabetes mellitus; G6PD deficiency glucose-6-phosphate dehydrogenase deficiency; GBS group B streptococcus; HELLP haemolysis, elevated liver enzymes, and low platelet count; hr hour; min minute; n number of participants/samples; N total number of participants/samples; NEC necrotising enterocolitis; NR not reported; OR odds ratio; RDS respiratory distress syndrome; rpm revolutions per minute; UTI urinary tract infection; wk week

Nicolle 2019[14]	
Citation	**Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis 2019;68(10):e83-e110.**
Aim	To provide evidence-based guidance on the screening and treatment of ASB in populations where ASB has been identified as common or potentially detrimental.
Last search date	June 2017
Population	Total population of adults and children (specifically includes separate data for pregnant women)
Intervention/ comparators	Screening vs. no screening Treatment vs. no treatment
Outcomes	Prevalence/incidence; pyelonephritis; preterm delivery; optimal duration of therapy;
Results	1. In pregnant women, we recommend screening for and treating ASB (strong recommendation, moderate-quality evidence). Remarks: A recent study in the Netherlands suggested that non-treatment of ASB may be an acceptable option for selected low-risk women. However, the committee felt that further evaluation in other populations was necessary to confirm the generalizability of this observation. We suggest a urine culture collected at 1 of the initial visits early in pregnancy. There is insufficient evidence to inform a

	recommendation for or against repeat screening during the pregnancy for a woman with an initial negative screening culture or following treatment of an initial episode of ASB. 2. In pregnant women with ASB, we suggest 4–7 days of antimicrobial treatment rather than a shorter duration (weak recommendation, low-quality evidence). Remarks: The optimal duration of therapy will vary depending on the antimicrobial given; the shortest effective course should be used
Comments	Infectious Diseases Society of America recommendations but based on a systematic review the results of which are reported as part of the guideline.
Abbreviations: ASB asymptomatic bacteriuria	

Smaill 2019[11]	
Citation	**Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2019, Issue 11. Art. No.: CD000490. DOI:10.1002/14651858.CD000490.pub4**
Aim	To assess the effect of antibiotic treatment for asymptomatic bacteriuria on the development of pyelonephritis and the risk of low birthweight and preterm birth.
Last search date	4 November 2018
Population	Pregnant women found, on antenatal screening, to have ASB
Intervention/ comparators	Any antibiotic regimen was compared with placebo or no treatment
Outcomes	Development of pyelonephritis; preterm birth less than 37 weeks; birthweight less than 2500 g; persistent bacteriuria; neonatal mortality or other serious adverse neonatal outcome; maternal side effects; costs; birthweight; gestational age; women's satisfaction, as measured by trial authors
Results	Included 15 studies, involving over 2000 women. Antibiotic treatment compared with placebo or no treatment may reduce the incidence of pyelonephritis (average risk ratio (RR) 0.24, 95% confidence interval (CI) 0.13 to 0.41; 12 studies, 2017 women; low-certainty evidence). Antibiotic treatment may be associated with a reduction in the incidence of preterm birth (RR 0.34, 95% CI 0.13 to 0.88; 3 studies, 327 women; low-certainty evidence), and low birthweight babies (average RR 0.64, 95% CI 0.45 to 0.93; 6 studies, 1437 babies; low-certainty evidence). There may be a reduction in persistent bacteriuria at the time of delivery (average RR 0.30, 95% CI 0.18 to 0.53; 4 studies; 596 women), but the results were inconclusive for serious adverse neonatal outcomes (average RR 0.64, 95% CI 0.23 to 1.79, 3 studies; 549 babies). There were very limited data on which to estimate the effect of antibiotics on other infant outcomes, and maternal adverse effects were rarely described. Overall, only one trial at low risk of bias across all domains; the other 14 studies were assessed as high or unclear risk of bias. Many studies lacked an adequate description of methods, and we could only judge the risk of bias as unclear, but in most studies, we assessed at least one domain at high risk of bias. We assessed the quality of the evidence for the three primary outcomes with GRADE software, and found low-certainty evidence for pyelonephritis, preterm birth, and birthweight less than 2500 g. Antibiotic treatment may be effective in reducing the risk of pyelonephritis in pregnancy, but our confidence in the effect estimate is limited given the low certainty of the evidence. There may be a reduction in preterm birth and low birthweight with antibiotic treatment, consistent

	with theories about the role of infection in adverse pregnancy outcomes, but again, the confidence in the effect is limited given the low certainty of the evidence.
Comments	Cochrane review.
Abbreviations: ASB asymptomatic bacteriuria; CI confidence interval; RCT randomised controlled trial; RR relative risk	

Wingert 2019[40]	
Citation	**Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347**. Also linked to: Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018. Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf
Aim	To provide recommendations on screening for ASB in pregnancy
Last search date	October 2017
Population	Pregnant women with ASB (women who are not at increased risk for asymptomatic bacteriuria)
Intervention/ comparators	Before vs. after ASB screening ASB screening vs. no screening Antibiotic treatment vs. no antibiotic treatment
Outcomes	Pyelonephritis; perinatal mortality; spontaneous abortion; preterm delivery; foetal abnormalities; low birth weight; neonatal sepsis; feasibility; acceptability; cost; equity; patient values and preferences.
Results	Systematic reviews on screening and treating asymptomatic bacteriuria in pregnancy found very low-quality evidence for a modest reduction in pyelonephritis among pregnant women and the number of low-birth-weight infants. Only scant and very low-quality evidence was available to infer harms associated with screening and treatment of asymptomatic bacteriuria in pregnancy. Patient values and preferences regarding screening for asymptomatic bacteriuria are variable and influenced by individual perspectives regarding the small potential benefit of antibiotic use, as well as potential harms associated with antibiotic use in pregnancy. A weak recommendation in favour of screening is warranted given the small but uncertain benefit of screening for asymptomatic bacteriuria, variation in women's values and preferences, and the judgment that harms associated with this long-standing practice in Canada are likely minimal. Some women who are not at increased risk of urinary tract infections in pregnancy and are more concerned with potential harms of antibiotics may choose not to be screened for asymptomatic bacteriuria; women at increased risk of urinary tract infections in pregnancy should follow guidance for higher risk populations.

	Guideline recommendation was: *We recommend screening pregnant women once during the first trimester with urine culture for asymptomatic bacteriuria (weak recommendation; very low-quality evidence).*
Comments	Systematic review and accompanying guidelines.
Abbreviations: ASB asymptomatic bacteriuria	

Question 5: How benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy?

a) **How benefits and harms of screening and treatment inform women decisions to undergo screening for bacterial infections during pregnancy?**
b) **How do women weigh the benefits and harms of a screening and treatment for bacterial infections during pregnancy?**

Table 35. Studies relevant to criterion 12

ID	Study details	Population	Testing
Kazemier 2015[13, 34] Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis* 2015;15(11):1324-33.	**Study design:** Prospective cohort study **Level of evidence**: Level 2b (Oxford Centre for Evidence-based Medicine – Levels of Evidence - March 2009) **Geographical location:** Netherlands **Study aim:** To assess the maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy in a national prospective cohort study **Study conclusions:** In women with an uncomplicated singleton pregnancy, ASB is not associated with preterm birth. ASB showed a significant association with pyelonephritis, but the absolute risk of pyelonephritis in untreated asymptomatic bacteriuria is low. These findings question a routine screen-treat policy for ASB in pregnancy. **Outcomes assessed:** • Composite of pyelonephritis,* delivery before 34 wks gestation, or both (primary outcome)	**No. of participants:** 5132 eligible, 4283 analysed **Inclusion criteria:** Women aged ≥18 years with singleton pregnancy without symptoms of UTI at 16–22 wks of gestation **Exclusion criteria:** History of spontaneous preterm delivery <34 wks; signs of threatening preterm delivery; foetal congenital malformations; use of antibiotics within 2 wks of screening; known G6PD deficiency or allergy to nitrofurantoin or risk factors for complicated UTI (pre-gestational diabetes mellitus, immunosuppressive medication, functional or structural abnormalities of the urinary tract). **Stage of pregnancy:** 16–22 wks of gestation **Antenatal risk factors for ASB**: NR.	**Timing:** 16–22 wks gestation **Setting:** 8 hospitals and 5 ultrasound centres **Sample collection method:** Mid-stream urine sample **Number of samples per patient:** Single **Test description:** Single dipslide (UricultW, Orion Diagnostica, Espoo, Finland) consisting of two different culture media (cysteine lactose electrolyte deficient medium and MacConkey medium) – reported to have 98.0% sensitivity and 99.6% specificity to detect ASB in pregnancy. Inoculated with urine at hospital, ultrasound centre or midwifery practices. Dipslides were sent by mail to laboratory for infectious diseases in Groningen, the Netherlands the same day. Laboratory technicians read the dipslide directly when incubated for 2-3 days at room temperature. If no colonies formed, the dipslide was incubated for another 24 hrs at 35°C. **Confirmatory methodology:** None - Urinary culture was not feasible in the Dutch antenatal care system since 70% of Dutch women attend

	• Adverse neonatal outcome (death or severe morbidity) • Neonatal death before discharge from the neonatal ward • Severe neonatal morbidity** • Neonatal birthweight • Congenital abnormalities • Time to delivery • Spontaneous preterm birth rate 32 to 37 wks • Admission to neonatal ICU • Maternal morbidity (including UTI; gestational diabetes; pregnancy induced hypertension; pre-eclampsia; HELLP syndrome; kidney stones; cholestasis; thromboembolic events; non-spontaneous labour onset; epidural/spinal analgesia during labour; endometritis within 6wk of delivery; mastitis within 6wks of delivery) • Costs • Chorioamnionitis (only mentioned in protocol) • No. of days maternal admission for (threatened) preterm labour and/or pyelonephritis (only mentioned in protocol) • Number of women willing to take part in subsequent RCT comparing antibiotic treatment versus no treatment		antenatal care at a midwifery practice where there is no direct access to a microbiology laboratory to perform the cultures. **Contamination:** Defined as >2 species present – excluded from the study **Definition of ASB:** Positive diplslide (≥1 × 10^5CFU/ml urine for single microorganism or ≥ 1 × 10^5 CFU/ ml for at least one microorganism when two are present) without any symptoms of UTI.

Summary of results:

5132 eligible women were screened for ASB of which 250 (5%) testing positive

Comparison
ASB-positive women who were untreated or given placebo during the linked RCT (n=208) versus ASB-negative women (n=4035)

Number of women willing to take part in subsequent RCT comparing antibiotic treatment versus no treatment
85/255 (33%) women who were confirmed as positive for ASB agreed to take part in the RCT. Of those who refused to take part in the RCT (170/255; 67%), 12 were lost to follow-up. Most of the remaining women (155/163 [94%]) who did not want to participate in the subsequent RCT made this choice because 'they did not want to receive antibiotics during pregnancy for an asymptomatic condition'.

Primary outcomes See Q1. What is the disease burden associated with ASB? **Secondary outcomes - maternal** See Q1. What is the disease burden associated with ASB? **Secondary outcomes - neonatal** See Q1. What is the disease burden associated with ASB?
Abbreviations: ASB asymptomatic bacteriuria; CFU colony forming units; hr hour; min minute; n number of participants; UTI urinary tract infection; wk week

Wingert 2019[40]	
Citation	**Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347**. Also linked to: Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018. Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf
Aim	To provide recommendations on screening for ASB in pregnancy
Last search date	October 2017
Population	Pregnant women with ASB (women who are not at increased risk for asymptomatic bacteriuria)
Intervention/ comparators	Before vs. after ASB screening ASB screening vs. no screening Antibiotic treatment vs. no antibiotic treatment
Outcomes	Pyelonephritis; perinatal mortality; spontaneous abortion; preterm delivery; foetal abnormalities; low birth weight; neonatal sepsis; feasibility; acceptability; cost; equity; patient values and preferences.
Results	Systematic reviews on screening and treating asymptomatic bacteriuria in pregnancy found very low-quality evidence for a modest reduction in pyelonephritis among pregnant women and the number of low-birth-weight infants. Only scant and very low-quality evidence was available to infer harms associated with screening and treatment of asymptomatic bacteriuria in pregnancy.

	Patient values and preferences regarding screening for asymptomatic bacteriuria are variable and influenced by individual perspectives regarding the small potential benefit of antibiotic use, as well as potential harms associated with antibiotic use in pregnancy. A weak recommendation in favour of screening is warranted given the small but uncertain benefit of screening for asymptomatic bacteriuria, variation in women's values and preferences, and the judgment that harms associated with this long-standing practice in Canada are likely minimal. Some women who are not at increased risk of urinary tract infections in pregnancy and are more concerned with potential harms of antibiotics may choose not to be screened for asymptomatic bacteriuria; women at increased risk of urinary tract infections in pregnancy should follow guidance for higher risk populations. Guideline recommendation was: *We recommend screening pregnant women once during the first trimester with urine culture for asymptomatic bacteriuria (weak recommendation; very low-quality evidence).*
Comments	Systematic review and accompanying guidelines.
Abbreviations: ASB asymptomatic bacteriuria	

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below.

Table 36. Question 1: Risk of bias in primary studies (JBI checklist for cohort studies)[28]

Each checklist item was judged for each study and one of the following responses assigned: Yes, No, Unclear or Not applicable. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

JBI checklist item (cohort studies)	Kazemier 2015[13, 34]
1. Were the 2 groups similar & recruited from the same population?	Yes – both groups are from same source population and inclusion criteria are clear
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	Yes – all women were screened for ASB in the same way
3. Was the exposure measured in a valid and reliable way?	Yes – used dip slide test which has satisfactory performance according to systematic review data[35]
4. Were confounding factors identified?	Yes - baseline differences in current smoking status
5. Were strategies to deal with confounding factors stated?	Yes – odds ratio estimations for maternal & neonatal outcomes adjusted for smoking, educational status, assisted conception and pre-existent hypertension
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes – women with urinary tract symptoms were excluded
7. Were the outcomes measured in a valid and reliable way?	Yes - Primary and secondary outcomes were defined and measured using prospectively collected data obtained by a validated linkage procedure between the midwifery registry, the obstetrics registry, and the neonatology registry
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes – participants followed up to 6 weeks after delivery
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes – follow-up not complete. Reasons for loss to follow-up shown on patient flow diagram.
10. Were strategies to address incomplete follow up utilised?	Yes – data imputation was used for patients lost to follow-up and those with contaminated dip slides.
11. Was appropriate statistical analysis used?	Yes – analyses adjusted for confounding variables
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias) – single sample
Abbreviations: ASB asymptomatic bacteriuria; JBI Joanna Briggs Institute	

JBI checklist item (cohort studies)	Naresh 2011[33]
1. Were the 2 groups similar & recruited from the same population?	Yes – both groups are from same source population
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	No – all women were screened for ASB in the same way, but urine cultures were collected earlier in the negative urine culture group (11.6 versus 12.2 weeks, p=0.02)
3. Was the exposure measured in a valid and reliable way?	No – cultures were used to screen for ASB but the time point at which cultures were taken differed between the two outcome groups
4. Were confounding factors identified?	Yes – baseline differences in chronic hypertension; self-reported pregravid weight >200lbs; prior pre-term delivery; timing of urine collection
5. Were strategies to deal with confounding factors stated?	Yes – analyses were adjusted for maternal age, race, parity, presence of multiples, presence of foetal anomalies, history of prior preterm birth, smoking, pregestational diabetes, maternal anaemia, maternal cardiac disease, maternal chronic hypertension, gestational hypertension (including preeclampsia and eclampsia), pregravid weight, and socioeconomic status.
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear for pyelonephritis
7. Were the outcomes measured in a valid and reliable way?	No – ASB was measured using a non-standard definition. Data for other outcomes was collected retrospectively from hospital discharge records and the research database.
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Unclear – obstetric outcomes assessed at time of delivery but length of follow up unclear for pyelonephritis
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes – it appeared that all recruited participants were included in the analysis
10. Were strategies to address incomplete follow up utilised?	Not applicable
11. Was appropriate statistical analysis used?	Yes – logistic regression used and results presented with odds ratios and 95% confidence intervals
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias) – single sample
Abbreviations: ASB asymptomatic bacteriuria; JBI Joanna Briggs Institute	

JBI checklist item (cohort studies)	Schneeberger 2018[15]
1. Were the 2 groups similar & recruited from the same population?	Yes – both groups are from same source population
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	Yes – all women were screened for ASB in the same way
3. Was the exposure measured in a valid and reliable way?	Yes –cultures were used for ASB screening

4. Were confounding factors identified?	Unclear – maternal baseline characteristics were tabulated but not presented per groups with ASB positive or negative test results
5. Were strategies to deal with confounding factors stated?	No – cross-tabulation of variables presented but no regression analyses to adjust for confounding factors
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes – the only relevant outcome was preterm birth and women were assessed for the exposure antenatally
7. Were the outcomes measured in a valid and reliable way?	Yes - Primary and secondary outcomes were defined and measured using prospectively collected data and obtained by questionnaire or medical record (hospital, midwifery clinic or GP).
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes – participants followed up to 6 weeks after delivery
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	No – incomplete follow-up data is apparent and not explained further. For missing data on the primary and secondary endpoints complete case analyses per exposure were performed.
10. Were strategies to address incomplete follow up utilised?	Unclear – no information
11. Was appropriate statistical analysis used?	No – descriptive approach only
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias) – some patients provided more than one sample but these were not consecutive
Abbreviations: ASB asymptomatic bacteriuria; JBI Joanna Briggs Institute	

Table 37. Question 2: Risk of bias in systematic reviews (ROBIS)[26]

Each checklist item was judged for each study and one of the following responses assigned: Probably Yes, Yes, Probably No, No, or Not enough information. The risk of bias was assigned one of the following responses: Low risk; High risk; Unclear risk. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Rogozinska E, Formina S, Zamora J, Mignini L, Khan KS. Accuracy of Onsite Tests to Detect Asymptomatic Bacteriuria in Pregnancy: A Systematic Review and Meta-analysis. *Obstet Gynecol* 2016;128(3):495-503.			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objective clearly and eligibility criteria clearly defined.	Probably Yes	Low risk
1.2 Were the eligibility criteria appropriate for the review question?	Eligibility criteria appears appropriate.	Probably Yes	
1.3 Were eligibility criteria unambiguous?	Eligibility criteria appears unambiguous.	Probably Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Studies with a case–control design, studies where the reference standard was not reported or used a different definition of bacteriuria than specified were excluded as this design and variation in reference standard were associated with bias.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No restrictions based on sources of information were reported.	Probably Yes	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Major databases such as MEDLINE, EMBASE, Web of Science, Scopus, and a specialized database of Latin-American literature were searched for studies published from database inception to August 2014 with no language restrictions.	Yes	High risk
2.2 Were methods additional to database searching used to identify relevant reports?	The search was updated to June 2015 and was supplemented by a hand search of the references from the included publications. The ClinicalTrials.gov register database was screened to identify any recently completed studies.	Yes	

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	The search strategy was reported however, a diagnostic test accuracy (DTA) study search filter was used. This is not advised due to the risk of missing relevant studies	Probably No	
2.4 Were restrictions based on date, publication format, or language appropriate?	No date or language restrictions	Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two independent reviewers (E.R. and S.F.) screened references and full text of previously selected articles. The consensus on the eligibility of evaluated publications was reached through discussion or consultation with a third reviewer (K.S.K.).	Probably Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	Data were extracted independently by two of the authors (E.R. and S.F.) onto a piloted sheet and discrepancies were discussed between reviewers.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	The risk of bias and applicability of included studies were assessed by two independent reviewers (E.R. and S.F.) using the QUADAS-2 tool10 tailored for this review.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	The risk of bias and applicability of included studies were assessed by two independent reviewers (E.R. and S.F.) using theQUADAS-2 tool10 tailored for this review. Any disagreements over quality assessment were resolved by a third reviewer (K.S.K.).	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	The synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	Analyses were predefined and followed.	Probably Yes	

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	The analyses were suitable for the review question.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Results of a sensitivity analysis based on study quality (ROB, description of urine sample) were reported and found that findings were generally robust.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Results of a sensitivity analysis based on study quality (ROB, description of urine sample) were reported and found that findings were generally robust.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	The overall quality of included studies was moderate.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	A diagnostic test accuracy study search filter was used. This is not advised due to the risk of missing relevant studies	High risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Table 30. Question 2: Risk of bias in primary studies (QUADAS-2)

Study: McIsaac 2005[12]
McIsaac W, Carroll JC, Biringer A, Bernstein P, Lyons E, Low DE and Permaul JA. *Screening for asymptomatic bacteriuria in pregnancy. JOGC* 2005;27(1):20-4.
DOMAIN 1: PATIENT SELECTION
A. Risk of Bias
Describe methods of patient selection:
All women presenting for antenatal care to 2 obstetricians and 6 family doctors affiliated to a large teaching hospital in Toronto, Canada between July 1996 and April 1998 were invited to participate. Urine cultures were excluded if the woman had symptoms of dysuria or had taken antibiotics within 1 wk of the antenatal visit.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Four screening strategies to detect ABU in pregnancy were compared: (1) urine dipstick testing at each antenatal visit using the LEN dipstick (Uristix 4, Bayer Pharmaceuticals) followed by a urine culture (sample taken at the same visit) if dipstick positive; (2) a single urine culture < 20 wks gestation; (3) two urine cultures, one < 20 wks and the other at 28 wks gestation; (4) three urine cultures, one < 20 wks, one at 28 wks and the third at 36 wks gestation. A positive LEN test strip was defined as either > trace leukocyte or positive for nitrite. The sampling method for urine culture was midstream urine sample. A standardised method was used to perform urine cultures in the same laboratory. A positive urine culture was defined as growth of a single organism at $\geq 10^3$ CFU/mL or two organisms at $\geq 10^5$ CFU/mL. No further details were provided for urine culture sampling or analysis methods.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes for LEN, No for urine culture methods
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**
DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: The reference standard was urine culture. The study authors had planned to collect a 2nd urine sample for all positive urine cultures for the purposes of confirmation but < 50% of women provided this. In light of this, ASB was defined as a single positive urine culture (positive = growth of a single organism at $\geq 10^3$ CFU/mL or two organisms at $\geq 10^5$ CFU/mL) in a woman without symptoms. The total number of ASB cases (reference standard positives) in the study population was defined as number of asymptomatic women with a positive urine culture, identified from any of the three urine culture strategies or by a culture prompted by a positive LEN test.	
Is the reference standard likely to correctly classify the target condition?	Unclear

Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**
DOMAIN 4: FLOW AND TIMING	
A. Risk of Bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: For screening strategy 1, some women did not receive the dipstick test at each antenatal visit (proportion receiving the test ranged from 68.3% to 83.0%). Reasons for missing the dipstick test were not explained. Urine cultures were only performed for women with a positive dipstick test and not for those with a negative test. A total of 2945 urine cultures were obtained from 1050 women across all time points. The number of urine cultures obtained per screening strategy is as follows: (1) 420; (2) 814; (3) 1732; (4) 2553. The number of planned urine cultures per time point (i.e. relating to screening strategies 2 to 4) were: (2) 814; (3) 918; (3) 821. Less than 50% of women provided a sample for a second urine culture. The missing data for urine cultures were not explained further. *Describe the time interval and any interventions between index test(s) and reference standard:* For strategy 1, a sample confirmatory urine culture was taken at the same visit. This was not reported, for urine culture strategies, but is likely to have varied considerably as wide ranges of timing are reported for each planned urine culture i.e. screening strategies 2 to 4: (2) 5 to 19 weeks gestation; (3) 20 to 32 weeks gestation; (4) 33 to 40 weeks gestation).	
Was there an appropriate interval between index test(s) and reference standard?	Unclear
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**
Key: ASB asymptomatic bacteriuria; CFU colony forming units; LEN leukocyte-esterase-nitrite; n number of participants/samples; hr hour; min minute; N total number of participants/samples; NPV negative predictive value; NR not reported; PPV positive predictive value; rpm revolutions per minute; UTI urinary tract infection; wk week	

Table 38. Question 3: Risk of bias in systematic reviews (ROBIS)[26]

Each checklist item was judged for each study and one of the following responses assigned: Probably Yes, Yes, Probably No, No, or Not enough information. The risk of bias was assigned one of the following responses: Low risk; High risk; Unclear risk. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. *BMC Pregnancy Childbirth* 2016;16(1):336.			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria clearly defined.	Yes	Unclear risk
1.2 Were the eligibility criteria appropriate for the review question?	Eligibility criteria was appropriate.	Yes	
1.3 Were eligibility criteria unambiguous?	Eligibility criteria was unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	No publication date restrictions.	Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No language restrictions. Both published and unpublished studies were included. Only full-text documents (e. g. journal article or clinical study report) were included.	Probably Not	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Primary studies and secondary publications were searched for in MEDLINE (1946 to January 2016) and EMBASE (1974 to January 2016) via Ovid, and in the Cochrane Central Register of Controlled Trials (January 2016).	Yes	High risk
2.2 Were methods additional to database searching used to identify relevant reports?	Reference lists of retrieved systematic reviews were searched by hand. In addition, web-based clinical trial registries were screened (ClinicalTrials.gov, International Clinical Trials Registry Platform Search Portal, and the EU Clinical Trials Register). Publications cited in comments addressed to the Federal Joint Committee, the decision-making body in the German statutory healthcare system and IQWiG's main commissioning body were also screened.	Yes	

	Persons and parties who had submitted written comments on the preliminary report were asked to provide any additional relevant studies.		
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy fully reported but unlikely to have included all relevant database indexing terms and free text synonyms	Probably No	
2.4 Were restrictions based on date, publication format, or language appropriate?	Primary studies and secondary publications were searched for in MEDLINE (1946 to January 2016) and EMBASE (1974 to January 2016) via Ovid, and in the Cochrane Central Register of Controlled Trials (January 2016). No further restrictions reported.	Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers independently screened titles and abstracts of retrieved citations to identify potentially eligible primary and secondary publications. The full texts of these articles were obtained and independently evaluated by the same two reviewers applying the full set of inclusion and exclusion criteria. All documents retrieved from nonbibliographic sources were also screened for eligibility or relevant information on studies. Disagreements were resolved by consensus.	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	The individual steps of the data extraction and risk of bias assessment were conducted by one author and checked by another; disagreements were resolved by consensus.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Risk of bias was assessed for each outcome and rated these risks as “high” or “low”. In individual studies the risk of bias was assessed by determining the adequacy of the following quality criteria: generation of random allocation sequence, allocation concealment, blinding of participants and investigators, and selective outcome reporting.	Probably Yes	

3.5 Were efforts made to minimise error in risk of bias assessment?	The individual steps of the data extraction and risk of bias assessment were conducted by one author and checked by another; disagreements were resolved by consensus.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All analyses were pre-defined	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Synthesis appeared appropriate.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Meta-analyses were not feasible, so a narrative synthesis was used. Differences between the studies were discussed.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Sensitivity analyses were performed to explore the potential impact of missing data.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Three out of four had high risk of bias. Studies were assessed individually.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	No – list of search terms not comprehensive and only full text reports were included which means that some relevant studies may have been missed.	High risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2019;322(12):1195-205. Also reported in: Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: an updated systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 183 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US), 2019 [accessed 17.10.19] Available from: https://www.ncbi.nlm.nih.gov/books/NBK547176/			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Research questions clearly listed. Appendix A Table 1 details inclusion and exclusion criteria.	Yes	High risk
1.2 Were the eligibility criteria appropriate for the review question?	Research questions clearly listed. Appendix A Table 1 details inclusion and exclusion criteria. Criteria thorough and appropriate for review questions	Yes	
1.3 Were eligibility criteria unambiguous?	Appendix A Table 1 details inclusion and exclusion criteria. Eligibility criteria clear and unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Restricted to countries rated high or very high on the human development index	Probably yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Restricted to English-language only	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	MEDLINE, PubMed Publisher - Supplied Records, and the Cochrane Collaboration Central Registry of Controlled Trials were searched.	Probably Yes	Low risk
2.2 Were methods additional to database searching used to identify relevant reports?	Reference lists of other previously published reviews, meta-analyses, and primary studies were examined to identify additional potential studies for inclusion. Searches were supplemented with suggestions from experts and articles identified through news and table-of-contents alerts, such as those produced by the USPSTF Scientific Resource Center LitWatch activity. ClinicalTrials.gov (https://ClinicalTrials.gov/) was also searched for ongoing trials.	Yes	

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy fully reported and appears appropriate.	Probably Yes	
2.4 Were restrictions based on date, publication format, or language appropriate?	Restricted to English language (This restriction has already been marked down in previous question)	Probably Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers independently screened the title and abstract of all identified articles to determine if the study met our a priori inclusion and exclusion criteria. Two reviewers then independently evaluated the full-text articles of all potentially relevant studies against the complete inclusion and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion.	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	For all included studies, one reviewer extracted key elements into standardized abstraction forms. A second reviewer checked the data for accuracy.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	For each study, general characteristics (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race/ethnicity, setting, country), analytic methods, definitions of outcomes measures, and results were abstracted.	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to have been collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies. We assigned each study a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies. We assigned each study a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**

4.1 Did the synthesis include all studies that it should?	The synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All predefined analyses were followed.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	We synthesized data on the benefits and harms of ASB screening and treatment for general adult populations separately from studies of pregnant women. Health outcomes and harms were sparsely and inconsistently reported in the studies conducted among general adult populations and in studies of screening conducted among pregnant women, precluding meta-analysis. For these outcomes, we described findings in the review text and tables and conducted narrative synthesis. Outcomes for the treatment of screen-detected ASB in pregnancy were analysed with random effects meta-analysis to calculate the pooled differences when data were sufficient.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	We examined statistical heterogeneity among the pooled studies using standard $\chi 2$ tests and estimated the proportion of total variability in point estimates using the I2 statistic.	Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Symptomatic UTI and Pyelonephritis: Visual inspection of a funnel plot revealed some asymmetry, and the Egger test approached statistical significance ($p = 0.08$). Low birth weight: There were too few studies available for this outcome to support the Egger test or assessment of publication bias with a funnel plot	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Sensitivity analyses dropping studies from meta-analysis that were deemed to have particularly high risk of bias demonstrated a greater pooled risk reduction and lower statistical heterogeneity	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	Restricting to countries rated high or very high on Human Development Index is reasonable considering need to use data from countries with similar clinical setting to the US. Restricting searches and inclusion criteria to English language only may mean studies have been missed.	High risk	

	There may be other countries with similar clinical settings to the US which may have studies published in other languages. This limitation is acknowledged as a limitation by the authors.	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk
HIGH RISK OF BIAS		

Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347.

Also reported in:
Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018.

Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf

Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria were predefined for each research question and adhered to.	Yes	High risk
1.2 Were the eligibility criteria appropriate for the review question?	The eligibility criteria were appropriate for each review question.	Probably Yes	
1.3 Were eligibility criteria unambiguous?	The eligibility criteria were unambiguous.	Probably Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Study type restriction for each specific question appear appropriate. No restriction to publication date.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	English and French language restrictions.	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**

2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Broad range of databases searched for each question including MEDLINE, Embase, Cochrane Library, CINAHL, PubMed and PsycINFO.	Probably Yes	Unclear risk
2.2 Were methods additional to database searching used to identify relevant reports?	References lists of systematic reviews were checked for additional studies	Probably Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy reported for each research question. All appear thorough and appropriate.	Probably Yes	
2.4 Were restrictions based on date, publication format, or language appropriate?	Limited to full texts published in English and French may lead to language bias. Language restriction has already been penalised in previous domain. 'Probably no' refers to including full texts only.	Probably No	
2.5 Were efforts made to minimise errors in selection of studies?	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	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	One reviewer independently extracted data, and another reviewer verified all data. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to have been collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	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-	Probably Yes	

	based Management appraisal tool for cross-sectional studies, and the Cochrane Risk of Bias tool for trials.		
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers independently assessed the methodological quality of each included study. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All predefined analyses followed or departures explained.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	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). When data were not pooled, we provided a narrative summary of findings. The synthesis appeared appropriate.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	We conducted sensitivity analyses for methodological issues (e.g., risk of bias) when substantial heterogeneity was found in meta-analysis. Heterogeneity was reduced.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Funnel plots and Egger's test were planned to detect small-study bias when there were at least eight studies in a meta-analysis. Where conducted, the funnel plot appeared symmetrical. The Egger's test was conducted, and the result approached significance, but was inconclusive (p=0.065). Note: this p-value only applies to the funnel plot for antibiotic treatment versus placebo/no treatment.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Biases remain after synthesis. Quality of evidence is low as indicated on GRADE.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	English and French language restrictions. Restriction to full text publications.	Unclear risk	

	Biases remain after synthesis.	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk
HIGH RISK OF BIAS		

Table 39. Question 4: Risk of bias in systematic reviews (ROBIS) [26]

Each checklist item was judged for each study and one of the following responses assigned: Probably Yes, Yes, Probably No, No, or Not enough information. The risk of bias was assigned one of the following responses: Low risk; High risk; Unclear risk. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Allen VM, Yudin MH. No. 276 - Management of group B streptococcal bacteriuria in pregnancy. J Obstet Gynaecol Can 2018;40(2):e181-6.			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria clearly defined.	Yes	Unclear risk
1.2 Were the eligibility criteria appropriate for the review question?	Eligibility criteria was appropriate.	Yes	
1.3 Were eligibility criteria unambiguous?	Eligibility criteria was unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	No publication date restrictions.	Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Limited to English language	Probably Not	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Primary studies and secondary publications were searched for in Medline, PubMed, and the Cochrane database. Embase was not searched so may have missed relevant data but unclear.	Probably Not	Unclear risk
2.2 Were methods additional to database searching used to identify relevant reports?	Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.	Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy was not reported.	No information	
2.4 Were restrictions based on date, publication format, or language appropriate?	Language restriction to English applied in line with the inclusion criteria but no further restrictions were apparent	Yes	
2.5 Were efforts made to minimise errors in selection of studies?	No information	Unclear	

Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	No information	Unclear	Unclear risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Limited study details available in the journal publication	No	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No information	Unclear	
3.5 Were efforts made to minimise error in risk of bias assessment?	No information	Unclear	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Unclear risk
4.2 Were all predefined analyses followed or departures explained?	No information	Unclear	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	No information	Unclear	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	No information	Unclear	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No information	Unclear	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No information	Unclear	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	This risk is unclear due to a lack of methodological and other details.	Unclear risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
UNCLEAR RISK OF BIAS			

Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. *BMC Pregnancy Childbirth* 2016;16(1):336.			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria clearly defined.	Yes	Unclear risk
1.2 Were the eligibility criteria appropriate for the review question?	Eligibility criteria was appropriate.	Yes	
1.3 Were eligibility criteria unambiguous?	Eligibility criteria was unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	No publication date restrictions.	Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No language restrictions. Both published and unpublished studies were included. Only full-text documents (e. g. journal article or clinical study report) were included.	Probably Not	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Primary studies and secondary publications were searched for in MEDLINE (1946 to January 2016) and EMBASE (1974 to January 2016) via Ovid, and in the Cochrane Central Register of Controlled Trials (January 2016).	Yes	High risk
2.2 Were methods additional to database searching used to identify relevant reports?	Reference lists of retrieved systematic reviews were searched by hand. In addition, web-based clinical trial registries were screened (ClinicalTrials.gov, International Clinical Trials Registry Platform Search Portal, and the EU Clinical Trials Register). Publications cited in comments addressed to the Federal Joint Committee, the decision-making body in the German statutory healthcare system and IQWiG's main commissioning body were also screened. Persons and parties who had submitted written comments on the preliminary report were asked to provide any additional relevant studies.	Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy reported but list of search terms was not comprehensive	Probably No	

2.4 Were restrictions based on date, publication format, or language appropriate?	Primary studies and secondary publications were searched for in MEDLINE (1946 to January 2016) and EMBASE (1974 to January 2016) via Ovid, and in the Cochrane Central Register of Controlled Trials (January 2016). No further restrictions reported.	Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers independently screened titles and abstracts of retrieved citations to identify potentially eligible primary and secondary publications. The full texts of these articles were obtained and independently evaluated by the same two reviewers applying the full set of inclusion and exclusion criteria. All documents retrieved from nonbibliographic sources were also screened for eligibility or relevant information on studies. Disagreements were resolved by consensus.	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	The individual steps of the data extraction and risk of bias assessment were conducted by one author and checked by another; disagreements were resolved by consensus.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Risk of bias was assessed for each outcome and rated these risks as “high” or “low”. In individual studies the risk of bias was assessed by determining the adequacy of the following quality criteria: generation of random allocation sequence, allocation concealment, blinding of participants and investigators, and selective outcome reporting.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	The individual steps of the data extraction and risk of bias assessment were conducted by one author and checked by another; disagreements were resolved by consensus.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Low risk

4.2 Were all predefined analyses followed or departures explained?	All analyses were pre-defined	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Synthesis appeared appropriate.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Meta-analyses were not feasible so a narrative synthesis was used. Differences between the studies were discussed.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Sensitivity analyses were performed to explore the potential impact of missing data.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Three out of four had high risk of bias. Studies were assessed individually.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	No - list of search terms not comprehensive and only full text reports were included which means some relevant studies may have been missed.	High risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2019;322(12):1195-205. Also reported in: Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: an updated systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 183 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US), 2019 [accessed 17.10.19] Available from: https://www.ncbi.nlm.nih.gov/books/NBK547176/			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Research questions clearly listed. Appendix A Table 1 details inclusion and exclusion criteria.	Yes	High risk

1.2 Were the eligibility criteria appropriate for the review question?	Research questions clearly listed. Appendix A Table 1 details inclusion and exclusion criteria. Criteria thorough and appropriate for review questions	Yes	
1.3 Were eligibility criteria unambiguous?	Appendix A Table 1 details inclusion and exclusion criteria. Eligibility criteria clear and unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Restricted to countries rated high or very high on the human development index	Probably yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Restricted to English-language only	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	MEDLINE, PubMed Publisher - Supplied Records, and the Cochrane Collaboration Central Registry of Controlled Trials were searched.	Probably Yes	Low risk
2.2 Were methods additional to database searching used to identify relevant reports?	Reference lists of other previously published reviews, meta-analyses, and primary studies were examined to identify additional potential studies for inclusion. Searches were supplemented with suggestions from experts and articles identified through news and table-of-contents alerts, such as those produced by the USPSTF Scientific Resource Center LitWatch activity. ClinicalTrials.gov (https://ClinicalTrials.gov/) was also searched for ongoing trials.	Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy fully reported and appears appropriate.	Probably Yes	
2.4 Were restrictions based on date, publication format, or language appropriate?	Restricted to English language (This restriction has already been marked down in previous question)	Probably Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers independently screened the title and abstract of all identified articles to determine if the study met our a priori inclusion and exclusion criteria. Two reviewers then independently evaluated the full-text articles of all potentially relevant studies against the complete inclusion and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion.	Yes	

Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	For all included studies, one reviewer extracted key elements into standardized abstraction forms. A second reviewer checked the data for accuracy.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	For each study, general characteristics (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race/ethnicity, setting, country), analytic methods, definitions of outcomes measures, and results were abstracted.	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to have been collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies. We assigned each study a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies. We assigned each study a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	The synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All predefined analyses were followed.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	We synthesized data on the benefits and harms of ASB screening and treatment for general adult populations separately from studies of pregnant women. Health outcomes and harms were sparsely and inconsistently reported in the studies conducted among general adult populations and in studies of screening conducted among pregnant women, precluding meta-analysis. For these outcomes, we described findings in the review text and tables and conducted narrative synthesis.	Probably Yes	

	Outcomes for the treatment of screen detected ASB in pregnancy were analysed with random effects meta-analysis to calculate the pooled differences when data were sufficient.		
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	We examined statistical heterogeneity among the pooled studies using standard χ2 tests and estimated the proportion of total variability in point estimates using the I2 statistic.	Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Symptomatic UTI and Pyelonephritis: Visual inspection of a funnel plot revealed some asymmetry, and the Egger test approached statistical significance (p = 0.08). Low birth weight: There were too few studies available for this outcome to support the Egger test or assessment of publication bias with a funnel plot	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Sensitivity analyses dropping studies from meta-analysis that were deemed to have particularly high risk of bias demonstrated a greater pooled risk reduction and lower statistical heterogeneity	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	Restricting to countries rated high or very high on Human Development Index is reasonable considering need to use data from countries with similar clinical setting to the US. Restricting searches and inclusion criteria to English language only may mean studies have been missed. There may be other countries with similar clinical settings to the US which may have studies published in other languages. This limitation is acknowledged as a limitation by the authors.	High risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Koves B, Cai T, Veeratterapillay R, Pickard R, Seisen T, Lam TB, et al. Benefits and Harms of Treatment of Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. *Eur Urol* 2017;72(6):865-868.			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	PICO defined in supplementary material	Yes	Unclear risk
1.2 Were the eligibility criteria appropriate for the review question?	The eligibility criteria appeared appropriate for the review question.	Yes	
1.3 Were eligibility criteria unambiguous?	The eligibility criteria appeared unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	No restrictions reported.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Congress abstracts were excluded, given the lack of detailed information available in these publications.	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Highly sensitive electronic searches were undertaken to identify published comparative studies in relevant databases including Medline, Embase, and the Cochrane Central Register of Controlled Trials.	Yes	High
2.2 Were methods additional to database searching used to identify relevant reports?	The database search was supplemented by additional sources, including the reference lists of included studies and any relevant systematic reviews identified by the EAU Urological Infections Guideline Panel, to also collect evidence from before the start date of our systematic search	Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy was reported however, it is not likely to be optimal and may have missed relevant studies. It could have been developed further e.g. they don't include many synonyms. Also, the filters they use for excluding studies focusing solely on animals or children don't look optimal.	Probably No	
2.4 Were restrictions based on date, publication format, or language appropriate?	No language restrictions were applied. Searches were limited to studies published from January 2000 to November 2016. No justification was given for this.	Probably No	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers screened all abstracts and full-text articles for inclusion independently (B.K. and T.C. or R.V.). Disagreement was resolved by discussion or by consulting an arbiter (B.W.).	Yes	
Domain 3: Data collection and study appraisal			

Question	Evidence	Rating	Overall domain rating
3.1 Were efforts made to minimise error in data collection?	Two reviewers independently extracted data using a data extraction form.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results.	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	Relevant study results were collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Risk of bias assessment using the Cochrane RoB Tool, and quality assessment using the Grading of Recommendations, Assessment, Development and Education (GRADE) approach were performed by two reviewers working independently.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Risk of bias assessment using the Cochrane RoB Tool, and quality assessment using the Grading of Recommendations, Assessment, Development and Education (GRADE) approach were performed by two reviewers working independently.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	For data analysis, descriptive statistics were used to summarise baseline characteristic data. We planned to perform meta-analyses for outcomes reported by more than one RCT. Nonrandomised studies were excluded from the meta-analysis because of the intrinsic biases associated with such studies, which, if pooled, can result in erroneous and misleading estimates. For studies not included in the meta-analysis, a narrative synthesis approach was used to summarise the results.	Probably Yes	High risk
4.2 Were all predefined analyses followed or departures explained?	Predefined analyses were followed where possible.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Synthesis was appropriate	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Statistical heterogeneity was apparent in some forest plots but was not investigated.	Probably No	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	A subgroup analysis was performed for studies using placebo and no treatment as control groups to see	Probably No	

	whether there are any differences between using different controls.		
4.6 Were biases in primary studies minimal or addressed in the synthesis?	GRADE findings were integrated into the narrative describing the estimates of effect.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	Conference abstracts were excluded; the search strategy had flaws and may have missed relevant studies; the observed statistical heterogeneity was not addressed and information on the quality of evidence was integrated into the synthesis but not the conclusions	High risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis 2019;68(10):e83-e110.

UK NSC external review – Antenatal screening for asymptomatic bacteriuria

Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Clear question presented and PICO mentioned but study selection criteria not provided.	Unclear	Unclear
1.2 Were the eligibility criteria appropriate for the review question?	No information provided	Unclear	
1.3 Were eligibility criteria unambiguous?	No information provided	Unclear	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	No information provided	Unclear	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No information provided	Unclear	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Searched MEDLINE, EMBASE and CENTRAL	Probably Yes	Unclear
2.2 Were methods additional to database searching used to identify relevant reports?	Handsearched reference lists and contacted authors of included studies	Probably Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information provided although mentioned in supplemental file	Unclear	
2.4 Were restrictions based on date, publication format, or language appropriate?	Restricted to English language or any language with English abstract; search dates appeared appropriate in relation to this work updating previous guidelines; no information about publication format	Unclear	
2.5 Were efforts made to minimise errors in selection of studies?	Two reviewers carried out independent screening at title and abstract and full text stages. Disagreements were resolved through discussion.	Probably Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	Two reviewers carried out independent data extraction. Data were finalised through discussion with the guideline panel.	Probably Yes	Low
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Study details outlined within a narrative discussion	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	It appeared that all relevant study results were considered	Probably Yes	

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Evidence summaries were prepared by the panel members using GRADE	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers carried out independent risk of bias assessment. Assessments were finalised through discussion with the guideline panel.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	It appeared that all relevant studies were included	Probably Yes	Unclear
4.2 Were all predefined analyses followed or departures explained?	Analyses not pre-specified	Unclear	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Narrative synthesis presented with no attempt at meta-analysis. Explanation for this approach not provided	Unclear	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Not discussed	Unclear	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not discussed	Unclear	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Used GRADE to summarise the quality of he overall body of evidence	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	Impact of potential sources of bias not discussed	Unclear	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Probably Yes	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Probably Yes	
UNCLEAR RISK OF BIAS			

Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2019, Issue 11. Art. No.: CD000490. DOI:10.1002/14651858.CD000490.pub4			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objective and eligibility criteria clearly defined.	Yes	Low risk
1.2 Were the eligibility criteria appropriate for the review question?	The eligibility criteria appeared appropriate.	Yes	
1.3 Were eligibility criteria unambiguous?	The eligibility criteria appeared unambiguous.	Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Crossover trials were not eligible for inclusion. No reason was given for this. This restriction seems reasonable given the nature of the treatment comparison.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	No restrictions	Yes	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist, and contains trials identified from: 1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); 2. weekly searches of MEDLINE Ovid; 3. weekly searches of Embase Ovid; 4. monthly searches of CINAHL EBSCO; 5. hand-searches of 30 journals and the proceedings of major conferences; 6. weekly current awareness alerts for a further 44 journals, plus monthly BioMed Central email alerts	Yes	Low risk
2.2 Were methods additional to database searching used to identify relevant reports?	ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) were searched for unpublished, planned, and ongoing trial reports on 4 November 2018, using the search methods detailed in Appendix 1. The reference lists of retrieved studies were also searched.	Yes	

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Full search strategy available and appears appropriate.	Probably Yes	
2.4 Were restrictions based on date, publication format, or language appropriate?	No language or date restrictions were applied.	Yes	
2.5 Were efforts made to minimise errors in selection of studies?	Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. Any disagreement was resolved through discussion.	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	Both review authors independently extracted the data, using the agreed form and discrepancies were resolved through discussion.	Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results.	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to be collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Two review authors independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two review authors independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Any disagreement was resolved by discussion.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	The synthesis appeared to include all studies that it should.	Probably Yes	Unclear risk
4.2 Were all predefined analyses followed or departures explained?	Analyses predefined and followed.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	The synthesis was likely to be appropriate.	Probably Yes	

4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Pre-specified subgroup analyses were carried out and heterogeneity was visible in some subgroups This was considered in the GRADE assessment and used to mark down the quality evidence. This was also acknowledged in the discussion section.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	The review authors stated 'There was no strong evidence of funnel plot asymmetry by visual assessment' however the funnel plot doesn't look symmetrical. Also, it represented several subgroups with small numbers of studies within each one, so difficult to interpret. It wasn't clear how they defined studies as being at overall ROB and therefore not clear why they couldn't do their sensitivity analysis based on this	Not enough information	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	GRADE tables were used to assess the certainty of the evidence.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	There is a lack of information about the search strategy and exploration of robustness	Unclear risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
UNCLEAR RISK OF BIAS			

Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347.

Also reported in:
Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018.

Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf

Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria were predefined for each research question and adhered to.	Yes	High risk
1.2 Were the eligibility criteria appropriate for the review question?	The eligibility criteria were appropriate for each review question.	Probably Yes	
1.3 Were eligibility criteria unambiguous?	The eligibility criteria were unambiguous.	Probably Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Study type restriction for each specific question appear appropriate. No restriction to publication date.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	English and French language restrictions.	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Broad range of databases searched for each question including MEDLINE, Embase, Cochrane Library, CINAHL, PubMed and PsycINFO.	Probably Yes	Unclear risk
2.2 Were methods additional to database searching used to identify relevant reports?	References lists of systematic reviews were checked for additional studies	Probably Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy reported for each research question. All appear thorough and appropriate.	Probably Yes	
2.4 Were restrictions based on date, publication format, or language appropriate?	Limited to full texts published in English and French may lead to language bias. Language restriction has already been penalised in previous domain. 'Probably no' refers to including full texts only.	Probably No	
2.5 Were efforts made to minimise errors in selection of studies?	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	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**

3.1 Were efforts made to minimise error in data collection?	One reviewer independently extracted data, and another reviewer verified all data. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to have been collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	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.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers independently assessed the methodological quality of each included study. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	
Domain 4: Synthesis and findings			
Question	**Evidence**	**Rating**	**Overall domain rating**
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All predefined analyses followed or departures explained.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	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). When data were not pooled, we provided a narrative summary of findings. The synthesis appeared appropriate.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	We conducted sensitivity analyses for methodological issues (e.g., risk of bias) when substantial heterogeneity was found in meta-analysis. Heterogeneity was reduced.	Probably Yes	

4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Funnel plots and Egger's test were planned to detect small-study bias when there were at least eight studies in a meta-analysis. Where conducted, the funnel plot appeared symmetrical. The Egger's test was conducted, and the result approached significance, but was inconclusive (p=0.065). Note: this p-value only applies to the funnel plot for antibiotic treatment versus placebo/no treatment.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Biases remain after synthesis. Quality of evidence is low as indicated on GRADE.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	English and French language restrictions. Restriction to full text publications. Biases remain after synthesis.	Unclear risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	
HIGH RISK OF BIAS			

Table 40. Question 4: Risk of bias in primary studies (Cochrane Risk of Bias tool for RCTs)[27]

Each domain was assessed as low, unclear or high risk of bias. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Kazemier 2015[13]			
Bias	**Domain**	**Supporting text**	**Decision**
Selection bias	**Random sequence generation**	Web based database with computerised randomisation	Low risk
	Allocation concealment	Web based central allocation	Low risk
Performance bias	**Blinding of participants**	Double-blind	Low risk
	Blinding of caregivers	Double-blind	Low risk
Detection bias	**Blinding of outcome assessment**	Blinded to researchers until after analysis	Low risk
Attrition bias	**Incomplete outcome data**	ITT analysis	Low risk
Reporting bias	**Selective reporting**	All assessed outcomes reported	Low risk
Other bias	**Other sources of bias**	Terminated early	Unclear risk
Summary of risk of bias		**Number of criteria "high risk of bias"**	0
		Number of criteria "low risk of bias"	7
		Number of criteria "unclear risk of bias"	1

Table 41. Question 5: Risk of bias in systematic reviews (ROBIS)[26]

Each checklist item was judged for each study and one of the following responses assigned: Probably Yes, Yes, Probably No, No, or Not enough information. The risk of bias was assigned one of the following responses: Low risk; High risk; Unclear risk. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347. Also reported in: Asymptomatic Bacteriuria in Pregnancy. *Canadian Task Force on Preventive Health Care* 2018. Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf			
Domain 1: Study eligibility criteria			
Question	**Evidence**	**Rating**	**Overall domain rating**
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Objectives and eligibility criteria were predefined for each research question and adhered to.	Yes	High risk
1.2 Were the eligibility criteria appropriate for the review question?	The eligibility criteria were appropriate for each review question.	Probably Yes	
1.3 Were eligibility criteria unambiguous?	The eligibility criteria were unambiguous.	Probably Yes	
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Study type restriction for each specific question appear appropriate. No restriction to publication date.	Probably Yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	English and French language restrictions.	Probably No	
Domain 2: Identification and selection of studies			
Question	**Evidence**	**Rating**	**Overall domain rating**
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Broad range of databases searched for each question including MEDLINE, Embase, Cochrane Library, CINAHL, PubMed and PsycINFO.	Probably Yes	Unclear risk
2.2 Were methods additional to database searching used to identify relevant reports?	References lists of systematic reviews were checked for additional studies	Probably Yes	
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Search strategy reported for each research question. All appear thorough and appropriate.	Probably Yes	

2.4 Were restrictions based on date, publication format, or language appropriate?	Limited to full texts published in English and French may lead to language bias. Language restriction has already been penalised in previous domain. 'Probably no' refers to including full texts only.	Probably No	
2.5 Were efforts made to minimise errors in selection of studies?	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	Yes	
Domain 3: Data collection and study appraisal			
Question	**Evidence**	**Rating**	**Overall domain rating**
3.1 Were efforts made to minimise error in data collection?	One reviewer independently extracted data, and another reviewer verified all data. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	Low risk
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Sufficient study characteristics were available to interpret the results	Probably Yes	
3.3 Were all relevant study results collected for use in the synthesis?	All relevant study results appear to have been collected for use in the synthesis.	Probably Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	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.	Probably Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Two reviewers independently assessed the methodological quality of each included study. Disagreements on data extraction or methodological quality assessments were resolved through consensus or consultation with a third reviewer.	Probably Yes	
Domain 4: Synthesis and findings			

Question	Evidence	Rating	Overall domain rating
4.1 Did the synthesis include all studies that it should?	Synthesis included all studies that it should.	Probably Yes	Low risk
4.2 Were all predefined analyses followed or departures explained?	All predefined analyses followed or departures explained.	Probably Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	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). When data were not pooled, we provided a narrative summary of findings. The synthesis appeared appropriate.	Probably Yes	
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	We conducted sensitivity analyses for methodological issues (e.g., risk of bias) when substantial heterogeneity was found in meta-analysis. Heterogeneity was reduced.	Probably Yes	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Funnel plots and Egger's test were planned to detect small-study bias when there were at least eight studies in a meta-analysis. Where conducted, the funnel plot appeared symmetrical. The Egger's test was conducted, and the result approached significance, but was inconclusive (p=0.065). Note: this p-value only applies to the funnel plot for antibiotic treatment versus placebo/no treatment.	Probably Yes	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Biases remain after synthesis. Quality of evidence is low as indicated on GRADE.	Probably Yes	
OVERALL RATING OF RISK OF BIAS			
Question	**Evidence**	**Rating**	
Did the interpretation of findings address all of the concerns identified in domains 1 to 4?	English and French language restrictions. Restriction to full text publications. Biases remain after synthesis.	Unclear risk	
Was the relevance of identified studies to the review's research question appropriately considered?	Yes	Low risk	
Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes	Low risk	

HIGH RISK OF BIAS

Table 42. Question 5: Risk of bias in primary studies (JBI checklist for cohort studies)[28]

Each checklist item was judged for each study and one of the following responses assigned: Yes, No, Unclear or Not applicable. Each judgement was made with reference to the particular questions and outcomes of interest to this systematic review.

JBI checklist item (cohort studies)	Kazemier 2015[13, 34]
1. Were the 2 groups similar & recruited from the same population?	Yes – both groups are from same source population and inclusion criteria are clear
2. Were the exposures measured similarly to assign people to the exposed & unexposed groups?	Yes – all women were screened for ASB in the same way
3. Was the exposure measured in a valid and reliable way?	Yes – used dip slide test which has satisfactory performance according to systematic review data[35]
4. Were confounding factors identified?	Yes - baseline differences in current smoking status
5. Were strategies to deal with confounding factors stated?	Yes – odds ratio estimations for maternal & neonatal outcomes adjusted for smoking, educational status, assisted conception and pre-existent hypertension
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes – women with urinary tract symptoms were excluded
7. Were the outcomes measured in a valid and reliable way?	Yes - Primary and secondary outcomes were defined and measured using prospectively collected data obtained by a validated linkage procedure between the midwifery registry, the obstetrics registry, and the neonatology registry
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes – participants followed up to 6 weeks after delivery
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes – follow-up not complete. Reasons for loss to follow-up shown on patient flow diagram.
10. Were strategies to address incomplete follow up utilised?	Yes – data imputation was used for patients lost to follow-up and those with contaminated dip slides.
11. Was appropriate statistical analysis used?	Yes – analyses adjusted for confounding variables
12. Topic-specific criterion: first voided urine sample confirmed with at least a second consecutive sample?	No (high risk of bias) – single sample
Abbreviations: ASB asymptomatic bacteriuria; JBI Joanna Briggs Institute	

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table .

Table 33. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	13
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	27, 53, 66
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	33, 49, 71
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		

3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	24, 79
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	79
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	**Error! Bookmark not defined.**
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: Quality assessment: 33, 49, 71
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	28, 46, 67
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	42, 49, 71
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?,	44, 51, 74
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted?	75

		Are there gaps in the evidence highlighted by the review?
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.

References

[1] Public Health England. *UK NSC: evidence review process. Updated 5 September 2017. Guidance [Internet]*: Public Health England, 2017 [accessed 17.10.19] Available from: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

[2] Wingert A, Pillay J, Featherstone R, Gates M, Sebastianski M, Shave K, et al. *Screening for asymptomatic bacteriuria in pregnancy: systematic review and meta-analysis [Internet]*. Edmonton, Alberta: Evidence Review and Synthesis Centre, University of Alberta, 2017 [accessed 17.10.19] Available from: https://canadiantaskforce.ca/wp-content/uploads/2018/06/Screening-for-Asymptomatic-Bacteriuria-in-Pregnancy-Final-Report-13Oct2017_v2.pdf

[3] Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2019;68(10):1611-1615.

[4] Scottish Intercollegiate Guidelines Network, Healthcare Improvement Scotland. *Management of suspected bacterial urinary tract infection in adults. SIGN 88 [Internet]*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2012 [accessed 17.10.19] Available from: http://www.sign.ac.uk/sign-88-management-of-suspected-bacterial-urinary-tract-infection-in-adults.html

[5] National Institute for Health and Care Excellence. *Antenatal care for uncomplicated pregnancies. NICE clinical guideline 62 [Internet]*. London: National Institute for Health and Care Excellence, 2008 [accessed 17.10.19] Available from: https://www.nice.org.uk/guidance/cg62

[6] Nicolle LE. Asymptomatic bacteriuria: when to screen and when to treat. *Infect Dis Clin North Am* 2003;17(2):367-94.

[7] Guinto VT, De GB, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2010, Issue 9. Art. No.: CD007855. DOI: 10.1002/14651858.CD007855.pub2

[8] Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. *Am J Obstet Gynecol* 2014;210(3):219.e1-6.

[9] Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev* 2015, Issue 11. Art. No.: CD000491. DOI: 10.1002/14651858.CD000491.pub3

[10] Allen VM, Yudin MH. No. 276 - Management of group B streptococcal bacteriuria in pregnancy. *J Obstet Gynaecol Can* 2018;40(2):e181-6.

[11] Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2019, Issue 11. Art. No.: CD000490. DOI: 10.1002/14651858.CD000490.pub4

[12] McIsaac W, Carroll JC, Biringer A, Bernstein P, Lyons E, Low DE, et al. Screening for asymptomatic bacteriuria in pregnancy. *J Obstet Gynaecol Can* 2005;27(1):20-4.

[13] Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis* 2015;15(11):1324-33.

[14] Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2019;68(10):e83-e110.

[15] Schneeberger C, Erwich J, van den Heuvel ER, Mol BWJ, Ott A, Geerlings SE. Asymptomatic bacteriuria and urinary tract infection in pregnant women with and without diabetes: Cohort study. *Eur J Obstet Gynecol Reprod Biol* 2018;222:176-181.

[16] Moore A, Doull M, Grad R, Groulx S, Pottie K, Tonelli M, et al. Recommendations on screening for asymptomatic bacteriuria in pregnancy. *CMAJ* 2018;190(27):E823-E830.

[17] Public Health England. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme [Internet]. London: PHE, 2015 [accessed 2.4.20]. Available from: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme

[18] Ullah A, Barman A, Ahmed I, Salam A. Asymptomatic bacteriuria in pregnant mothers: a valid and cost-effective screening test in Bangladesh. *J Obstet Gynaecol* 2012;32(1):37-41.

[19] UK National Screening Committee. *Screening for asymptomatic bacteriuria in pregnancy: external review against programme appraisal criteria for the UK National Screening Committee (UK NSC). Version: 2*. London: NSC, 2011. 15p.

[20] UK National Screening Committee. *Antenatal screening for asymptomatic bacteriuria. External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). Version: Final [Internet]*: UK National Screening Committee, 2017 [accessed 17.10.19] Available from: https://legacyscreening.phe.org.uk/asymptomaticbacteriuria

[21] UK National Screening Committee. *Commissioning document: antenatal screening for asymptomatic bacteriuria*. London: NSC, 2019. 13p.

[22] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019) [Internet]*: Cochrane, 2019 [accessed 17.10.19]. Available from: www.training.cochrane.org/handbook

[23] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 17.10.19] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[24] UK National Screening Committee. *The UK NSC Reporting Checklist for Evidence Summaries (ReCESs). Version 4.2*: UK National Screening Committee, 2019

[25] Nicolle LE. Updated Guidelines for Screening for Asymptomatic Bacteriuria. *JAMA* 2019;322(12):1152-1154.

[26] Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016;69:225-34.

[27] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

[28] Joanna Briggs Institute. *The Joanna Briggs Institute critical appraisal tools for use in JBI systematic reviews: checklist for cohort studies [Internet]*. Adelaide: JBI, 2017 [accessed 2.4.20] Available from: https://joannabriggs.org/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Cohort_Studies2017_0.pdf

[29] Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36.

[30] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40-6.

[31] Canadian Agency for Drugs and Technologies in Health. *PRESS - Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E) [Internet]*. Ottawa: CADTH, 2016 [accessed 17.10.19] Available from: https://www.cadth.ca/resources/finding-evidence/press

[32] Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.

[33] Naresh A, Simhan HN. Association of polymicrobial growth from urine culture with adverse pregnancy outcomes. *Am J Perinatol* 2011;28(7):537-42.

[34] Kazemier BM, Schneeberger C, De Miranda E, Van Wassenaer A, Bossuyt PM, Vogelvang TE, et al. Costs and effects of screening and treating low risk women with a singleton pregnancy for asymptomatic bacteriuria, the ASB study. *BMC Pregnancy Childbirth* 2012;12:52.

[35] Rogozinska E, Formina S, Zamora J, Mignini L, Khan KS. Accuracy of onsite tests to detect asymptomatic bacteriuria in pregnancy: a systematic review and meta-analysis. *Obstet Gynecol* 2016;128(3):495-503.

[36] Ontario Medical Association, Ontario Ministry of Health and Long-Term Care. *Ontario antenatal record 1 [Internet]*. Ontario: OMA, [n.d.] [accessed 2.4.20]. 2p. Available from: http://individual.utoronto.ca/dtsang/misc/antenatal/1.pdf

[37] Ontario Medical Association, Ontario Ministry of Health and Long-Term Care. *Ontario antenatal record 2 [Internet]*. Ontario: OMA, [n.d.] [accessed 2.4.20]. 2p. Available from: http://individual.utoronto.ca/dtsang/misc/antenatal/2.pdf

[38] Centre for Evidence-Based Medicine. Oxford Centre for Evidence-based Medicine – levels of evidence (March 2009) [Internet]. Oxford: CEBM, 2020 [accessed 2.4.20]. Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

[39] Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2019;322(12):1195-205.

[40] Wingert A, Pillay J, Sebastianski M, Gates M, Featherstone R, Shave K, et al. Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. *BMJ OPEN* 2019;9(3):e021347.

[41] Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. *BMC Pregnancy Childbirth* 2016;16(1):336.

[42] Hsu J, Brożek JL, Terracciano L, Kreis J, Compalati E, Stein AT, et al. Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines. *Implement Sci* 2011;6(1):62.

[43] Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64(4):380-2.

[44] Koves B, Cai T, Veeratterapillay R, Pickard R, Seisen T, Lam TB, et al. Benefits and harms of treatment of asymptomatic bacteriuria: A systematic review and meta-analysis by the European Association Of Urology Urological Infection Guidelines Panel. *Eur Urol* 2017;72(6):865-8.

[45] Butters L, Howie CA. Awareness among pregnant women of the effect on the fetus of commonly used drugs. *Midwifery* 1990;6(3):146-54.

[46] Twigg MJ, Lupattelli A, Nordeng H. Women's beliefs about medication use during their pregnancy: a UK perspective. *Int J Clin Pharm* 2016;38(4):968-76.

[47] Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health behavior during pregnancy. *Patient Educ Couns* 2014;96(2):171-8.

[48] Sanz E, Gómez-López T, Martínez-Quintas MJ. Perception of teratogenic risk of common medicines. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2001;95(1):127-31.

[49] Nordeng H, Ystrøm E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010;66(2):207-14.

[50] Bianchi-Jassir F, Seale AC, Kohli-Lynch M, Lawn JE, Baker CJ, Bartlett L, et al. Preterm birth associated with group B streptococcus maternal colonization worldwide: systematic review and meta-analyses. *Clin Infect Dis* 2017;65(suppl_2):S133-42.

[51] Asymptomatic bacteriuria in pregnancy. *Canadian Task Force on Preventive Health Care* 2018;190(27):E823-30.

[52] Henderson JT, Webber EM, Bean SI. *Screening for asymptomatic bacteriuria in adults: an updated systematic review for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 183 [Internet]*. Rockville, MD: Agency for Healthcare Research and Quality (US), 2019 [accessed 17.10.19] Available from: https://www.ncbi.nlm.nih.gov/books/NBK547176/

[53] Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, De Miranda E, et al. Maternal and neonatal consequences of asymptomatic bacteriuria in pregnancy-the ASB trial. *Reproductive sciences.* 2014;21(3 SUPPL. 1):255A.

[54] Versi E, Chia P, Griffiths DJ, Harlow BL. Bacteriuria in pregnancy: a comparison of Bangladeshi and Caucasian women. *Int Urogynecol J* 1997;8(1):8-12.

[55] Meis PJ, Michielutte R, Peters TJ, Wells HB, Sands RE, Coles EC, et al. Factors associated with preterm birth in Cardiff, Wales. I. Univariable and multivariable analysis. *Am J Obstet Gynecol* 1995;173(2):590-6.

[56] Nazareth I, King M. Decision making by general practitioners in diagnosis and management of lower urinary tract symptoms in women. *BMJ* 1993;306(6885):1103-6.

[57] Gehani M, Kapur S, Bhardwaj P, Nag V, Balasubramaniam SM, Kammili N, et al. Unmet need of antenatal screening for asymptomatic bacteriuria: a risk factor for adverse outcomes of pregnancy. *Indian J Community Med* 2019;44(3):193-8.

[58] Deville WL, Yzermans JC, van Duijn NP, Bezemer PD, van der Windt DA, Bouter LM. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol* 2004;4:4.

[59] Aigere EO, Okusanya BO, Eigbefoh JO, Okome GB. Enhanced urinalysis in the detection of asymptomatic bacteriuria in pregnancy. *Niger* 2013;23(2):105-9.

[60] Ajayi AB, Nwabuisi C, Aboyeji PO, Fowotade A, Fakeye OO. Reliability of urine multistix and gram stain in the detection of asymptomatic bacteriuria in pregnancy. *West Afr J Med* 2010;29(5):339-43.

[61] Awonuga DO, Fawole AO, Dada-Adegbola HO, Olola FA, Awonuga OM. Asymptomatic bacteriuria in pregnancy: evaluation of reagent strips in comparison to microbiological culture. *African Journal of Medicine & Medical Sciences* 2011;40(4):377-83.

[62] Azhari S, Yazd MM, Moghaddam MHS, Zadeh SE. Accuracy of urine dipslide to detect asymptomatic bacteriuria in pregnancy. *Iran J Obstet Gynecol Infertil* 2012;15(3):7-12.

[63] Balamurugan S, Shah C, Jayapriya S, Priyadarshini S, Jeya M, Ramesh RK. Reagent strip testing (RST) for asymptomatic bacteriuria (ASB) in pregnant women: A cost-effective screening tool in under-resourced settings. *J Clin Diagn Res* 2012;6(4 Suppl. 2):671-3.

[64] Demilie T, Beyene G, Melaku S, Tsegaye W. Diagnostic accuracy of rapid urine dipstick test to predict urinary tract infection among pregnant women in Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. *BMC Res Notes* 2014;7:481.

[65] Dhanalakshmi TA, Nagarathnamma D, Venkatesha D, Basavaraja HC. Screening tests for asymptomatic bacteriuria in pregnant women. *Journal of Pure and Applied Microbiology* 2012;6(3):1309-12.

[66] Eigbefoh JO, Isabu P, Okpere E, Abebe J. The diagnostic accuracy of the rapid dipstick test to predict asymptomatic urinary tract infection of pregnancy. *J Obstet Gynaecol* 2008;28(5):490-5.

[67] Gutierrez-Fernandez J, Lara A, Bautista MF, de Dios Luna J, Polo P, Miranda C, et al. Performance of the Sysmex UF1000i system in screening for significant bacteriuria before quantitative culture of aerobic/facultative fast-growth bacteria in a reference hospital. *J Appl Microbiol* 2012;113(3):609-14.

[68] Jayalakshmi J, Jayaram VS. Evaluation of various screening tests to detect asymptomatic bacteriuria in pregnant women. *Indian Journal of Pathology & Microbiology* 2008;51(3):379-81.

[69] Kacmaz B, Cakir O, Aksoy A, Biri A. Evaluation of rapid urine screening tests to detect asymptomatic bacteriuria in pregnancy. *Jpn J Infect Dis* 2006;59(4):261-3.

[70] Karabulut A. Asymptomatic bacteriuria in pregnancy: can automated urinanalysis be helpful for detection? *J Turk Ger Gynecol Assoc* 2007;8(4):367-71.

[71] Kodikara H, Seneviratne H, Kaluarachchi A, Corea E. Diagnostic accuracy of nitrite dipstick testing for the detection of bacteriuria of pregnancy. *Public Health* 2009;123(5):393-4.

[72] Kovavisarach E, Vichaipruck M, Kanjanahareutai S. Reagent strip testing for antenatal screening and first meaningful of asymptomatic bacteriuria in pregnant women. *J Med Assoc Thai* 2008;91(12):1786-90.

[73] Kovavisarach E, Romyen S, Kanjanahareutai S. Diagnostic performance of reagent strip testing for antenatal screening of asymptomatic bacteriuria using single- and double-urine culture criteria. *J Med Assoc Thai* 2017;100(10):1045-1049.

[74] Mangalgi S, Sajjan A. Asymptomatic bacteriuria in pregnancy. *J Krishna Inst Med Sci Univ* 2018;7(3):35-42.

[75] Mignini L, Carroli G, Abalos E, Widmer M, Amigot S, Nardin JM, et al. Accuracy of diagnostic tests to detect asymptomatic bacteriuria during pregnancy. *Obstet Gynecol* 2009;113(2 Pt 1):346-52.

[76] Nct. Screening and Treating Asymptomatic Bacteriuria Every Trimester and Preterm Birth. *https://clinicaltrials.gov/show/NCT03274960* 2017.

[77] Okusanya BO, Aigere EO, Eigbefoh JO, Okome GB, Gigi CE. Is a chlorhexidine reaction test better than dipsticks to detect asymptomatic bacteriuria in pregnancy? *J Obstet Gynaecol* 2014;34(1):21-4.

[78] Onakoya JA, Amole OO, Ogunsanya OO, Tayo O. Comparing the specificity and sensitivity of nitrate and leucocyte tests on multistick in screening for urinary tract infections amongst pregnant women at Lagos State University Teaching Hospital Ikeja, Nigeria. *Niger* 2008;18(2):61-3.

[79] Tamayo J, Gomez-Garces JL, Alos JI. Evaluation of Granada agar plate for detection of streptococcus agalactiae in urine specimens from pregnant women. *J Clin Microbiol* 2004;42(8):3834-6.

[80] Teppa RJ, Roberts JM. The uriscreen test to detect significant asymptomatic bacteriuria during pregnancy. *J Soc Gynecol Investig* 2005;12(1):50-3.

[81] Thakre SS, Dhakne SS, Thakre SB, Thakre AD, Ughade SM, Kale P. Can the Griess Nitrite Test and a Urinary Pus Cell Count of >=5 Cells Per Micro Litre of Urine in Pregnant Women be Used for the Screening or the Early Detection of Urinary Tract Infections in Rural India? *J Clin Diagn Res* 2012;6(9):1518-22.

[82] Iarikov D, Wassel R, Farley J, Nambiar S. Adverse events associated with fosfomycin use: review of the literature and analyses of the FDA Adverse Event Reporting System Database. *Infect Dis Ther* 2015;4(4):433-58.

[83] Khawaja AR, Khan FB, Dar TI, Bhat AH, Wani MS, Wazir BS. Fosfomycin tromethamine. Antibiotic of choice in the female patient: A multicenter study. *Cent European J Urol* 2015;68(3):371-5.

[84] Lumbiganon P, Villar J, Laopaiboon M, Widmer M, Thinkhamrop J, Carroli G, et al. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. *Obstet Gynecol* 2009;113(2 Pt 1):339-45.

[85] Estebanez A, Pascual R, Gil V, Ortiz F, Santibanez M, Perez Barba C. Fosfomycin in a single dose versus a 7-day course of amoxicillin-clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. *Eur J Clin Microbiol Infect Dis* 2009;28(12):1457-64.

[86] Bayrak O, Cimentepe E, Inegol I, Atmaca AF, Duvan CI, Koc A, et al. Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimesterof pregnancy? *Int Urogynecol J* 2007;18(5):525-9.

[87] Vousden N, Shennan AH. 1 Day of nitrofurantoin was not as effective as 7 days for asymptomatic bacteriuria in pregnancy. *Evid Based Med* 2009;14(4):113.

[88] Lumbiganon P, Villar J, Laopaiboon M, Widmer M, Thinkhamrop J, Carroli G, et al. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. *Obstet Gynecol Surv* 2009;64(6):359-60.

[89] Rafal'skiĭ VV, Dovgan EV, Kozyrev Iu V, Gustovarova TA, Khlybova SV, Novoselova AV, et al. The efficacy and safety of cefixime and amoxicillin/clavulanate in the treatment of asymptomatic bacteriuria in pregnant women: a randomized, prospective, multicenter study. *Urologiia (moscow, russia : 1999)* 2013(5):24, 26-8.

[90] Nct. Management of Sub-Clinical Bacteriuria in Pregnancy. *https://clinicaltrials.gov/show/NCT03275623* 2017.

[91] Nct. Treatment of Asymptomatic Bacteriuria in Pregnancy. *https://clinicaltrials.gov/show/NCT02911662* 2016.

[92] Nct. the Use of Fosfomycin as a Single Dose Oral Treatment of Asymptomatic Bacteriuria. *https://clinicaltrials.gov/show/NCT03548129* 2018.

[93] Urinary tract infection (lower): antimicrobial prescribing : guidance (NG109). 2018.