UK National Screening Committee

Antenatal screening for asymptomatic bacteriuria

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

Version: Draft 3

Solutions for Public Health

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://legacy.screening.nhs.uk/screening-recommendations.php and the policy review process is described in detail at https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process

Abbreviations List

ASB	Asymptomatic Bacteriuria
CFU	Colony Forming Unit
CI	Confidence Interval
HPF	High Power Field
ml	Millilitres
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
OIF	Oil-Immersion Field
PPV	Positive Predictive Value
OR	Odds Ratio
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Risk Ratio
UK	United Kingdom
UK NSC	UK National Screening Committee

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from Public Health England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Plain English Summary

Asymptomatic bacteriuria (ASB) is a urinary tract infection that does not have any symptoms. If untreated, pregnant women are at greater risk of developing pyelonephritis (a kidney infection). This can lead to fever, breathing problems and kidney failure in the mother. It can also cause premature birth and still birth.

This document reviews new evidence about screening women for ASB while they are pregnant. It looks at evidence published between October 2010 and April 2016. The aim of a screening programme for ASB would be to prevent pyelonephritis.

The UK National Screening Committee (UK NSC) published its last review in 2011. This recommended against introducing a screening programme for ASB in the UK. The current review looked at some key questions:

1. How many pregnant women have ASB in the UK?
2. What happens to women if ASB in pregnancy is not treated?
3. What would be the best way of screening for ASB infection in pregnancy?
4. How effective are treatments such as antibiotics for ASB in pregnant women?

This review of the evidence found that the UK NSC still cannot recommend screening.

1. How many pregnant women have ASB in the UK?
There was no new evidence to answer this question.

2. What happens to women if ASB in pregnancy is not treated?
A study in the Netherlands found that ASB in pregnancy was less harmful than expected. This led to the study stopping early. There is no evidence about whether the UK would have the same results.

3. What would be the best way of screening for ASB infection in pregnancy?
There was no new evidence on when or how often to test for ASB in pregnancy. The most effective way of screening pregnant women for ASB remains uncertain.

4. How effective are treatments such as antibiotics for ASB in pregnant women?
A recent study found that treating ASB had no effect on reducing pyelonephritis and premature birth. This contrasts with the evidence reported in the 2011 UK NSC review. This had suggested that antibiotics could reduce pyelonephritis by around 75%. Limitations with both studies mean that the benefit of antibiotics is uncertain.
A systematic review looked at whether to give antibiotics once or as a short course. It found there was no difference in cure rates, recurrence of ASB, pyelonephritis or preterm birth rates. But when only good quality studies were included results suggested that a short course of antibiotics may lead to a better outcome.

As the questions could not be answered, the review concluded that a population screening programme should not be introduced in the UK.

Executive Summary

This document reviews new evidence published between October 2010 and April 2016 on antenatal population screening for asymptomatic bacteriuria.

Background

Asymptomatic bacteriuria (ASB) is a potentially serious urinary tract infection without symptoms. It is defined as a positive culture (≥10^5CFU/ml urine) of the same uropathogen in a patient without urinary symptoms. Women with untreated ASB are at risk of developing pyelonephritis. Pregnant women with pyelonephritis have an increased risk of maternal and fetal mortality and morbidity, including maternal fever, acute respiratory distress, acute renal failure, stillbirth and preterm birth.

Previous findings

The current UK NSC policy is that the systematic antenatal population screening for asymptomatic bacteriuria is not recommended. Clinical practice guidelines for routine pregnancy clinics are covered by guidance from the National Institute of Health and Care Excellence (NICE, clinical guideline 62). This recommends that women should be offered a test for ASB early in pregnancy.

The previous UK NSC external review of antenatal screening for ASB was published in 2011. The 2011 review concluded that there was insufficient information to recommend a population screening programme. The gaps in the evidence related to the prevalence of ASB, the impact of screening on pyelonephritis, the optimum test and its timing and frequency during pregnancy and the optimal treatment strategy.

The current review

The current review explores the volume, quality and direction of the literature published since 2010 and focuses on key questions relating to the conclusions of the previous review. The aim of the review is to inform discussion on whether the recent evidence provides a sufficient basis on which to recommend the introduction of an antenatal population screening programme for ASB in the UK.

The key questions considered in this review are:

- what is the incidence of asymptomatic bacteriuria in the UK?
- what are the outcomes of untreated asymptomatic bacteriuria in pregnancy?
- what is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
- what are the effects of antimicrobial treatment for asymptomatic bacteriuria in pregnant women to prevent adverse outcomes?

The review found that there are still a number of areas where the UK NSC criteria for introducing a population screening programme are uncertain or not met:

- there was an absence of new evidence available to provide updated information on the incidence or prevalence of ASB in the UK.
- one study considered the outcomes of untreated ASB in a Dutch population that could be considered analogous to the UK. The number of cases of pyelonephritis (2.4%) and

preterm delivery (1.0%) in this population was lower than previously reported in the published literature, causing recruitment into the study to be terminated early. The women in this study had pregnancies described as uncomplicated and the prevalence of ASB in the population was at the lower end of the range found in the UK. In the absence of any updated information on the current prevalence of ASB or pyelonephritis in the UK it is uncertain how applicable the results of this study are to a UK population of pregnant women.

- the new studies on screening test performance identified in this review do not provide sufficiently robust evidence to recommend a particular screening test. No new evidence was identified on the timing of testing during pregnancy or the frequency/ repetitions of the test. The optimum population screening strategy for detecting ASB in pregnancy remains uncertain.
- the most recent RCT evidence found no difference between treated and untreated ASB patients for risk of pyelonephritis, delivery before 34 weeks or on a range of secondary maternal and neonatal outcomes. This contrasts with the results of a systematic review available to the 2011 UK NSC review and recently updated (with no new studies identified), which suggests that the risk of pyelonephritis is reduced with antibiotics compared to placebo or no treatment (by approximately 75%). In light of the contrasting results and methodological limitations with both studies the effects of antimicrobial treatment for ASB in pregnant women to prevent adverse outcomes is uncertain.
- a systematic review on the duration of treatment for ASB found no significant difference in cure rates, recurrence of ASB, pyelonephritis or preterm birth rates between a short course or single dose of antibiotics. However, a sub-group analysis found that a short course of antibiotics may lead to a better outcome in good quality studies (based on limited data). A single dose of antibiotics is associated with fewer side effects.

Recommendation

The review concluded that, at present, the evidence base is insufficient to recommend a UK systematic population antenatal screening programme for asymptomatic bacteriuria.

Introduction

Asymptomatic bacteriuria (ASB) is a potentially serious urinary tract infection that does not have any symptoms. It is defined as a positive culture (≥10^5CFU/ml urine) of the same uropathogen in a patient without urinary symptoms[1]. Previously, the presence of bacteria in 2 consecutive urine samples was required for a positive result. However, a single voided midstream urine sample is accepted as an adequate and practical alternative[2]. The most common causative organisms are Escherichia coli (E.coli), Staphylococcus saprophyticus, Klebsiella spp, Enterobacter spp, Proteus spp and Enterococcus spp[3].

Women with untreated ASB are at greater risk of developing pyelonephritis (a kidney infection). Pregnant women with pyelonephritis are at increased risk of maternal and fetal mortality and morbidity, including maternal fever, acute respiratory distress, acute renal failure, stillbirth and preterm birth[4]. Acute pyelonephritis is also associated with anaemia and pre-eclampsia[1].

Clinical practice guidelines for routine pregnancy clinics are covered by guidance from the National Institute of Health and Care Excellence[5]. This recommended 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."

Basis for current recommendation

The current UK NSC policy is that systematic population antenatal screening for ASB is not recommended. The previous UK NSC external review of antenatal screening for ASB was produced in 2011[6]. The review concluded that testing for asymptomatic bacteriuria in early pregnancy is an established part of antenatal care packages, but a systematic population screening programme was not recommended. While there was value in continuing to recommend screening, and there were no evidence of harm due to such practice, there was insufficient information to recommend a population screening programme.

The Committee also noted that current practice overlaps with guidance in other areas and the consequences of recommending withdrawal of screening are uncertain at this point.

Current update review and approach taken

The current review considers antenatal screening for ASB and was prepared by Solutions for Public Health, in discussion with the UK National Screening Committee (UK NSC).

The current evidence summary was developed using a rapid review methodology and assessed using the UK NSC reporting checklist for evidence summaries. The key questions addressed in the current review were developed by the UK NSC and are based on the key areas where ASB did not meet the criteria for a screening programme in the last 2011 UK NSC review. The aim of the current review is to update the evidence in these key areas, namely around the UK incidence of ASB, the outcomes of untreated ASB in pregnancy, the performance of screening strategies for detecting ASB and the effects of antimicrobial treatment. The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

A systematic literature search of 3 databases was conducted by the UK NSC in April 2016 for new evidence published since October 2010. The search was structured around the issues raised in the 2011 UK NSC external review. A total of 867 unique references were identified and sifted by title and abstract by the UK NSC for potential relevance to the review. Details of the databases searched, search terms and a flow diagram summarising the references

identified are presented in the Search Strategy section at the end of this report. Seventy-three references were sent to Solutions for Public Health for further appraisal and possible inclusion in the final review. Selection and appraisal of studies was undertaken by one reviewer. Any queries were resolved through discussion with a second reviewer or with the UK NSC.

Overall, 26 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. This includes papers where relevance could not be determined from the title or abstract alone. Reasons for excluding studies at the abstract stage included studies where there full text was not available in English, studies published only as a conference abstract which do not provide sufficient information for appraisal, papers published prior to 2010, discussion papers and papers that did not address the specific population or questions of interest in this review.

Each section below provides information on the evidence selection process and number of included studies for the given criterion.

The review was quality assured by a second senior reviewer who was not involved with the writing of the review in accordance with Solutions for Public Health's quality assurance process.

Table 1: Key questions for current review of antenatal screening for asymptomatic bacteriuria

Criterion*	Key Questions	# Studies Included
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 the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.	What is the incidence of asymptomatic bacteriuria in the UK?	0
	What are the outcomes of untreated asymptomatic bacteriuria in pregnancy?	1
4. There should be a simple, safe, precise and validated screening test.	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?	7
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 shouldn't be further considered.	What are the effects of antimicrobial treatment for asymptomatic bacteriuria in pregnant women to prevent adverse outcomes?	3

* UK NSC evidence review criteria (January 2016)

Appraisal against UK NSC Criteria[†]

Each of the key questions and their associated criteria are considered in turn below.

Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were considered in determining the quality of the identified evidence, including study design and methodology, risk of bias and applicability of the evidence.

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 the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.

Key Question: What is the incidence of asymptomatic bacteriuria in the UK?

Key Question: What are the outcomes of untreated asymptomatic bacteriuria in pregnancy?

Sub-question: What is the incidence of low birthweight, pyelonephritis and preterm birth in women with ASB?

The UK NSC briefing note[7] states that studies done within the UK should be prioritised, but that other studies done in Western populations analogous to the UK pregnancy cohort could also be included.

The 2011 UK NSC review[6] found that the prevalence of ASB in pregnancy varied from 2.5% to 15% in different studies. In UK studies, the prevalence varied from 2% to 12%. Most of these studies collected data from the first trimester of pregnancy. The 2011 review also discussed outcomes of ASB, and reported 1 study with prevalence rates for pyelonephritis of 24.8% in pregnant women with untreated ASB compared to 3.2% for treated ASB. An association between ASB and low birthweight and preterm birth was reported, with an odds ratio of having a medically indicated preterm delivery of 2.0 (95%CI 1.5 to 2.8) with ASB compared to no ASB[6].

Description of the evidence

In the current review, of the 26 studies identified as potentially relevant during title and abstract sifting, 9 related to this criterion. After review of the full texts 1 study was included. Reasons for excluding studies at this stage included populations not analogous to the UK, populations that combined symptomatic and asymptomatic patients and did not provide separate results for asymptomatic patients and a descriptive review of studies that were separately identified and considered.

No new studies on the incidence or prevalence of ASB in the UK were identified. One study presented results for pregnant women with untreated ASB in a Dutch population that could be considered analogous to the UK.

[†]These criteria are available online at UK NSC evidence review criteria (January 2016)

In a cohort study set in the Netherlands, Kazemir et al (2015)[8] tested 5,132 women aged 18 years and over with a singleton pregnancy of between 16 and 22 weeks for ASB. A dipslide test on a single urine sample generated 255 (5.0%) results that were positive for ASB. Of these, 208 women were untreated because they either declined treatment or were randomised to the placebo arm of an embedded randomised controlled trial (RCT). This RCT is described in further detail later in this review. In this population of 208 untreated, ASB positive women there were 5 cases of pyelonephritis (2.4%), 2 cases of preterm delivery (<34 weeks) (1.0%) and 17 cases where the neonate was small for its gestation age (<10th percentile) (8.2%).

The prevalence of ASB in the study population was at the lower end of the range found in the UK. The cohort study and embedded RCT were suspended early due to the low incidence of the primary outcomes (pyelonephritis and preterm delivery). The women in this study had pregnancies that were described as uncomplicated. The exclusion criteria for this study were women with a history of preterm delivery before 34 weeks; warning signs of an imminent preterm delivery; fetal congenital malformations; antibiotic use within 2 weeks of screening; known glucose-6-phosphate dehydrogenase deficiency; hypersensitivity to nitrofurantoin or risk factors for complicated urinary tract infection (eg pre-gestational diabetes mellitus, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract). Further details of this study are provided in Appendix Tables 1 (for the cohort study) and 9 (for the embedded RCT).

Discussion

No new evidence on the incidence or prevalence of ASB in the UK was identified. In the previous review the UK prevalence ranged from 2% to 12%. No new information to change or update this estimate was identified.

Only one study considered the outcomes of untreated ASB in a population of Dutch women that could be considered analogous to the UK. The 5 cases (2.4%) of pyelonephritis identified in the women who were positive for the ASB but did not receive treatment in this study was lower than the 24.8% of pyelonephritis cases in untreated women with ASB reported in the 2011 UK NSC review. The study was terminated early due to the cases of pyelonephritis and preterm delivery in this population being fewer than expected from published figures. The women included in this study all had pregnancies that were described as uncomplicated and the prevalence of ASB in the population was at the lower end of the UK range of 2% to 12% specified in the 2011 UK NSC review. In the absence of any updated information on the current prevalence of ASB or pyelonephritis in the UK it is uncertain how applicable the results of this study are to a UK population of pregnant women.

Summary: Criterion 1 uncertain

Overall, there was an absence of new evidence to answer the key questions about the epidemiology of ASB and the outcomes of untreated ASB in a UK population or population analogous to the UK. In the absence of such evidence it is uncertain if this criterion is met.

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

Key Question: What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?

The UK NSC review protocol states that of interest in this question is the accuracy of tests, the timing of testing during pregnancy and the optimal frequency/ repetitions of the test[7].

The 2011 UK NSC review[6] stated that the gold standard test for ASB is urine culture, but that it can also be detected by dipstick methods. Sensitivity and specificity values of 98.0% and 99.6% were reported for urine culture and 53.0% and 92.0% for dipstick. Two urine specimens is the gold standard, but the 2011 review acknowledged that testing a single midstream specimen is a more practical alternative. There was no strong evidence around the timing of when samples should be taken.

Description of the evidence

In the current review, of the 26 studies identified as potentially relevant during title and abstract sifting, 11 related to this criterion. After review of the full texts, 7 studies were included. Reasons for excluding studies at this stage included populations that combined symptomatic and asymptomatic patients and did not provide separate results for asymptomatic patients and studies focusing on sampling methods rather than test performance. In addition, 2 of the studies on screening test performance identified as potentially relevant from their abstracts were not available as full text (Aigere 2013[9] and Ajayi 2010[10]) and could therefore not be included in this review. In both cases the journal issue in which the article was published was not listed in the journal's electronic archive (ie it was not possible to obtain an electronic version of the article). From the limited information available in the abstract, the design and results of these studies appear to be similar to the other studies on test performance identified and included.

The 7 studies presenting results on test performance for ASB are introduced below and their results are summarised in Table 2:

- Okusanya et al (2014)[11] tested 150 pregnant women in Nigeria for ASB using a dipstick test and a chlorhexidine reaction test
- Ullah et al (2012)[12] tested 600 pregnant women in Bangladesh for ASB using dipstick tests and leucocyte count and gram staining by microscopic analysis
- Dhanlakshmi et al (2012)[13] tested 750 pregnant women in India for ASB using a urine wet mount test, gram staining, catalase test and triphenyl tetrazolium chloride test
- Awonuga et al (2011)[14] tested 205 pregnant women in Nigeria for ASB using dipstick tests
- Demilie et al (2014)[15] tested 367 pregnant women in Ethiopia for ASB using dipstick tests. Of these 330 were asymptomatic and only tests reported separately for this group have been included in this review
- Balamurugan et al (2012)[16] tested 100 pregnant women in India for ASB using dipstick tests. This study reported test results for the presence of nitrates or leucocytes singly and combinations of nitrates, leucocytes, blood and protein. Only the results for nitrate and leucocyte singly or combined are reported in Table 2. The addition of blood and or protein as a marker did not improve on the test performance of nitrate and leucocyte combined
- Gayathree et al (2010)[17] tested 900 pregnant women in India for ASB using dipstick and gram staining tests

All 7 studies tested a single midstream urine sample using urine culture as the reference standard. In 4 studies the timing of the testing in the pregnancy was not stated. In the remaining 3 studies the percentage of the sample tested in each of the 3 pregnancy trimesters was reported, however, test performance results were not reported separately for women tested during different trimesters. Further details of these studies are presented in Appendix Tables 2 to 8.

Table 2: Test performance for screening tests for ASB

Test	Prevalence ASB	Sensitivity*	Specificity*	PPV*	NPV*	Study
Dipstick – nitrate	4.7%	42.9%	93.7%	25.0%	97.1%	Okusanya et al 2014[11]
	Not reported	35.7%	98.0%	62.5%	94.3%	Demilie et al 2014[15]
	4.0%	29.2% (95%CI 14.9 to 49.2)	99.7% (95%CI 98.7 to 99.9)	77.8% (95%CI 45.3 to 93.7)	97.1% (95%CI 95.4 to 98.2)	Ullah et al 2012[12]
	13.0%	61.6% (95%CI 32.3 to 84.7)	71.3% (95%CI 60.4 to 80.2)	24.0%	93.0%	Balamurugan et al 2012[16]
	10.7%	36.4%	98.4%	72.7%	92.9%	Awonuga et al 2011[14]
	6.8%	71.0%	99.3%	88.0%	97.9%	Gayathree et al 2010[17]
Dipstick – leukocyte esterase	4.7%	14.3%	79.0%	3.2%	95.0%	Okusanya et al 2014[11]
	Not reported	50.0%	89.1%	29.8%	95.1%	Demilie et al 2014[15]
	4.0%	33.3% (95%CI 18.0 to 53.3)	79.5% (95%CI 76.0 to 82.6)	6.3% (95%CI 3.3 to 12.0)	96.6% (95%CI 94.6 to 97.9)	Ullah et al 2012[12]
	13.0%	84.6% (95%CI 53.7 to 97.3)	71.3% (95%CI 60.4 to 80.2)	31.0%	96.0%	Balamurugan et al 2012[16]
	10.7%	31.8%	94.5%	41.2%	92.0%	Awonuga et al 2011[14]
	6.8%	61.3%	92.8%	38.8%	97.0%	Gayathree et al 2010[17]
Dipstick – nitrate and leukocyte	4.7%	14.3%	97.9%	25.0%	96.0%	Okusanya et al 2014[11]
	4.0%	25.0% (95%CI 12.0 to 44.9)	99.7% (95%CI 98.7 to 99.9)	75.0% (95%CI 40.9 to 92.9)	96.9% (95%CI 95.2 to 98.1)	Ullah et al 2012[12]

	10.7%	50.0%	92.9%	45.8%	93.9%	Awonuga et al 2011[14]
	6.8%	53.2%	100%	100%	96.7%	Gayathree et al 2010[17]
Dipstick – nitrate or leukocyte	13%	92.3% (95%CI 64.0 to 99.8)	82.8% (95%CI 73.2 to 90.0)	45.0%	99.0%	Balamurugan et al 2012[16]
Gram staining	4.0%	91.7% (95%CI 74.2 to 97.7)	97.2% (95%CI 95.5 to 98.3)	57.9% (95%CI 42.2 to72.1)	99.6% (95%CI 98.7 to 99.9)	Ullah et al 2012[12]
	6.8%	90.3%	99.0%	87.5%	98.3%	Gayathree et al 2010[17]
	7.9%	98.3%	100%	100%	99.8%	Dhanlakshmi et al 2012[13]
Chlorhexidine reaction	4.7%	100%	54.0%	9.7%	100%	Okusanya et al 2014[11]
Leucocyte count	4.0%	62.5% (95%CI 42.7 to 78.8)	64.9% (95%CI 60.9 to 68.7)	6.9% (95%CI 4.2 to 11.1)	97.6% (95%CI 95.6 to 98.8)	Ullah et al 2012[12]
Urine wet mount	7.9%	27.1%	100%	100%	94.1%	Dhanlakshmi et al 2012[13]
Catalase test	7.9%	100%	95.5%	65.6%	100%	Dhanlakshmi et al 2012[13]
Triphenyl tetrazolium chloride test	7.9%	95.4%	98.2%	82.0%	99.6%	Dhanlakshmi et al 2012[13]

*95% CI reported where available

Discussion

The 7 studies included were similar in their design. However, the test performance results varied considerably. For example, for the 6 studies reporting the results of dipstick nitrate tests the sensitivity ranged from 29.2% to 71.0%, specificity ranged from 71.3% to 99.7%, PPV ranged from 24.0% to 88.0% and NPV ranged from 93.0% to 97.9%. Whilst some individual studies reported reasonable accuracy scores for ASB screening tests, the lack of consistency in the results between the different studies suggests that these results should be interpreted with caution. Urine culture was used as the reference standard in all of the studies and remains the gold standard test for detecting ASB. None of the studies were conducted in the UK.

The quality of each study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) framework. The QUADAS-2 framework is used to assess the quality of primary test accuracy studies and includes 5 domains on patient selection, the index test, the reference standard, test strategy flow and timing and applicability[‡].

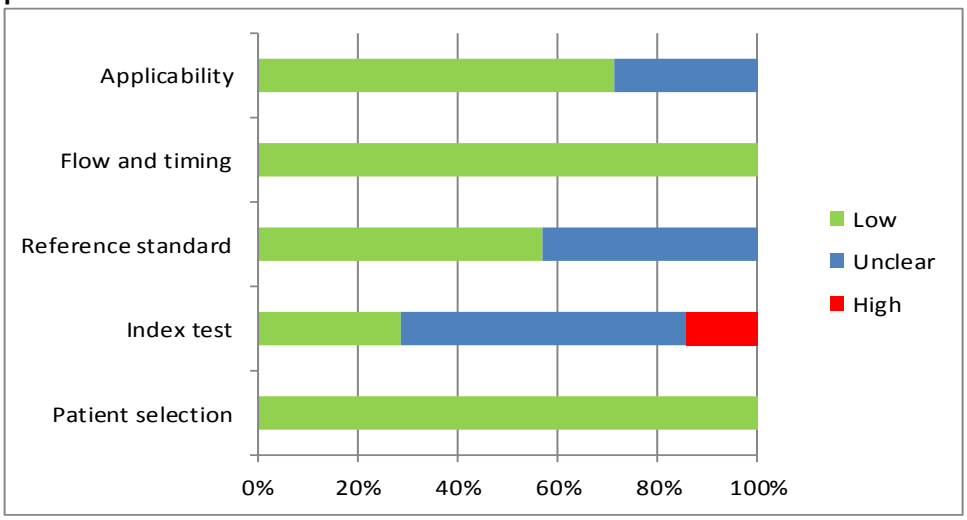
The scores for each area are summarised in Figure 1. The scores indicate a low risk of bias for all 7 studies in the test strategy flow and timing domain. This low risk scores reflects the fact that all studies used the same urine sample for the index and reference standard tests, all participants received the same reference standard and all patients were included in the analysis. All 7 studies also had a low risk of bias in the patient selection domain. This low risk score reflects the fact that all of the studies recruited women attending antenatal care clinics during the study period (a consecutive rather than a random sample), all studies avoided a case-control study design and all studies avoided inappropriate exclusions.

In the applicability domain, 5 of the 7 studies were considered to be at low risk of bias as, although the studies were not set in the UK, the prevalence of ASB identified was within the range found in the UK and the index tests and reference standards used are available in the UK. In the remaining two studies the risk of bias was unclear due to a lack of information on the prevalence of ASB in the study population in 1 study and a prevalence that was slightly higher than the range found in the UK in another study.

The main area where there was unclear or high risk of bias (in 5 of the 7 studies) was in the index test. This was due to lack of clarity about whether the assessors were blinded to the results or lack of information about the threshold for judging a positive screening test result. The same lack of clarity about blinding for the reference standard test resulted in an unclear risk of bias rating in 3 of the 7 studies. Further details on the QUADAS-2 scores are provided in Appendix tables 2 to 8.

[‡] The patient selection domain considers the study design, the population sample and the patient exclusions; the index test domain considers assessor blinding and the process for determining the threshold to be used; the reference standard domain considers test performance and assessor blinding; the test strategy and flow and timing domain considers the interval between the test and reference standard and whether all patients received the reference standard and were included in the analysis; the applicability domain considers applicability to a UK screening population and the relevance of the test and reference standard to the UK.

Figure 1: Summary of the QUADAS framework results for the 7 studies assessing test performance



These studies provide information on test performance for various screening tests for ASB, however the timing of testing during the pregnancy was not addressed. When the gestational age of the study population was reported it generally included women in more than 1 pregnancy trimester and results were not presented separately for women tested at different stages in the pregnancy. All of the studies used a single urine sample for testing so these studies do not provide any information on the optimum frequency or repetitions of testing.

Summary: Criterion 4 not met

The new studies on screening tests identified in this review do not provide sufficiently robust evidence to recommend a particular screening test. The 2011 UK NSC review found that there is no strong evidence around the timing of when samples should be taken. No new evidence was identified on the timing of testing during pregnancy or the frequency/ repetitions of the test. The optimum screening strategy for detecting ASB in pregnancy remains unclear and this criterion is therefore 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 shouldn't be further considered.

Key Question: What are the effects of antimicrobial treatment for asymptomatic bacteriuria in pregnant women to prevent adverse outcomes?

The UK NSC review protocol states that of interest in this question is the type of antimicrobial treatment, the timing of treatment (eg early vs late pregnancy), the duration and dose of treatment, and negative outcomes in the mother or baby[7].

The 2011 UK NSC review[6] stated that ASB is treated with oral antibiotics and reported a meta-analysis demonstrating a reduced risk of pyelonephritis with antibiotics compared to no antibiotics in women with ASB. The most appropriate choice of antibiotic or duration of treatment was not clear.

Description of the evidence

In the current review, of the 26 studies identified as potentially relevant during title and abstract sifting, 6 related to this criterion. After review of the full texts, 3 studies were included. Reasons for excluding studies at this stage included a study comparing outcomes for asymptomatic and symptomatic patients and descriptive reviews of studies included in available systematic reviews.

A Cochrane review on antibiotics for ASB in pregnant women was recently updated (Smaill and Vazquez 2015[2]). An earlier version of this review (Smaill and Vazquez 2009[18]) was included in the 2011 UK NSC review[6]. No new RCTs were identified for the 2015 update of the Cochrane review and there was no change to the review's conclusions. As such this review does not provide any new evidence and the results are only briefly summarised here and the study is not included in the appendix tables.

Smaill and Vazquez[2:18] identified 14 RCTs including almost 2,000 women. In the meta-analysis the risk of pyelonephritis was reduced with antibiotics compared to placebo or no treatment (RR 0.23 95%CI 0.13 to 0.41). This equates to an approximately 75% reduction in the incidence of pyelonephritis with treatment of ASB. The risk of preterm birth (<37 weeks) (RR 0.27 95%CI 0.11 to 0.62) and low birthweight (<2,500g) (RR 0.64 95%CI 0.45 to 0.93) were also reduced with antibiotics. Several different antibiotic treatment regimens were used in the included studies with variation in the duration of treatment (from a single dose to treatment continuing up to or after delivery). Many studies used antibiotics that are no longer used routinely for the treatment of bacteriuria which introduces some uncertainty about the applicability of the results. The studies included in the meta-analyses were of low quality with an unclear or high risk of bias reducing confidence in the results observed.

Kazemir et al (2015)[8] conducted a double-blind RCT embedded within a multi-centre cohort study in the Netherlands. The RCT included 85 women aged ≥18 years with a singleton pregnancy of between 16 and 22 weeks gestation who tested positive for ASB in the cohort study and agreed to take part in the RCT. Of these, 40 received treatment (with the antibiotic nitrofurantoin) and 45 received placebo. An additional group of 4 women who were negative for ASB in the cohort study were invited to participate in the trial. These women all received placebo but were not included in the RCT analysis. This group was included so that women participating in the RCT were blinded to their bacteriuria status. Enrolment into the RCT and cohort study was stopped early due to the low incidence of the primary outcomes (pyelonephritis and/or delivery before 34 weeks). An intention to treat analysis was performed and found no significant difference between the treatment and placebo groups for risk of pyelonephritis (RD -2.2 95%CI -23.4 to 19.0) or delivery before 34 weeks (RD 2.5 95%CI -18.8 to 23.6). There were also no significant differences between the treatment and placebo groups on a range of secondary maternal and neonatal outcomes (further details of these outcomes are

provided in the appendix). The authors also performed an additional analysis that compared the 40 women who received treatment to a combined 'untreated' group consisting of the 45 women in the placebo group and a further 163 women who tested positive for ASB but who declined to participate in the RCT. This analysis also found no significant difference between the treated and untreated groups for risk of pyelonephritis (RD -2.4 95%CI -19.2 to 14.5), delivery before 34 weeks (RD -1.5 95%CI -15.3 to 18.5) or on secondary maternal and neonatal outcomes.

All RCT participants and assessors were blinded to bacteriuria status and treatment allocation. However due to the early suspension of recruitment into the RCT and cohort study the study was underpowered to detect a change so the results should be treated with caution. This study used a single urine test for ASB. Five of the 255 women who tested positive in the cohort study and were randomised to the RCT were later found not to have ASB. Due to the intention-to-treat analysis these women were retained in their assigned group for the RCT. In previous studies, 2 or 3 positive urine samples have often been used to define a positive result. It is possible that some of the women who tested positive did not have persistent bacteriuria and may not have been included if a second test had been required. The population of this study was women with uncomplicated pregnancies. Women were excluded if they had a history of preterm delivery before 34 weeks, warning signs of an imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 weeks of screening, known glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin or risk factors for complicated urinary tract infection (eg pre-gestational diabetes mellitus, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract). Further details of this study are provided in Appendix Table 9.

A 2015 Cochrane review (Widmer et al 2015[3]) considered the duration of treatment for ASB during pregnancy. This review identified 13 studies, involving 1,622 women, all of which compared single-dose to short course (4 - 7 days) treatments including a variety of different antibiotics. Eleven of the 13 studies were conducted in high income countries (Austria, Belgium, Denmark, Italy, New Zealand, Spain, UK and US). Overall, there was no significant difference in cure rates[§], recurrence of ASB, pyelonephritis or preterm birth rates. The single study that included birthweight as an outcome found that low birthweight was reduced for longer antibiotic treatment compared to a single dose (RR 1.7 95%CI 1.1 to 2.6). A pooled analysis of 12 studies did find that women receiving a single dose of any antibiotic had fewer side effects compared to women receiving a short course (RR 0.7 95%CI 0.6 to 0.9).

The studies included in this Cochrane review were generally thought to lack evidence of sufficient rigour in the design, conduct and analysis of the results, with areas of high or unclear risk of bias including blinding of participants and assessors and lack of information on the study population and compliance with the treatment regimen. A sub-group analysis including only the 2 studies which were rated as good quality found that cure rates were improved for short course treatment compared to a single dose of the same antibiotic (RR 1.7 95%CI 1.3 to 2.3). Further details of this study are provided in Appendix Table 10.

[§] a negative culture following initial treatment

Discussion

The literature search for this review identified an updated Cochrane review (with no new studies identified) on the use of antibiotics for ASB, and a 2015 RCT published after the search date of the Cochrane review. The Cochrane review did not identify any new RCTs published since the previous UK NSC review and retained the conclusion cited in the previous UK NSC review that the risk of pyelonephritis is reduced with antibiotics compared to placebo or no treatment (by approximately 75%). The risk of preterm birth and low birthweight were also reduced with antibiotics. This contrasts with the results of a 2015 RCT which found no difference between treated and untreated patients for risk of pyelonephritis, delivery before 34 weeks or on secondary maternal and neonatal outcomes.

The 2015 RCT had a strong methodological design but recruitment was suspended early and the study was therefore underpowered to detect a difference between the 2 groups. The population of the RCT was women with pregnancies described as uncomplicated and the number of cases of pyelonephritis and preterm birth was lower than expected. The studies included in the Cochrane review were considered to be of unclear or high risk of bias and many of the antibiotics are no longer routinely used for the treatment of bacteriuria which also introduces uncertainty about the quality and applicability of these results.

A second Cochrane review investigated the duration of treatment. Overall there was no difference between a single dose and a short course of treatment for cure rates, recurrence of ASB, pyelonephritis or preterm birth rates. Women who received a single dose of antibiotic did have fewer side effects. There were a number of areas of unclear or high risk of bias in the included studies. A sub-group analysis that only included the 2 good quality studies found that cure rates were improved for a short course of treatment compared to a single dose. This review suggests that a longer duration of antibiotics may lead to a better outcome in good quality studies (based on limited data) but that a single dose is associated with fewer side effects.

No new studies investigating the type or dose of antimicrobial treatment or the timing of treatment were identified.

Summary: Criterion 9 not met

Although the effects of antimicrobial treatment has been investigated in RCTs the inconsistency in the results of the systematic review of older trials and the results of a more recent RCT, combined with limitations in both studies leads to uncertainty about the effectiveness of treatment for ASB. A review on the duration of treatment suggests that a longer duration of antibiotics may lead to a better outcome in good quality studies (based on limited data) but that a single dose is associated with fewer side effects. In light of these uncertainties this criterion is not met.

Conclusions and implications for policy

This report assesses systematic population antenatal screening for asymptomatic bacteriuria against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if new evidence published since 2010 supports a recommendation for antenatal screening for asymptomatic bacteriuria in the UK.

The volume, quality and direction of new evidence published since October 2010 does not indicate that systematic population antenatal screening for asymptomatic bacteriuria should be recommended in the UK. Several uncertainties remain across key criteria, including:

- there was an absence of new evidence to provide updated information on the incidence or prevalence of ASB in the UK.
- one study considered the outcomes of untreated ASB in a Dutch population that could be considered analogous to the UK. The number of cases of pyelonephritis (2.4%) and preterm delivery (1.0%) in this population was lower than previously reported in the published literature, causing recruitment into the study to be terminated early. The women in this study had pregnancies described as uncomplicated and the prevalence of ASB in the population was at the lower end of the range found in the UK. In the absence of any updated information on the current prevalence of ASB or pyelonephritis in the UK it is uncertain how applicable the results of this study are to a UK population of pregnant women.
- the new studies on screening test performance identified in this review do not provide sufficiently robust evidence to recommend a particular screening test. No new evidence was identified on the timing of testing during pregnancy or the frequency/ repetitions of the test. The optimum population screening strategy for detecting ASB in pregnancy remains uncertain.
- the most recent RCT evidence found no difference between treated and untreated ASB patients for risk of pyelonephritis, delivery before 34 weeks or on a range of secondary maternal and neonatal outcomes. This contrasts with the results of a systematic review available to the previous UK NSC review and recently updated (with no new studies identified), which suggests that the risk of pyelonephritis is reduced with antibiotics compared to placebo or no treatment (by approximately 75%). In light of the contrasting results and methodological limitations with both studies the effects of antimicrobial treatment for ASB in pregnant women to prevent adverse outcomes is uncertain.
- a systematic review on the duration of treatment for ASB found no significant difference in cure rates, recurrence of ASB, pyelonephritis or preterm birth rates between a short course or single dose of antibiotics. However, a sub-group analysis found that a short course of antibiotics may lead to a better outcome in good quality studies (based on limited data). A single dose of antibiotics is associated with fewer side effects.

Recommendation

The review concluded that, at present, the evidence base is insufficient to recommend a UK systematic antenatal population screening programme for asymptomatic bacteriuria.

Limitations

Overall, this review identified few new studies addressing the key questions of interest.

Search strategy

A literature search on asymptomatic bacteriuria screening in pregnancy was performed by Elaine Garrett for the UK NSC in April 2016.

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: Medline Oct 2010-April Week 2 2016; Embase 2010-2016 April 22, Cochrane Library 2010-2016.

SEARCH STRATEGY

Medline (OVID interface). Similar searches were carried out in the other databases.

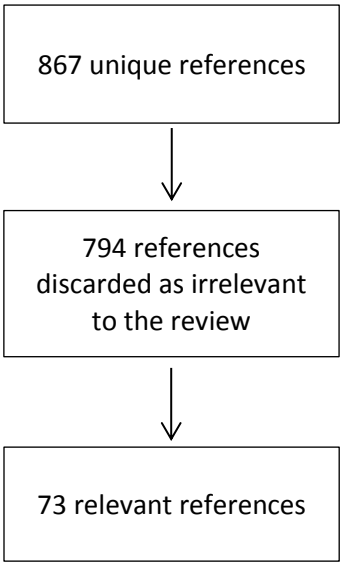
1 Bacteriuria/
2 (asymptomatic$ adj2 bacteriuria$).tw.
3 1 or 2
4 exp pregnancy/ or exp pregnancy complications/
5 (pregnan* or ante?natal* or ante natal* or pre?natal* or pre natal*).mp.
6 exp Infant, Newborn/
7 exp fetus/
8 exp "congenital, hereditary, and neonatal diseases and abnormalities"/
9 perinatal care/ or postnatal care/ or preconception care/ or prenatal care/
10 exp Prenatal Diagnosis/
11 exp "diagnostic techniques and procedures"/ or mass screening/
12 or/4-11
13 3 and 12
14 Bacteriuria/di
15 13 or 14
16 (20101* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dc.
17 15 and 16

Table 3: Results of the literature search

Database	No. of citations retrieved	Exclusive
Medline	342	332
Medline in Process	249	248
Embase	373	270
Cochrane Library	31	17
Total	**995**	**867**

After 128 duplicated were removed, 867 unique references were sifted by title and abstract, and where necessary and available the full text, for potential relevance to the review. 73 papers remained and were passed to the SPH reviewer for further consideration.

Figure 2: Flow diagram summarising the results of the reference sifting process



These 73 references were classified as presented in Table 4

Table 4: Summary of the relevant references by category

Category	**No. of citations**
Systematic reviews	4
Non-systematic reviews	7
Guidelines	1
Preventing the condition	2
Incidence/prevalence of condition *including:* *Europe (2)* *Australia (1)* *USA (1)*	4
Risk factors	2
Adverse outcomes	15
Identification – screening tests	22
Treatment	10
Screening programmes	6
Total	**73**

Key question PICOS**

Question	What is the incidence of ASB in the UK?
Sub-questions	N/A
Population	All pregnant women
Intervention	N/A
Comparator	N/A
Outcomes	Outcomes should reflect the likelihood of developing a serious complication in the newborn and mother
Inclusion criteria	Comparative observational studies eg cohorts, case controls, and systematic reviews (SRs) of these

Question	What are the outcomes of untreated ASB in pregnancy?
Sub-questions/comments	Studies that are done within the UK should be prioritised; other studies done in western populations that are analogous to the UK pregnancy cohort can also be included. Report outcomes by first, second and third trimester What is the incidence of low birthweight, pyelonephritis and preterm birth in women with ASB?
Population	Women with ASB
Intervention	Standard care
Comparator	Depending on standard care treatment vs no treatment
Outcomes	• Low birthweight • Pyelonephritis • UTI • Preterm birth
Inclusion criteria	Comparative observational or control studies eg cohorts, case controls, and systematic reviews (SRs) of these

Question	What is the performance of screening strategies for detecting ASB infection in pregnancy?
Sub-questions/comments	This question should look at: • Tests (accuracy etc) • Timing of testing during pregnancy • Frequency/repetitions of the test
Population	All pregnant women
Intervention	• Urine culture • Dipstick
Comparator	Open
Outcomes	Study reporting clinical performance measures, and SRs of these • Sensitivity • Specificity

** Population, Intervention, Comparator, Outcomes

	• False positive rate • False negative rate • PPV/NPV

Question	What are the effects of antimicrobial treatment for ASB in pregnant women to prevent adverse outcomes?
Sub-questions/comments	For the studies identified note: • Type of antimicrobial treatment • Timing of treatment (eg early vs late pregnancy) • Duration and dose of treatment • Negative outcomes in the mother • Negative outcomes in the baby
Population	Women with ASB
Intervention	Antibiotic therapies with UK marketing authorisation for use in pregnancy For example: • Amoxicillin • Nitrofurantoin • Trimethoprim • Cefalexin
Comparator	Active management (non-pharmacological)
Outcomes	• Rate of pyelonephritis • Rate of UTI • Low birthweight • Preterm birth
Inclusion criteria	RCTs prioritised, prospective comparative observational studies included if RCTs not available. Also systematic reviews of these studies.

Appendix Tables

Appendix number	1
Relevant criteria	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 the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	What are the outcomes of untreated asymptomatic bacteriuria in pregnancy?
Publication details	Kazemier BM. Koningstein FN. Schneeberger C. 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 Infectious Diseases 2015, 15: 1324-33

Study details	Multicentre cohort study
Study objectives	To assess the maternal and neonatal consequences of treated and untreated ASB in pregnancy
Inclusions	Women aged ≥18 years with a singleton pregnancy of between 16 and 22 weeks gestation
Exclusions	Women with a history of preterm delivery before 34 weeks, warning signs of an imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 weeks of screening, known glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin or risk factors for complicated urinary tract infection (eg pre-gestational diabetes mellitus, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract)
Population	Pregnant women (n=5,132) attending 8 hospitals and 5 ultrasound centres in the Netherlands
Intervention/ test	N/a
Comparator	N/a
Results	In the population of 208 untreated ASB positive women there were: • 5 cases of pyelonephritis (2.4%) • 42 urinary tract infections that were treated with antibiotics during pregnancy (20.2%) • 2 cases of preterm delivery (<34 weeks) (1.0%) • 17 cases where the neonate was small for its gestation age (<10th percentile) (8.2%)
Comments	Enrolment into the study was stopped early due to the low incidence of the primary outcomes (pyelonephritis and/or delivery before 34 weeks) The population in this study were women with uncomplicated pregnancies. It is uncertain how applicable the results are to a general UK population sample. This study used a single urine test for ASB. Five of the 255 women who tested positive in the cohort study and were randomised to the RCT were later found not to have ASB. It is possible that some of the women who tested positive did not have persistent bacteriuria and may not have been included if a second test had been required.

Appendix number	2
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	Okusanya BO. Aigere EOS. Eigbefoh JO. Okome GBO. Gigi CE. Is a chlorhexidine reaction test better than dipsticks to detect asymptomatic bacteriuria in pregnancy. Journal of Obstetrics and Gynaecology 2014, 34: 21-24

Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick and chlorhexidine reaction test performance in screening for ASB
Inclusions	Lack of symptoms such as dysuria, urine frequency, subrapubic and loin pain or vaginal discharge
Exclusions	Use of antibiotics for any reason or antibiotic treatment in the preceding 2 weeks
Population	150 asymptomatic pregnant women in Nigeria
Test	A single sample of urine was collected using a midstream clean catch technique. The tests performed were: • Dipstick test for nitrate and leukocyte esterase activity. A result was considered positive if the colour on the reagent square was positive for each portion • Chlorhexidine reaction test. A cloudy colour was considered a positive result after 5 drops of chlorhexidine were added to 10 drops of urine
Comparator / reference standard	Urine culture. A positive test contained >10^5 bacteria/ ml urine
Results	Seven women had positive urine cultures (4.7%) ***Dipstick test for nitrate*** Sensitivity: 42.9% PPV: 25.0% Specificity: 93.7% NPV: 97.1% ***Dipstick test for leucocyte esterase*** Sensitivity: 14.3% PPV: 3.2% Specificity: 79.0% NPV: 95.0% ***Dipstick test for leucocyte esterase and nitrate*** Sensitivity: 14.3% PPV: 25.0% Specificity: 97.9% NPV: 96.0% ***Chlorhexidine reaction test*** Sensitivity: 100% PPV: 9.7% Specificity: 54.0% NPV: 100% 95% confidence intervals not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending an antenatal clinic during the study period
Case-control design avoided?	Yes	Low	
Inappropriate exclusions avoided?	Yes	Low	

Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Unclear	Unclear	The index tests were performed by researchers at the antenatal clinic and the reference standard by laboratory scientists at a laboratory. However the paper makes no reference to blinding so it is not clear if other results were known
Threshold pre-specified?	Yes	Low	Each test had a pre-defined definition of a positive result
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	The index tests were performed by researchers at the antenatal clinic and the reference standard by laboratory scientists at a laboratory. However the paper makes no reference to blinding so it is not clear if other results were known
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was divided into 3 containers and used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Yes	Low	The prevalence of ASB identified was within the range found in the UK
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The point in the pregnancy when testing took place was not reported. No information was provided on the stage or trimester of the women who participated in the study

Appendix number	3
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	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 Research Notes 2014, 7: 481
Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick test performance in screening for ASB
Inclusions	Pregnant women attending an antenatal check
Exclusions	Women who had taken antibiotics in the previous 7 days
Population	Asymptomatic pregnant women in Ethiopia (n=330). The population also included 37 symptomatic women. Only the results for asymptomatic women are reported. Gestational age ranged from 16 to 38 weeks
Test	A single sample of urine was collected using a midstream clean catch technique. The tests performed were: • Dipstick test for nitrate and leukocyte esterase activity
Comparator / reference standard	Urine culture. A positive test contained >10^5 bacteria/ ml urine
Results	The number of positive results identified by the reference standard was not reported ***Dipstick test for nitrate*** Sensitivity: 35.7% PPV: 62.5% Specificity: 98.0% NPV: 94.3% ***Dipstick test for leucocyte esterase*** Sensitivity: 50.0% PPV: 29.8% Specificity: 89.1% NPV: 95.1% 95% confidence intervals not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for antenatal care at 1 centre during the study period
Case-control design	Yes	Low	

avoided?			
Inappropriate exclusions avoided?	Yes	Low	
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to other test results
Threshold pre-specified?	Yes	Low	
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to other test results
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	The prevalence of ASB identified by the reference standard test was not reported
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The point in the pregnancy when testing took place was not reported. The number of cases of ASB identified by the reference standard was not reported

Appendix number	4
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	Ullah A. Barman A. Ahmed I. Salam A. Asymptomatic bacteriuria in pregnant mothers: a valid and cost-effective screening test in Bangladesh. Journal of Obstetrics and Gynaecology 2012, 32: 37-41
Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick, gram staining and leucocyte count test performance in screening for ASB
Inclusions	Pregnant women attending a routine antenatal check and free of any symptoms of urinary tract infection
Exclusions	Women who had taken antibiotics in the previous 48 hours
Population	Asymptomatic pregnant women in Bangladesh (n=600)
Test	A single sample of urine was collected using a midstream clean catch technique. The tests performed were: • Dipstick test for nitrate and leukocyte esterase activity. A result was considered positive according to standard colour charts • Leucocyte count assessed microscopically in centrifuged urine samples. A range of cut-off points for a positive test were considered • Gram staining assessed microscopically in uncentrifuged urine. Bacteria were counted per oil-immersion field. A range of cut-off points for a positive test were considered
Comparator / reference standard	Urine culture. A positive test contained $>10^5$ bacteria/ ml urine
Results	24 women had positive urine cultures (4%) ***Dipstick test for nitrate*** Sensitivity: 29.2% (95%CI 14.9 to 49.2) PPV: 77.8% (95%CI 45.3 to 93.7) Specificity: 99.7% (95%CI 98.7 to 99.9) NPV: 97.1% (95%CI 95.4 to 98.2) ***Dipstick test for leucocyte esterase*** Sensitivity: 33.3% (95%CI 18.0 to 53.3) PPV: 6.3% (95%CI 3.3 to 12.0) Specificity: 79.5% (95%CI 76.0 to 82.6) NPV: 96.6% (95%CI 94.6 to 97.9) ***Dipstick test for leucocyte esterase and nitrate*** Sensitivity: 25.0% (95%CI 12.0 to 44.9) PPV: 75.0% (95%CI 40.9 to 92.9) Specificity: 99.7% (95%CI 98.7 to 99.9) NPV: 96.9% (95%CI 95.2 to 98.1) ***Gram staining (≥1OIF)*** Sensitivity: 91.7% (95%CI 74.2 to 97.7) PPV: 57.9% (95%CI 42.2 to 72.1) Specificity: 97.2% (95%CI 95.5 to 98.3) NPV: 99.6% (95%CI 98.7 to 99.9) ***Leucocyte count (≥6/HPF)*** Sensitivity: 62.5% (95%CI 42.7 to 78.8) PPV: 6.9% (95%CI 4.2 to 11.1) Specificity: 64.9% (95%CI 60.9 to 68.7) NPV: 97.6% (95%CI 95.6 to 98.9)

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for routine antenatal care at 1 hospital during the study period
Case-control design avoided?	Yes	Low	
Inappropriate exclusions avoided?	Yes	Low	
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Yes	Low	The authors specify that results were interpreted without knowledge of other test results
Threshold pre-specified?	No	High	A range of cut-off values were considered for each of the index tests
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Yes	Low	The authors specify that results were interpreted without knowledge of other test results
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Yes	Low	The prevalence of ASB identified was within the range found in the UK
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK

Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The point in the pregnancy when testing took place was not reported. No information was provided on the stage or trimester of the women who participated in the study

Appendix number	5
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	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): 1309-1312
Study details	Prospective observational study of screening test performance
Study objectives	To investigate gram staining, urine wet mount, catalase test and triphenyl tetrazolium chloride test performance in screening for ASB
Inclusions	Pregnant women in the first, second or third trimester attending an antenatal check at 1 hospital and free of any symptoms of urinary tract infection
Exclusions	Non stated
Population	Asymptomatic pregnant women in India (n=750)
Test	A single sample of urine was collected using a midstream clean catch technique Gram stain, urine wet mount, catalase test and triphenyl tetrazolium chloride test were assessed in uncentrifuged urine. The cut-off levels used for a positive test was not reported
Comparator / reference standard	Urine culture. A positive test contained >10^5 bacteria/ ml urine
Results	59 women had positive urine cultures (7.9%) ***Gram staining*** Sensitivity: 98.3% Specificity: 100% ***Urine wet mount*** Sensitivity: 27.1% Specificity: 100% ***Catalase test*** Sensitivity: 100% Specificity: 95.5% ***Triphenyl tetrazolium chloride test*** Sensitivity: 95.4% Specificity: 98.2%

	PPV and NPV were not reported by the study authors, but were calculated for this review in Table 1 in the main section of the report. 95% confidence intervals not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for antenatal care at 1 hospital during the study period
Case-control design avoided?	Yes	Low	
Inappropriate exclusions avoided?	Yes	Low	Only women with symptoms of urinary tract infection were excluded
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to other test results
Threshold pre-specified?	Unclear	Unclear	No details provided on the cut-off levels used to indicate a positive test
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to other test results
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Yes	Low	The prevalence of ASB identified was within the range found in the UK

Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study did not state if women who were taking or had recently taken antibiotics were excluded from the study. No information was provided on the cut-off levels used to indicate a positive test or the blinding of test assessors.

This study involved testing of a single urine sample. The point in the pregnancy when testing took place was not reported

Appendix number	6
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	Balamurugan S. Shah C. Jayapriya S. et al. Reagent strip testing (RST) for asymptomatic bacteriuria (ASB) in pregnant women: a cost-effective screening tool in under-resourced settings. Journal of Clinical and Diagnostic Research 2012, 64(4) (Suppl-2): 671-673
Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick test performance in screening for ASB
Inclusions	Pregnant women attending a routine antenatal check and free of any symptoms of urinary tract infection
Exclusions	Women who had taken antibiotics in the previous 2 weeks
Population	Asymptomatic pregnant women in India (n=100). Of these 15% were in the first trimester, 45% in the second trimester and 40% in the third trimester
Test	A single sample of urine was collected using a midstream clean catch technique. Dipstick tests for nitrate and leukocyte esterase activity were performed singly and in combination with blood and protein markers. Only the results for nitrate and leucocyte singly or combined are reported. The addition of blood and or protein as a marker did not improve on the test performance of nitrate and leucocyte combined.
Comparator / reference standard	Urine culture. A positive test contained $>10^5$ bacteria/ ml urine
Results	13 women had positive urine cultures (13%) ***Dipstick test for nitrate***

	Sensitivity: 61.6% (95%CI 32.3 to 84.7) PPV: 24.0% Specificity: 71.3% (95%CI 60.4 to 80.2) NPV: 93.0% ***Dipstick test for leucocyte esterase*** Sensitivity: 84.6% (95%CI 53.7 to 97.3) PPV: 31.0% Specificity: 71.3% (95%CI 60.4 to 80.2) NPV: 96.0% ***Dipstick test for leucocyte esterase or nitrate*** Sensitivity: 92.3% (95%CI 64.0 to 99.8) PPV: 45.0% Specificity: 82.8% (95%CI 73.2 to 90.0) NPV: 99.0% Confidence intervals for PPV and NPV were not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for antenatal care at 1 clinic during the study period
Case-control design avoided?	Yes	Low	
Inappropriate exclusions avoided?	Yes	Low	
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Yes	Low	The authors specify that this was a blinded study
Threshold pre-specified?	Yes	Low	
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Yes	Low	The authors specify that this was a blinded study
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants	Yes	Low	

receive same reference standard?			
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Unclear	Unclear	The ASB prevalence of 13% was slightly higher than the range found in the UK
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The proportion of women in each of the 3 pregnancy trimesters was reported, but test performance was not reported for testing at different stages of the pregnancy.

The confidence intervals reported for the sensitivity and specificity results were wide

Appendix number	7
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	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 and Medical Science 2011, 40: 377-383
Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick test performance in screening for ASB
Inclusions	Pregnant women attending first antenatal visit
Exclusions	Women with symptoms of acute urinary tract infection and women who were on or had been on antibiotic treatment prior to booking
Population	Asymptomatic pregnant women in Nigeria (n=205). The mean gestational age was 20.9 weeks (range 6 to 40 weeks)
Test	A single sample of urine was collected using a midstream clean catch technique. A dipstick test for nitrate and leukocyte esterase activity was used. A result was considered positive according to the colour charts on the reagent strip bottle

Comparator / reference standard	Urine culture. A positive test contained >10^5 bacteria/ ml urine
Results	22 women had positive urine cultures (10.7%) Dipstick test for nitrate Sensitivity: 36.4% PPV: 72.7% Specificity: 98.4% NPV: 92.9% ***Dipstick test for leucocyte esterase*** Sensitivity: 31.8% PPV: 41.2% Specificity: 94.5% NPV: 92.0% ***Dipstick test for leucocyte esterase and nitrate*** Sensitivity: 50.0% PPV: 45.8% Specificity: 92.9% NPV: 93.9% 95% confidence intervals not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for their first antenatal visit at 1 hospital during the study period
Case-control design avoided?	Yes	Low	
Inappropriate exclusions avoided?	Yes	Low	
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Yes	Low	Index tests were performed before the reference standard test
Threshold pre-specified?	Yes	Low	Each test had a pre-defined definition of a positive result
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Yes	Low	The scientists performing the urine culture were blinded to the results of the reagent strip

Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Yes	Low	The prevalence of ASB identified was within the range found in the UK
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The gestational age of the study population ranged from 6 to 40 weeks. Test performance results were not presented separately for different stages in the pregnancy

Appendix number	8
Relevant criteria	Criterion 4: There should be a simple, safe, precise and validated screening test
Relevant key question	What is the performance of screening strategies for detecting asymptomatic bacteriuria infection in pregnancy?
Publication details	Gayathree L. Shetty S. Deshpande SR. Venkatesha DT. Screening for asymptomatic bacteriuria in pregnancy: an evaluation of various screening tests at the Hassan district hospital, India. Journal of Clinical and Diagnostic Research 2010, 4: 2702-2706
Study details	Prospective observational study of screening test performance
Study objectives	To investigate dipstick and gram staining test performance in screening for ASB
Inclusions	Pregnant women attending a routine antenatal check and free of any symptoms urinary tract infection
Exclusions	Women who had taken antibiotics in the previous 2 weeks; pregnancy induced diabetes mellitus / hypertension; pyrexia; known congenital anomalies of the urinary tract

Population	Asymptomatic pregnant women in India (any gestational age) (n=900). A control group of 50 non-pregnant women was also included in the study but not used in the calculations of test performance
Test	A single sample of urine was collected using a midstream clean catch technique. The tests performed were: • Dipstick test for nitrate and leukocyte esterase activity • Gram staining assessed microscopically in uncentrifuged urine. Bacteria were counted per oil-immersion field. A positive result had ≥1 bacteria/ oil immersion field (OIF)
Comparator / reference standard	Urine culture. A positive test contained >10^5 bacteria/ ml urine
Results	62 women had positive urine cultures (6.8%) ***Dipstick test for nitrate*** Sensitivity: 71.0% PPV: 88.0% Specificity: 99.3% NPV: 97.9% ***Dipstick test for leucocyte esterase*** Sensitivity: 61.3% PPV: 38.8% Specificity: 92.8% NPV: 97.0% ***Dipstick test for leucocyte esterase and nitrate*** Sensitivity: 53.2% PPV: 100% Specificity: 100% NPV: 96.7% ***Gram staining (≥1OIF)*** Sensitivity: 90.3% PPV: 87.5% Specificity: 99.0% NPV: 98.3% 95% confidence intervals not reported

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Yes	Low	Women attending for antenatal care at 1 hospital during the study period
Case-control design avoided?	Yes	Low	A control group of 50 non-pregnant women was included in the study but not used in the calculations of test performance
Inappropriate exclusions avoided?	Yes	Low	
Domain II: Index Test			
Index test results interpreted without	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to

knowledge of reference standard results?			other test results
Threshold pre-specified?	Yes	Low	
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Yes	Low	Urine culture used as the reference standard
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	No details provided on who performed the tests and whether they were blinded to other test results
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Yes	Low	One urine sample was used for the index tests and reference standard
Did all participants receive same reference standard?	Yes	Low	
All patients included in analysis?	Yes	Low	
Applicability			
Applicable to UK screening population of interest?	Yes	Low	The prevalence of ASB identified was within the range found in the UK
Applicable to UK screening test of interest?	Yes	Low	The tests are applicable to the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Yes	Low	Urine culture is recognised as the gold standard for identifying ASB

Other comments

This study involved testing of a single urine sample. The women could be of any gestational age and the point in the pregnancy when testing took place was not reported

Appendix number	9
Relevant criteria	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 shouldn't be further considered.
Relevant Key question	What are the effects of antimicrobial treatment for asymptomatic bacteriuria in pregnant women to prevent adverse outcomes?
Publication details	Kazemier BM. Koningstein FN. Schneeberger C. 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 Infectious Diseases 2015, 15: 1324-33
Study details	Double-blind placebo RCT embedded within a multicentre cohort study. Enrolment into the RCT and cohort study was stopped early due to the low incidence of the primary outcomes (pyelonephritis and/or delivery before 34 weeks)
Study objectives	To assess the maternal and neonatal consequences of treated and untreated ASB in pregnancy
Inclusions	Women aged ≥18 years with a singleton pregnancy of between 16 and 22 weeks gestation, without symptoms of urinary tract infection, who tested positive for ASB
Exclusions	Women with a history of preterm delivery before 34 weeks; warning signs of an imminent preterm delivery; fetal congenital malformations; antibiotic use within 2 weeks of screening; known glucose-6-phosphate dehydrogenase deficiency; hypersensitivity to nitrofurantoin or risk factors for complicated urinary tract infection (eg pre-gestational diabetes mellitus, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract)
Population	Pregnant women (n=85) attending 8 hospitals and 5 ultrasound centres in the Netherlands who tested positive for ASB in the cohort study (on a single dipslide test) were randomised to the treatment or control groups An additional group of 4 women who were negative for ASB in the cohort study were invited to participate in the trial. These women all received placebo but were not included in the RCT analysis. This group was included so that women were blinded to their bacteriuria status The remaining cohort population (total n= 5132) who did not participate in the RCT were also followed-up separately. Follow-up results were available for 248 (95%) of the ASB positive women and 4035 (95%) of the ASB negative women
Intervention/ test	Antibiotic treatment with nitrofurantoin (100mg twice daily for 5 consecutive days) (n=40)
Comparator	Placebo (ASB positive women) (n=45)
Results	The first set of results presented is from the intention-to-treat analysis of the RCT participants **Pyelonephritis:** • no significant difference between the treatment and placebo group (RD -2.2 95%CI -23.4 to 19.0)

	Delivery < 34 weeks: • no significant difference between the treatment and placebo group (RD 2.5 95%CI -18.8 to 23.6) There were also no significant differences between the treatment and placebo groups on a range of secondary maternal and neonatal outcomes. The maternal outcomes assessed included: symptomatic urinary tract infection (UTI) treated with antibiotics during pregnancy; recurrent UTI treated with antibiotics during pregnancy; UTI treated with antibiotics postpartum (within 6 weeks); antibiotics during pregnancy other than for UTI; gestational diabetes; pregnancy induced hypertension; pre-eclampsia; HELLP; kidney stones; cholestasis; thrombo-embolic events; non-spontaneous onset of labour; epidural/ spinal analgesia during labour; endometritis (within 6 weeks of delivery); mastitis (within 6 weeks of delivery). The neonatal outcomes included gestational age at delivery <37 weeks, <32 weeks and <28 weeks; birthweight mean SGA <P10 or SGA<5; perinatal death; composite severe morbidity (respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, bronchopulmonary disease, sepsis); admission to a neonatal intensive care unit; neonatal sepsis confirmed with culture; congenital abnormalities The second set of results presented compares the women who received treatment (n=40) to a group of untreated women which combined the women from the cohort who tested positive but did not participate in the RCT (n=163) and the placebo group from the RCT (n=45) **Pyelonephritis:** • no significant difference between the treatment and non-treatment group (RD -2.4 95%CI -19.2 to 14.5) **Delivery < 34 weeks:** • no significant difference between the treatment and non-treatment group (RD -1.5 95%CI -15.3 to 18.5) There were also no significant differences between the treatment and placebo groups on the secondary maternal and neonatal outcomes
Comments	All RCT participants and assessors were blinded to bacteriuria status and treatment allocation This study was designed as an RCT but stopped early due to the low incidence of the primary outcomes. Outcomes were reported for the RCT intention-to-treat analysis and for a separate analysis that included RCT and cohort participants. However due to the small number of participants, the RCT was underpowered and therefore the results should be treated with caution The population in this study were women with uncomplicated pregnancies. It is therefore uncertain how applicable the results are to a general population sample This study used a single urine test for ASB. Five of the 255 women who tested positive

	in the cohort study and were randomised to the RCT were later found not to have ASB. Due to the intention-to-treat analysis these women were retained in their assigned group for the RCT. In previous studies 2 or 3 positive urine samples have often been used to define a positive result. It is possible that some of the women who tested positive did not have persistent bacteriuria and may not have been included if a second test had been required

Appendix number	10
Relevant criteria	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 shouldn't be further considered.
Relevant Key question	What are the effects of antimicrobial treatment for asymptomatic bacteriuria in pregnant women to prevent adverse outcomes?
Publication details	Widmer M. Lopez I. Gülmezoglu AM. Mignini L. Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 11. Art No.: CD000491. DOI: 10.1002/14651858.CD000491.pub3
Study details	Systematic review and meta-analysis
Study objectives	To assess the effects of different durations of treatment for ASB in pregnancy
Inclusions	All RCTs and quasi-RCTs comparing regimens of different durations for the treatment of ASB during pregnancy, including those that compared different duration of different antimicrobial agents as well as different durations of the same agent
Exclusions	Trials comparing different therapeutic agents with the same duration of administration
Population	This review identified 13 studies, involving 1,622 women, all comparing single-dose to short course (4 - 7 days) treatments including a variety of different antibiotics. Eleven of the 13 studies were conducted in high income countries (Austria, Belgium, Denmark, Italy, New Zealand, Spain, UK and US)
Intervention/ test	Antibiotic treatment – single dose
Comparator	Antibiotic treatment – longer duration regimens
Results	**Cure rate** (a negative culture following initial treatment)**:** • no difference between single-dose antibiotic versus short course treatment using any antibiotic (RR 1.3 95%CI 0.9 to 1.9) (13 studies) • in a sub-group analysis of 2 studies rated as good quality, cure rates improved with short course treatment compared to single dose for different durations of the same antibiotic (RR 1.7 95%CI 1.3 to 2.3)

	• no differences found in sub-group analysis of studies on different regimens of the same agent, or different regimens for different agents **Recurrent ASB** (relapse/ recurrence by same organism or by a different strain within 6 weeks of initial infection): • no difference between single-dose antibiotic versus short course treatment using any antibiotic (RR 1.1 95%CI 0.8 to 1.7) (8 studies) • no differences found in subgroup analysis of different durations of the same antibiotic and different durations of different antibiotics **Pyelonephritis:** • no difference between single-dose antibiotic versus short course treatment using different durations of the same antibiotic (RR 3.1 95%CI 0.5 to 17.6) (2 studies) **Preterm birth rates** (<37 weeks): • no difference between single-dose antibiotic versus short course treatment using different durations of the same antibiotic (RR 1.2 95%CI 0.8 to 1.8) (3 studies) **Low birthweight rates** (<2,500g): • lower low birthweight rates for longer treatment compared to single dose treatment using different durations of the same antibiotic (RR 1.7 95%CI 1.1 to 2.6) (1 study) **Side effects** • women receiving a single dose of any antibiotic had fewer side effects compared to women receiving short course treatment using different durations of the same antibiotic (RR 0.7 95%CI 0.6 to 0.9) (12 studies) • subgroup analysis of trials testing different durations of the same antibiotic and different durations of different antibiotics also found fewer side effects for women receiving a single dose of antibiotic
Comments	The studies were generally thought to lack evidence of sufficient rigour in the design, conduct and analysis of the results with areas of high or unclear risk of bias including blinding of participants and assessors, and lack of information on the study population and compliance with the treatment regimen

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