

Appendix 2 (as supplied by the authors): GRADE EVIDENCE-TO-DECISION FRAMEWORK

Question

Should we screen women for asymptomatic bacteriuria in pregnancy?

POPULATION: Pregnant women	BACKGROUND: Asymptomatic bacteriuria (ASB) - synonymous with asymptomatic urinary tract infection (UTI) - signifies a significant quantitative count of bacteria in the urine without symptoms of a lower (acute cystitis) or upper urinary tract (acute pyelonephritis) infection. ^{1,2} There is a 2-10% prevalence of ASB in premenopausal, ambulatory women, ¹ but due to anatomical and physiological changes (e.g., urinary stasis - difficulty emptying the bladder due to hormonal changes and pressure from the expanding uterus) to the urinary tract in pregnancy there are theoretical reasons to suspect a greater chance of progression to symptomatic UTI and other pregnancy complications (e.g., maternal kidney infection, preterm delivery). ^{1,3} Numerous risk factors for ASB
INTERVENTION: Screening for asymptomatic bacteriuria	
COMPARISON: No screening	
MAIN OUTCOMES: Benefits (reduction in): Pyelonephritis; spontaneous abortion; perinatal mortality; preterm delivery Harms: fetal abnormalities; maternal mortality; maternal sepsis; neonatal sepsis; low birth weight	
SETTING: Primary care and prenatal care in Canada	

Appendix to: Moore A, Doull M, Grad R, et al; for the Canadian Task Force on Preventive Health Care. Recommendations on screening for asymptomatic bacteriuria in pregnancy. *CMAJ* 2018. doi: 10.1503/cmaj.171325.

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PERSPECTIVE:

Population

in pregnancy have been identified, with a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract most cited.^{1,2,8}

Current Canadian practice is to screen all asymptomatic pregnant women for ASB in early pregnancy with the intention to treat positive results. The SOGC also recommends screening in each trimester for women with a history of recurrent UTIs.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	<p>Is the problem a priority?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Current Canadian practice is to screen asymptomatic pregnant women for ASB in the first trimester of pregnancy with antibiotic treatment for positive screens. There is considerable variation in the reported risk of pyelonephritis associated with untreated ASB in pregnant women, depending on the setting and date of the report^{4,5,6,7}. There is an association between clinical signs of pyelonephritis and maternal respiratory insufficiency, septicemia, renal dysfunction and anemia, as well as preterm birth and low birth weight^{8,9}. A recent study found asymptomatic bacteriuria was not associated with preterm birth⁴. Hence, the relationship between ASB and pregnancy complications is somewhat uncertain. An up-to-date guideline that considers evidence on the potential harms and benefits of screening for ASB in pregnancy, as well as women's values and preferences regarding screening and resultant outcomes is needed.</p>	
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p><u>BENEFITS – SCREENING (reduction in all)</u></p>	

Screening compared to no screening for asymptomatic bacteriuria in pregnant women

Patient or population: asymptomatic bacteriuria in pregnant women

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

Intervention: screening

Comparison: no screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no screening	Risk with screening				
Maternal mortality	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal mortality.
Maternal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal sepsis.
Pyelonephritis	Median		RR 0.28 (0.15 to 0.54)	5659 (3 observational studies)	⊕○○○ VERY LOW ^{1,a}	We are very uncertain about the effects of screening on pyelonephritis.
	18 per 1,000	13 fewer per 1,000 (from 8 fewer to 16 fewer)				

	Perinatal mortality	Median 19 per 1,000	4 more per 1,000 (from 19 fewer to 1,000 more)	RR 1.21 (0.01 to 102.93)	724 (2 observational studies)	⊕○○○ VERY LOW ^{1,b}	We are very uncertain about the effects of screening on perinatal mortality.
	Spontaneous abortion	55 per 1,000	2 fewer per 1,000 (from 32 fewer to 70 more)	RR 0.96 (0.41 to 2.27)	370 (1 observational study)	⊕○○○ VERY LOW ^{1,c}	We are very uncertain about the effects of screening on spontaneous abortion.
	Neonatal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on neonatal sepsis.
	Preterm delivery	Median 13 per 1,000	102 more per 1,000 (from 9 fewer to 1,000 more)	RR 8.70 (0.32 to 240.07)	722 (2 observational studies)	⊕○○○ VERY LOW ^{1,d}	We are very uncertain about the effects of screening on preterm delivery.

		<p>Low birthweight 0 per 1,000 0 per 1,000 (0 to 0) not estimable (0 studies) - No study reported on low birthweight.</p>	
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio</p>			
<p>GRADE Working Group grades of evidence</p> <p>High quality: We are very confident that the true effect lies close to that of the estimate of the effect</p> <p>Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p>Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p>Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>			
<p><u>BENEFITS – TREATMENT, LINKED EVIDENCE</u> (reduction in all)</p>			

Treatment compared to no treatment for asymptomatic bacteriuria

Patient or population: asymptomatic bacteriuria

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

Intervention: treatment

Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with treatment				
Maternal mortality	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal mortality.
Maternal sepsis	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal sepsis.
Pyelonephritis	Median	176 fewer per 1,000 (from 137 fewer to 202 fewer)	RR 0.24 (0.13 to 0.41)	2017 (12 RCTs)	⊕⊕○○ LOW ^{1,a}	There may be a reduction in pyelonephritis from treatment.
	232 per 1,000					

	Perinatal mortality	Median	RR 0.96 (0.27 to 3.39)	1104 (6 RCTs)	⊕○○○ VERY LOW ^{1, b}	We are very uncertain about the effects of treatment on perinatal mortality.
		40 per 1,000	2 fewer per 1,000 (from 29 fewer to 97 more)			
	Spontaneous abortion	Median	RR 0.60 (0.11 to 3.10)	379 (2 RCTs)	⊕○○○ VERY LOW ^{1, c}	We are very uncertain about the effects of treatment on spontaneous abortion.
		33 per 1,000	13 fewer per 1,000 (from 30 fewer to 70 more)			
Neonatal sepsis	Median	RR 0.22 (0.01 to 4.54)	154 (2 RCTs)	⊕○○○ VERY LOW ^{1, d}	We are very uncertain about the effects of treatment on neonatal sepsis.	
	22 per 1,000	17 fewer per 1,000 (from 22 fewer to 79 more)				
	Median					

<p>Preterm delivery</p> <p>158 per 1,000</p>	<p>68 fewer per 1,000 (from 125 fewer to 88 more)</p>	<p>RR 0.57 (0.21 to 1.56)</p>	<p>533 (4 RCTs)</p>	<p>⊕○○○ VERY LOW ^{1,e}</p>	<p>We are very uncertain about the effects of treatment on preterm delivery.</p>
<p>Low birth weight</p>	<p>Median</p> <p>118 per 1,000</p>	<p>44 fewer per 1,000 (from 12 fewer to 65 fewer)</p>	<p>RR 0.63 (0.45 to 0.90)</p>	<p>1522 (7 RCTs)</p> <p>⊕○○○ LOW ^{1,f}</p>	<p>There may be a reduction in low birth weight from treatment.</p>
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio</p>					
<p>GRADE Working Group grades of evidence</p> <p>High quality: We are very confident that the true effect lies close to that of the estimate of the effect</p> <p>Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p>Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p>Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>					

UNDESIRABLE EFFECTS								
	<p>How substantial are the undesirable anticipated effects?</p> <p><input type="radio"/> Large</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Varies</p> <p>X Don't know</p>	<u>HARMS – SCREENING</u>						
		Maternal serious harm(s)	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal serious harms.
		Neonatal serious harm: fetal abnormalities	11 per 1,000	5 more per 1,000 (from 8 fewer to 85 more)	RR 1.50 (0.25 to 8.87)	372 (1 observational study ⁴⁵)	⊕○○○ VERY LOW ^{1,e}	We are very uncertain about the effects of screening on fetal abnormalities.
		<u>HARMS – TREATMENT</u>						
		Maternal serious harm(s)	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	No study reported on maternal serious harms.
Neonatal serious harm: fetal abnormalities		Median 19 per 1,000	9 fewer per 1,000 (from 15 fewer to 8 more)	RR 0.49 (0.17 to 1.43)	821 (4 RCTs)	⊕○○○ VERY LOW ^{1,g}	We are very uncertain about the effects of treatment on harms (fetal abnormalities).	

		<p>Neonatal serious harm: hemolytic anemia</p> <p>0 per 1,000</p> <p>0 per 1,000 (0 to 0)</p> <p>not estimable</p> <p>265 (1 RCT)</p> <p>⊕○○○ VERY LOW^{1, h}</p> <p>We are very uncertain about the effects of treatment on harms (hemolytic anemia).</p>	
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <p>X Very low</p> <p><input type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>Screening: Very Low – the overall quality of evidence for the critical outcomes is very low. We are very uncertain about the absolute effects of screening on the critical outcomes.</p> <p>Treatment (linked evidence): Very Low – the overall quality of evidence for the critical outcomes is very low. We are very uncertain about the absolute effects of treatment for ASB on critical outcomes.</p>	
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <p><input type="radio"/> Important uncertainty or variability</p> <p>X Possibly important uncertainty or variability</p> <p><input type="radio"/> Probably no important</p>	<p>No study provided evidence on how women weigh the benefits and harms of screening and/or treatment of asymptomatic bacteriuria; six studies provided indirect evidence, specifically with inconsistent and sometimes conflicting opinions of antibiotic use during pregnancy and perception of teratogenic risks from medications used in pregnancy.</p> <p>The patient preferences report by the Knowledge Translation Group at St. Michael’s Hospital undertaken on behalf of the CTFPHC indicates that women placed more importance on benefits rather than harms when making decisions about asymptomatic bacteriuria screening because screening itself was not seen as harmful.. Some women also seemed to separate the benefits and harms of screening versus treatment and viewed screening as less harmful. Some women indicated</p>	<p>A recently published study from The Netherlands included from the search update for treatment evidence reported that a significant proportion of women (61%) opted out of their treatment trial</p>

	<p>uncertainty or variability</p> <ul style="list-style-type: none"> ○ No important uncertainty or variability 	<p>that they would assess the benefits and harms of treating after their decision to screen because of some concerns about antibiotic use in pregnancy. Past experience with antibiotic use, pregnancy complications, as well as unknown harms to babies and mothers influenced women’s preferences both in favour and against treatment of ASB in pregnancy</p>	<p>due to concerns with using antibiotics for an asymptomatic condition. It is important to note that screening for ASB is not part of routine prenatal care in the Netherlands.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">BALANCE OF EFFECTS</p>	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	<p>Considering critical outcomes we are uncertain that the benefits of screening outweigh the harms. There is low quality evidence that treatment modestly reduces the incidence of pyelonephritis and the number of low birth weight infants. There was a lack of evidence on serious harms of screening or treatment.</p>	

RESOURCES REQUIRED	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A cost-effectiveness analysis was not conducted as part of the systematic review. Urine samples are a routine part of pre-natal care in Canada and are used for various tests including ASB. Task force members considered the cost of screening for ASB to be relatively low compared to the overall costs of prenatal care in Canada</p>	<p>Cost of urine culture/laboratory cost: Median cost of urine culture test across Canada: \$15.00 CDN (Alberta Health Services); \$19.57 (BC Lab Services, fee schedule)</p>
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 		

COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 		
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input checked="" type="radio"/> Don't know 	<p>Low socioeconomic status has been identified as a risk factor for ASB in pregnancy. However, the evidence review could not assess this in a subgroup analysis.</p>	<p>Screening for ASB is currently a routine part of prenatal care in Canada so if a recommendation is made against screening it is possible that populations with higher rates of ASB and subsequent</p>

			complications may be adversely affected.
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <p> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know </p>	<p>Possible stakeholder groups include: pregnant women, physicians/midwives/nurses engaged in prenatal care, SOGC, government/health system stakeholders.</p> <p>Physicians/Midwives/Nurses: Currently in Canada, screening for ASB is part of standard prenatal care – so in the judgement of the CTFPHC, screening is acceptable to these stakeholders. Further, urine cultures are used routinely in prenatal care and thus the task force does not think there will be any additional burden.</p> <p>Women: As above, screening for ASB and the collection of urine for screening are routine prenatal care in Canada. Women do not experience any harms from providing urine samples. However, findings from the patient values and preferences report are mixed – with women weighing benefits more heavily than harms for both screening and treatment. Screening is done with the intention to treat and findings from the systematic review on patient values suggest that some women are less comfortable taking antibiotics during pregnancy. Overall, it is unclear whether the intervention is acceptable to all women.</p> <p>SOGC/Specialty stakeholders: SOGC and most prenatal guidelines (e.g, BC prenatal care pathway) include screening for ASB in early pregnancy as standard practice. The intervention is likely acceptable to this group.</p> <p>Government/Health system: As screening for ASB is part of routine care it is acceptable to system level stakeholders.</p>	
FEASIBILITY	<p>Is the intervention feasible to implement?</p>	<p>Yes, screening is part of standard prenatal care in Canada and urine culture, the gold standard method of testing for ASB is widely practiced. Thus, in the judgment of the task force, the</p>	

	<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	intervention is feasible.	
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Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				

	JUDGEMENT							IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should we screen women for asymptomatic bacteriuria in pregnancy?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention X	Strong recommendation for the intervention ○
RECOMMENDATION	<p>The Task Force recommends <i>recommend screening pregnant women once during the first trimester with urine culture for asymptomatic bacteriuria (Weak recommendation; very low quality evidence).</i></p> <p><i>This recommendation applies to pregnant women who are not experiencing symptoms of a UTI and are not at increased risk for ASB.</i></p>				
JUSTIFICATION	<p>Very low quality evidence was found for the benefits and harms of screening for ASB in pregnancy. Low quality, evidence was found for effectiveness of treating screen-identified women with ASB to modestly reduce the incidence of pyelonephritis and the number of low birth weight infants.</p> <p>It is a longstanding practice in Canada to provide routine screening and treatment of ASB in pregnancy and this may contribute to the low prevalence of pyelonephritis among pregnant women in Canada. In addition, the resources required to provide such screening are relatively modest. Therefore, in the judgement of the task force, the potential benefits of screening outweigh possible harms, and a weak recommendation in favor of screening is warranted. This recommendation places a relatively higher priority on the small but uncertain benefit of screening for ASB and a relatively lower priority on the lack of evidence regarding serious harms associated with antibiotic use for pregnant mothers and their babies.</p>				

	<p>The recommendation is weak because of uncertainty regarding the benefits of screening as well as the variable preferences of women regarding antibiotic treatment in pregnancy.</p>
SUBGROUP CONSIDERATIONS	<p>No data was available to inform specific recommendations or considerations for vulnerable groups.</p> <p>As with prenatal care generally, we encourage clinicians to attend to the specific needs of high risk women. This weak recommendation does not apply to women who are at increased risk for ASB.</p>
IMPLEMENTATION CONSIDERATIONS	<p>Clinicians should understand the risk factors for ASB and urinary tract infections in pregnancy and should engage their pregnant patients in a shared decision making process to determine the best course of action.</p> <p>A weak recommendation in favour of screening highlights the need for shared decision-making with patients. Women who are interested in a small, uncertain potential reduction in the risk of pyelonephritis and/or low birthweight will be more likely to choose screening for ASB. Women who are more concerned with potential harms of antibiotics may be more likely to choose not be screened.</p> <p>Some women who are not at increased risk of urinary tract infections in pregnancy and are more concerned with potential side-effects and harms of antibiotics for their babies and themselves, may chose not to be screened for ASB, and would opt for antibiotic treatment in the event of UTI symptoms. Women who are more concerned with the potential, but uncertain benefit of ASB screening and are less concerned with potential harms of antibiotics in pregnancy may choose screening for ASB.</p>
MONITORING AND EVALUATION	<p>Awareness of this recommendation may lead some pregnant women who are not at high risk and their clinicians to question routine ASB screening, while also increasing clinician understanding of the importance of screening in high risk women. Awareness of this recommendation therefore is a performance measure for this guideline.</p>
RESEARCH PRIORITIES	<ul style="list-style-type: none"> - High quality ASB screening and treatment trials. - More information is also needed on independent factors that place some groups of women at clinically important risk for ASB (e.g. vulnerable groups)

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| | <ul style="list-style-type: none">- Studies evaluating rates of ASB among pregnant women in Canada are recommended to inform accurate baseline risk.- Further research to confirm best practice for diagnosis such as the number of repeat urine cultures.- Preference-based studies on how Canadian women weigh ASB screening outcomes would be clinically useful to understand the proportion of women choosing screening. |
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