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Screening for Asymptomatic Bacteriuria in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Screening for asymptomatic bacteriuria can identify patients for whom treatment might be beneficial for preventing symptomatic infection and other health outcomes.

OBJECTIVE To systematically review benefits and harms of asymptomatic bacteriuria screening and treatment in adults, including during pregnancy, to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed (publisher-supplied records), and Cochrane Collaboration Central Registry of Controlled Trials; surveillance through May 24, 2019.

STUDY SELECTION Randomized clinical trials (RCTs) and observational studies on benefits and harms of screening for asymptomatic bacteriuria; RCTs on benefits and harms of asymptomatic bacteriuria treatment. Eligible populations included unselected, asymptomatic individuals without known urinary tract conditions.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction by 2 reviewers. Random-effects meta-analysis was conducted to estimate benefits of the interventions.

MAIN OUTCOMES AND MEASURES Symptomatic infection; function, morbidity, mortality; pregnancy complications and birth outcomes.

RESULTS Nineteen studies (N = 8443) meeting inclusion criteria were identified. Two cohort studies (n = 5289) found fewer cases of pyelonephritis in the cohorts of screened pregnant women (0.5%) than within retrospective comparisons of unscreened cohorts (2.2% and 1.8%); the larger study estimated a statistically significant relative risk of 0.30 (95% CI, 0.15-0.60). No studies examined screening in nonpregnant populations. Among 12 trials of asymptomatic bacteriuria screening and treatment during pregnancy (n = 2377; 1 conducted within past 30 years), there were reduced rates of pyelonephritis (range, 0%-16.5% for the intervention group and 2.2%-36.4% for the control group; pooled risk ratio [RR], 0.24 [95% CI, 0.14-0.40]; 12 trials) and low birth weight (range, 2.5%-14.8% for the intervention group and 6.7%-21.4% for the control group; pooled RR, 0.64 [95% CI, 0.46-0.90]; 7 trials). There was no significant difference in infant mortality (pooled RR, 0.98 [95% CI, 0.29-3.26]; 6 trials). Five RCTs of asymptomatic bacteriuria treatment in nonpregnant adults (n = 777) did not report any significant differences in risk of infection, mobility, or mortality. Limited evidence on harms of screening or treatment was available, and no statistically significant differences were identified.

CONCLUSIONS AND RELEVANCE Screening and treatment for asymptomatic bacteriuria during pregnancy was associated with reduced rates of pyelonephritis and low birth weights, but the available evidence was not current, with only 1 study conducted in the past 30 years. Benefits of asymptomatic bacteriuria treatment in nonpregnant adult populations were not found. Trial evidence on harms of asymptomatic bacteriuria antibiotic treatment was limited.

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Asymptomatic bacteriuria is defined as the presence of a significant bacterial colony count in urine (≥10^5 colony-forming units/mL of a single bacterial species) in the absence of any of the typical signs or symptoms of a urinary tract infection.[1] During pregnancy, asymptomatic bacteriuria is present in an estimated 2% to 10% of women and has been associated with an increased risk of symptomatic infection, including pyelonephritis.[2,3] Rates of pyelonephritis during pregnancy are low in the United States, possibly owing to asymptomatic bacteriuria screening and treatment as part of standard prenatal care.[4,5] In general adult populations, women have higher rates of asymptomatic bacteriuria than men, and prevalence increases after menopause for women and older (>90 years) men. In 2008, the US Preventive Services Task Force (USPSTF) concluded there was a high level of certainty that the net benefit of screening pregnant women for asymptomatic bacteriuria was substantial and recommended screening for asymptomatic bacteriuria with urine culture for pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit (A recommendation). The USPSTF concluded with moderate certainty that the harms of screening men and nonpregnant women for asymptomatic bacteriuria outweigh the benefits and recommended against screening for asymptomatic bacteriuria in men and nonpregnant women (D recommendation). The aim of this systematic review was to update the evidence on benefits and harms of screening and treatment of screen-detected asymptomatic bacteriuria to inform the USPSTF recommendation update.[6,7]

Methods

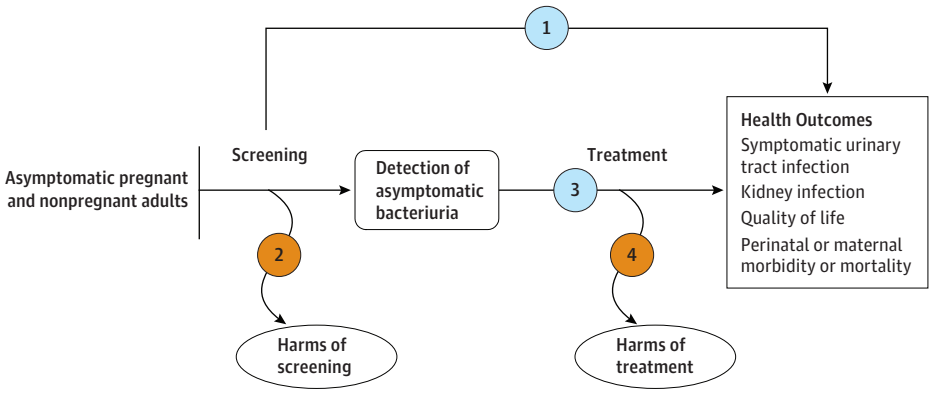
Scope of Review

The USPSTF commissioned this review to evaluate evidence on the benefits and harms of screening and treatment of asymptomatic bacteriuria in adults, including pregnant women. Four key questions (KQs) were drafted to address screening (KQ1, KQ2) and treatment (KQ3, KQ4), as shown in **Figure 1**. Methodological details, including those for study selection and a list of excluded studies, and detailed results including descriptive tables and forest plots, are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/asymptomatic-bacteriuria-in-adults-screening1.

Data Sources and Searches

In addition to considering all studies from the previous reviews on this topic for inclusion in the current review,[6,9,10] a comprehensive search of MEDLINE, PubMed (publisher-supplied records), and the Cochrane Collaboration Central Registry of Controlled Trials for literature published through September 7, 2018, was conducted (eMethods in the Supplement). The reference lists of other previously published reviews, meta-analyses, and primary studies were examined and ClinicalTrials.gov was searched to identify additional relevant studies or ongoing trials. After September 2018, ongoing surveillance continued through article alerts and targeted searches of high-impact journals to identify major studies published in the

Figure 1. Analytic Framework: Screening for Asymptomatic Bacteriuria in Adults

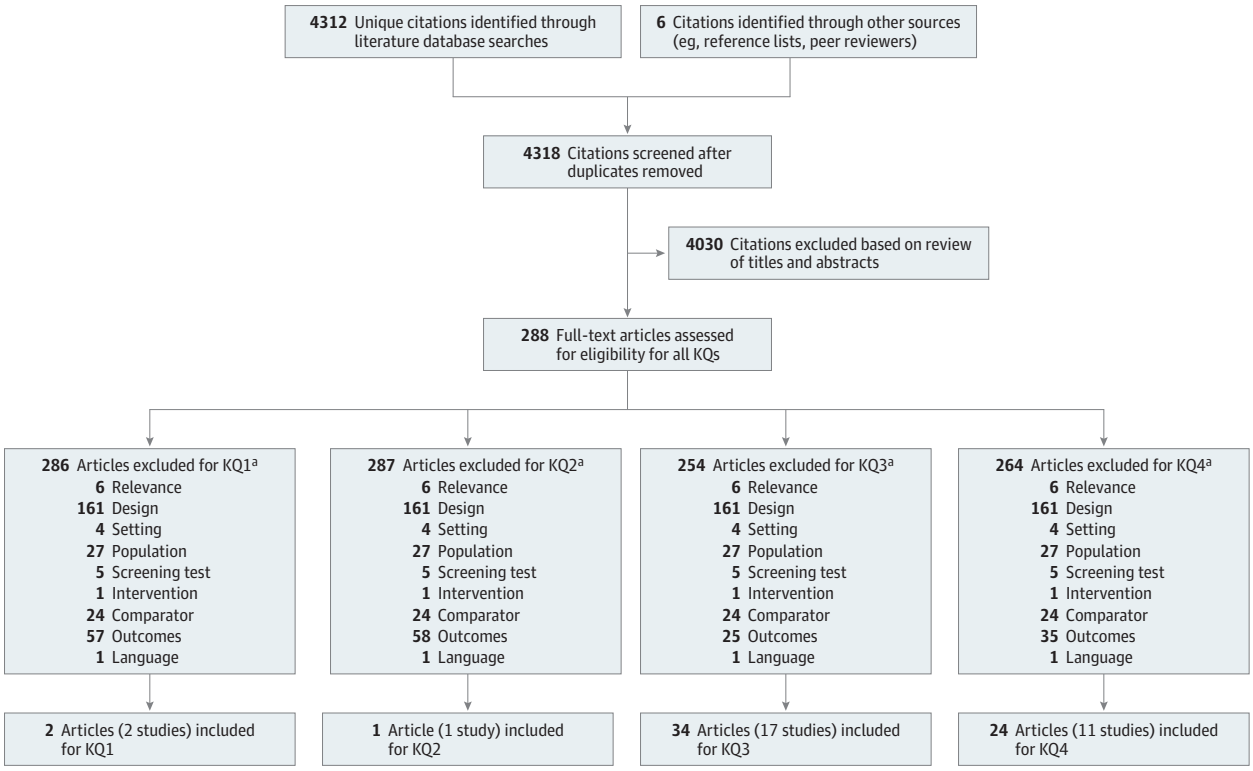


Key questions

1. Does screening for asymptomatic bacteriuria improve health outcomes among adults, including pregnant women?
2. What are the harms of screening for asymptomatic bacteriuria?
3. Does treatment of screen-detected asymptomatic bacteriuria improve health outcomes?
4. What harms are associated with treatment of screen-detected asymptomatic bacteriuria?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for interpretation of the analytic framework.[8]

Figure 2. Literature Search Flow Diagram: Screening for Asymptomatic Bacteriuria in Adults



[a] Reasons for exclusion: Relevance: Study aim was not relevant. Design: Study did not use an included design or was not a primary research article. Setting: Study conducted in an eligible setting, including studies conducted in a country not classified as "high" or "very high" on the Human Development Index in 2016. Population: Study conducted in an ineligible population, including studies conducted in individuals who were institutionalized, were symptomatic of a urinary tract infection, or had recurrent urinary tract infections, or in which screening was related to a surgical procedure. Screening test: Ineligible screening test including screening performed via catheter or suprapubic aspiration. Intervention: Intervention was out of scope. Comparator: Ineligible comparator, including comparative effectiveness studies. Outcomes: No relevant outcomes or incomplete outcomes reporting. Language: Publication not in English. KQ indicates key question.

interim that could affect the conclusions or understanding of the evidence and affect the related USPSTF recommendation. The last surveillance was conducted on May 24, 2019, and resulted in the addition of no new studies.

Study Selection

Two reviewers reviewed 4138 abstracts and 288 full-text articles against a priori inclusion and exclusion criteria (**Figure 2**; eTable 1 in the Supplement). The review was defined to focus on adults (≥18 years) and pregnant women of any age who were asymptomatic for, and not in specialty care for, conditions of the urinary tract; not immunocompromised; and not undergoing surgical or catheterization procedures. Studies among community-dwelling adults, including those living in independent or assisted living facilities, were included, but studies conducted in hospital or institutional settings were not. For general adult populations, we included studies conducted in countries categorized as "very high" on the Human Development Index (HDI) in 2016. For pregnant women, the scope was expanded slightly to include studies with an HDI of "high" or "very high" because asymptomatic bacteriuria screening and treatment in pregnancy is standard-of-care, established practice in many "very high" HDI countries, and not an active area of research.

For all KQs, we included randomized clinical trials to assess the benefits and harms of screening (KQ1 and KQ2) and treatment (KQ3 and KQ4) for asymptomatic bacteriuria in asymptomatic pregnant and nonpregnant adults. In addition, for KQ1 and KQ3 among pregnant women, observational cohort studies with a comparator of no screening or no treatment were included because prior evidence and recommendations established a standard practice of asymptomatic bacteriuria screening and treatment, and movement away from trial research for the topic. For KQ2 and KQ4, observational cohort studies with or without a comparison group were also included, as well as registry studies.

Data Extraction and Quality Assessment

Included studies were assessed for risk of bias by 2 independent reviewers according to prespecified criteria (eTable 2 in the Supplement),[8,11] and discrepancies were resolved after discussion with a third reviewer. Because of the historical nature of the evidence, a more lenient quality rating of studies was used to allow for changes in trial reporting standards over time. To support sensitivity analyses, studies were flagged as "high risk of bias" if there were notable problems with reporting or procedures related to concerns about diagnostic criteria or definitions of outcomes, treatment allocation, baseline characteristics of participants (eg, miss-

ing or unbalanced study groups), or high suspicion of selective outcome reporting. One reviewer extracted key descriptive and outcome data into standardized abstraction forms, and a second reviewer checked the data for accuracy.

Data Synthesis and Analysis

Summary tables describing study design, population, and intervention characteristics were created separately for nonpregnant adult and pregnant populations. Data were synthesized separately for each KQ. Given the small number of included studies, a narrative synthesis was provided of study results for all KQs evaluated in adult, nonpregnant populations. Similarly, for KQ1 and KQ2 in pregnant populations, data were summarized narratively and in tables.

Quantitative pooling of KQ3 and KQ4 outcomes related to asymptomatic bacteriuria treatment in pregnant populations was conducted with random-effects meta-analyses that applied the DerSimonian and Laird[12] method to calculate pooled differences in mean changes or pooled risk ratios (for binary outcomes). When pooling fewer than 10 studies, sensitivity analyses using a restricted maximum likelihood model with Knapp-Hartung correction for small samples were calculated and reported if different from the DerSimonian and Laird result. Details of the data analysis methods are included in the full report.

Statistical heterogeneity among the pooled studies was evaluated with standard χ^2 tests and the I^2 statistic to estimate the proportion of total variability in point estimates.[13] Funnel plots were used to examine outcomes for potential small-study effects (a possible indication of publication bias), and the Egger test was conducted if 10 or more studies were available to statistically assess whether study size was associated with study results.[14] Sensitivity analyses were conducted after removing studies with high risk of bias from meta-analysis.

Stata version 15.1 (StataCorp) was used for all analyses. All significance testing was 2-sided, and results were considered statistically significant if the *P* value was .05 or less.

The strength of the overall body of evidence for each key question was graded as high, moderate, low, or insufficient based on the consistency, precision, and limitations of the body of evidence related to each outcome. For more details on review methods, see the full report.

Results

Two reviewers independently assessed 4318 abstracts and reviewed 288 full-text articles. In total, 19 studies (1 good quality, 18 fair quality; N = 8443) of asymptomatic bacteriuria screening or treatment were included in this review.[15-33] Of these, 14 were conducted with pregnant populations: 2 comparative cohort studies of screening effectiveness and harms (KQ1, KQ2) and 12 trials of the effectiveness and harms of asymptomatic bacteriuria treatment (KQ3, KQ4). Five trials examined the effectiveness and harms of asymptomatic bacteriuria treatment (KQ3, KQ4) among nonpregnant adults, primarily women and older adults.

Effectiveness of Screening

Key Question 1. Does screening for asymptomatic bacteriuria improve health outcomes among adults, including pregnant women?

Pregnant Populations

Two fair-quality cohort studies (n = 5289)[15,16] compared a screened cohort with an unscreened historical comparison group to assess the association of maternal and perinatal outcomes with implementation of an asymptomatic bacteriuria screening and treatment program (**Table 1**). In a study conducted in Spain (n = 4917), 77 of screened participants (4.7%) were diagnosed with asymptomatic bacteriuria. There were 9 cases of pyelonephritis (0.5%) diagnosed in this screened cohort and 60 cases (1.8%) in the historical comparison cohort (risk ratio [RR], 0.30 [95% CI, 0.15-0.60]). In a study conducted in Turkey (n = 372), 17 participants (9.3%) screened positive for asymptomatic bacteriuria, and there were 4 pyelonephritis cases (2.2%) in the unscreened cohort and 1 (0.54%) in the screened cohort. No birth or infant outcomes were reported in the Spanish study,[15] and the Turkish study reported no significant difference in the weight of newborns (data not reported) or premature births (screened, 11.8% [22/186] vs unscreened, 9.7% [18/186]).[16] Low event rates, study size, and reporting inconsistencies limited the ability to draw conclusions for other outcomes in this study (eTable 3 in the Supplement).

Nonpregnant Adult Populations

No studies were identified that addressed the benefits of screening for asymptomatic bacteriuria in the general adult population.

Harms of Screening

Key Question 2. What are the harms of screening for asymptomatic bacteriuria?

Pregnant Populations

The Turkish cohort study described above reported on potential harms of the screening program (such as fetal abnormalities and intrauterine death) and found no evidence of harms associated with the screening program.[16] Two congenital abnormalities were reported in the unscreened cohort (1.1%), compared with 3 in the screening cohort (1.6%); however, the 3 congenital abnormalities were observed among infants of women who screened negative for asymptomatic bacteriuria and presumably were not prescribed antibiotics to treat asymptomatic bacteriuria (eTable 3 in the Supplement).

Nonpregnant Adult Populations

No studies were identified that addressed the harms of screening for asymptomatic bacteriuria in the general adult population.

Effectiveness of Treament

Key Question 3. Does treatment of screen-detected asymptomatic bacteriuria improve health outcomes?

Pregnant Populations

Twelve trials of pregnant women screened for asymptomatic bacteriuria and randomized to either a treatment or control condition were included (n = 2377).[17-20,22-27,29,33] All but 2[29,33] were published in the 1960s or 1970s (Table 1). The 2 most recently published studies were conducted in the Netherlands (2015)[33] and Ireland (1987).[29] Among the 10 early studies, 3 were conducted in the United States[18,20,25] and the remainder in Great Britain,[19,23,26] Jamaica,[22] and Australia.[17,24,27] Most studies were conducted in the obstetrics/gynecology clinics of hospitals, with 7 specifying

Table 1. Summary of Study Characteristics, by Population[a]

Source	Study Design (No. of Participants)	Country	Population	Race/Ethnicity (%)[b]	Confirmatory Culture Required	ASB Prevalence, No. Positive/No. Screened (%)	Age, Mean (Range)	KQ
Pregnant Women								
Brumfitt et al,[26] 1975	RCT (414)	Great Britain	Pregnant women, <32 wk gestation	Asian: 9.7 West Indian: 10.6	NR	426/20 000 (2.1)	26.4 (NR)	3
Elder et al,[25] 1971	RCT (289)	United States	Pregnant women, <32 wk gestation	White: 39.9 Other: 60.1	Yes	362/9156 (4.0)[c]	25.1 (NR)	3, 4
Foley et al,[29] 1987	RCT (220)	Ireland	Pregnant women	NR	No	220/6883 (3.2)	NR	3
Furness et al,[27] 1975	RCT (206)	United States	Pregnant women	NR	No	226/5256 (4.3)	NR	3, 4
Gratacos et al,[15] 1994	Cohort (4917[d])	Spain	Pregnant women, <25 wk gestation	NR	Yes	77/1652 (4.7)	NR	1
Gold et al,[18] 1966	RCT (65)	United States	Pregnant women	Puerto Rican: 6.0[e] Other white: 9.0[e] Nonwhite: 85.0[e]	Yes	65/1281 (5.1)	NR	3, 4
Kazemier et al,[33] 2015	RCT (85)	The Netherlands	Pregnant women (≥18 y), 16-22 wk gestation	White: 92.0[f]	No	255/5132 (5.0)	29 (NR)[f]	3, 4
Kincaid-Smith et al,[17] 1965	RCT (116)	United States	Pregnant women, <26 wk gestation	NR	Yes	160/4000 (4.0)[g]	NR	3, 4
Little et al,[19] 1966	RCT (265)	Great Britain	Pregnant women, 12 wk gestation (mean)	NR	Yes	265/5000 (5.3)	NR (10-≥40)	3
Pathak et al,[22] 1969	RCT (178)	Jamaica	Pregnant women, <24 wk gestation	NR	Yes	217/7602 (2.9)	NR	3, 4
Savage et al,[20] 1967	RCT (203)	United States	Pregnant women, <32 wk gestation	White: 52.0[h] African American: 46.0[h] Other: 2.0[h]	Yes	245/6327 (3.9)	NR	3
Uncu et al, 2002[16]	Cohort (372[d])	Turkey	Pregnant women, <33 wk gestation	NR	No	23/247 (9.3)	27.7 (NR)	1, 2
Williams et al,[23] 1969	RCT (163)	Great Britain	Pregnant women, <30 wk gestation	NR	Yes	211/5542 (3.8)	NR	3, 4
Wren et al,[24] 1969	RCT (173)	United States	Pregnant women	NR	Yes	183/3604 (5.1)	NR	3
General Adult Populations								
Abrutyn et al,[30] 1994	Nonrandomized CCT (358)	United States	Women (mean age, 81.9 y)	NR	Yes	NR	81.9 (NR)	3
Asscher et al,[21] 1969	RCT (94)	Wales	Women (20-65 y)	NR	Yes	107/3578 (3.0)	NR (20-65)	3, 4
Boscia et al,[28] 1987	RCT (124)	United States	Women (≥65 y)	NR	Yes	124/603 (20.6)	85.8 (70-100)	3, 4
Giamarellou et al,[31] 1998	RCT (96)	Greece	Older adults (83.9% women; ≥65 y)	NR	Yes	106/455 (23.3)	83.3 (NR)	3, 4
Harding et al,[32] 2002	RCT (105)	Canada	Women with diabetes (>16 y)	NR	Yes	135/1900 (7.1)	55.3 (NR)	3, 4

Abbreviations: ASB, asymptomatic bacteriuria; CCT, controlled clinical trial; KQ, key question; NR, not reported; RCT, randomized clinical trial.

[a] All studies in table were fair quality except for Harding et al,[32] which was good quality.

[b] Racial/ethnic categories as reported in original publications.

[c] Number invited.

[d] Included in cohort.

[e] Baseline characteristics for entire screened cohort.

[f] Intervention group only; control group NR.

[g] Calculated.

[h] Estimated from figure.

screening at the first prenatal visit,[17-19,23,24,26,27] 2 specifying screening by a certain week of gestation in pregnancy,[25,33] and 3 indicating pregnant women with no mention of the timing of study recruitment.[20,22,29] Information on the characteristics of the study participants was sparsely reported. Only 3 studies reported the mean age of randomized women (range, 25-29 years).[25,26,33]

Exclusion criteria were generally not specified or limited (eg, hypertensive, chronic renal insufficiency, recent urinary tract infection) in most included studies. The most recent trial had an aim of enrolling a low-risk study population and thus excluded women at risk of preterm birth and other health conditions.[33] The percentage of pregnant women screened who were diagnosed with asymptomatic bacteriuria ranged from 2.1% to 5.3% across the included studies. The most recent study identified 5.0% of women who were screened with dip slide as positive for asymptomatic bacteriuria.[33] Treatments for screen-detected asymptomatic bacteriuria varied widely across the included studies with respect to timing, dosage, duration, and medication. Sulfonamides were the most common

Table 2. Pooled Effects of Asymptomatic Bacteriuria Treatment in Pregnancy, by Outcome

Health Outcome	No. Studies	No. Observations	Outcome Event Rate in Control Group (%)	Pooled RR (95% CI) Associated With Intervention	I^2, %
Pyelonephritis[a]	12	2068	212/1023 (20.7)	0.24 (0.14 to 0.40)	56.9
Low birth weight[b]	7	1522	99/753 (13.1)	0.64 (0.46 to 0.90)	15.8
Mean birth weight, g	5	1070	3210.5 (628.6)[c]	15.51 (−91.17 to 122.18)[d]	52.5
Preterm birth[e]	4	493	27/217 (12.4)	0.81 (0.38 to 1.73)	34.8
Perinatal mortality[f]	6	1103	21/574 (3.6)	0.98 (0.29 to 3.26)	52.3
Hypertensive disorders of pregnancy[g]	5	889	31/465 (6.7)	1.21 (0.76 to 1.93)	0
Congenital malformations among infants	5	961	12/472 (2.5)	0.44 (0.16 to 1.22)	0

Abbreviation: RR, risk ratio.

[a] Defined by the study.

[b] Birth weight less than 2500 g or small for gestational age (below the 10th percentile for gestational age).

[c] Mean (SD).

[d] Mean difference (95% CI).

[e] Birth prior to 37- or 38-weeks' gestation or study-defined "premature birth."

[f] Perinatal mortality includes fetal and infant deaths occurring at more than 20 weeks' gestation and less than 1 week postpartum.

[g] Toxemia, preeclampsia, HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome.

class of antibiotics, but many specific antibiotic formulations are no longer used (eg, sulfamethizole, sulfadimethoxine). The treatment dosage and duration in most of the studies were higher and longer than what is more common to contemporary practice. Five studies were judged to have particularly high risk of bias because of multiple concerns related to randomization and inconsistencies or a lack of clarity regarding the participant characteristics and outcomes.[20,23,24,26,27]

The most commonly reported health outcome was pyelonephritis (12 studies); other perinatal health outcomes were less consistently reported (**Table 2**). Rates of pyelonephritis in the control group were much lower in the 2 most recent studies[29,33] than in older literature (2.2% and 2.5% vs 7%-36%), and 8 of the 12 included studies reported pyelonephritis rates greater than 20% among women with asymptomatic bacteriuria in the untreated/placebo group. Higher rates of pyelonephritis were observed in the control group (placebo or no treatment) than in the treated group in all but 1 study.[29] The pooled effect estimate indicated a significant risk reduction associated with asymptomatic bacteriuria treatment (pooled RR, 0.24 [95% CI, 0.14-0.40]); rates of pyelonephritis ranged from 0% to 16.5% in the intervention group and from 2.2% to 36.4% in the control group. Sensitivity analyses that eliminated 5 studies deemed to have particularly high risk of bias demonstrated a greater pooled risk reduction and lower statistical heterogeneity (pooled RR, 0.19 [95% CI, 0.11-0.34]). Visual inspection of a funnel plot including all studies reporting this outcome showed a somewhat asymmetric distribution, suggesting potential reporting bias, with the Egger test showing $P = .08$.

Seven studies reported differences in infants with low birth weight (<2500 g or small for gestational age [weight below the 10th percentile for gestational age]) among women treated or untreated for asymptomatic bacteriuria (Table 2).[17,19,20,24-26,33] The proportion of infants with low birth weight ranged from 2.5% to 14.8% in the intervention groups and from 6.7% to 21.4% in the control groups. A statistically significant reduction in the risk of low birth weight was reported in 2 studies,[20,24] and the pooled estimate was also statistically significant, with low statistical heterogeneity (pooled RR, 0.64 [95% CI, 0.46-0.90]). Sensitivity analysis removing studies with the highest risk of bias led to exclusion of the statistically significant studies and a no longer significant pooled effect (pooled RR, 0.86 [95% CI, 0.57-1.31]). There were too few studies available for this outcome to support the Egger test or assessment of publication bias with a funnel plot. Results from 5 studies reporting mean birth weight[24-27,33] were inconsistent and did not show a statistically significant association. Few small and clinically heterogeneous studies reported results for preterm birth, limiting conclusions that can be drawn from the null pooled estimate.

Six studies reported perinatal mortality.[17,19,20,24,25,33] Three of the trials found effects in the direction of treatment benefit, and the other 3 in the direction of treatment harms. Probably reflecting small sample sizes, none of the studies reported statistically significant effects, and the pooled estimate was null (pooled RR, 0.98 [95% CI, 0.29-3.26]). The small number and size of the included studies in the sensitivity analysis, however, resulted in an analysis underpowered for evaluating this rare outcome. Event rates ranged from 0% to 6.6% in the intervention group and from 0% to 7.3% in the control group.

Nonpregnant Adult Populations

Five included trials (n = 777) examined the effectiveness of antibiotic treatment in general adult populations with screen-detected asymptomatic bacteriuria (Table 1).[21,28,30-32] These studies were conducted in the United States (2 studies),[28,30] Canada,[32] the United Kingdom,[21] and Greece.[31] Two studies of adult women recruited individuals from medical centers,[21,32] with 1 of these studies limited to women with diabetes.[32] Three studies were conducted among older adults (mean age, 81.9-85.8 years) residing in independent living facilities.[28,30,31] Two of the 3 studies among older adults were limited to women,[28,30] and the third was mostly women (83.9%).[31] In general, population characteristics were sparsely reported across studies. The study of asymptomatic bacteriuria treatment in women with diabetes was rated as good quality,[32] and the 4 remaining studies were rated fair quality.

Four studies reported on the rate of symptomatic infection or pyelonephritis, with none finding a statistically significant difference between treatment and control groups across a range of time

points (eTable 4 in the Supplement). One study among men and women older adults reported on mobility as an outcome and found no difference at 6 months.[31] The study excluded individuals who needed help performing activities of daily living at enrollment and used a subjective proxy measure of good mobility (ie, complete independence) determined by the physician and head nurse of the independent living pavilions. All 3 trials specific to older adults reported mortality by treatment group as a primary or secondary outcome, with no trial finding a statistically significant difference (eTable 5 in the Supplement). One trial conducted among women that analyzed mortality as the primary outcome reported 18% mortality over the course of 100 months of follow-up, compared with 20% in the control group (hazard ratio, 0.92 [95% CI, 0.50-1.47]).[30] Two additional studies that measured mortality as a secondary outcome found no statistically significant effect of treatment at 6 months of follow-up.[28,31]

Harms of Treatment

Key Question 4. What harms are associated with treatment of screen-detected asymptomatic bacteriuria?

Pregnant Populations

Seven of the included studies for KQ3 described above reported potential harms of treatment of screen-detected asymptomatic bacteriuria.[18-20,24,25,27,33] Five studies reported on congenital malformations in the intervention and control groups (Table 2).[19,24,25,27,33] Few cases were reported, and more cases were observed in the control groups than in the intervention groups in all but 1 study.[19] The pooled estimate was not statistically significant (pooled RR, 0.44 [95% CI, 0.16-1.22]). Cases of congenital malformation ranged from 0% to 1.6% in the intervention group and from 1.4% to 4.2% in the control groups. Evidence related to other infant and maternal harms of asymptomatic bacteriuria treatment in pregnancy was sparsely and inconsistently reported, and there was a lack of evidence on long-term neonatal outcomes after antibiotic treatment of asymptomatic bacteriuria in pregnancy. Two studies provided information on maternal adverse reactions to medications.[19,24] For ampicillin treatment, vaginitis and diarrhea were reported.[24] For nalidixic acid and nitrofurantoin treatment, rashes and nausea were reported.[19,24]

Nonpregnant Adult Populations

Two studies of treatment in nonpregnant adult women[21,32] and 2 studies in older adults[28,31] reported on rates of adverse events associated with treatment of asymptomatic bacteriuria. One study among nonpregnant women reported that there were no adverse drug reactions among the 49 women treated with nitrofurantoin therapy.[21] The study among women with diabetes (n = 105) reported higher rates of treatment-related adverse events (not specified) among those treated with trimethoprim-sulfamethoxazole compared with placebo, but the difference was not statistically significant (18.1% of women, compared with 6.0%; RR, 3.45 [95% CI, 0.90-14.29]).[32] One study among older adults reported that no adverse medication reactions occurred among the 63 women treated with trimethoprim.[28] Another reported that 2 of 32 women (6%) assigned to daily ofloxacin therapy withdrew because of adverse events (vertigo and gastrointestinal tract symptoms).[31] Treatment was found to not affect hematocrit, serum bilirubin level, or serum urea nitrogen level, but a mild reduction in serum creatinine level was seen in the treatment groups.

Discussion

A summary of the evidence for this review is reported in **Table 3**. For general nonpregnant adult populations, no evidence identified health benefits associated with screening or treatment of screen-detected asymptomatic bacteriuria. This is consistent with findings in reviews by others, including the Infectious Diseases Society of America.[2,34] Concerns about potential overuse of antimicrobial treatment and the development of resistance to treatment are therefore highlighted in discussions regarding clinical practice for asymptomatic people, including elderly persons and those with diabetes.

Few studies of asymptomatic bacteriuria screening or treatment in pregnant populations have been conducted in the past 40 years; historical evidence established asymptomatic bacteriuria screening and treatment as standard obstetric practice in the United States. The most consistent finding from the available trials indicates that treatment of asymptomatic bacteriuria in pregnancy was associated with a lower risk of pyelonephritis, even when the studies at highest risk of bias were excluded in sensitivity analysis. Other outcomes were less consistently reported, raising concerns about possible selective reporting or publication bias.

The sparse, less rigorous reporting and research methods seen in the earlier scientific era could contribute to risk of bias. In addition, the applicability of historic evidence to current clinical settings and populations is limited because of changes over time in population characteristics, delivery of care, and treatment protocols for asymptomatic bacteriuria. The only recently conducted study of the treatment of asymptomatic bacteriuria is a randomized trial conducted in the Netherlands,[33] where asymptomatic bacteriuria screening and treatment are not standard care. This study focused on a low-risk population, and event rates and study power were too low to draw conclusions about the effectiveness of treatment from this study alone. It does, however, provide important contextual information about the course of untreated asymptomatic bacteriuria in a modern population.

More recent evidence on the association between asymptomatic bacteriuria and pyelonephritis, and between these infections and pregnancy health outcomes, is important to consider when interpreting the historical evidence. In most of the studies conducted before 1980, rates of pyelonephritis in pregnant women with untreated asymptomatic bacteriuria were at least 10-fold greater than more recently observed. Rates of 2.2% and 2.5% were reported in the 2 most recent trials, yet in 8 of the earlier trials rates were above 20%, with 2 trials reporting that 36% and 33% of women in the control group developed pyelonephritis.[17,24] The much lower incidence of pyelonephritis in more recent studies may be owing to a range of factors, such as changes in population health status, more stringent diagnostic criteria, better recognition and treatment of lower urinary tract infections, changes in health behaviors, and differences in the infectious microorganisms circulating in the population. Regardless of the reasons, this difference would result in lower absolute differences in risk, meaning a higher number needed to treat to

Table 3. Summary of Evidence by Key Question and Population

Population	Studies, Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Screening Effectiveness						
Pregnant women	2 Retrospective cohort studies (5289 observations)	Fewer cases of pyelonephritis occurred in pregnant women included in a screening cohort compared with retrospective cohort of unscreened women	Direction of effects consistent and 1 study with adequate precision	Fair-quality studies with risk of bias due to limited information about how cohort was identified, characteristics of women in comparison cohorts, ascertainment bias, selective reporting	Low for a benefit of screening for prevention of pyelonephritis in pregnancy based on 2 fair-quality cohort studies	One study conducted in a hospital in Spain 24 y ago and another in Turkey 16 y ago; may not be entirely applicable to current US hospital settings and populations
General adult populations	No studies	NA	NA	NA	NA	NA
KQ2: Screening Harms						
Pregnant women	1 Retrospective cohort study (372 observations)	No harms of screening were identified Number of congenital abnormalities similar between groups and none in screen-positive women	Consistency NA Imprecise (small No. of participants, few events)	Limited reporting on potential harms of screening and treatment, low No. of participants for detecting rare harms	Insufficient for the absence of screening harms based on 1 fair-quality cohort study	Small study conducted in Turkey 16 y ago; may not be entirely applicable to current US hospital settings and populations
General adult populations	No studies	NA	NA	NA	NA	NA
KQ3: Treatment Effectiveness						
Pregnant women	12 RCTs (2369 observations)	Treatment of screen-detected ASB in pregnancy reduced the risk of pyelonephritis (5.5% vs 20.7%; pooled RR, 0.24 [95% CI, 0.14-0.41]; 12 studies, n = 2068) and low birth weight infants (8.3% vs 13.1%; pooled RR, 0.64 [95% CI, 0.46-0.90]; 7 studies, n = 1522) Other birth outcomes were less consistently reported, and statistically significant differences were not found in pooled analyses	Consistent and precise for pyelonephritis Consistent but less precise for low birth weight Imprecise and inconsistent for other perinatal outcomes, including perinatal mortality, mean birth weight, and preterm birth	Risk of bias present or difficult to assess in all studies; limited reporting of baseline characteristics; problems with blinding, randomization, selective reporting, and outcome definitions	Moderate for benefit of treatment on pyelonephritis from 12 fair- quality RCTS (including 5 with high risk of bias) Low for benefit of treatment on low birth weight from 7 fair- quality studies (including 3 with high risk of bias)	Most studies conducted >40 y ago, and many of the treatment protocols and medications are no longer used in clinical practice Rates of pyelonephritis as much as 10-fold higher in historical trials compared with estimates from modern prenatal care
General adult populations	5 studies (4 RCTs, 1 nonrandomized CCT; 777 observations)	Mortality: 3 trials in older adults found no difference in mortality over 6 to 100 mo of follow-up Mobility: 1 trial in older adults found no effect on mobility at 6 mo Symptomatic infection/ pyelonephritis: 4 trials (including 2 in older adults) found no difference in the rate of symptomatic infection	Consistent for no benefit; imprecise Treatment ranged from a single dose of treatment to daily treatment over 3 mo	Lack of reporting of population characteristics Some studies lacked reporting on randomization, allocation, and outcome assessment	Low	Evidence primarily applies to women (84%-100% women in each study); 3 studies limited to older adults (2 of 3 limited to older women); 1 study limited to women with diabetes

(continued)

Table 3. Summary of Evidence by Key Question and Population (continued)

Population	Studies, Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ4: Treatment Harms						
Pregnant women	7 RCTs (1286 observations)	Five studies reported congenital malformations with effect in direction of benefit, but null All other outcomes sparsely reported and did not provide evidence of harms or rule out harms	Inconsistent; imprecise	Risk of bias present or difficult to assess in all studies; limited reporting of baseline characteristics; problems with blinding, randomization, selective reporting, and outcome definitions	Insufficient for absence of treatment harms	Most studies conducted >40 y ago, and many of the treatment protocols and medications no longer used in clinical practice
General adult populations	4 RCTs (419 observations)	Minimal reporting of adverse events Most studies reported no adverse events or only on those few patients who withdrew from the trials based on adverse events One study of treatment of women with diabetes found higher rates of adverse events among women in the treatment group	Inconsistent; imprecise	Limited data reporting Unclear reporting bias	Insufficient	Evidence is limited to mostly women (84%-100% women in each study)

Abbreviations: ASB, asymptomatic bacteriuria; CCT, controlled clinical trial; KQ, key question; NA, not applicable; RCT, randomized clinical trial; RR, risk ratio.

prevent a single case of pyelonephritis. Assuming 2.5% incidence, for example, 25 women in 1000 with asymptomatic bacteriuria would develop pyelonephritis in the absence of treatment, and applying the pooled RR of 0.24 from this review, 19 cases of pyelonephritis would be prevented for every 1000 women treated for asymptomatic bacteriuria with antibiotics during pregnancy.

Understanding of the harms of antibiotic use has increased greatly in the 40 years since the seminal trials of asymptomatic bacteriuria treatment in pregnancy were conducted. The emergence of antibiotic-resistant bacteria and the rare but rising incidence of *Clostridium difficile* infection—including during pregnancy[35-37]—have shifted clinical practice toward a more cautious approach to antibiotic use.[38] Most recently, research on the microbiome has led to discoveries of protective bacterial colonization, including in the renal system, and growing concern that perturbations caused by antibiotic exposure may influence health.[39] In light of this shift in understanding, selection of the type of antibiotic, duration of use, and indications for prescription have become more targeted.

Observational evidence from large health system cohorts have provided complementary evidence that pyelonephritis contributes to poor maternal and fetal health outcomes.[5,40,41] These studies also note that asymptomatic bacteriuria in pregnancy often occurs along with other risk factors associated with poor birth outcomes.[41-44] Associations of asymptomatic bacteriuria and pyelonephritis with poor birth outcomes could therefore also in part arise from shared underlying risk factors. Several risk factors associated with the development of pyelonephritis have been identified, including younger age, nulliparity, fewer years of education, black or Hispanic race/ethnicity, smoking during pregnancy, late initiation of prenatal care, and pregestational diabetes. Thus, women at risk of developing pyelonephritis in pregnancy, particularly women with limited access to health care, are at risk of poor birth outcomes for a host of reasons. Ensuring adequate screening and interventions for those at high risk for poor outcomes may require system- and policy-level interventions to facilitate early and regular access to prenatal health care.

Limitations

This study has several limitations. First, the review focused on English-language evidence from countries ranked "very high" and "high" (for pregnant women) on the HDI, and it is possible that relevant evidence in other languages or settings may exist. Recent evidence reviews on this topic, however, did not identify additional studies that would apply to women obtaining care in the United States.[34,45] Second, the review scope was limited to trials designed to assess the effectiveness of treatment. Cohort studies could also have been included in the general adult population, but for this topic cohort studies were expected to have too many threats to internal validity to draw conclusions about effects of asymptomatic bacteriuria treatment in the absence of randomized comparisons. For harms of treatment, general studies of the effects of antibiotic treatment in pregnancy would not be sufficiently guarded against risk of bias from the health consequences of underlying conditions that would require antibiotics. Thus, for treatment benefits and harms, the scope was narrowly defined for study design. Nevertheless, no major cohort studies were identified that would have strengthened the review conclusions if included.

Conclusions

Screening and treatment for asymptomatic bacteriuria during pregnancy was associated with reduced rates of pyelonephritis and low birth weights, but the available evidence was not current, with only 1 study conducted in the past 30 years. Benefits of asymptomatic bacteriuria treatment in nonpregnant adult populations were not found. Trial evidence on harms of asymptomatic bacteriuria antibiotic treatment was limited.

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Drafting of the manuscript: Henderson, Bean.
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REFERENCES

1. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am*. 2014;28(1):1-13. doi:10.1016/j.idc.2013.09.003

2. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America [published online March 21, 2019]. *Clin Infect Dis*. doi:10.1093/cid/ciy1121

3. Nicolle LE. Asymptomatic bacteriuria: when to screen and when to treat. *Infect Dis Clin North Am*. 2003;17(2):367-394. doi:10.1016/S0891-5520(03)00008-4

4. Duff P. Pyelonephritis in pregnancy. *Clin Obstet Gynecol*. 1984;27(1):17-31. doi:10.1097/00003081-198403000-00006

5. Hill JB, Sheffield JS, McIntire DD, Wendel GD Jr. Acute pyelonephritis in pregnancy. *Obstet Gynecol*. 2005;105(1):18-23. doi:10.1097/01.AOG.0000149154.96285.a0

6. U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. 2008;149(1):43-47. doi:10.7326/0003-4819-149-1-200807010-00009

7. Lin K, Fajardo K; U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. 2008;149(1):W20-W24. doi:10.7326/0003-4819-149-1-200807010-00009-w1

8. U.S. Preventive Services Task Force. *U.S. Preventive Services Task Force Procedure Manual*. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

9. US Preventive Services Task Force. *Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force*. 2nd ed. Baltimore, MD: Agency for Healthcare Research and Quality; 1996.

10. US Preventive Services Task Force. *Screening for Asymptomatic Bacteriuria: Recommendation Statement*. Rockville, MD: Agency for Healthcare Research and Quality; 2004.

11. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Hospital website. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed September 12, 2017.

12. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28(2):105-114. doi:10.1016/j.cct.2006.04.004

13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

15. Gratacós E, Torres PJ, Vila J, Alonso PL, Cararach V. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. *J Infect Dis*. 1994;169(6):1390-1392. doi:10.1093/infdis/169.6.1390

16. Uncu Y, Uncu G, Esmer A, Bilgel N. Should asymptomatic bacteriuria be screened in pregnancy? *Clin Exp Obstet Gynecol*. 2002;29(4):281-285.

17. Kincaid-Smith P, Bullen M. Bacteriuria in pregnancy. *Lancet*. 1965;1(7382):395-399. doi:10.1016/S0140-6736(65)90001-2

18. Gold EM, Traub FB, Daichman I, Terris M. Asymptomatic bacteriuria during pregnancy. *Obstet Gynecol*. 1966;27(2):206-209.

19. Little PJ. The incidence of urinary infection in 5000 pregnant women. *Lancet*. 1966;2(7470):925-928. doi:10.1016/S0140-6736(66)90534-4

20. Savage WE, Hajj SN, Kass EH. Demographic and prognostic characteristics of bacteriuria in pregnancy. *Medicine (Baltimore)*. 1967;46(5):385-407. doi:10.1097/00005792-196709000-00002

21. Asscher AW, Sussman M, Waters WE, et al. The clinical significance of asymptomatic bacteriuria in the nonpregnant woman. *J Infect Dis*. 1969;120(1):17-26. doi:10.1093/infdis/120.1.17

22. Pathak UN, Tang K, Williams LL, Stuart KL. Bacteriuria of pregnancy: results of treatment. *J Infect Dis*. 1969;120(1):91-103. doi:10.1093/infdis/120.1.91

23. Williams GL, Campbell H, Davies KJ. Urinary concentrating ability in women with asymptomatic bacteriuria in pregnancy. *Br Med J*. 1969;3(5664):212-215. doi:10.1136/bmj.3.5664.212

24. Wren BG. Subclinical renal infection and prematurity. *Med J Aust*. 1969;2(12):596-600.

25. Elder HA, Santamarina BA, Smith S, Kass EH. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. *Am J Obstet Gynecol*. 1971;111(3):441-462. doi:10.1016/0002-9378(71)90793-9

26. Brumfitt W. The effects of bacteriuria in pregnancy on maternal and fetal health. *Kidney Int Suppl*. 1975;4:S113-S119.

27. Furness ET, McDonald PJ, Beasley NV. Urinary antiseptics in asymptomatic bacteriuria of pregnancy. *N Z Med J*. 1975;81(539):417-419.

28. Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D. Therapy vs no therapy for bacteriuria in elderly ambulatory nonhospitalized women. *JAMA*. 1987;257(8):1067-1071. doi:10.1001/jama.1987.03390080057030

29. Foley ME, Farquharson R, Stronge JM. Is screening for bacteriuria in pregnancy worthwhile? *Br Med J (Clin Res Ed)*. 1987;295(6592):270. doi:10.1136/bmj.295.6592.270

30. Abrutyn E, Mossey J, Berlin JA, et al. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? [published correction appears in *Ann Intern Med*. 1994;121(11):901]. *Ann Intern Med*. 1994;120(10):827-833. doi:10.7326/0003-4819-120-10-199405150-00003

31. Giamarellou H, Dontas A, Zorbas P, Staszewska-Pistoni M, Xirouchaki E, Petrikkos G. Asymptomatic bacteriuria in freely voiding elderly subjects: long-term continuous vs pulse treatment with ofloxacin. *Clin Drug Investig*. 1998;15(3):187-195. doi:10.2165/00044011-199815030-00003

32. Harding GK, Zhanel GG, Nicolle LE, Cheang M; Manitoba Diabetes Urinary Tract Infection Study Group. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med*. 2002;347(20):1576-1583. doi:10.1056/NEJMoa021042

33. 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 Infect Dis*. 2015;15(11):1324-1333. doi:10.1016/S1473-3099(15)00070-5

34. Canadian Task Force on Preventive Health Care (CTFPHC). Asymptomatic Bacteriuria in Pregnancy (2018). CTFPHC website. https://canadiantaskforce.ca/guidelines/published-guidelines/asymptomatic-bacteriuria/. 2018. Accessed July 16, 2018.

35. Ruiter-Ligeti J, Vincent S, Czuzoj-Shulman N, Abenhaim HA. Risk factors, incidence, and morbidity associated with obstetric *Clostridium difficile* infection. *Obstet Gynecol*. 2018;131(2):387-391. doi:10.1097/AOG.0000000000002422

36. Kuntz JL, Yang M, Cavanaugh J, Saftlas AF, Polgreen PM. Trends in *Clostridium difficile* infection among peripartum women. *Infect Control Hosp Epidemiol*. 2010;31(5):532-534. doi:10.1086/652454

37. Cózar-Llistó A, Ramos-Martinez A, Cobo J. *Clostridium difficile* infection in special high-risk populations. *Infect Dis Ther*. 2016;5(3):253-269. doi:10.1007/s40121-016-0124-z

38. Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep*. 2016;65(6):1-12. doi:10.15585/mmwr.rr6506a1

39. Antunes-Lopes T, Vale L, Coelho AM, et al; EAU Young Academic Urologists (YAU) Functional Urology Working Group. The role of urinary microbiota in lower urinary tract dysfunction: a systematic review [published online September 27, 2018]. *Eur Urol Focus*. doi:10.1016/j.euf.2018.09.011

40. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. *Am J Obstet Gynecol*. 2014;210(3):219.e1-219.e6. doi:10.1016/j.ajog.2013.10.006

41. Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales, II: indicated and spontaneous preterm birth. *Am J Obstet Gynecol*. 1995;173(2):597-602. doi:10.1016/0002-9378(95)90288-0

42. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. *Eur J Clin Invest*. 2008;38(suppl 2):50-57. doi:10.1111/j.1365-2362.2008.02009.x

43. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. *Arch Med Sci*. 2015;11(1):67-77. doi:10.5114/aoms.2013.39202

44. Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales, I: univariable and multivariable analysis. *Am J Obstet Gynecol*. 1995;173(2):590-596. doi:10.1016/0002-9378(95)90287-2

45. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2015;(8):CD000490.