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Screening for Asymptomatic Bacteriuria in Adults: An Updated Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To update the USPSTF's previous recommendation statement on Screening for Asymptomatic Bacteriuria in Adults, we systematically reviewed evidence on the benefits and harms of screening for asymptomatic bacteriuria (ASB) and treatment for pregnant women, nonpregnant women, and men.

Data Sources: MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Collaboration Central Registry of Controlled Trials for literature published through September 7, 2018.

Study Selection: Two researchers independently reviewed 4,318 titles and abstracts and 288 full-text articles against prespecified inclusion criteria, then abstracted data from included studies. English-language randomized trials and observational studies were included to assess the direct health benefits and potential harms of screening for ASB. Randomized trials with control conditions of placebo or no treatment were included to evaluate the benefits and harms of ASB treatment, with observational studies also included for assessment of potential treatment harms among pregnant women. Included study populations were asymptomatic community-dwelling adults (ages 18+), not undergoing treatment or specialized care related to surgical or urologic procedures, including catheterization. Pregnant women of any age were also included and studied as a separate population. Due to the historical nature of the evidence, more lenient quality rating of studies was employed to allow for changes in trial reporting standards over time.

Data Analysis: We synthesized data on the benefits and harms of ASB screening and treatment for general adult populations separately from studies of pregnant women. Health outcomes and harms were sparsely and inconsistently reported in the studies conducted among general adult populations and in studies of screening conducted among pregnant women, precluding meta-analysis. For these outcomes, we described findings in the review text and tables and conducted narrative synthesis. Outcomes for the treatment of screen-detected ASB in pregnancy were analyzed with random effects meta-analysis to calculate the pooled differences when data were sufficient. We examined statistical heterogeneity among the pooled studies using standard $\chi 2$ tests and estimated the proportion of total variability in point estimates using the I^2 statistic. We generated funnel plots and conducted the Egger tests for small-study effects for all pooled analyses that included at least 10 studies. Using established methods, we assessed the strength of evidence for each question.

Results: We included 19 studies of screening or treatment for ASB reported in 36 publications. Fourteen of the included studies were conducted among pregnant women; two of them examining the effectiveness and/or harms of screening (N=5,289) and 12 examining the effectiveness and harms of treatment (N=2,377). Five included studies examined the effectiveness and harms of treatment among adult men and nonpregnant women (N=777), with most primarily focused on women. Reporting on the characteristics of study participants was sparse in the included literature, and all but one included were judged to be fair quality in risk of bias assessments.

Screening: Of the two cohort studies on screening in pregnant women, one conducted in Spain (N=4,917) identified a three-fold reduction in risk for pyelonephritis in unadjusted comparisons on a retrospective unscreened and screened cohort. The other cohort study of screening in pregnant women was conducted in Turkey (N=372) and had low statistical power for comparisons of health outcomes in a screened and unscreened cohort due to rarity of outcome events. For health outcomes related to ASB screening in adult men/nonpregnant women, no eligible studies were identified for inclusion in the review.

Treatment: Twelve trials of ASB treatment among pregnant women (N=2,377) and five trials of ASB treatment among general adult populations (N=777) were included. Screening with culture testing was used in all but one recent included study. Antibiotic treatment was the most common intervention, but the treatment protocols varied considerably across studies. Data from 12 trials provided evidence that treatment of ASB in pregnancy reduces the risk of pyelonephritis (pooled relative risk [RR], 0.24 [95% CI, 0.14 to 0.40], k=12, n=2,068, I2 56.9%). Seven treatment studies reported infant outcomes, demonstrating a reduction in low birthweight (<2500g or or small for gestational age [SGA; weight below the 10th percentile for gestation age]) (pooled RR, 0.64 [95% CI, 0.46 to 0.90], k=7, n=1,522, I2 15.8.6%). Data on potential harms and adverse effects of antibiotic treatment of ASB in pregnancy were sparsely reported in the trials, and power was low for observing rare outcomes. A pooled analysis from five studies reporting congenital malformations was null (pooled RR, 0.44 [95% CI, 0.16 to 1.22], k=5, n=961, I2 0%). Adverse reactions to medications were reported, including vaginitis, diarrhea, rashes, and nausea.

Five trials (N=777) addressed the benefits of treating screen-detected ASB general adult populations, focused on women and older adults. Four trials were conducted only in women, and the fifth trial was primarily among older adult women (84%). Treatment was variable across the trials, ranging from a single dose to 3 months of daily antibiotics. Overall, no study found a difference in mortality, mobility, or rates of symptomatic infections between treated and untreated individuals. Data were inconsistently reported in the four studies reporting harms because they did not report any adverse events or identified few or no patients who withdrew from the study based on adverse events.

Limitations: This review was limited to English-language evidence, primarily from trials conducted in high and very high HDI countries. Risk of bias was judged to be high or difficult to assess due to limitations in reporting in many of the included studies. Most of the trials among pregnant women were conducted over 40 years ago, many using treatment protocols and scientific methods that are no longer commonly employed.

Conclusions: In pregnancy, there is some evidence that treatment of urine culture screen-detected ASB confers a benefit to maternal and infant health, but most of the evidence is from an earlier era. We did not find evidence that treatment of ASB in nonpregnant populations is beneficial to health, based on a limited number of trials conducted mainly among older women. Information on harms was limited in the included studies, but established and emerging evidence highlights the importance of antibiotic stewardship to limit the development of antibiotic resistance and rising awareness of potential harms associated with antibiotic exposure, including changes to the microbiome that increasingly are found to have consequences for health.

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Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2008 recommendation on Screening for Asymptomatic Bacteriuria in Adults.[1]

Condition Background

Condition Definition

Asymptomatic bacteriuria (ASB) is defined as the presence of a significant bacterial colony count present in a person without any of the typical signs or symptoms of a urinary tract infection (UTI).[2] The typical symptoms of UTI depend on the parts of the urinary tract involved. Acute onset cystitis involves the lower urinary tract and is often accompanied by symptoms of dysuria, urinary frequency, urinary urgency, bladder pain, pyuria, and hematuria. Acute pyelonephritis is a more serious infection involving the kidneys. Typical signs and symptoms include flank pain, fever, nausea and vomiting.

The quantitative criteria for defining a significant bacterial count in a urine culture test is at least 10^5 colony-forming units (CFU) per milliliter of a single bacterial species.[3] Recommended sampling procedures to confirm diagnosis of ASB differ for men and women, with two consecutive voided urine specimens cultured positively a few days apart for diagnosis in women, and only one positively cultured urine specimen for diagnosis in men.[3]

Prevalence and Burden

Pregnant Women

During pregnancy ASB is present in an estimated 2 to 10 percent of women.[3, 4] The risk of cystitis and pyelonephritis is higher among pregnant women with ASB, but the incidence of pyelonephritis in pregnant women is low in the United States, likely due to widespread adoption of ASB treatment in pregnancy.[5, 6] One large retrospective cohort study of insured women in the United States with singleton deliveries occurring from 1993–2010 found very low rates of pyelonephritis in pregnancy (0.5%) with incidence rising over time, which the authors attribute to increases in other risk factors in the study population (e.g., maternal age, diabetes).[7] Another prospective study from 2000 to 2001 reported higher pyelonephritis hospitalization rates during pregnancy of 1.4 percent.[6] The majority of cases occurred during the second trimester (53%) and a minority of cases (3%) had previously screened positive for ASB. In both studies, pyelonephritis was associated with higher rates of perinatal complications (e.g., septicemia, respiratory distress, low birthweight, spontaneous preterm birth) in adjusted analyses.[6, 7]

General Adult Populations

The prevalence of ASB varies by age and sex, with women having the highest prevalence at all stages of life. Estimates for nonpregnant, premenopausal adult women range from 1 to 6 percent.[3, 8] Prevalence after menopause increases with age, to above 10 percent after age 70 and up to 22 percent above age 90.[3, 9] In young healthy men, ASB is rare, but increases with age to <5 percent among community-dwelling men in midlife and older age, and just above 5 percent among men over age 90. The prevalence of ASB is three to four times higher among women with diabetes than healthy women.[10]

Etiology and Natural History

By definition, ASB occurs when the urinary tract is colonized with pathogenic bacteria from the gastrointestinal tract. Escherichia coli (E. coli) infection is most common, but other bacteria (e.g., Klebsiella spp., Proteus mirabilis) and group B streptococci [GBS] are also observed.[9, 11] These pathogenic bacteria are also associated with symptomatic infections. The presence of bacteria in the urine was until recently considered pathogenic, as urine was thought to be normally sterile. The presence of commensal non-pathogenic bacteria has been established in more science with the development of new culture media and DNA testing techniques.[12] Thus, ASB refers to colonization of the urinary tract with noncommensal bacterial species.

Pregnant Women

Early observational evidence and a more recent study among pregnant females found associations of ASB with a heightened risk of UTI, including acute pyelonephritis, as well as adverse pregnancy outcomes, especially low birth weight and preterm birth.[4, 13-16]

A mechanism explaining a relationship between ASB and adverse birth outcomes has not been clearly established, but there is some evidence that women with ASB are at increased risk for pyelonephritis. In turn, pyelonephritis in pregnancy has been associated with worse pregnancy outcomes in observational studies.[7, 17, 18] It is unclear whether ASB in the absence of progression to symptomatic infection is related to poor birth outcomes; an observational study of nearly 40,000 births in Wales found no association between ASB and preterm birth when accounting for medical and social confounders, but the study did not describe ASB treatment protocols during the study.[19, 20] Notably, these studies and others find that ASB in pregnancy often occurs along with other risk factors associated with poor birth outcomes, including older maternal age, low socioeconomic status, multiparity, and diabetes.[4, 21] Observed associations of ASB with poor birth outcomes may thus arise in part from a constellation of risk factors, in addition to the risk for pyelonephritis.

General Adult Populations

Although ASB is found when screening nonpregnant individuals, and is associated with increased rates of other outcomes, evidence is mixed and the causal pathways have not been established to explain how ASB could contribute to worse health outcomes. Among women with type 2 diabetes, the risk of UTI is increased with ASB, but this association of ASB with UTI is

not consistently seen for type I diabetes.[22] ASB also has not been consistently associated with other negative health outcomes for nonpregnant adults, and treatment of ASB has not been found to be associated with decreased morbidity or mortality.[3, 23]

Risk Factors

Pregnant Women

During pregnancy, physiologic changes affecting the urinary tract, such as compression of the bladder, ureteral dilation, urinary stasis, and changes in urine pH, are thought to account for an increased risk of ASB and UTI.[4, 24]

General Adult Populations

Women are predisposed to infections of the urinary tract,[4] including ASB, owing to the location and length of the female urethra, which facilitates urinary tract colonization with bacterial strains from the gastrointestinal tract. Sexual activity also increases the risk of ASB (and UTI) in women.[8] The risk of ASB also is greater for men and women with diabetes, owing to glycosuria and the neurologic and immunologic complications of diabetes. Aging is associated with higher rates of ASB due to physiologic changes to the urinary tract as well as rising prevalence of health conditions associated with ASB risk (e.g., diabetes, incontinence, dementia). In older women, decreasing estrogen levels and changes in vaginal pH reduce vaginal colonization with protective *Lactobacilli* spp, allowing for colonization from uropathogenic bacteria such as *E. coli* and *Enterococcus* spp, with consequent higher risks of ASB and UTI. Rising rates of ASB in older men are thought to be related to prostate hypertrophy and changes in urine flow, and possibly changes in bactericidal activity of prostate secretions.[25]

Screening

Pregnant Women

The rationale for ASB screening at least once during pregnancy is supported by historical evidence from the 1960s and 1970s finding that antibiotic treatment of screen-detected ASB reduces cystitis and pyelonephritis in pregnancy, and prevents preterm delivery and low birthweight. Screening for and treatment of ASB is undertaken to reduce risk of symptomatic ascending infections of the urinary tract.

Urine culture is currently recommended for ASB screening in pregnancy and is necessary to definitively diagnose ASB.[1, 3] A "clean catch" urine specimen, involving cleansing of the vulva and perianal area and midstream collection, is generally sought to reduce bacterial contamination of the sample, with some evidence highlighting the importance of midstream collection.[26] The sterility of sample collection materials and handling of the samples, including transport times and storage temperature, can also affect culture findings. A second urine specimen is recommended for confirmation of ASB in pregnancy, as transient ASB and contamination of the sample are not uncommon,[3, 27] but this may not be widely practiced. Rapid onsite urine dipstick and dipslide

tests are often used for screening in clinical practice, with reflexive culture for positive findings.[28]

General Adult Populations

Current practice does not include routine screening of adults, other than pregnant women, for ASB in primary care. Identification and treatment of ASB is recommended prior to transurethral resection of the prostate or other urologic procedures for which mucosal bleeding is anticipated.[3]

Treatment Approaches

Pregnant Women

The choice of antibacterial regimen for treatment of ASB (and UTI) during pregnancy depends on considerations of treatment effectiveness, safety in pregnancy, and observed local and regional levels of bacterial resistance.[4] Amoxicillin, cephalexin, and nitrofurantoin are commonly used to treat ASB and lower UTI infections in pregnancy, but the evidence to weigh effectiveness, optimal routes of administration, regimen, or class is limited. Followup culture to verify cure is recommended by the American College of Obstetrics and Gynecology and American Academy of Pediatrics, but with recognition that evidence is incomplete with regard to the recommendation.[29]

General Adult Populations

Treatment is not recommended for screen-detected ASB in any general adult populations in primary care other than pregnant individuals.

Current Clinical Practice and Recent Recommendations

Pregnant Women

Most antenatal care guidelines include routine screening for ASB early in pregnancy, but there is no consensus for the optimal timing and screening frequency.[4, 30] Screening at the first prenatal visit in the United States can include a culture test or onsite urinalysis, dipstick, or dipslide test for bacteriuria, with reflexive laboratory urine culture to confirm positive findings. Most practice guidelines recommend urine culture screening for ASB due to the suboptimal performance of currently available point of care tests.[28] Most clinical guidelines suggest screening once, early in pregnancy or at the first prenatal visit (**Table 1**). Guidelines for diagnosis of ASB recommend a second sample for confirmatory culture in screened positive women, but a single screening test with reflexive culture is commonly practiced.[27] Recent guidelines, including those from the Infectious Diseases Society of America, Canadian Task Force on Preventive Health Care and European Association of Urology have stated that these recommendations are based on limited evidence of a benefit of screening.[3, 31, 32]

General Adult Populations

In general, guidelines do not recommend screening for ASB in non-pregnant adults (**Table 1**). The European Association of Urology and Infectious Diseases Society of America recommend that patients should be screened and treated for ASB prior to urological procedures breaching the mucosa. [3, 31]

Previous USPSTF Recommendation

Pregnant Women

Since 1996, the USPSTF has maintained an **A recommendation** for screening for ASB using urine culture in **pregnant women** once between 12 and 16 weeks' gestation. The original 1996 recommendation was subsequently reaffirmed in 2004 and again in 2008.[1, 33, 34] The most recent statement from the USPSTF for screening for ASB in pregnant women states there is a high level of certainty that the net benefit of screening **pregnant women** for ASB was substantial and recommended screening for ASB with urine culture for pregnant women at 12–16 weeks' gestation, or at the first prenatal visit (**A Recommendation**).[1]

General Adult Populations

The initial recommendation in 1996 stated there was insufficient evidence to recommend for or against screening in older adult women or women with diabetes, and that screening was not recommended in other asymptomatic adults or institutionalized older adults.[33] In 2004, these recommendations were combined into one recommendation against screening which was subsequently reaffirmed in 2008.[1, 34] The most recent statement from the USPSTF states that: the USPSTF concluded with moderate certainty that the harms of screening men and **nonpregnant** women for ASB outweigh the benefits and recommended against screening for ASB in men and nonpregnant women (**D Recommendation**).[1]

Chapter 2. Methods

Scope and Purpose

This systematic review addresses the benefits and harms of screening and treatment of asymptomatic bacteriuria in adults, including pregnant women. The USPSTF will use this review to update its 2008 recommendation on this topic.[1]

Key Questions and Analytic Framework

We developed an Analytic Framework (**Figure 1**) and four Key Questions (KQs) to guide the literature search, data abstraction, and data synthesis.

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?

Data Sources and Searches

In addition to considering all studies from the previous reviews on this topic for inclusion in the current review,[1, 33, 34] we performed 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. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**).

We also examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential studies for inclusion. We supplemented our searches with suggestions from experts and articles identified through news and table-of-contents alerts, such as those produced by the USPSTF Scientific Resource Center LitWatch activity. We also searched ClinicalTrials.gov (https://ClinicalTrials.gov/) for ongoing trials. We managed literature search results using EndNote® X7 (Thomson Reuters, New York, NY).

Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently screened the title and abstract of all identified articles using DistillerSR (Evidence Partners, Ottawa, Canada) to determine if the study met our *a priori* inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated the full-text articles of all potentially relevant studies against the complete inclusion and exclusion criteria. Disagreements in the abstract

and/or full-text review were resolved by discussion.

For all KQs, we included randomized controlled trials (RCTs) to assess the benefits and harms of screening (KQs 1 and 2) and treatment (KQs 3 and 4) for ASB in asymptomatic pregnant and non-pregnant adults. In addition, for KQs 1 and 3 among pregnant women, we included observational cohort studies with a comparator of no screening or no treatment. The inclusion of observational studies related to screening for and treatment of asymptomatic bacteriuria is due to prior evidence from trials and ensuing recommendations which have established a standard practice of screening and treatment. For KQs 2 and 4, we also included observational cohort studies with or without a comparison group as well as registry studies. We excluded case control studies, case series and case reports, and qualitative studies.

We included studies among asymptomatic community-dwelling adults, including those in independent or assisted living, ages 18 years and older. Asymptomatic pregnant women of any age as well as individuals with common chronic conditions, such as diabetes mellitus (type 1 or type 2), were included. Studies conducted exclusively among individuals who were hospitalized or institutionalized (e.g., nursing homes) were excluded as findings would not be generalizable to primary care. We excluded studies conducted among individuals with symptoms of or suspected UTI (cystitis or pyelonephritis), or with a history of recurrent UTIs, or individuals seen in specialty care for treatment or followup of conditions affecting the urinary tract (e.g., prostate cancer). Dialysis patients or individuals having a catheter, urinary stent, nephrostomy tube, or patients being tested in preparation for urological procedures were also excluded. In addition, we excluded studies conducted exclusively in recipients of a kidney or organ transplant, pregnant women with sickle cell disease, immunocompromised individuals as well as individuals with spinal cord injuries.

Eligible settings included primary care clinics, prenatal or reproductive health clinics, obstetrics/gynecology clinics, and independent living facilities. For general adult populations, we included studies conducted in countries categorized as "very high" on the Human Development Index (HDI). For pregnant women, we expanded the scope slightly to include studies with an HDI of "high" or "very high" because ASB screening and treatment in pregnancy are standard of care, established practice in most "very high" HDI countries and not an active area of research. For KQs 1 and 2, we included screening with urine testing (e.g., urine culture or urinalysis with microscopy, dipstick, or dipslide screening, with or without reflex urine culture). We excluded studies of suprapubic aspiration and catheterization as screening techniques as these were viewed to not represent standard screening techniques in primary care and prenatal care. For KQs 3 and 4, we included medications or treatment interventions to prevent UTIs in patients with screen-detected ASB from at least one positive culture result. We did not exclude studies using lower screening thresholds (e.g., 10^4 CFU) or requiring specific bacterial species or numbers of species. We excluded studies of interventions to prevent ASB (e.g., cranberry extract).

General health outcomes for general adult populations and pregnant women included symptomatic UTI (e.g., cystitis and pyelonephritis), kidney failure, quality of life, and mortality. General harms included the adverse effects of treatment (e.g., allergic reactions, resistant infections). Pregnancy-specific health outcomes included complications of pregnancy associated with maternal or fetal morbidity, such as: preterm birth (before 37 weeks' gestation); low birth

weight (<2,500 g); hypertensive disorders of pregnancy (e.g., preeclampsia, eclampsia); sepsis and developmental abnormalities/malformations. Maternal and fetal or infant mortality outcomes (e.g., intrauterine death, stillbirth, neonatal death, fetal loss before term, spontaneous abortion, miscarriage, perinatal death, fetal loss after 20 weeks) were also included. In addition to the general outcomes and pregnancy-specific outcomes, fetal anomalies, stillbirth, and adverse effects of treatment were included to assess harms (KQs 2 and 4).

Quality Assessment and Data Abstraction

Two reviewers applied USPSTF design-specific criteria (**Appendix A Table 2**) to assess the methodological quality of all eligible studies. We assigned each study a quality rating of "good," "fair," or "poor." Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.

Good-quality studies were those that met nearly all of the specified quality criteria (e.g., comparable groups assembled initially and maintained over study, adequate followup, conservative data substitution methods for missing data, no evidence of selective outcome or analysis reporting), whereas fair-quality studies did not meet these criteria. Traditionally in USPSTF methods, studies that have serious threats to their internal validity related to the design or execution of the study would be rated as poor quality and excluded from the review. However, based on discussions with the USPSTF leads and consideration of the historical nature of the studies, with some dating to the 1960s, these studies were instead categorized as fair quality due to the changing standard of study reporting over time. Those studies that appeared to have the highest risk of bias were flagged to be dropped from meta-analysis as sensitivity analyses. Criteria for these "high risk" studies included those with multiple shortcomings such as a lack of reporting of criteria for ASB, no reporting of how treatments were allocated, no definition provided for pyelonephritis or other major outcomes, a lack of information on the baseline characteristics of participants and/or a serious imbalance in baseline characteristics, or a high suspicion of selective outcome reporting.

For all included studies, one reviewer extracted key elements into standardized abstraction forms in DistillerSR (Evidence Partners, Ottawa, Canada). A second reviewer checked the data for accuracy. For each study, we abstracted general characteristics (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race/ethnicity, setting, country), analytic methods, definitions of outcomes measures, and results.

Data Synthesis and Analysis

We created summary tables for all KQs describing study, population, and intervention characteristics (if applicable) and outcomes for qualitative evidence synthesis. Studies were grouped according to population: adult men and nonpregnant women (age ≥18) and pregnant women (of any age). We used these tables along with forest plots of the results to examine data for consistency, precision, and, for intervention trials, the relationship of effect size with key potential modifiers such as the definition of pyelonephritis, treatment duration, and study risk of

bias.

We synthesized data separately for each Key Question. Outcomes that were too few to support quantitative pooling due to the limited number of comparable studies are narratively summarized. For studies with enough clinically comparable outcomes reported, we conducted random-effects meta-analyses using the method of DerSimonian and Laird[35] (DL) to calculate the pooled relative risks. When pooling fewer than 10 studies, we conducted sensitivity analyses using a restricted maximum likelihood (REML) model with Knapp-Hartung correction for small samples and reported estimates only if they differed from the DL result. When available, we favored relative risks reported by study authors, but calculated crude effect estimates and confidence intervals when only p-values, raw percentages, or other estimates of effects were given.[36] For studies in pregnant populations we sought infant and maternal outcomes throughout pregnancy, delivery, and immediately postpartum.

For quantitative pooling of the effects of ASB treatment for pregnant women, we defined outcomes as follows: low birthweight (defined as birthweight less than 2500 grams or small for gestational age below the 10th percentile), mean birthweight, pyelonephritis (as defined by the study), and preterm birth (defined as birth prior to 37 or in rare instances before 38 weeks' gestation); if no definition was provided by the study authors (e.g., defined only as "premature birth") the outcome was included in pooled results for preterm birth. Perinatal mortality includes fetal and infant deaths occurring >20 weeks of gestation and <1 week postpartum, and when information was provided, study outcomes were grouped accordingly. Studies used differing definitions/criteria for pyelonephritis. We stratified analyses to explore whether pyelonephritis results were influenced by the clinical definition used by the study authors, categorized as: "strong" (definitions that required fever or chills), "moderate" (those requiring loin pain with or without fever), or "weak" (no criteria given or nonspecific diagnostic criteria). Other sensitivity analyses included an examination of pooled effects with the studies considered at "high risk of bias" excluded, and exploration of the effect of the duration of antibiotic treatment on study findings.

We examined statistical heterogeneity among the pooled studies by applying standard χ^2 tests and estimated the proportion of total variability in point estimates by using the I^2 statistic.[37] We followed the Cochrane Collaboration's general overlapping ranges for interpreting heterogeneity:[38] Less than 40 percent likely represents unimportant heterogeneity; 30 to 65 percent, moderate heterogeneity; 50 to 90 percent, substantial heterogeneity; and more than 75 percent, considerable heterogeneity. Funnel plots were used to examine outcomes for potential small-study effects (a possible indication of publication bias), and we conducted the Egger test if 10 or more studies were available, to assess the statistical significance of any imbalance in study size associated with individual study results.[39] We used Stata version 13.1 (Stata Corp LP, College Station, TX) for all quantitative analyses. All significance testing was two-sided. Results were considered statistically significant if the p-value was 0.05 or less.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each key question. We adapted the Evidence-based Practice Center approach,[40] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[41] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). Issues related to reporting bias or study quality are described under "other limitations" if detected. Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). We did not address the fifth required domain—directness—as it is implied in the structure of the key questions (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each key question according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from October 4, 2017, through October 25, 2017. In response to feedback, minor changes to the Research Plan were made to clarify the included population and relevant outcomes. The full draft report was shared with invited expert reviewers and federal partners. We compiled the comments received from these invited experts and addressed them in the report as appropriate. The draft version of this report was posted for public comment on the USPSTF Web site from April 23, 2019 to May 20, 2019. Comments received during this period were reviewed and considered. Changes requested by reviewers mainly pertained to the Recommendation Statement and not the Evidence Synthesis; therefore, no changes were made to the evidence or to our conclusions.

USPSTF Involvement

We worked with five USPSTF members at key points throughout this review, particularly when determining the scope and methods, and developing the Analytic Framework and KQs. After

revisions reflecting the public comment period, the USPSTF members approved the final analytic framework, KQs, and inclusion and exclusion criteria. AHRQ funded this review under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

Description of Included Studies

We reviewed 4,318 abstracts and 288 full-text articles. Following review of full-text articles and critical appraisal, we included 19 studies of screening or treatment for ASB,[42-60] reported in 36 publications (**Appendix A Figure 1; Appendix B**).[14, 15, 42-75] Only one study was published after the last USPSTF recommendation on this topic.[59] Fourteen of the included studies were conducted among pregnant women; 2 examining the effectiveness and/or harms of screening[42, 43] and 12 examining the effectiveness and harms of treatment.[44-46, 48, 49, 51, 53, 54, 56-59] Five included studies examined the effectiveness and harms of treatment among general adult populations, primarily women and older adults (**Table 2**).[50, 52 47, 55, 60]

Of the 288 articles reviewed, the most common reasons for exclusion were; not a study (e.g., literature summaries, commentaries) (k=101), lack of relevant outcomes or incomplete outcome reporting (k=25), or study design (k= 60). **Appendix C** contains a list of all excluded studies and the reasons for exclusion.

Key Question 1. Benefits of Screening for ASB

Pregnant Women

Summary of Results

Two retrospective observational cohort studies,[42, 43] comparing data on pregnant women before and after a routine screening program was introduced, provided limited evidence on the effects on pregnancy outcomes of screening for and treatment of ASB. One study reported five cases of pyelonephritis over the study period with only one case in the intervention group.[42] More cases of intrauterine death and intrauterine growth retardation were also reported in the unscreened control group in this study, but the small study n and low event rates limited statistical power for comparisons. The other study reported a statistically significant effect of screening for pyelonephritis; there were three times more cases of pyelonephritis reported in the unscreened cohort than the screened cohort.[43] The study did not report findings for any other health outcomes. Both of these observational studies were noted to have considerable risk of bias from missing data, selective outcome reporting, and possible underlying differences in the screened and unscreened cohorts.

Characteristics of Included Studies

Two fair-quality cohort studies (N=5,289)[42, 43] compared a screened cohort to an unscreened comparison group to assess the effects of implementing an ASB screening program on maternal and perinatal outcomes (**Table 2**). A study of 4,917 pregnant women conducted in Spain analyzed hospital data on women seen in prenatal care before 25 weeks' gestation and delivered at Hospital Clinic of Barcelona from the years 1987–1992.[43] Women who delivered from 1987 to

the end of 1990 were not routinely screened for ASB and were compared with women entering prenatal care from 1991 to the end of 1992 who were routinely screened for ASB. Similarly, a study of 372 pregnant women conducted in Bursa, Turkey, included women screened for ASB prior to 32 weeks' gestation during 1998–1999 (n=186) and a comparative retrospective control cohort that delivered at the hospital prior to the initiation of the ASB screening program (n=186).[42]

Population Characteristics

The population in the Spanish study[43] was not described apart from participant pregnancy status, and in the Turkish study a mean age of 28 was reported for both the screened and unscreened cohort.[42]

Both studies included screening at the first prenatal visit with neither reporting when exactly in pregnancy this tended to occur. In the Spanish study,[43] screening was conducted with culture and an ASB diagnosis required two positive tests for the same organism on culture. When ASB was diagnosed, it was treated based on antibiotic sensitivity testing. In the Turkish study, a single positive urine culture with count of $\geq 10^5$ colony forming units (CFU)/mL was used to diagnose ASB, which was treated with ampicillin, cephalexin or nitrofurantoin.[42]

Study Quality

Both studies were rated fair quality, with several factors contributing to an elevated risk of bias. Neither of the included studies provided details on the source of study outcome data, the procedures used to select the comparison cohort, or the characteristics of women in the screened and unscreened groups. In both cases, the comparison group was identified retrospectively, increasing the risk of bias from missing data, selective outcome ascertainment, or differences in the study group characteristics or composition. In the Turkish study, the time period during which the unscreened control group was selected and how the retrospective control group was identified (i.e., every patient or select patients) were not specified.[42]

Detailed Results by Outcome

Pyelonephritis

The Spanish study compared 1,652 women screened for ASB with 3,265 women in an unscreened retrospective comparison cohort.[43] In the screened cohort, 4.7 percent of pregnant women <25 weeks' gestation were diagnosed with ASB. A smaller proportion of women in the screening cohort (9/1,652 [0.5%]) compared with the unscreened cohort (60/3,265 [1.8%]) were diagnosed with pyelonephritis during their pregnancy—such that the risk was 3 times lower after implementation of routine screening and treatment (RR, 0.30 [95% CI, 0.15 to 0.60]) (**Table 3**).

The Turkish study of women <32 weeks' gestation reported results of ASB screening for 186 women (with "sufficient delivery records") compared with an unscreened control comprising 186 women.[42] In the screened group, 9.3 percent of women were diagnosed with ASB. There

was one case of pyelonephritis in the screened cohort and four cases in the unscreened control group.

Birth Outcomes

No birth or infant outcomes were reported in the Spanish study.[43] The Turkish study reported no significant difference in the weight of newborns (data NR). The rate of prematurity was not found to differ between the screened and unscreened cohort (11.8% [22/186] versus 9.7% [18/186]). The authors reported fewer cases of intrauterine death (1/186 versus 7/186) and intrauterine growth retardation (1/186 compared with 5/186) in the screened cohort than in the unscreened control (**Table 3**).[42] The study had low event rates and study N, and was therefore not adequately powered to detect group differences for these outcomes. Although the study text reported a statistically significant difference for intrauterine growth retardation, it is unclear from the study-reported numbers and methods what would account for this finding, and it was inconsistent with the absence of statistically significant differences reported for other outcomes with larger observed effects.

Hypertensive Disorders of Pregnancy

The Turkish study reported a lower rate of hypertension in pregnancy among women in the screened group than in the unscreened group (4.3% [8/186] versus 9.7% [18/186]) (**Table 3**).[42] It was unclear what might account for this difference, which approached statistical significance in an unadjusted comparison (calculated RR, 0.44 [95% CI, 0.20 to 1.0]).

General Adult Populations

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

Key Question 2. Harms of Screening for ASB

Pregnant Women

Only one cohort study comparing screened and unscreened pregnant women reported a potential harm of the screening program, with no meaningful differences reported.[42]

This study of 372 women conducted in Turkey,[42] described above, was included to assess potential harms of screening for ASB. Two congenital abnormalities were reported in the unscreened cohort (2/186) compared with three in the screening cohort (3/186); the three congenital abnormalities were observed among infants of women who screened ASB negative and presumably were not prescribed antibiotics to treat ASB. No other potential harms of screening for ASB and subsequent treatment with antibiotics were reported in the included studies, including no paradoxical effects on reported outcomes (**Table 3**).

General Adult Populations

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

Key Question 3. Benefits of Treating Screen-Detected ASB

Pregnant Women

Summary of Results

Twelve fair-quality trials,[44-46, 48, 49, 51, 53, 54, 56-59] most conducted over 40 years ago and many employing treatment protocols no longer used in modern clinical practice, provided evidence on the benefits of treating screen-detected ASB. Screening in the older studies was primarily conducted with an initial urine culture and a second culture test to confirm diagnosis. The only recent study, conducted in the Netherlands, used a single dipslide urine test to screen for ASB, focusing on a low risk patient population.[59] The sparse reporting and sometimes flawed methods used in this earlier era of medical research raise the risk of potential bias. With caveats regarding the limitations of the literature, the available trials provided evidence that treatment of ASB in pregnancy reduces the risk of pyelonephritis and the finding was robust in sensitivity analyses. Other outcomes were less likely to be reported across the included studies. Seven studies of treatment on the incidence of low birthweight in infants provided evidence of a benefit in pooled analysis, and the direction of effects were nearly all in the direction of a benefit. Fewer studies reported mean birthweight and rates of preterm birth, and findings in all but one individual study and the pooled analyses for these outcomes were null. Six studies reported differences in perinatal mortality,[44, 48, 49, 54, 56, 59] with more inconsistency in the direction of effects, and a null pooled effect.

Characteristics of Included Studies

Population Characteristics

Twelve trials of pregnant women screened for ASB and randomized to either a treatment or control condition were included (N = 2,377).[44-46, 48, 49, 51, 53, 54, 56-59] All but two[51, 59] were published in the 1960s or 1970s (**Table 4**). The two most recently published studies were conducted in the Netherlands (2015)[59] and Ireland (1987) (N=305).[51] Among the 10 early studies, three were conducted in the United States (N=557),[48, 56, 57] and the remainder in Great Britain,[45, 49, 58] Jamaica,[53] and Australia.[44, 46, 54] Most studies were conducted in the OB/GYN clinics of hospitals, with seven specifying screening at the first prenatal visit,[44-46, 49, 54, 57, 58] two specifying screening by a certain week of gestation in pregnancy,[48, 59] and three indicating pregnant women with no mention of the timing of study recruitment.[51, 53, 56]

Information on the characteristics of the study participants was very sparsely reported, but when available, reported higher smoking prevalence in earlier cohorts. There was limited reporting on race/ethnicity, and imbalances were seen. Only three studies reported the mean age of

randomized women (range 25-29).[48, 58, 59] Three studies reported smoking rates.[48, 58, 59] In one U.S. study published in 1971,[48] 52 percent of the pregnant women randomized were described as smokers. This study also reported race/ethnicity, described as 40 percent "white" and 60 percent "other."[48] In a 1975 study from Great Britain, 22 percent of pregnant women randomized were identified as smokers, with more in the control group (26%) than the intervention group (19%).[58] This study also reported the race/ethnicity for 20 percent of the study population as Asian or West Indian, with lower percentages in the control group (14%) relative to the intervention group (21%). The recent Netherlands study reported that 8 percent of women in the intervention group were smokers.[59] Smoking rates in the control group were not reported. This same study reported white race/ethnicity for 92 percent of the study participants. Estimates from the figure from another early U.S. study identified the race/ethnic composition of the study sample as 52 percent "white," 46 percent "African American," and 2 percent "other."[56] This study also reported fewer white participants and more high gravidity women in the control group compared with the intervention group (>5% difference).

Exclusion criteria were not specified or few (e.g., hypertensive, chronic renal insufficiency, recent UTI) in most of the included studies, and some referred to loss to study followup in describing exclusions. The most recent trial excluded women at risk of preterm birth and other health conditions with the aim of enrolling a low-risk study population.[59]

Screening procedures and definitions of ASB were variable across the included studies. Some specified the approach taken to obtain a clean-catch,[45, 48, 58] midstream urine sample,[44, 46, 49, 57, 59] while others simply described the sample as a clean catch.[51, 53, 54, 56] While most studies specified a midstream sample, not all were described as clean catch. Laboratory culture testing was the primary screening modality. Two studies,[46, 59] including the most recent, relied on dipslide testing. ASB positive women were most commonly defined as those with colony counts $\geq 10^5$ CFU/mL dilution of the same single bacterial species on two consecutive samples, with some studies defining fewer criteria (e.g., same organism not required, single sample) including the most recent trial which relied on a single sample. The percent of pregnant women screened who were diagnosed with ASB ranged from 2.1 to 5.3 percent across the included studies. The most recent study identified 5.0 percent of women screened with dipslide as ASB positive.[59]

Intervention Characteristics

Treatments for screen-detected ASB varied widely across the included studies with respect to timing, dosage, duration, and medication (**Table 5**). Antibiotics were the primary treatment in all of the studies with the exception of one that used renal antiseptics (i.e., methenamine hippurate, methenamine mandelate).[46] Sulfonamides were the most common class of antibiotics used, but many of the specific antibiotics tested in the studies are no longer used (e.g., sulfamethizole, sulfadimethoxine). Five of the studies used nitrofurantoin alone[53, 59] or as one of several antibiotic treatment options.[44, 49, 51] One study used tetracycline,[48] which is contraindicated and no longer used during pregnancy. The treatment dosage and duration in most of the studies were higher and longer than what is more common to contemporary practice. Four studies continued treatment from the time ASB was diagnosed until delivery or postpartum,[44, 46, 54, 57] resulting in continuous antibiotic use for weeks or months. Only five of the studies randomized women to an initial treatment lasting a week or less,[45, 51, 56, 58, 59] including one study using a single 2000mg

dose of sulphormethoxine[58] and another using a high dose of a sulfonamide no longer used in clinical practice (i.e., sulphadimidine, 1000mg, three times a day, seven days).[45]

Study Quality

All included studies for this key question were rated fair quality, having considerable risk of bias related to the trial methods and reporting. With one exception,[59] this body of evidence was generated prior to standardization in the conduct and reporting of randomized trials. Several studies did not describe how randomization was conducted, or they used a randomization and allocation technique that would potentially not be protected from bias in study implementation. Moreover, the absence of reporting on the baseline characteristics or balance in the study groups prevents assessment of the effectiveness of randomization. Definitions of study outcomes were also often limited or absent. For example, pyelonephritis was a key outcome in most studies, but a clinical definition was not always provided.[44, 51, 53, 57] Five studies were judged to have particularly high risk of bias due to multiple concerns related to randomization and inconsistencies or a lack of clarity regarding the participant characteristics and outcomes.[44-46, 56, 58]

Detailed Results by Outcome

Symptomatic UTI and Pyelonephritis

Two studies reported symptomatic lower UTIs.[51,59] One did not provide a clear definition but reported similar numbers of UTI cases in the treatment arm (4/100) and the control arm (5/120).[51] The other reported UTI cases treated with antibiotics during pregnancy in the treatment arm (4/40) and the control arm (8/45).[59] Although the numbers were higher in the CG, the relative risk was not statistically significant (calculated RR, 0.56 [95% CI, 0.02 to 8.93]) (**Appendix E Table 1**).

Twelve studies reported rates of pyelonephritis in trial intervention and control groups among pregnant women with screen-detected ASB (**Figure 2, Appendix E Table 1**).[44-46, 48, 49, 51, 53, 54, 56-59] Rates of pyelonephritis in the control group were 2.2 percent in the most recent study[59] and 2.5 percent in the second most recent study,[51] published in 1987. Rates of pyelonephritis in the older studies were considerably higher, ranging from 7 to 36 percent, with 8 of the 12 included studies reporting pyelonephritis rates greater than 20 percent among women with ASB in the untreated/placebo arm. Higher rates of pyelonephritis were observed in the control group (placebo or no treatment) than in the treated group in all but one study.[51] Eight of the 12 studies reported statistically significant reductions in pyelonephritis,[44, 45, 48, 49, 53, 54, 56, 58] and overall, the pooled estimate suggested a four-fold risk reduction (pooled RR, 0.24 [95% CI, 0.14 to 0.40], k=12, n = 2,068, I^2 56.9%). Sensitivity analyses dropping studies from meta-analysis that were deemed to have particularly high risk of bias demonstrated a greater pooled risk reduction and lower statistical heterogeneity (pooled RR, 0.19 [95% CI, 0.11 to 0.34], k=7, n=1,184, I^2 15.6%) (**Appendix D Figure 1**). Analyses stratified by the extent to which pyelonephritis was defined using specific diagnostic criteria did not reveal a clear pattern, with statistically significant reductions seen for studies regardless of the strength of the definition provided (**Appendix D Figure 2**). Visual inspection of plots sorted by treatment duration suggested that findings were

not driven by longer treatment protocols that are no longer used. Visual inspection of a funnel plot revealed some asymmetry, and the Egger test approached statistical significance (p = 0.08).

Birth Outcomes

Overall, fewer studies reported birth outcomes, and findings were mixed. Pooled analyses, where possible, suggested a reduction in low birth weight, but the finding was tempered by the loss of statistical significance in a sensitivity analysis removing the highest-risk studies. Studies were not adequately powered to evaluate rare outcomes such as perinatal mortality.

Low birthweight. Seven studies reported differences in low birthweight infants (<2,500 grams or small for gestational age [SGA; weight below the 10th percentile for gestation age]) among women treated or untreated for ASB (**Figure 3, Appendix E Table 2**).[44, 48, 49, 54, 56, 58, 59] The proportion of low birthweight infants ranged from 2.5 to 14.8 percent in the study intervention groups and from 6.7 to 21.4 percent in the study control groups. A statistically significant reduction in the risk of low birthweight was reported in two studies,[44, 56] and the pooled estimate was also statistically significant, with low statistical heterogeneity (pooled RR, 0.64 [95% CI, 0.46 to 0.90], k=7, n=1,522, I^2 15.8%). A sensitivity analysis removing studies with the highest risk of bias led to exclusion of the statistically significant studies, and loss of a significant pooled effect (pooled RR, 0.86 [95% CI, 0.57 to 1.31], k=4, n=745, I^2 0%) (**Appendix D Figure 3**). 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 five studies reporting mean birthweight[44, 46, 48, 58, 59] were inconsistent and did not show a statistically significant effect (**Figure 4, Appendix E Table 3**).

Preterm Birth. Three studies reported differences in preterm birth defined as <37 weeks' gestation[44, 57, 59] and one study used <38 weeks' gestation[46] to define preterm birth (**Figure 5, Appendix E Table 2**).[44, 46, 57, 59] One study considered to be at higher risk of bias reported a statistically significant benefit for the intervention group,[44] and the remaining three trials reported nonstatistically significant differences in the direction of a control group benefit. Few small and clinically heterogeneous studies reported this outcome, limiting conclusions that can be drawn from the null pooled estimate.

Perinatal mortality. Six studies reported perinatal mortality (**Figure 6, Appendix E Table 4**).[44, 48, 49, 54, 56, 59] Half of the trial effects were in the direction of treatment benefit and the other half in the direction of treatment harms, but owing to small numbers, none of the studies reported statistically significant effects, and the pooled estimate was null (pooled RR, 0.98 [95% CI, 0.29 to 3.26], k=6, n=1,103, I^2 52.3%). A sensitivity analysis eliminating two studies with the highest risk of bias was also null (pooled RR 1.93 [95% CI 0.84, 4.45]) (**Figure 4 in Appendix D**).[44, 56] The small number and size of the included studies in the sensitivity analysis, however, results in an underpowered analysis for evaluating this rare outcome.

Hypertensive Disorders of Pregnancy

Five studies reported the occurrence of hypertensive disorders of pregnancy, primarily preeclampsia or 'toxemia' in the intervention and control groups (**Figure 7, Appendix E Table**

5),[44, 48, 49, 59] or noted whether there were significant differences.[54] None of the studies reported a statistically significant difference in cases between the intervention and control groups, with most reporting more cases in the intervention group. The pooled effect across studies was null for an increased risk in the intervention group (pooled RR, 1.21 [95% CI, 0.76 to 1.93], k=5, n=889, I^2 0%).

General Adult Populations

Summary of Results

One good-quality[55] trial and four fair-quality[47, 50, 52, 60] trials addressed the benefits of treating screen-detected ASB in general adult populations. In general, fair-quality studies lacked reporting on the randomization and allocation of participants, as well as methods for outcome assessment. Four trials[47, 50, 52, 55] were conducted only in women, and the fifth trial[60] was primarily in older women (83.9%). All studies had sparse reporting of participant characteristics. Treatment was variable across the trials ranging from a single dose to 3 months of daily antibiotics. No study found a difference the rates of symptomatic infections, mobility, or mortality between treated and untreated individuals.

Characteristics of Included Studies

Population Characteristics

We identified five trials (N=777) examining the effectiveness of antibiotic treatment in general adult populations with screen-detected ASB (**Table 6**).[47, 50, 52, 55, 60] These studies were conducted in the United States (two studies),[47, 52] Canada,[55] the United Kingdom,[50] and Greece.[60] Two studies of adult women (N=199) recruited individuals from medical centers.[50, 55] One study conducted in Wales included women ages 20–65 without diabetes.[50] The study conducted in Canada was limited to women with diabetes (mean age 55.3 years) recruited from endocrinology clinics and tertiary care.[55] Three studies were conducted among older adults (N= 578) residing in independent living facilities.[47, 52, 60] Two of the three studies among older adults were limited to women,[47, 52] and the third was mostly women (83.9%).[60] The mean age of participants across the studies among older adults ranged from 81.9 to 85.8 years.

In general, population characteristics were sparsely reported across studies, with none reporting on participant race, ethnicity, or smoking status.

All five studies included individuals who had two consecutive positive screening cultures from clean catch, mid-stream urine samples using a cutoff of greater than the 10^5 CFU/ml.

Intervention Characteristics

The two studies of women with and without diabetes randomized women to short-term (1-2 weeks) antibiotics or placebo treatment (**Table 7**).[52, 55] Within the three studies of older adults, treatment was more variable; two studies examined short-term antibiotic treatment ranging from a single dose to 3 days,[47, 52] and one study treated individuals with antibiotics either daily or

intermittently for 3 months (two intervention arms).[60] All three studies were initiated with a "no treatment" control condition; however, at the midpoint of one study the control condition was changed to a placebo.[52] In all studies, individuals who did not clear the infection were retreated with an additional course or courses of antibiotics.

Study Quality

The study of ASB treatment in diabetic women was rated as good quality,[55] and the four remaining studies were rated fair quality. The fair-quality studies lacked information about blinding and randomization. The percentage of individuals included in followup (reported or assumed) was generally high at 12 months (87 to 100%).[47, 50, 60] In one study that reported findings through 3 years of followup, fewer than half (46.7%) were retained for the entire study (mean followup 2 years).[55] One study did not provide information allowing for calculation of the number of participants lost to followup.[52] The Greek study, conducted in older adults,[60] reported earlier preliminary results of the study in an extended abstract,[68] but the reported results and time points provided in the preliminary abstract did not match those reported in the final publication. Therefore, results from the final publication were used.[60]

Detailed Results by Outcome

Symptomatic UTI and Pyelonephritis

Four studies reported on the rate of symptomatic infection or pyelonephritis; no study found a statistically significant difference. The study among nonpregnant women reported that during 1 year of followup, symptomatic infections developed in 36.7 percent of those in the treatment group and 35.6 percent of the placebo group, (RR, 1.03 [95% CI, 0.60, 1.77) (Table 8).[50] In the study among adult women with diabetes,[55] there were no significant difference in the rates of symptomatic UTI between the treatment (0.80 per 1,000 person days) and placebo groups (0.83 per 1,000 person days) (RR, 0.97 [95% CI, 0.61 to 1.54]) over a followup of up to 36 months (mean followup 2 years). Rates of pyelonephritis were also not different between treatment (0.13 per 1,000 person days) and placebo groups (0.28 per 1,000 person days) (RR, 0.47 [95% CI, 0.18 to 1.23]). The majority of women in both groups had no symptomatic episodes, with approximately a quarter of the women in each arm accounting for over 80 percent all reported infections. Two women in each study group developed clinically significant renal failure.

Two studies in older adults reported symptomatic infections during followup. One study in older adult women reported that during the 6-month followup, 16.4 percent of women in the no-therapy control group and 7.9 percent of women in the treatment group developed symptoms of a UTI; however, this difference was not statistically significant (p=0.15).[47] Another reported that there were no cases of sepsis or septic shock occurred during the 6-month study followup.[60]

Mobility

Only one study, in older adults, reported on mobility as an outcome and found no effect on mobility at 6 months.[60] This study excluded individuals who needed help performing activities of daily living at enrollment and used a subjective measure of good mobility (i.e., complete

independence) as classified by the physician and head nurse of the independent living pavilions.

Mortality

The two studies of adult nonpregnant women (with and without diabetes) did not report effects of treatment on mortality.[52, 55] All three trials specific to older adults reported on the effect of treatment on mortality, with no trial finding a difference in mortality between the treated and untreated groups (Table 9). One study examined the effect of treatment on mortality as its primary outcome and reported that 18 percent of treated women died over the course of 100 months of followup compared with 20 percent in the control group (HR, 0.92 [95% CI, 0.50 to 1.47]).[52] Two additional studies that measured mortality as a secondary outcome found no effect on treatment at 6 months.[47, 60]

Key Question 4. Harms of Treating Screen-Detected ASB

Pregnant Women

Summary of Results

There was no statistically significant evidence of harms associated with treatment of screen-detected ASB. Adverse reactions to antibiotics were reported, such as vaginitis and diarrhea, but there was no evidence of major fetal developmental harms related to treatment (e.g., congenital malformations). Evidence on infant and maternal harms of ASB treatment in pregnancy was sparsely and inconsistently reported (seven studies), and there was a lack of evidence on long term neonatal outcomes following antibiotic treatment of ASB in pregnancy. Overall, thefindings did not identify or rule out potential harms.

Detailed Results by Outcome

Characteristics of Included Studies

Seven of the studies included for Key Question 3 and described above reported potential harms of treatment of screen-detected ASB.[44, 46, 48, 49, 56, 57, 59] One study used tetracycline,[48] which is contraindicated and no longer used during pregnancy.

Infant and Fetal Harms

Five studies reported on congenital malformations in the intervention and control groups (**Figure 8, Appendix E Table 6**).[44, 46, 48, 49, 59] Although the number of cases were small, all but one study reported fewer in the intervention group than in the control group.[49] The pooled estimate was not statistically significant (pooled RR, 0.44 [95% CI, 0.16 to 1.22], k=5, n=961, I^2 0%). The estimate was similar, but even less precise, in a sensitivity analysis removing two high risk of bias studies.

Two studies reported infant jaundice. One study did not report any cases in either study group.[57] The other study using tetracycline for treatment and reported similar numbers in the intervention

(4.0% [5/126]) and control group (2.8% [4/144]).[48] This same study reported cases of respiratory distress, including respiratory distress syndrome and "other causes of respiratory embarrassment," with more events in the intervention group (6/126) than in the CG (4/144). The difference was not statistically significant (calculated), but power was limited for drawing comparisons. The most recent of the included studies reported two cases of neonatal sepsis confirmed with culture in the control group and zero in the intervention group (**Table 10**).[59]

Maternal Harms

Complications of pregnancy and delivery were inconsistently and sparsely reported in two of the studies, but where available did not indicate potential harms of treatment for third-trimester hemorrhage,[48] premature rupture of the membranes,[48] nonspontaneous onset of labor,[59] or cesarean section before onset of labor.[48] An undefined composite variable of "other maternal complications" was reported in an older study using tetracycline,[48] with more events in the control group (11/127) than the intervention group (21/145) but no statistical difference (calculated) (**Table 10**).

Two studies provided information on maternal adverse reactions to medications.[44, 49] For ampicillin treatment, vaginitis and diarrhea were reported.[44] For nalidixic acid and nitrofurantoin treatment, rashes and nausea were reported.[44, 49]

General Adult Populations

Summary of Results

Four studies reported on the potential harms of treatment in nonpregnant and older adults. Overall, data was inconsistently reported and limited for drawing conclusions about potential harms.

Detailed Results by Outcome

Characteristics of Included Studies

Two studies of treatment in nonpregnant adult women[50, 55] and two studies in older adults[47, 60] reported on rates of adverse events associated with treatment of ASB.

Adverse Reactions

The study among nonpregnant women reported that there were no adverse drug reactions from among the 49 women treatment with nitrofurantoin therapy.[50] The study among diabetic women (N=105) reported higher rates of treatment-related adverse events (not specified) associated with treatment with trimethoprim-sulfamethoxazole; 18.1 percent compared with 6.0 percent of women treated with placebo (RR 3.45, [95% CI, 0.90 to 14.2]).[55]

One study among older adults reported that no adverse medication reactions occurred among the 63 women treated with trimethoprim.[47] Another reported that 6.3 percent (2/32) of women

assigned to daily ofloxacin therapy withdrew due to adverse events (vertigo and gastrointestinal tract symptoms).[60] The authors stated that in general those assigned to "pulse treatment" (i.e., treatment 3 days of every 2 weeks) generally accepted therapy more easily than those assigned to continuous therapy, but numbers of overall adverse events in each group were not reported. Treatment was found to not affect hematocrit, serum bilirubin or blood urea, but a mild reduction in serum creatinine was seen in the treatment groups.

Chapter 4. Discussion

Summary of Evidence

Our review of the literature on ASB screening and treatment revealed limited evidence for drawing conclusions on benefits and harms of this practice for general adult populations and pregnant women and their infants (**Table 11**). Only one study has been published since the last USPSTF recommendation on this topic.[59] There was limited interval validity, with considerable risk of bias in the evidence included for both pregnant and nonpregnant populations. The external validity and applicability of the evidence base, particularly in the studies of pregnant women, was also poor, as most were conducted over 40 years ago and many of the treatment protocols and medications are no longer used in clinical practice. The results of most of the studies among pregnant women included in this review do not warrant strong conclusions about effects of screening and treatment as practiced in modern U.S. clinical populations and health care settings. Nevertheless, current practice is derived from these early studies that sought to determine whether treatment of ASB (primarily with antibiotics) could improve pregnancy and birth outcomes.

Direct evidence on the benefits and potential harms of screening was limited in pregnant and nonpregnant populations, and the preponderance of evidence contributing to this review was on the effects of treating screen-detected ASB. Two fair-quality comparative retrospective cohort studies of screening in pregnant women (N=2,019) found fewer cases of pyelonephritis in screened than in unscreened women. No harms of screening were identified but reporting on potential harms was extremely limited.

Evidence that treatment of screen-detected ASB reduces the incidence of pyelonephritis in pregnancy was found, based on the 12 included trials (N=2,068) reporting this outcome. A reduced risk of low birthweight infants was also seen based on seven trials reporting this outcome (N=1,522), but the finding was less robust. There were fewer studies reporting low birthweight overall, and statistical significance was not retained when the three studies with high risk of bias were dropped from meta-analysis. Benefits and harms for other birth and infant outcomes were very limited. Some adverse reactions to medication, including diarrhea, rash, and nausea, were reported.

No evidence on the effect of screening for ASB in diabetic women, nonpregnant women, or older adults was identified. There was no evidence from five included studies that treatment of ASB improved mobility, mortality, or renal health outcomes among older adults, or UTIs (including pyelonephritis) among diabetic or nonpregnant women (N=777). Reporting on potential harms of treatment was very limited and nonspecific; however, two cases of patient withdrawal due to of vertigo and gastrointestinal symptoms were reported in one study.

Comparison With Other Reviews

A recent review of the evidence on ASB screening and treatment in pregnancy for the Canadian Task Force on Preventive Health Care (CTFPHC)[76] had very similar findings to those of our

current review and was based on much of the same evidence. In pregnancy, a significant reduction on the rate of pyelonephritis was seen in studies comparing screening to no screening. In addition, trials on ASB treatment among pregnant women found similar, statistically significant reductions in the rates of pyelonephritis and low birth weight. Effects on other outcomes including preterm birth, perinatal mortality, and congenital malformations were similar to those found in the current review. The authors of the review for the Canadian Task Force noted similar limitations of the literature with regard to quality and applicability, noting that there is great uncertainty if the magnitude of the effects seen are true and to what extent they can be applied to practice today based on evidence that the incidence of pyelonephritis in untreated ASB may be substantially lower than that reported in the historical literature.[76] The Canadian Task Force also considered evidence on patient outcome evaluations and on cost-effectiveness that were not included in our review. Overall, their findings led to a weak recommendation in favor of screening, and included recognition of patient valuations, noting that some women's preferences may vary such that those more concerned with potential harms or risks of antibiotic use may choose not to be screened or treated for ASB.[32]

A 2015 review by the Cochrane Collaboration (conducted prior to publication of the recent Netherlands study[59]) found a similar reduction in the risk of pyelonephritis and low birth weight. This review similarly noted the low or very low quality of evidence for all outcomes with the potential for high risk of bias in many studies. Two additional recent reviews came to similar conclusions and noted that inconsistency in the evidence base and the high risk of bias noted in the older trial evidence do not provide a strong foundation for current ASB-screening practices.[31, 77]

Reviews of treatment in general adult populations have similarly found that there is no evidence of clinical benefit from treating ASB.[23, 31, 78] A systematic review of screening and treatment in asymptomatic adults reported only a slightly increased risk of symptomatic UTIs among individuals with ASB than those without, and treatment did not reduce the risk of subsequent UTI.[23] The review also did not find associations of ASB with consequential health indicators or outcomes, such as kidney dysfunction, hypertension, cancer, or mortality.

Contextual Issues for ASB Screening and Treatment in Pregnant Women

Onsite ASB Screening Test Accuracy in Pregnancy

In its previous recommendation, the USPSTF stated that no tests available at that time had high enough sensitivity and negative predictive value in pregnant women to replace urine culture as the preferred screening test. It called for research to develop a screening test that could reduce the use of laboratory urine culture, which is more labor-intensive and costly than onsite screening urine tests. All but two of the included trials of pregnant women in this review relied on laboratory urine culture tests for screening. Two studies, including the most recent study, relied on a dipslide test that can be used for screening onsite with visual interpretation after overnight incubation and can also sent to a laboratory for culture. Recent literature on the performance of onsite urine tests, including onsite interpretation of the dipslide test, did not suggest that newer more accurate tests have become available since the previous review.

Available onsite urinalysis tests generally have higher specificity than sensitivity. A recent systematic review of onsite, point-of-care tests to detect ASB in pregnancy with urine culture as the reference standard found 27 studies of 9 different screening tests: dipstick (nitrites positive), dipstick (leucocytes or nitrites positive), chlorhexidine reaction, uriscreen catalase, Griess test, urinalysis, dipslide with gram staining, dipslide (Uricult), and dipslide (Microstix-3).[28] Urine dipstick the most commonly reported test. The literature search was updated through June 2016 and included 27 studies published between 1981 and 2010. Seven studies were conducted in the United States, seven in India, three in Nigeria, and one each in Ethiopia, Germany, South Africa, Turkey, Pakistan, Thailand, Argentina, Spain, Venezuela, and the United Kingdom (n=13,641 pregnant women). For studies using the dipslide with gram staining (k=6, n=3201), sensitivity ranged from 0.76 to 0.92 and specificity ranged from 0.86 to 0.99. The pooled sensitivity was 0.86 (95% CI, 0.80 to 0.91) and specificity was 0.97 (95% CI, 0.93 to 0.99). For the dipstick test combining positive nitrites and leukocytes (k=8, n=5,940), sensitivity ranged from 0.45 to 0.92 and specificity ranged from 0.63 to 0.97. The pooled sensitivity was 0.73 (95% CI, 0.59 to 0.83) and specificity was 0.89 (95% CI, 0.79 to 0.94). Finally, sensitivity for the dipstick test using positive nitrates only ranged from 0.15 to 1.00 and specificity ranged from 0.71 to 1.00 (k=21, n=9491), with a pooled sensitivity of 0.55 (95% CI, 0.42 to 0.67) and specificity of 0.99 (95% CI, 0.98 to 0.99). Ideally a screening test would maximize sensitivity, but some of these studies and their pooled findings suggest that onsite testing methods could fail to identify a significant number of women with ASB. Due to the lack of sensitivity and specificity of rapid screening tests for detecting ASB in pregnant women, these are not recommended for screening and guidance from the WHO recommends use of onsite testing only for settings where culture is unavailable or resources are very limited.

Limited Evidence on ASB Screening Test Timing and Frequency

There is little evidence available on the optimal timing and frequency of ASB screening in pregnancy. In the included studies, screening occurred anywhere from the 12th week of gestation to delivery. Screening generally was conducted only once over the course of pregnancy; the first prenatal visit, ideally in the first trimester, is usually recommended. One of the included trials screened women at every prenatal visit, and found that nearly one third did not screen positive for ASB at the first visit, but were diagnosed within 2 to 7 visits. Observational evidence is limited, but suggests ASB rates may increase as pregnancy progresses toward closer to term, and that detection of ASB may increase with more frequent screening.[79] A nonrandomized study among underserved pregnant women seen in a hospital-based midwifery practice compared women screened with culture at the first prenatal visit. Thereafter they receive screening with a urine dipstick test either on an indicated basis (symptoms or underling health condition) or routinely at every prenatal visit. Rates of pyelonephritis and UTI were no worse (based on noninferiorty statistical tests) among women with indicated rather than routine testing over the course of pregnancy, suggesting that further screening after a single culture at the first prenatal visit may not improve health outcomes. Overall, evidence on the test type, timing and frequency is limited. In the absence of more updated evidence, approaches other than culture screening at the first prenatal visit have not been supported in diagnostic accuracy or in randomized or nonrandomized comparative studies.

Association of ASB and Pyelonephritis in Pregnancy With Health Outcomes

The most consistent and robust effect observed with ASB treatment during pregnancy was a reduction in pyelonephritis infections. More infrequent outcomes, such as low birthweight, were less precisely estimable because there were fewer trials and low birthweight event rates were lower than for pyelonephritis in most of the older trials. Some of the included pregnancy outcomes where a relationship with ASB treatment was not evident, such as intrauterine growth restriction and hypertensive disorders of pregnancy may have less direct physiologic relationships to ASB and are more likely to be confounded by factors such as maternal smoking rates and pregnancy history. Evidence on the association between ASB and pyelonephritis, and between ASB and pyelonephritis on pregnancy health outcomes is needed to interpret the historical evidence.

In most of the studies conducted prior to 1980, rates of pyelonephritis in pregnant women with untreated ASB were at least 10-fold greater than currently observed. In the two most recent studies, rates of 2.2 percent and 2.5 percent were reported, yet in eight of the studies conducted earlier, rates were above 20 percent– in two of the older studies over one-third developed pyelonephritis.[44, 54] The much lower incidence of pyelonephritis in more recent studies conducted may be owing to a range of factors. These include different health status, smoking rates, or other characteristics of enrolled populations from an earlier era, more stringent diagnostic criteria, better recognition and treatment of lower urinary tract infections, changes in behaviors, and differences in the infectious microorganisms circulating in the population. Regardless of the reasons for lower pyelonephritis incidence, it corresponds to lower absolute differences in risk, meaning higher number needed to treat (NNT) to prevent a case of pyelonephritis. Assuming 2.5 percent incidence, 25 women in 1,000 with ASB would develop pyelonephritis in the absence of treatment. Applying the pooled RR of 0.24 from this review, 19 cases (estimate ranges from 15 to 21 from RR 95% CI) of pyelonephritis would be prevented for every 1,000 women treated for ASB with antibiotics during pregnancy (NNT 53, ranging from 45 to 67 from RR 95% CI).

The one recent study included in this review, from the Netherlands, provides data on the clinical course of untreated ASB. For the trial, a low-risk cohort of asymptomatic women aged 18 or older with a singleton pregnancy ranging from 16-22 weeks' gestation were screened using a single sample screening with dipslide culture ($>10^5$ CFU/ml). While some of these women consented to be included in the randomized trial following a positive screening result, 163 women with ASB opted not to be included in the trial. These women and the 45 women with ASB randomized to placebo were compared with the 4,035 women in the cohort who did not screen positive for ASB. Most women who chose not to participate declined because they did not wish to receive antibiotics during pregnancy. The ASB-positive women who were untreated or given placebo and the ASB-negative women were similar at baseline was apart from a higher rate of smoking among ASB-positive women (11% versus 6%, $p<0.004$) compared with those without ASB. The incidence of pyelonephritis was higher among untreated ASB-positive women (2.4% versus 0.6%; adjusted OR, 3.9 [95% CI: 1.4 to 11.4]). There were no differences in birth outcomes, but low event rates due to the exclusion of pregnant women at risk for preterm birth and other complications limited statistical power for these outcomes. In addition, defining ASB with a single sample result may have included more women with transient ASB, potentially

dampening differences between groups in the effect of treatment. Nevertheless, this pragmatic trial in a population that included women with untreated ASB for comparison offers some modern evidence points to the need for additional research to understand ASB and pyelonephritis risk in current pregnant populations.

Large observational studies have found that pyelonephritis in pregnancy is associated with negative health outcomes, including low birthweight. A large retrospective cohort study of women delivering singletons in Kaiser Permanente Southern California (KPSC) hospitals from 1993–2010 (n=546,092) found that 5.3 per 1,000 women were diagnosed with acute pyelonephritis and 0.5 percent of pregnant women were hospitalized for the condition. In this cohort, pyelonephritis was found to be independently associated with anemia, septicemia, acute renal failure, respiratory distress/adult respiratory distress syndrome, spontaneous preterm birth (<37 weeks and 33–36 weeks), low birth weight (1500–2499 g), chorioamnionitis, and primary cesarean delivery.[7] The analysis was adjusted for maternal age, race/ethnicity, education, prenatal care, gravida, chronic hypertension, pregestational and gestational diabetes, smoking during pregnancy, and year of delivery. Another cohort study from 1988–2010 conducted among women with singleton deliveries and prenatal care in Israel (n=219,612) found that 0.07 percent of women were admitted to the hospital with acute pyelonephritis. In this cohort, pyelonephritis was associated with induction of labor, suspected fetal distress, placental abruption, preterm delivery (<37 weeks), and Apgar <7 at 1 minute. In a multivariate regression model from this cohort, acute pyelonephritis was an independent risk factor for preterm delivery (OR, 2.6 [95% CI, 1.7 to 3.9]).[18] A prospective cohort study conducted in Texas from 2000–2001 (n=32,282) found 1.4 percent of women were admitted for acute pyelonephritis during pregnancy (14 per 1000 deliveries). Complications included anemia (23%), transient renal dysfunction (2%), respiratory insufficiency (7%), preterm birth <37 weeks (5%), preterm birth <32 weeks, and birth weight <2500 g. These rates were not higher than the usual rates observed at the study hospital, and the authors concluded that acute pyelonephritis was not associated with preterm delivery, small for gestational age, or increased rates of adverse pregnancy outcomes. The authors suggested that this could be due to improvements in treatment and aggressive followup care.[6]

This observational evidence is consistent with the premise that pyelonephritis contributes to poor maternal and fetal health outcomes but does not rule out other possibilities. Notably, observational studies indicate that ASB in pregnancy often occurs along with other risk factors associated with poor birth outcomes, including older maternal age, low socioeconomic status, multiparity, and diabetes.[4, 19-21] Associations of ASB and pyelonephritis with poor birth outcomes could therefore also in part arise from shared underlying risk factors or confounders that cannot be fully accounted for in observational studies.

Potential Risks of Antibiotic Exposure in Pregnancy

Antibiotics account for 80 percent of all prescribed medication in pregnancy, with guidance available for clinicians on the best approaches to infection treatment in pregnancy.[11, 80, 81] Information on the adverse effects of antibiotic treatment is limited, as clinical trials of medication safety are often not feasible and potentially unethical in pregnant women.[80] Consequently, there is little direct evidence establishing the safety of antibiotic use in pregnancy,

but animal studies and observational evidence, as well as clinical experience, underlie the safety profiles outlined for different classes of antibiotics in pregnancy. Penicillins, cephalosporins, and aztreonam are generally considered safe in pregnancy, with fosfoymcin and nitrofurantoin commonly used for treating ASB during pregnancy in modern practice. Other classes of antibiotics (e.g., tetracyclines, fluoroquinolones) are associated with harms and not advised, or advised only for use in midpregnancy (e.g., trimethoprim-sulfamethoxazole).[27]

Literature on potential longer-term adverse events related to antibiotic prophylaxis in pregnancy has been inconsistently reported and the studies are subject to high risk of bias. A systematic review of 30 studies of intrapartum prophylaxis for a variety of indications (e.g., GBS prevention, preterm labor) found that all of the included trials or observational studies had a high risk of bias. Results from seven cohort studies consistently showed that treatment altered the infant microbiome up to 90 days after delivery; however, it is unclear whether these alterations are related to any clinically meaningful adverse health effects. Six studies showed mixed evidence related to whether treatment led to increased antibiotic resistance in infants. Data were most limited related to long-term adverse events. One RCT comparing the results of 7-year-old children whose mothers had received treatment for preterm labor found a higher rate of cerebral palsy in mothers who had receive treatment with erythromycin (53/1611 [3%] and 27/1562 [2%]; OR, 1.93 [95% CI, 1.21 to 3.09) or amoxicillin-clavulanate (50/1587 [3%] and 30/1586 [2%]; OR, 1.69 [95% CI, 1.07 to 2.67). In addition, there was some limited evidence that rates of bowel problems and functional impairment were higher among children whose mothers were treated with erythromycin. However, the review notes that this study was limited by the multiple statistical comparisons conducted on a relatively small sample size, with additional analysis conducted on diabetes, behavioral problems, education attainment, attention deficit hyperactivity disorder, and other developmental problem not finding significance. In addition, the authors note that the biological plausibility of an increased risk of cerebral palsy is unknown.

In pregnant women, there is limited preliminary evidence pointing to possible longer term health effects for children whose mothers were exposed to antibiotics in pregnancy (for various indications). Characteristics of the microbiome as passed from mother to child may underlie risks for conditions thought to have an immune component.[80, 82-85]Obesity and asthma in childhood may be associated with changes to the microbiome,[85-88] and recent observational data suggest that antibiotic exposure during pregnancy may lead to alterations in the maternal microbiome.[89] A 2013 prospective cohort study conducted in Denmark (n=668) examined the effect of antibiotic administration during pregnancy on vaginal bacteria colonization at gestational week 36.[89] Results showed that women who received oral antibiotics during any trimester had an increased rate of colonization by *Staphylococcus* species, compared with women who did not receive any antibiotic treatment during pregnancy (adjusted OR, 1.63 [95% CI, 1.06 to 2.52], p=0.028).[89] Moreover, the increase in vaginal *Staphylococcus* species was associated with UTI antibiotics administered during any trimester in pregnancy (adjusted OR, 1.90 [95% CI, 1.08 to 3.33, p 0.026).[89] Emerging evidence has suggested that changes in the maternal microbiome may also induce perinatal complications, such as spontaneous abortion,[90] congenital malformations,[91] and low birth weight. The evidence base on this topic is evolving but highlights the need for a more thorough consideration of potential longer-term adverse consequences of ASB treatment in pregnancy.

Contextual Issues for ASB Screening in General Adult Populations

Association of ASB With Health Outcomes in General Adult Populations

The absence of effects of ASB treatment on health outcomes in the available trials may suggest that there is not a plausible mechanism whereby ASB influences mobility or mortality, or that observed associations of ASB and declining health are not causal relationships. ASB may instead be a marker for age and immune functioning. In addition, high rates of antibiotic use in the care of older adults in contact with the health care system for a range of health conditions may subsume potential effects of ASB screening and treatment. Overall, high rates of antibiotic use in older adults may subsume potential effects ASB screening and treatment; there was evidence in the studies that despite no differences in mobility or mortality, screening was associated with more antibiotic treatment overall, even accounting for differences in days of antibiotics used for ASB treatment.

Prospective cohort studies have shown that women with ASB (including women with diabetes and premenopausal and postmenopausal women) are at increased risk for symptomatic UTIs, but the presence of ASB has not be associated with long-term adverse events. In addition, treatment of ASB has not been found to decrease the frequency of symptomatic infections or future episodes of ASB. Prospective studies of ambulatory older adult males have also found no association between ASB and adverse outcomes or changes in survival. Therefore, screening for ASB in these populations has not been indicated in other practice guidelines. Despite the recommendations not to screen, ASB remains one of the most common causes of antimicrobial overprescribing in acute and long-term care. Within a systematic review of rates of ASB treatment, 45 percent of individuals with ASB who did not have an indication for treatment received inappropriate antimicrobial treatment with women and those with a gram-negative bacteriuria having higher rates of inappropriate treatment. The CDC has stated that antibiotic resistance is among the great public health threats today, leading to an estimated 2 million infections and 23,000 deaths per year in the United States. Antibiotic stewardship is the effort to measure and improve prescribing to ensure antibiotics are used only when needed, minimize underuse of antibiotics when indicated, and ensure proper dosing when indicated. The CDC has offered guidance on the core elements of antibiotic stewardship programs in hospital, nursing home, and outpatient settings.[92-94]

While studies among adults in long-term care facilities were excluded from this review, prospective studies of antimicrobial treatment for ASB in these settings have not found an association of treatment with a decreased rate of infection or improvements in survival or symptoms; however, treatment has been associated with significantly increased rates of adverse antimicrobial effects and reinfection with treatment resistant organisms. Therefore, screening for ASB in institutionalized adults has not been indicated in other practice guidelines.[3]

Limitations of the Evidence and Future Research Needs

We focused on English-language evidence from countries with high and very high (for pregnant women) on the Human Development Index (2016), 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. The review scope was limited to trials for assessing effects of treatment. Cohort studies could also have been included in the general adult population, but for this topic we expected too many threats to internal validity to draw conclusions about effects of ASB 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 effects of underlying conditions that would require antibiotics. Thus, for treatment benefits and harms, the scope was narrowly defined for study design. We are not aware, however, of any major cohort studies evaluating effects whether antibiotic treatment of ASB during pregnancy or in general adult populations exist that would have strengthened our review conclusions if included. Only one ongoing study with limited applicability was identified (**Appendix F**).

The included studies were found to have substantial risk of bias, with only one good-quality study included; a study of ASB treatment in women with diabetes.[55] Most of the trials among pregnant women were conducted over 40 years ago, using treatment protocols and scientific methods that are no longer commonly employed. In some studies, the evaluation of study quality was hindered by a lack of information, such as about the study groups at baseline, whereas in other studies the information provided raised questions about the methodologic rigor. The limited reporting on harms, including longer term harms was also a limitation of the evidence reviewed. Finally, selective outcome reporting and possibly publication bias are suggested by the limited number of included studies reporting important outcomes, such as low birthweight and preterm birth.

Our understanding of the harms of antibiotic use have greatly increased in the 40 years since the seminal trials of ASB treatment in pregnancy were conducted. The emergence of antibiotic resistant bacterium, and the rare but rising incidence of *Clostridium difficile* infection including during pregnancy,[95-97] have shifted clinical science toward a more cautious approach to antibiotic use.[92] 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 impact health.[12] In light of this shift in understanding, selection of the type of antibiotic, duration of use, and indications for prescription have become more targeted.

Newer understandings of the human microbiome and the role of bacterial colonization in maintaining health are resulting in exploratory studies on the potential impact of antibiotic treatment on protective bacterial colonization.[98-100] The urinary tract is not a sterile environment as once thought, and the potential for bacterial colonization to serve as a protective factor have led to new thinking about ASB.[12] While some cases of ASB may pose a health risk, ASB is increasingly understood to be a benign condition for some adults, depending on the characteristics of the bacteria and the host environment. The effects of antibiotic use on commensal bacterial colonization of the gut and reproductive tract have also been associated with vaginal infections and inflammatory digestive conditions for adults.[101-104] Further research

is needed to better understand whether previously unrecognized consequences of antibiotic exposure at different stages of the life span may need to be mitigated or taken into account when weighing the net benefit of ASB screening programs. Theoretical and evident harms, such as the development of antibiotic resistance and increased future infection risk from elimination of protective bacteria in the urinary tract, are of particular concern for general adult populations where health benefits from treatment have not been established.

Data on current ASB screening practices in the United States was not found, and there is likely to be variation in practice across different types of primary care settings. Further research is needed to understand current screening approaches, and the extent to which screening with culture is practiced, in accordance with the trial evidence and longstanding recommendations. ASB is commonly defined as two consecutive voided urine specimens with isolation of the same bacterial species at a count of $\geq 10^5$ CFU/mL in both. This CFU/mL cutpoint and the requirement that it be observed for a single bacterial organism was applied in most of the included studies in this review. Several also required more than one positive culture result on subsequent samples. In current clinical practice, typically only one voided specimen is obtained, and diagnosis and treatment decisions are often made without repeat sample collection and culture.

Evidence was not found that would allow us to draw conclusions about the importance of different screening threshold and diagnostic confirmation criteria for obtaining ASB treatment benefits. None of the included studies specified a lower screening threshold for ASB; for example, GBS ASB is an indicator of vaginal colonization at a lower threshold (10^4 CFU/mL) and is treated with intrapartum intravenous antibiotics to prevent newborn sepsis.[21, 105] Colonization with GBS is more commonly detected through recommended vaginal culture screening later in pregnancy.[21, 105] The available screening approaches and practices in prenatal care have changed over time since the evidence on ASB treatment in pregnancy was generated. Culture-based screening remains useful for guiding the selection of antibiotic treatment when the result is positive, which is particularly important during pregnancy due to the reduced number of safe treatment alternatives. The range of sensitivities and specificities reported above suggest that some tests (e.g., dipslide with gram staining) could be further investigated to assess whether they may achieve reasonable test performance for onsite for screening in certain settings when combined with reflex culture.

In the United States, where screening for ASB in pregnancy is a longstanding practice, pyelonephritis rates are low. A cohort study from 2005 estimated 1.4 percent incidence of pyelonephritis[6] and a more recent, large KPSC cohort study reported even lower, but rising, rates of acute pyelonephritis in pregnancy (4.6 per 1,000 births to 5.9 per 1,000 births, p for trend <.001).[7] Several risk factors associated with the condition 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. 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 risk for poor outcomes may require system- and policy-level interventions to facilitate early and regular access to prenatal health care.

Conclusions

As with previous reviews on this topic, we did not identify benefits from screening and treatment of ASB in general adult and elderly populations based on evidence that focused primarily on women. For pregnant women, evidence almost entirely from an earlier era indicated potential benefits from screening and treatment of ASB among pregnant women. Due to the historical nature of the evidence, more lenient quality rating of studies was employed to allow for changes in trial reporting standards over time. The findings are likely subject to considerable risk of bias, however, and treatment protocols used in several studies are no longer used in clinical practice. Evidence of a reduction in the risk of pyelonephritis was the most consistent and precise finding of a treatment benefit, and there was less convincing evidence that ASB treatment reduced the risk of having a low birthweight infant, and publication bias or selective reporting may have inflated the effect. Adverse reactions to medication were reported, including nausea, diarrhea and rashes, but reporting was limited. More serious harms of treatment were sparsely reported and were not statistically significant in individual studies or meta-analysis. Evidence from the only recent trial highlights a need for additional research to update the medical literature that informs ASB screening and treatment practices.

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Figure 1. Analytic Framework

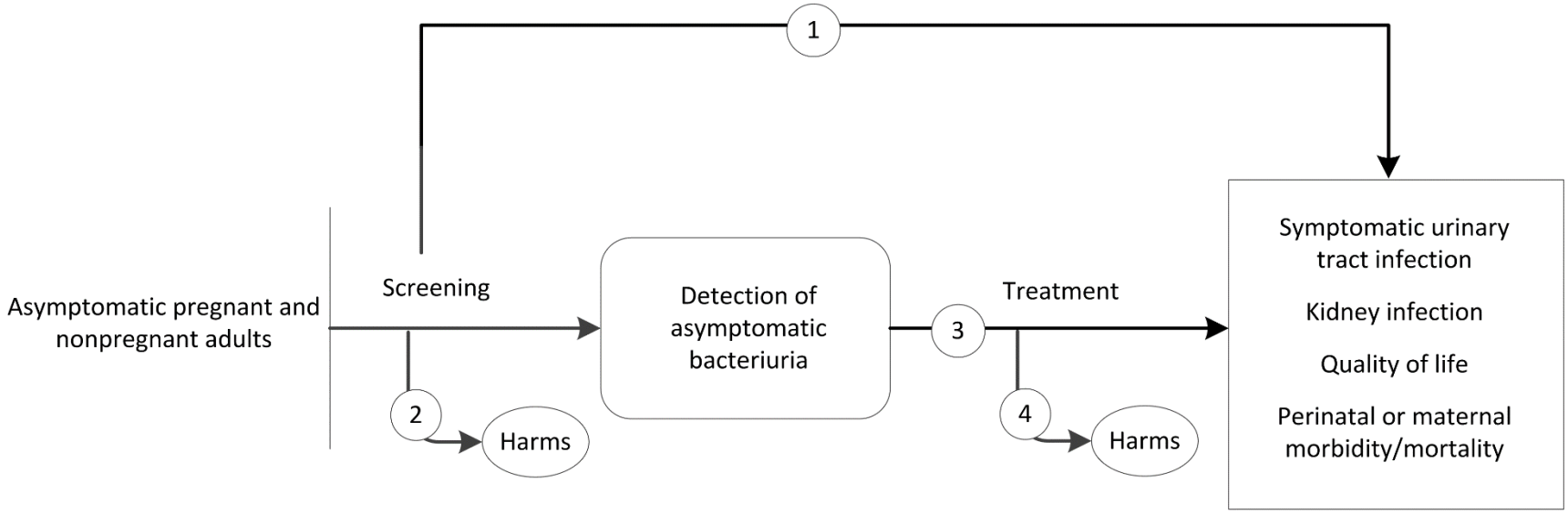
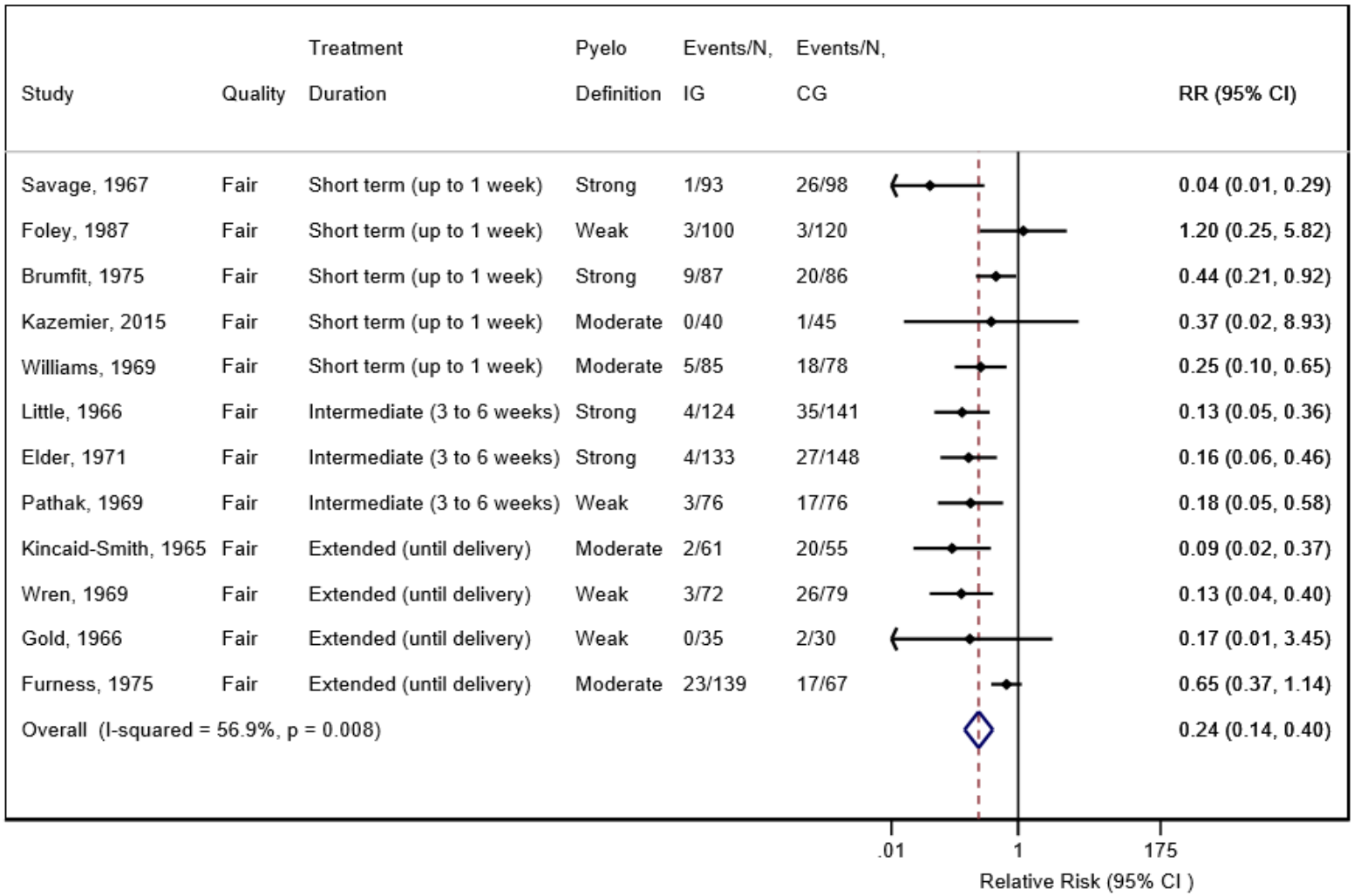
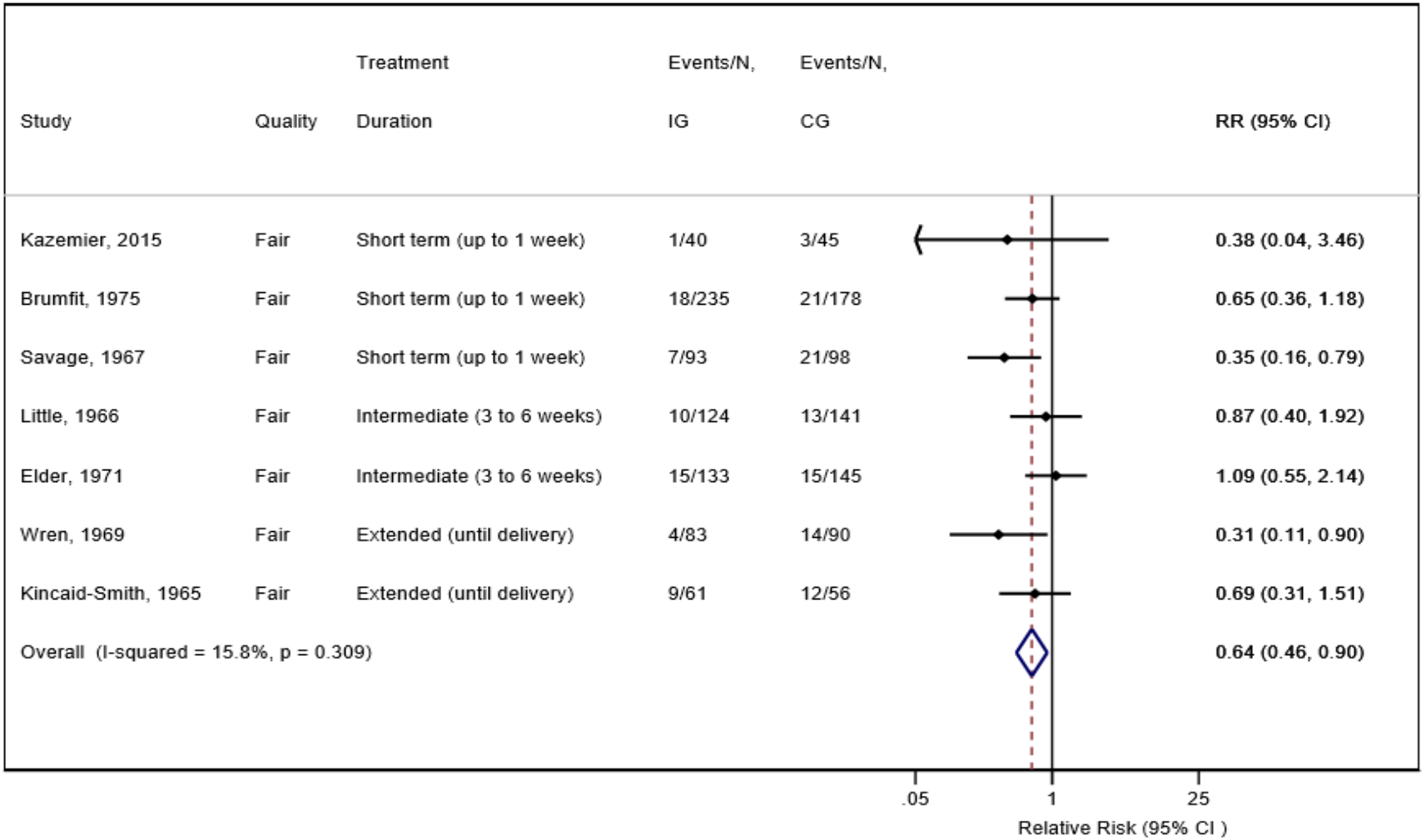


Figure 2. Pooled Analysis of Rates of Pyelonephritis Among Treated Pregnant Women Compared With Controls



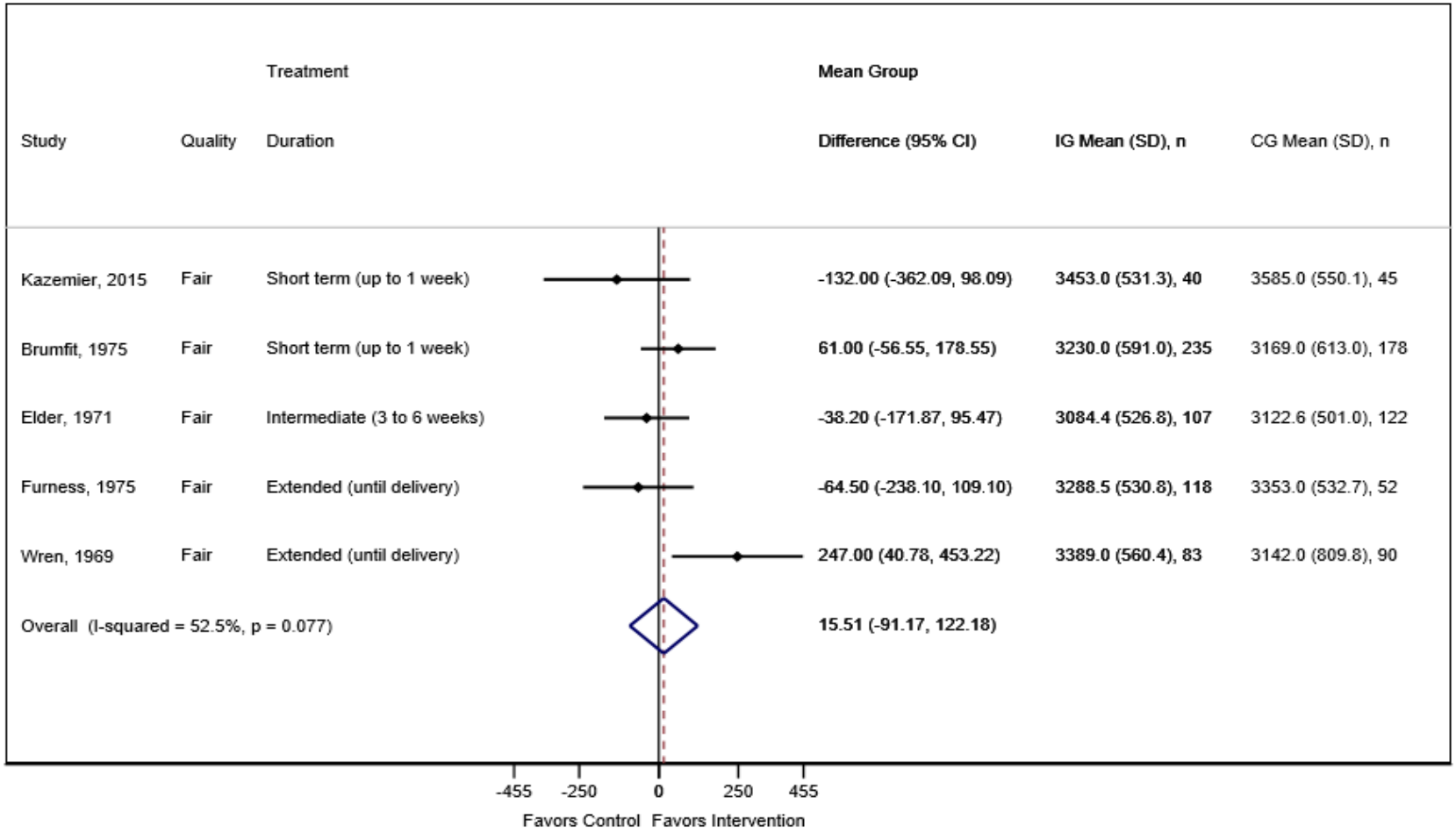
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; pyelo = pyelonephritis; RR = relative risk

Figure 3. Pooled Analysis of Rates of Low Birth Weight Among Treated Pregnant Women Compared With Controls



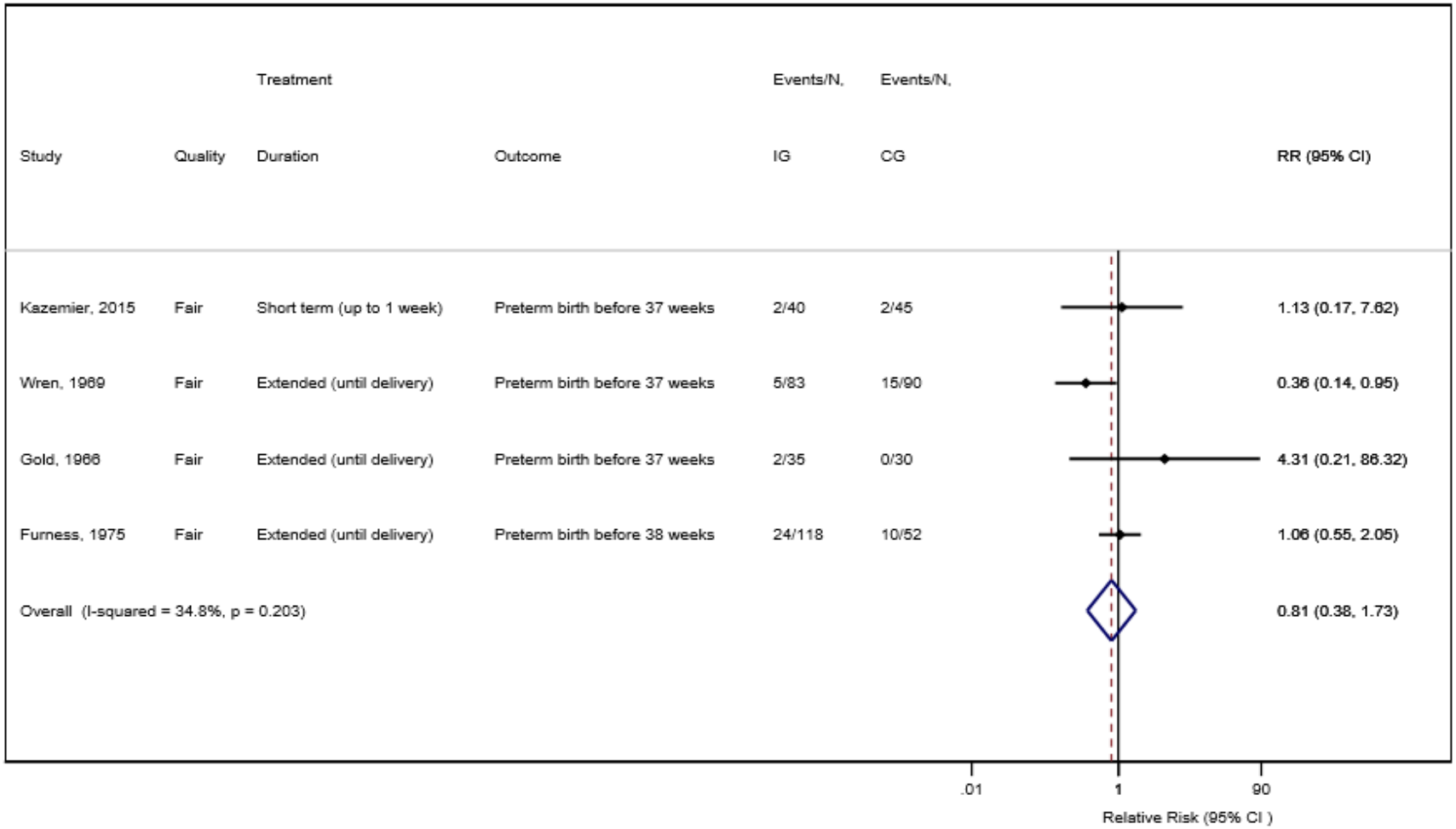
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Figure 4. Pooled Analysis of Mean Birth Weight (Grams) of Infants Born to Treated Pregnant Women Compared With Those Born to Controls



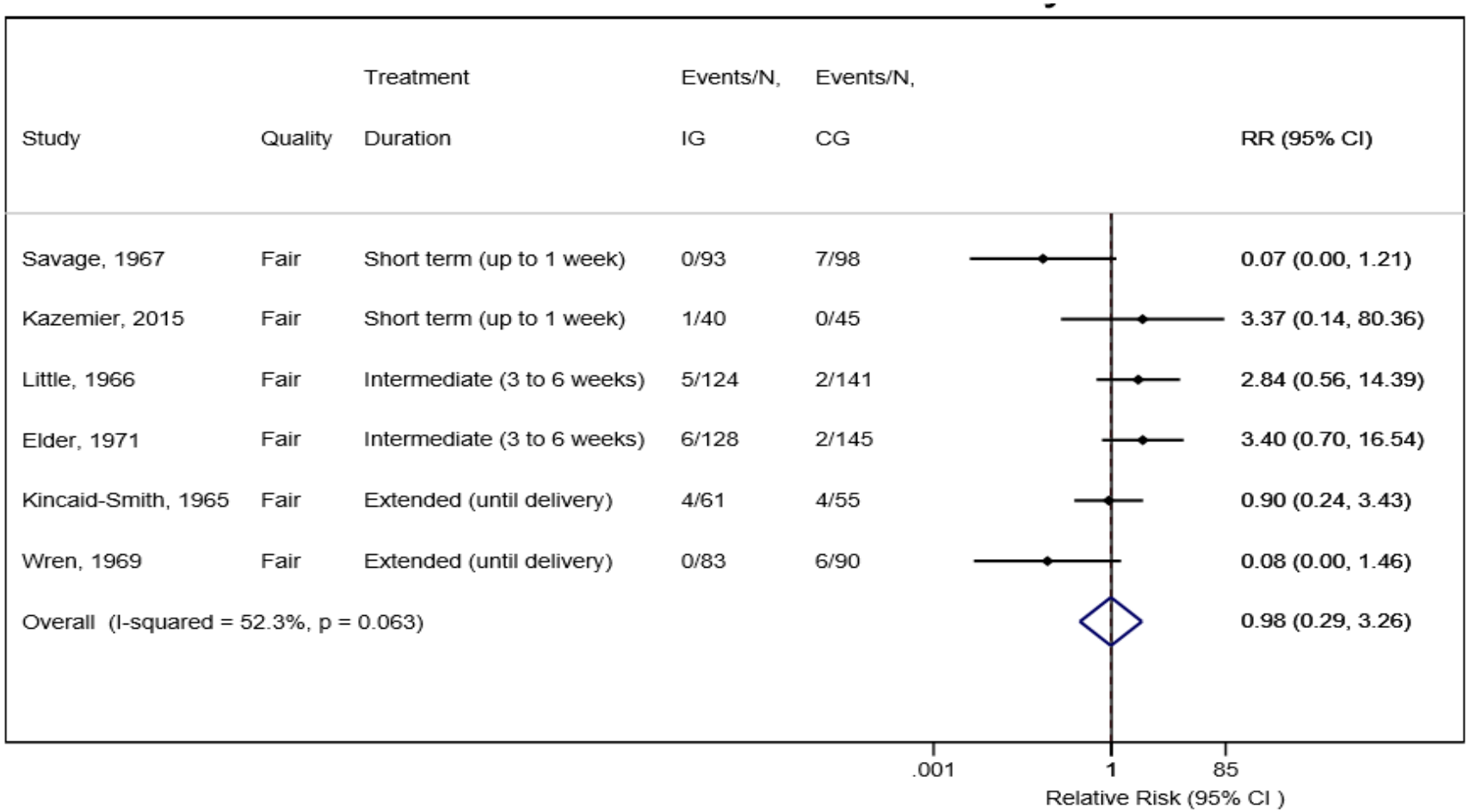
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; n = number of participants; SD = standard deviation

Figure 5. Pooled Analysis of Rates of Preterm Birth Among Treated Pregnant Women Compared With Controls



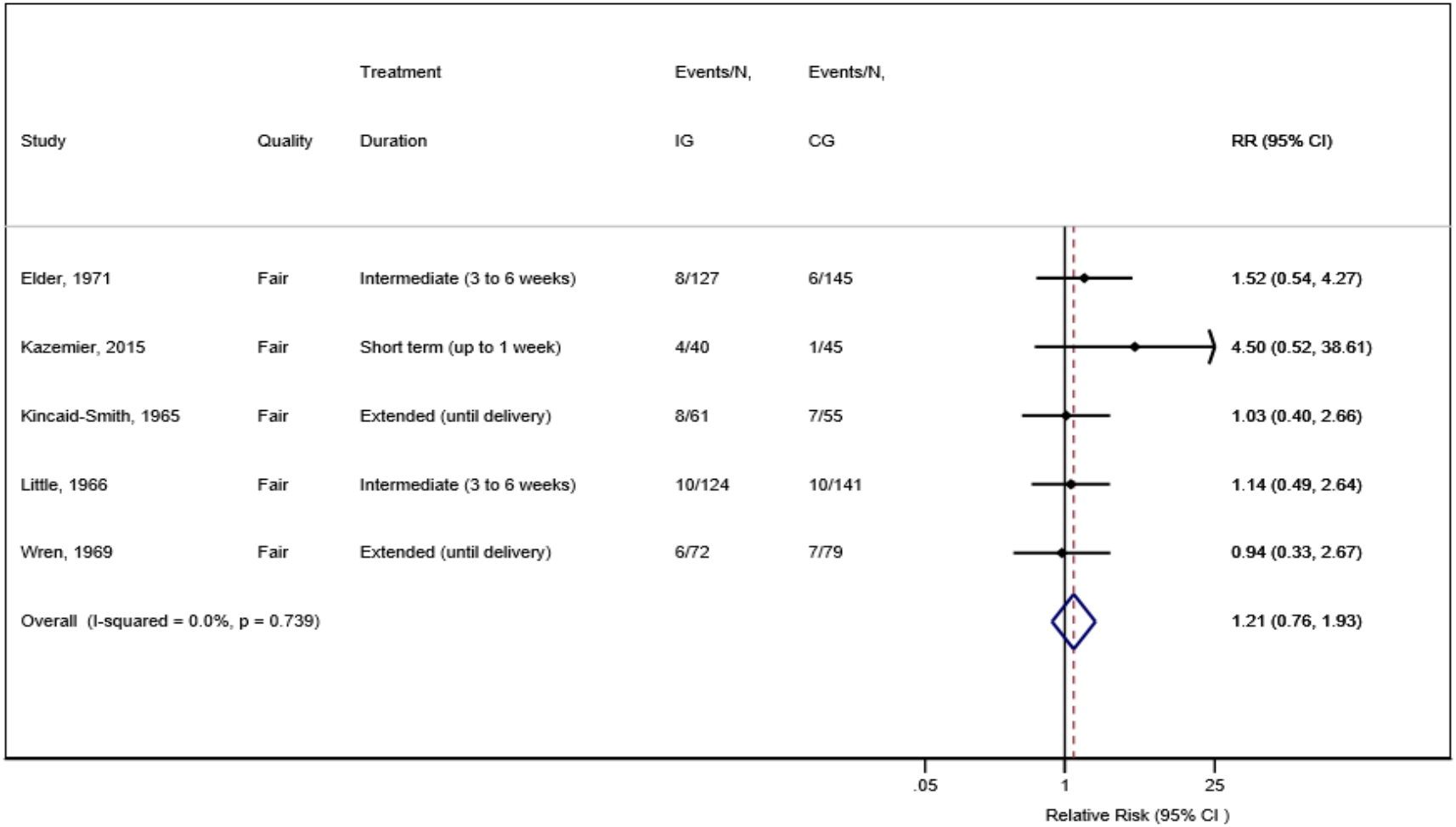
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Figure 6. Pooled Analysis of Rates of Perinatal Mortality Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls



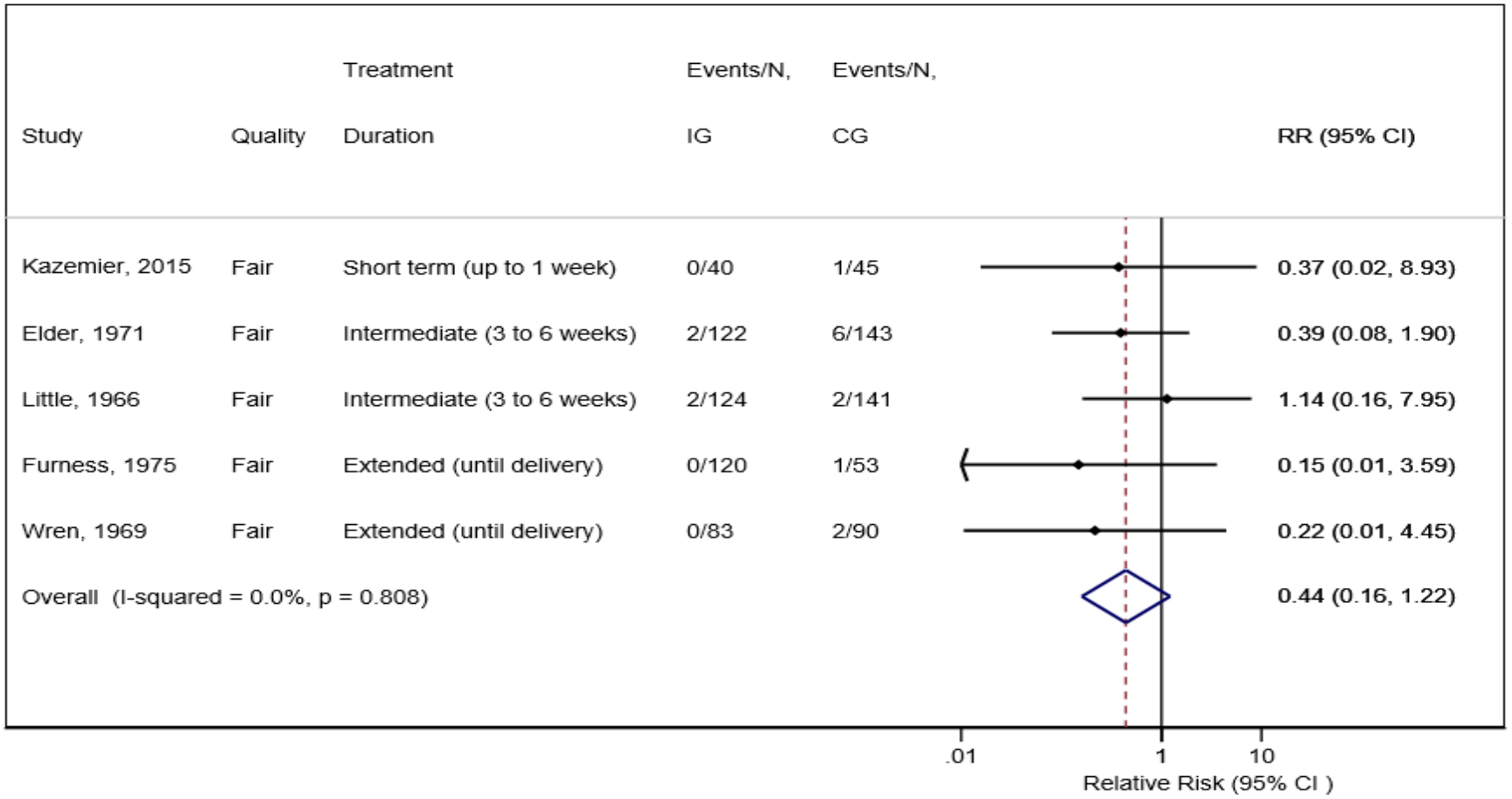
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Figure 8. Pooled Analysis of Rates of Congenital Malformations Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Figure 8. Pooled Analysis of Rates of Congenital Malformations Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Table 1. Recent Guidelines on the Screening and Treatment of Asymptomatic Bacteriuria

Organization, Year	Recommendation(s) for pregnant women	Recommendation(s) for non-pregnant adults
Infectious Diseases Society of America, 2019[3]	Screen and treat pregnant women (strong recommendation, moderate-quality evidence) In pregnant women with ASB, 4-7 days of antimicrobial treatment rather than a shorter duration is recommended (weak recommendation, low-quality evidence)	Screen for and treat ASB prior to urological procedures breaching the mucosa. Do not screen for or treat asymptomatic bacteriuria in: healthy non-pregnant women. older adults, patients with diabetes, catheterized patients, or those undergoing elective non urologic surgery.
Canadian Task Force on Preventive Health Care, 2018[106]	Screen pregnant women once during the first trimester with urine culture for ASB (weak recommendation; very low-quality evidence)	No recommendation
National Institute for Health and Care Excellence, U.K., 2018[107] (2008)[108]	Routinely screen by midstream urine culture early in pregnancy Offer an immediate antibiotic prescription to pregnant women with asymptomatic bacteriuria	Do not screen for or treat asymptomatic bacteriuria in men and non-pregnant women
European Association of Urology, 2017[31]	Short-course treatment should continue to be recommended for pregnant women, although this is challenged by the results of a recent high-quality study finding no difference in neonatal outcomes	Screen for and treat ASB prior to urological procedures breaching the mucosa.
ACOG Committee on Obstetric Practice[109] and American Academy of Pediatrics, 2017[110]	No specific screening recommendation If urine culture performed early in pregnancy, treat asymptomatic bacteriuria and do a test of cure	Screening for and treatment of asymptomatic bacteriuria is not recommended in nonpregnant, premenopausal women.
Scottish Intercollegiate Guidelines Network, 2012[111]	Treat asymptomatic bacteriuria detected during pregnancy with an antibiotic. Women with bacteriuria confirmed by a second urine culture should be treated and have repeated urine cultures at each antenatal visit until delivery Women who do not have bacteriuria in the first trimester should not have repeat urine cultures	Do not treat non-pregnant women (of any age) with asymptomatic bacteriuria with an antibiotic. Do not treat catheterized patients with asymptomatic bacteriuria with an antibiotic
American Academy of Family Physicians, 2008[112]	Screen pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit, if after that time	Do not screen for asymptomatic bacteriuria in men and nonpregnant women

Abbreviations: ABU: asymptomatic bacteriuria; ACOG: American College of Obstetricians and Gynecologists; ASB: asymptomatic bacteriuria; UK = United Kingdom; US = United States

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	QR	Population	Country	Study design	N	KQ
Gratacos, 1994[43]	Fair	Pregnant women	ESP	Cohort	4917*	KQ1
Uncu, 2002[42]	Fair	Pregnant women	TUR	Cohort	372*	KQ1,KQ2
Brumfit, 1975[58]	Fair	Pregnant women	GBR	RCT	414	KQ3
Elder, 1971[48]	Fair	Pregnant women	US	RCT	289	KQ3,KQ4
Foley, 1987[51]	Fair	Pregnant women	IRL	RCT	220	KQ3
Furness, 1975[46]	Fair	Pregnant women	AUS	RCT	206	KQ3,KQ4
Gold, 1966[57]	Fair	Pregnant women	US	RCT	65	KQ3,KQ4
Kazemier, 2015[59]	Fair	Pregnant women	NLD	RCT	85	KQ3,KQ4
Kincaid-Smith, 1965[54]	Fair	Pregnant women	AUS	RCT	116	KQ3
Little, 1966[49]	Fair	Pregnant women	GBR	RCT	265	KQ3,KQ4
Pathak, 1969[53]	Fair	Pregnant women	JAM	RCT	178	KQ3
Savage, 1967[56]	Fair	Pregnant women	US	RCT	203	KQ3,KQ4
Williams, 1969[45]	Fair	Pregnant women	GBR	RCT	163	KQ3
Wren, 1969[44]	Fair	Pregnant women	AUS	RCT	173	KQ3,KQ4
Abrutyn, 1994[52]	Fair	Older adults	US	Nonrand CCT	358	KQ3
Asscher, 1969[50]	Fair	Adults	WLS	RCT	94	KQ3,KQ4
Boscia, 1987[47]	Fair	Older adults	US	RCT	124	KQ3,KQ4
Giamarellou, 1998[60]	Fair	Older adults	GRC	RCT	96	KQ3,KQ4
Harding, 2002[55]	Good	Adults with diabetes	CAN	RCT	105	KQ3,KQ4

* Included in cohort

Abbreviations: AUS = Australia; CAN = Canada; CCT = clinical controlled trial; ESP = Spain; GBR = Great Britain; GRC = Greece; IRL = Ireland; JAM = Jamaica; KQ = Key Question; N = number of participants; NLD = Netherlands; Nonrand = nonrandomized; QR = quality rating; RCT = randomized controlled trial; TUR = Turkey; US = United States; WLS = Wales

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	Outcome	Events in Screening Cohort n/N (%)	Events in Unscreened Cohort n/N (%)	RR (95% CI)
Uncu, 2002[42]	Fetal abnormalities	3/186 (1.6%)	2/186 (1.1%)	1.5 (0.25 to 8.87)
	Hypertension	8/186 (4.3%)	18/186 (9.7%)	0.44 (0.20 to 1)
	Intrauterine death*	1/186 (0.5%)	7/186 (3.8%)	0.14 (0.02 to 1.15)
	Intrauterine growth retardation*	1/186 (0.5%)	5/186 (2.7%)	0.20 (0.02 to 1.7)†
	Prematurity*	22/186 (11.8%)	18/186 (9.7%)	1.22 (0.68 to 2.2)
	Pyelonephritis*	1/186 (0.5%)	4/186 (2.2%)	0.25 (0.03 to 2.22)†
Gratacos, 1994[43]	Pyelonephritis‡	9/1652 (0.5%)	60/3265 (1.8%)	0.30 (0.15 to 0.60)§

* Definition NR

† The study reported a statistically significant between group difference ($p \leq 0.05$), but based on the reported data and methods, it is unclear what accounted for this result

‡ Fever, flank pain, tenderness in the costovertebral angle, and positive urine culture

§ Study reported inverse calculation of RR: 3.37 (1.68 to 6.78)

Abbreviations: CI = confidence interval; n = number of events; mos = months; N = number of participants; NR = not reported; NS = not significant; RR = relative risk

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	QR	Study design	Country	Population criteria	ASB screening tool detail	ASB prevalence (N pos./N screened)	N rand	Mean age (range)	Smoker (%)	Race/ Ethnicity (%)
Brumfit, 1975[58]	Fair	RCT	GBR	Pregnant women, <32 weeks' gestation Exclusion criteria: Home delivery, abortion, treatment before confirmation of bacteriuria, other complicating factors (not specified)	Culture Cutoff: NR Detail: NR	426/20000 (2.1%)	414	26.4 (NR)	22.2	Asian: 9.7 Other: 10.6*
Elder, 1971[48]	Fair	RCT	US	Pregnant women, <32 weeks' gestation Exclusion criteria: Treated for UTI prior to the first obstetric visit, delivered or aborted after registering but before first obstetric visit, transferred prenatal care after registration	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	362/9156† (4.0%)	289	25.1 (NR)	51.6	White: 39.9 Other: 60.1
Foley, 1987[51]	Fair	RCT	IRL	Pregnant women Exclusion criteria: NR	NR Cutoff: >10^5 CFU/ml Detail: One positive test of a single organism	220/6883 (3.2%)	220	NR	NR	NR
Furness, 1975[46]	Fair	RCT	AUS	Pregnant women Exclusion criteria: NR	Dipslide Cutoff: ≥10^5 CFU/ml Detail: One positive test of a single organism	226/5256 (4.3%)	206	NR	NR	NR
Gold, 1966[57]	Fair	RCT	US	Pregnant women Exclusion criteria: Failed to return to the clinic, aborted, delivered at other hospitals, found to be not pregnant, ectopic pregnancy, transferred to other care, delivered by private physician	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	65/1281 (5.1%)	65	NR	NR	White: 9.0‡ Hisp: 6.0§ Other: 85.0‖
Kazemier, 2015[59]	Fair	RCT	NLD	Pregnant women (age ≥ 18 years), 16-22 weeks' gestation Exclusion criteria: Prior preterm birth (<34 weeks), symptoms of UTI, signs of preterm delivery, congenital malformations, antibiotic use at screening, known G6PD deficiency, allergy to nitrofuran	Dipslide Cutoff: ≥10^5 CFU/ml Detail: One positive test of a single organism	255/5132 (5.0%)	85	29¶ (NR)	8.0¶	White: 92.0¶

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	QR	Study design	Country	Population criteria	ASB screening tool detail	ASB prevalence (N pos./N screened)	N rand	Mean age (range)	Smoker (%)	Race/ Ethnicity (%)
Kincaid-Smith, 1965[54]	Fair	RCT	AUS	Pregnant women, <26 weeks' gestation Exclusion criteria: NR	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of a single organism	160/4000# (4.0%)	116	NR	NR	NR
Little, 1966[49]	Fair	RCT	GBR	Pregnant women, 12 weeks' gestation (mean) Exclusion criteria: NR	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	265/5000 (5.3%)	265	NR (10-40+)	NR	NR
Pathak, 1969[53]	Fair	RCT	JAM	Pregnant women, <24 weeks' gestation Exclusion criteria: Blood pressure >130/90 mm Hg	NR Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	217/7602 (2.9%)	178	NR	NR	NR
Savage, 1967[56]	Fair	RCT	US	Pregnant women, <32 weeks' gestation Exclusion criteria: Clinical diagnosis of chronic renal insufficiency	Culture Cutoff: >10^5 CFU/ml Detail: Three positive tests of the same organism	245/6327 (3.9%)	203	NR	NR	White: 52.0** AA: 46.0** Other: 2.0**
Williams, 1969[45]	Fair	RCT	GBR	Pregnant women, <30 weeks' gestation Exclusion criteria: NR	Culture Cutoff: >10^5 CFU/ml Detail: Two positive tests of the same organism	211/5542 (3.8%)	163	NR	NR	NR
Wren, 1969[44]	Fair	RCT	AUS	Pregnant women Exclusion criteria: NR	Culture Cutoff: NR Detail: Two positive tests of the same organism	183/3604 (5.1%)	173	NR	NR	NR

* West Indian
† Number invited
‡ Baseline characteristics for entire screened cohort "other white"
§ Puerto Rican
‖ Non-white
¶ IG only, CG age NR
# Calculated
** Estimated from figure

Abbreviations: AUS = Australia; CFU/ml = colony forming units/milliliter; GBR = Great Britain; IRL = Ireland; JAM = Jamaica; N = number of participants; NLD = Netherlands; NR = not reported; rand = randomized; pos = positive; QR = quality rating; RCT: randomized controlled trial; US: United States

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	IG	Intervention type	Intervention details	Treatment duration	CG Condition
Brumfit, 1975[58]	IG1	Antibiotic	Sulphormethoxine: 2000 mg, (1 day)*	Short term (up to 1 week)	Placebo
Elder, 1971[48]	IG1	Antibiotic	Tetracycline: 250 mg, qid (6 weeks)	Intermediate (3 to 6 weeks)	Placebo
Foley, 1987[51]	IG1	Antibiotic	Sulphamethizole or Nitrofuratoin: NR†	Short term (up to 1 week)	No Treatment
Furness, 1975[46]	IG1	Urinary antiseptic	Methenamine hippurate (Hiprex): 1000 mg, bid (until delivery)	Duration of pregnancy	No Treatment
	IG2	Urinary antiseptic	Methenamine mandelate (Mandelamine): 1000 mg, qid (throughout pregnancy)	Duration of pregnancy	No Treatment
Gold, 1966[57]	IG1	Antibiotics (sequential)	Sulfadimethoxine: 500 mg, qd (through week 36)* Sulfadiazine: 1000 mg, tid (weeks 36 through delivery)	Duration of pregnancy	Placebo
Kazemier, 2015[59]	IG1	Antibiotic	Nitrofurantoin: 100 mg, bid (5 days)	Short term (up to 1 week)	Placebo
Kincaid-Smith, 1965[54]	IG1	Antibiotics (sequential)	Sulphamethoxydiazine: 500 mg (through week 30 of pregnancy)* Sulphadimidine: 1000 mg, tid (week 30 through delivery)	Duration of pregnancy	Placebo
Little, 1966[49]	IG1	Antibiotic	Sulphamethoxypyridazine (sulphonamide): 500 mg, qd (30 days)‡	Intermediate (3 to 6 weeks)	Placebo
Pathak, 1969[53]	IG1	Antibiotic	Nitrofuratoin: 100 mg, bid (3 weeks)	Intermediate (3 to 6 weeks)	Placebo
Savage, 1967[56]	IG1	Antibiotic	Sulfamethoxypyridazine: 500 mg, qd (1 week)	Short term (up to 1 week)	Placebo
Williams, 1969[45]	IG1	Antibiotic	Sulphadimidine: 1000 mg, tid (7 days)	Short term (up to 1 week)	No Treatment
Wren, 1969[44]	IG1	Antibiotics (sequential)	9 week treatment rotation until 1 to 6 weeks postpartum: Nitrofurantoin: 100 mg, bid (2 weeks); Ampicillin: 250 mg qid (1 week); Sulphurazole: 500 mg, qid (4 weeks); Nalidixic acid: 500 mg, qid (2 weeks)	Duration of pregnancy	No Treatment

* Dosing frequency NR
† Starting in 1981, treatment reduced over 6 years from sulphamethizole 600 mg or nitrofurantoin 300 mg TID for 14 days to sulphamethizole 300 mg and nitrofurantoin 150 mg for three days. Trial in 1985
‡ Primary treatment was changed from sulphamethoxypridazine to nitrofurantoin part way through trial, 44 participants treated with nitrofurantoin 100 mg, qd first line

Abbreviations: bid = two times per day; CG = control group; IG = intervention group; mg = milligram; NR = not reported; qd = once per day; qid = four times per day; tid = three times per day

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	QR	Study design	Country	FU (mos)	Population criteria	ASB screening tool detail	ASB prevalence (N positive/ N screened)	N rand	Mean age (range)	Female (%)
Abrutyn, 1994[52]	Fair	Nonrand CCT	US	100	Women (mean age: 81.9 years) Exclusion criteria: Indwelling catheters or those incapable of providing mid-stream clean-catch urine specimens	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	NR	358	81.9 (NR)	100
Asscher, 1969[50]	Fair	RCT	WLS	12	Women (age 20-65 years) Exclusion criteria: Diabetes, pregnant women, presence of urinary symptoms	Culture Cutoff: >10^5 CFU/ml Detail: Two positive tests of the same organism	107/3578 (3.0%)	94	NR (20-65)	100
Boscia, 1987[47]	Fair	RCT	US	6	Women (age ≥65 years) Exclusion criteria: Indwelling bladder catheter or incapable of giving a midstream clean-catch urine specimen	Culture Cutoff: >10^5 Detail: Two positive tests of the same organism	124/603 (20.6%)	124	85.8 (70-100)	100
Giamarellou, 1998[60]	Fair	RCT	GRC	6	Older adults (age ≥65 years) Exclusion criteria: Required help for activities of daily living, major musculoskeletal problems, incontinence, bladder cauterization, recent manipulations of the urinary tract, renal failure, (i.e. serum creatinine >2.0 m	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism within 1 week	106/455 (23.3%)	96	83.3 (NR)	83.9
Harding, 2002[55]	Good	RCT	CAN	36	Women with diabetes (age >16 years) Exclusion criteria: Pregnant women, serum creatinine level >2.25 mg/dL, or could not return for regular follow-up	Culture Cutoff: ≥10^5 CFU/ml Detail: Two positive tests of the same organism	135/1900 (7.1%)	105	55.3 (NR)	100

Abbreviations: CAN = Canada; CCT = clinical controlled trial; CFU/ml = colony forming units/milliliter; FU = followup; GRC = Greece; mg/dL = milligram/deciliter; mos = months; N = number of participants; NR = not reported; QR = quality rating; RCT = randomized controlled trial; US = United States; WLS = Wales

Table 7. Intervention Descriptions for Included Studies of Treatment for Asymptomatic Bacteriuria in General Adult Populations (k=5)

Author, Year	IG	Antibiotic details	CG Condition
Abrutyn, 1994[52]	IG1	Varied, based on susceptibility (single dose to 3 days)*	Placebo
Asscher, 1969[50]	IG1	Nitrofurantoin: 50 mg, qid (1 week)	Placebo
Boscia, 1987[47]	IG1	Trimethoprim: 200 mg, qd (1 day)	No Treatment
Giamarellou, 1998[60]	IG1	Ofloxacin: 200 mg, bid (3 days); 200 mg, qd (3 months)	No Treatment
	IG2	Ofloxacin: 200 mg, bid (3 days every other week for 3 months)	No Treatment
Harding, 2002[55]	IG1	Trimethoprim-Sulfamethoxazole: 160/800 mg, bid (2 weeks)	Placebo

*****Treatment was selected based on susceptibility and history of drug allergy: trimethoprim, 200 mg, single dose; trimethoprim-sulfamethoxazole, 160mg/800mg, single dose; cefaclor, 500 mg, TID for 3 days; amoxicillin, 250 mg, TID for 3 days; carbenicllin indanyl sodium, dosage NR, QID for 3 days; macrodantin, 100 mg, BID for 3 days; or norfloxacin, 400 mg, single dose

Abbreviations: bid = two times per day; CG = control group; IG = intervention group; mg = milligram; NR = not reported; qd = once per day; qid = four times per day; tid = three times per day

Table 8. Results of Treatment for Asymptomatic Bacteriuria on Symptomatic Infections in General Adult Populations (k=4)

Pop	Author, Year	FU (mos)	Outcome	Description	IG	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Adults	Asscher, 1969[50]	12	Symptomatic UTI/Pyelonephritis	Complained of frequency and dysuria lasting 24 hr or more, or if she developed loin pain and fever	IG1	18/49 (36.7%)	16/45 (35.6%)	1.03 (0.60 to 1.77)
Adults with diabetes	Harding, 2002[55]	1.5	Treated for symptomatic infection		IG1	1/49 (2.0%)	2/50 (4.0%)	0.51 (0.05 to 5.45)
		36	Pyelonephritis	The presence of costovertebral-angle pain or tenderness and a positive urine culture (≥10^4 CFU of a urinary pathogen per ml) with or without systemic symptoms such as fever	IG1	0.13 per 1000 days	0.28 per 1000 days	0.47 (0.18 to 1.23)*
			Renal failure	Clinically significant renal failure	IG1	2/55 (3.6%)	2/50 (4.0%)	0.91 (0.13 to 6.21)
			Symptomatic UTI	Acute onset of symptoms of irritation of the lower tract, such as dysuria, urgency, and frequency, in the absence of fever or costovertebral-angle pain or tenderness, and in the presence of a positive urine culture (≥10^3 CFU of a urinary pathogen/ml)	IG1	0.80 per 1000 days	0.83 per 1000 days	0.97 (0.61 to 1.54)†
Older adults	Giamarellou, 1998[60]	6	Sepsis or shock	NR	IG1	0/32 (0.0%)	0/29 (0.0%)	NA
					IG2	0/32 (0.0%)	0/29 (0.0%)	NA
Older adults	Boscia, 1987[47]	6	Symptomatic UTI/Pyelonephritis	Symptoms of urinary tract infection (dysuria, urgency, frequency, suprapubic pain, flank pain, and fever)	IG1	5/63 (7.9%)	10/61 (16.4%)	0.48 (0.18 to 1.33)
		6	Treated for symptomatic infection	Antimicrobial therapy during the 6-month FU for symptomatic UTI infection	IG1	4/55 (7.3%)	8/55 (14.5%)	0.50 (0.16 to 1.56)

* Study reported inverse calculation of RR 2.13 (95% CI 0.81 to 5.62)
† Study reported inverse calculation of RR 1.03 (95% CI 0.65 to 1.65)

Abbreviations: CFU = colony forming units; CG = control group; CI = confidence interval; FU = followup; hr = hour; IG = intervention group; Int = intervention; ml = milliliter; n = number of events; N = number of participants; mos = months; N = number of participants; NR = not reported; NS = not significant; Pop = Population; RR = relative risk; UTI = urinary tract infection

Table 9. Results of Treatment for Asymptomatic Bacteriuria on Mortality in General Adult Populations (k=3)

Author, Year	FU (mos)	Int arm	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Boscia, 1987[47]	6	IG1	2/63 (3.2%)	3/61 (4.9%)	0.65 (0.11 to 3.73)
Giamarellou, 1998[60]	6	IG1	2/32 (6.3%)	2/29 (6.9%)	0.91 (0.14 to 6.03)
		IG2	0/32 (0.0%)	2/29 (6.9%)	0.18 (0.01 to 3.64)
Abrutyn, 1994[52]	100	IG1	30/166 (18.1%)	39/192 (20.3%)	0.92 (0.5 to 1.47)*

*Hazard ratio, calculated RR: 0.89 (0.58 to 1.37)

Abbreviations: CG = control group; CI = confidence interval; FU = followup; IG = intervention group; Int = intervention; n = number of events; mos = months; N = number of participants; NR = not reported; RR = relative risk

Table 10. Results of Treatment for Asymptomatic Bacteriuria in Pregnant Women on Maternal and Infant Complications (k=3)

Author, Year	Outcome	Description	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Elder, 1971[48]	Induced labor	Cesarean section performed before the onset of labor	19/133 (14.3%)	21/145 (14.5%)	0.99 (0.56 to 1.75)
	Jaundice	Neonatal jaundice noted during in the first 24 hours	5/126 (4.0%)	4/144 (2.8%)	1.43 (0.39 to 5.2)
	Other infant complications	NR	3/126 (2.4%)	8/144 (5.6%)	0.43 (0.12 to 1.58)
	Other maternal complications	NR	11/127 (8.7%)	21/145 (14.5%)	0.60 (0.30 to 1.19)
	Premature rupture of the membranes	Rupture occurred ≥12 hours before the onset of labor	14/127 (11.0%)	12/145 (8.3%)	1.33 (0.64 to 2.77)
	Respiratory distress	Respiratory distress syndrome and other causes of respiratory embarrassment	6/126 (4.8%)	4/144 (2.8%)	1.71 (0.49 to 5.94)
	Third-trimester hemorrhage		4/127 (3.1%)	4/145 (2.8%)	1.14 (0.29 to 4.47)
Gold, 1966[57]	Jaundice	NR	0/35 (0.0%)	0/30 (0.0%)	NA
Kazemier, 2015[59]	Composite severe morbidity	Respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, bronchopulmonary disease, sepsis	0/40 (0.0%)	2/45 (4.4%)	0.22 (0.01 to 4.54)*
	Neonatal sepsis confirmed with culture		0/40 (0.0%)	2/45 (4.4%)	0.22 (0.01 to 4.54)*
	Non-spontaneous onset of labor		13/40 (32.5%)	13/45 (28.9%)	1.13 (0.59 to 2.13)†
	Thrombo-embolic events		0/40 (0.0%)	0/45 (0.0%)	NA‡

* Study reported risk difference: -4.4 (-25.5 to 16.8)
† Study reported risk difference: 3.6 (-17.8 to 24.8)
‡ Study reported risk difference: 0 (-9.4 to 10.5)

Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; n = number of events; mos = months; N = number of participants; NR = not reported; RR = relative risk

Table 11. Summary of Evidence

Key Question	(Populations or Interventions)	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Screening effectiveness	Pregnant women	k=2 (n=5,289) Retrospective cohort studies Fair quality	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 one 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 two fair-quality cohort studies	One study conducted in a hospital in Spain 24 years ago and another in Turkey 16 years ago – may not be entirely applicable to current U.S. hospital settings and populations.
	General adult populations	k=0	NA	NA	NA	NA	NA
KQ2: Screening harms	Pregnant women	k=1 (n=372) Retrospective cohort study Fair quality	No harms of screening were identified. Number of congenital abnormalities similar between groups and none in screen-positive women.	Consistency NA Imprecise due to small n, few events	Limited reporting on potential harms of screening and treatment, low n for detecting rare harms.	Insufficient for the absence of screening harms based on one fair-quality cohort study	Small study conducted in Turkey 16 years ago – may not be entirely applicable to current U.S. hospital settings and populations
	General adult populations	k=0	NA	NA	NA	NA	NA

Table 11. Summary of Evidence

Key Question	(Populations or Interventions)	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ3: Treatment effectiveness	Pregnant women	k=12 RCTS (n=2,369)	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 to 0.41], k=12, n = 2,068) and low birthweight infants (8.3% vs 13.1%; pooled RR, 0.64 [95% CI, 0.46 to 0.90], k=7, n =1,522). 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 birthweight Imprecise and inconsistent for other perinatal outcomes, including perinatal mortality, mean birthweight, 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 birthweight from 7 fair-quality studies (including 3 with high risk of bias)	Most studies conducted over 40 years 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	k=5 (n=777) 4 RCTs, 1 nonrandomized CCT	Mortality: 3 trials in older adults found no difference in mortality over 6 to 100 months followup. Mobility: 1 trial in older adults found no effect on mobility at 6 months. 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 months.	Lack of reporting of population characteristics. Some studies lacked reporting on randomization, allocation, and outcome assessment.	Low	Evidence primarily applies to women (84-100% female in each study) Three studies limited to older adults (2 of 3 limited to older women) One study limited to women with diabetes

Table 11. Summary of Evidence

Key Question	(Populations or Interventions)	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ4: Treatment harms	Pregnant women	k=7 (n=1,286)	Five studies reported congenital malformations with effect in direction of benefit, but null. All other outcomes sparsely reported and did not provide evidence of 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 over 40 years ago, and many of the treatment protocols and medications are no longer used in clinical practice
	General adult populations	k=4 (n=419) 4 RCTs	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 arm.	Inconsistent Imprecise	Limited data reporting. Unclear reporting bias	Insufficient	Evidence is limited to mostly women (84-100% female in each study).

Abbreviations: CCT = clinical controlled trial; KQ = Key Question; NA = not applicable; RCT = randomized controlled trial

Appendix A. Literature Searches

Screening for asymptomatic bacteriuria | Search strategies
Smyth Lai, 12/5/2017

Sources searched:
Cochrane Central Register of Controlled Clinical Trials, via Wiley
MEDLINE, via Ovid
PubMed, publisher-supplied

Key:
/ = MeSH subject heading
* = truncation
* preceding a word = major focus
ab = word in abstract
exp = explode
fs = MeSH subheading
kf = keyword heading [word not phrase indexed]
kw = keyword
md = methodology
mp = mapping alias (searches within: Title (TI), Abstract (AB), Subject Headings Word (HW), Table of Contents Titles/Headings (TC), Original Title (OT), Test & Measures (TM), and Key Phrase Identifiers (ID) fields)
pt = publication type
ti = word in title

Cochrane Central Register of Controlled Trials : Issue 11 of 12, November 2017

#1 (bacilluria* or bacteriuria*):ti,ab,kw 932
#2 (asymptomatic* or nonsymptomatic or non-symptomatic):ti,ab,kw 7537
#3 (without or no or absence or absent):ti,ab,kw near/3 symptom*:ti,ab,kw 5096
#4 #2 or #3 12333
#5 (bacteria or infection*):ti,ab,kw and (bladder* or kidney* or urin* or genitourin* or urogenita*):ti,ab,kw 12374
#6 #4 and #5 448
#7 (colonization or colonisation):ti,ab,kw and (bladder* or kidney* or urin* or genitourin* or urogenita*):ti,ab,kw 175
#8 #1 or #6 or #7 in Trials 1292

MEDLINE
Database: Ovid MEDLINE(R) <1946 to November Week 4 2017>, Ovid MEDLINE(R) Epub Ahead of Print <December 04, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 04, 2017>, Ovid MEDLINE(R) Daily Update <December 04, 2017>

Screening trials, non-pregnant adults

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/

5. (asymptomatic or nonsymptomatic or non symptomatic or ((without or no or absence or absent) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Mass screening/
14. Antibody-Coated Bacteria Test, Urinary/
15. Microbial Sensitivity Tests/
16. Microscopy/
17. Reagent Kits, Diagnostic/
18. Reagent Strips/
19. Urinalysis/
20. Predictive Value of Tests/
21. "Sensitivity and Specificity"/
22. (detect* or predict* or screen*).ti,ab,kf.
23. (microb* adj2 test*).ti,ab,kf.
24. (micro-scopy or microscopy).ti,ab,kf.
25. culture*.ti,ab,kf.
26. (dip slide* or dipslide* or dip stick* or dipstick*).ti,ab,kf.
27. ((re-agent* or reagent) adj3 (strip* or test*)).ti,ab,kf.
28. strip* test*.ti,ab,kf.
29. urine test*.ti,ab,kf.
30. (urinalys* or urine analys*).ti,ab,kf.
31. ((accurac* or diagnostic) adj5 (algorithm* or test*)).ti,ab,kf.
32. diagnostic accurac*.ti,ab,kf.
33. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 12 and 33
35. *Bacteriuria/di, pc, mi, ur [Diagnosis, Prevention & Control, Microbiology, Urine]
36. 34 or 35
37. clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
38. (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
39. Random*.ti,ab.
40. control groups/ or double-blind method/ or single-blind method/
41. clinical trial*.ti,ab.
42. controlled trial*.ti,ab.
43. meta analy*.ti,ab.
44. 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 36 and 44
46. Animals/ not (Humans/ and Animals/)
47. 45 not 46
48. limit 47 to english language

49. remove duplicates from 48

Screening, pregnant women

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/
5. (asymptomatic or nonsymptomatic or non symptomatic or ((without or no or absence or absent) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Mass screening/
14. Antibody-Coated Bacteria Test, Urinary/
15. Microbial Sensitivity Tests/
16. Microscopy/
17. Reagent Kits, Diagnostic/
18. Reagent Strips/
19. Urinalysis/
20. Predictive Value of Tests/
21. "Sensitivity and Specificity"/
22. (detect* or predict* or screen*).ti,ab,kf.
23. (microb* adj2 test*).ti,ab,kf.
24. (micro-scopy or microscopy).ti,ab,kf.
25. culture*.ti,ab,kf.
26. (dip slide* or dipslide* or dip stick* or dipstick*).ti,ab,kf.
27. ((re-agent* or reagent) adj3 (strip* or test*)).ti,ab,kf.
28. strip* test*.ti,ab,kf.
29. urine test*.ti,ab,kf.
30. (urinalys* or urine analys*).ti,ab,kf.
31. ((accurac* or diagnostic) adj5 (algorithm* or test*)).ti,ab,kf.
32. diagnostic accurac*.ti,ab,kf.
33. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 12 and 33
35. *Bacteriuria/di, pc, mi, ur [Diagnosis, Prevention & Control, Microbiology, Urine]
36. 34 or 35
37. exp Pregnancy/
38. Pregnancy complications, infectious/
39. Pregnant women/
40. Prenatal care/
41. Prenatal diagnosis/

42. Perinatal care/
43. Peripartum period/
44. Maternal Health Services/
45. pregnan*.ti,ab,kf.
46. prenatal.ti,ab,kf.
47. pre natal.ti,ab,kf.
48. perinatal.ti,ab,kf.
49. peri natal.ti,ab,kf.
50. antenatal.ti,ab,kf.
51. ante natal.ti,ab,kf.
52. antepartum.ti,ab,kf.
53. ante partum.ti,ab,kf.
54. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 36 and 54
56. Animals/ not (Humans/ and Animals/)
57. 55 not 56
58. limit 57 to english language
59. remove duplicates from 58

Screening harms

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/
5. (asymptomatic or nonsymptomatic or non symptomatic or ((without or no or absence or absent) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Mass screening/
14. Antibody-Coated Bacteria Test, Urinary/
15. Microbial Sensitivity Tests/
16. Microscopy/
17. Reagent Kits, Diagnostic/
18. Reagent Strips/
19. Urinalysis/
20. Predictive Value of Tests/
21. "Sensitivity and Specificity"/
22. (detect* or predict* or screen*).ti,ab,kf.
23. (microb* adj2 test*).ti,ab,kf.
24. (micro-scopy or microscopy).ti,ab,kf.
25. culture*.ti,ab,kf.

26. (dip slide* or dipslide* or dip stick* or dipstick*).ti,ab,kf.
27. ((re-agent* or reagent) adj3 (strip* or test*)).ti,ab,kf.
28. strip* test*.ti,ab,kf.
29. urine test*.ti,ab,kf.
30. (urinalys* or urine analys*).ti,ab,kf.
31. ((accurac* or diagnostic) adj5 (algorithm* or test*)).ti,ab,kf.
32. diagnostic accurac*.ti,ab,kf.
33. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 12 and 33
35. *Bacteriuria/di, pc, mi, ur [Diagnosis, Prevention & Control, Microbiology, Urine]
36. 34 or 35
37. Mortality/
38. Morbidity/
39. Death/
40. safety.ti,ab,kf.
41. harm*.ti,ab,kf.
42. mortality.ti,ab,kf.
43. complication*.ti,ab,kf.
44. (death or deaths).ti,ab,kf.
45. (adverse adj2 (interaction* or response* or effect* or event* or reaction* or outcome*)).ti,ab,kf.
46. adverse effects.fs.
47. mortality.fs.
48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 36 and 48
50. Animals/ not (Humans/ and Animals/)
51. 49 not 50
52. limit 51 to english language
53. remove duplicates from 52

Treatment trials, non-pregnant adults

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/
5. (asymptomatic or nonsymptomatic or non symptomatic or ((without or no or absence or absent) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Anti-Bacterial Agents/
14. Antibiotic Prophylaxis/

15. Anti-Infective Agents, Urinary/
16. Drug Therapy, Combination/
17. Norfloxacin/
18. exp Penicillins/
19. exp Sulfonamides/
20. amoxicillin*.mp.
21. ampicillin*.mp.
22. (anti-bacteria* or antibacteria*).ti,ab,kf.
23. (anti-biotic* or antibiotic*).ti,ab,kf.
24. aztreonam*.mp.
25. cefadroxil*.mp.
26. cefepime*.mp.
27. ceftibuten*.mp.
28. ceftri?xone*.mp.
29. cefuroxime*.mp.
30. cephalexin*.mp.
31. cephalosporin*.mp.
32. cephradine*.mp.
33. clindamycin*.mp.
34. (co-trimoxazole* or cotrimoxazole*).mp.
35. cycloserine*.mp.
36. fosfomycin*.mp.
37. gentam#cin*.mp.
38. nalidixic acid*.mp.
39. nitrofurantoin*.mp.
40. penicillin*.mp.
41. piperacillin*.mp.
42. pivampicillin*.mp.
43. pivmecillinam*.mp.
44. sulfadimethoxine*.mp.
45. sulfadiazine*.mp.
46. sulfamethizole*.mp.
47. sulfamethoxazole*.mp.
48. sulfamethoxypyridazine*.mp.
49. sulfonamide*.mp.
50. sulphadimidine*.mp.
51. sulphonamide*.mp.
52. tetracycline*.mp.
53. vancomycin*.mp.
54. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 12 and 54
56. *Bacteriuria/dt, th [Drug therapy, Therapy]
57. 55 or 56
58. clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
59. (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.

60. Random*.ti,ab.
61. control groups/ or double-blind method/ or single-blind method/
62. clinical trial*.ti,ab.
63. controlled trial*.ti,ab.
64. meta analy*.ti,ab.
65. 58 or 59 or 60 or 61 or 62 or 63 or 64
66. 57 and 65
67. Animals/ not (Humans/ and Animals/)
68. 66 not 67
69. limit 68 to english language
70. remove duplicates from 69

Treatment, pregnant women

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/
5. (asymptomatic or nonsymptomatic or non symptomatic or ((without or no or absence or absent) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Anti-Bacterial Agents/
14. Antibiotic Prophylaxis/
15. Anti-Infective Agents, Urinary/
16. Drug Therapy, Combination/
17. Norfloxacin/
18. exp Penicillins/
19. exp Sulfonamides/
20. amoxicillin*.mp.
21. ampicillin*.mp.
22. (anti-bacteria* or antibacteria*).ti,ab,kf.
23. (anti-biotic* or antibiotic*).ti,ab,kf.
24. aztreonam*.mp.
25. cefadroxil*.mp.
26. cefepime*.mp.
27. ceftibuten*.mp.
28. ceftri?xone*.mp.
29. cefuroxime*.mp.
30. cephalexin*.mp.
31. cephalosporin*.mp.
32. cephradine*.mp.

33. clindamycin*.mp.
34. (co-trimoxazole* or cotrimoxazole*).mp.
35. cycloserine*.mp.
36. fosfomycin*.mp.
37. gentam#cin*.mp.
38. nalidixic acid*.mp.
39. nitrofurantoin*.mp.
40. penicillin*.mp.
41. piperacillin*.mp.
42. pivampicillin*.mp.
43. pivmecillinam*.mp.
44. sulfadimethoxine*.mp.
45. sulfadiazine*.mp.
46. sulfamethizole*.mp.
47. sulfamethoxazole*.mp.
48. sulfamethoxypyridazine*.mp.
49. sulfonamide*.mp.
50. sulphadimidine*.mp.
51. sulphonamide*.mp.
52. tetracycline*.mp.
53. vancomycin*.mp.
54. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 12 and 54
56. *Bacteriuria/dt, th
57. 55 or 56
58. exp Pregnancy/
59. Pregnancy complications, infectious/
60. Pregnant women/
61. Prenatal care/
62. Prenatal diagnosis/
63. Perinatal care/
64. Peripartum period/
65. Maternal Health Services/
66. pregnan*.ti,ab,kf.
67. prenatal.ti,ab,kf.
68. pre natal.ti,ab,kf.
69. perinatal.ti,ab,kf.
70. peri natal.ti,ab,kf.
71. antenatal.ti,ab,kf.
72. ante natal.ti,ab,kf.
73. antepartum.ti,ab,kf.
74. ante partum.ti,ab,kf.
75. 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. 57 and 75
77. Animals/ not (Humans/ and Animals/)
78. 76 not 77

79. limit 78 to english language
80. remove duplicates from 79

Treatment harms

1. Bacteriuria/
2. bacilluria*.ti,ab,kf.
3. bacteriuria*.ti,ab,kf.
4. Asymptomatic Infections/
5. (asymptomatic or ((without or no) adj3 symptom*)).ti,ab,kf.
6. 4 or 5
7. Urinary Tract Infections/
8. ((bacteria or infection*) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
9. 7 or 8
10. 6 and 9
11. ((colonization or colonisation) and (bladder* or kidney* or urin* or genitourin* or urogenita*)).ti,ab,kf.
12. 1 or 2 or 3 or 10 or 11
13. Anti-Bacterial Agents/
14. Antibiotic Prophylaxis/
15. Anti-Infective Agents, Urinary/
16. Drug Therapy, Combination/
17. Norfloxacin/
18. exp Penicillins/
19. exp Sulfonamides/
20. amoxicillin*.mp.
21. ampicillin*.mp.
22. (anti-bacteria* or antibacteria*).ti,ab,kf.
23. (anti-biotic* or antibiotic*).ti,ab,kf.
24. aztreonam*.mp.
25. cefadroxil*.mp.
26. cefepime*.mp.
27. ceftibuten*.mp.
28. ceftri?xone*.mp.
29. cefuroxime*.mp.
30. cephalexin*.mp.
31. cephalosporin*.mp.
32. cephradine*.mp.
33. clindamycin*.mp.
34. (co-trimoxazole* or cotrimoxazole*).mp.
35. cycloserine*.mp.
36. fosfomycin*.mp.
37. gentam#cin*.mp.
38. nalidixic acid*.mp.
39. nitrofurantoin*.mp.
40. penicillin*.mp.
41. piperacillin*.mp.
42. pivampicillin*.mp.

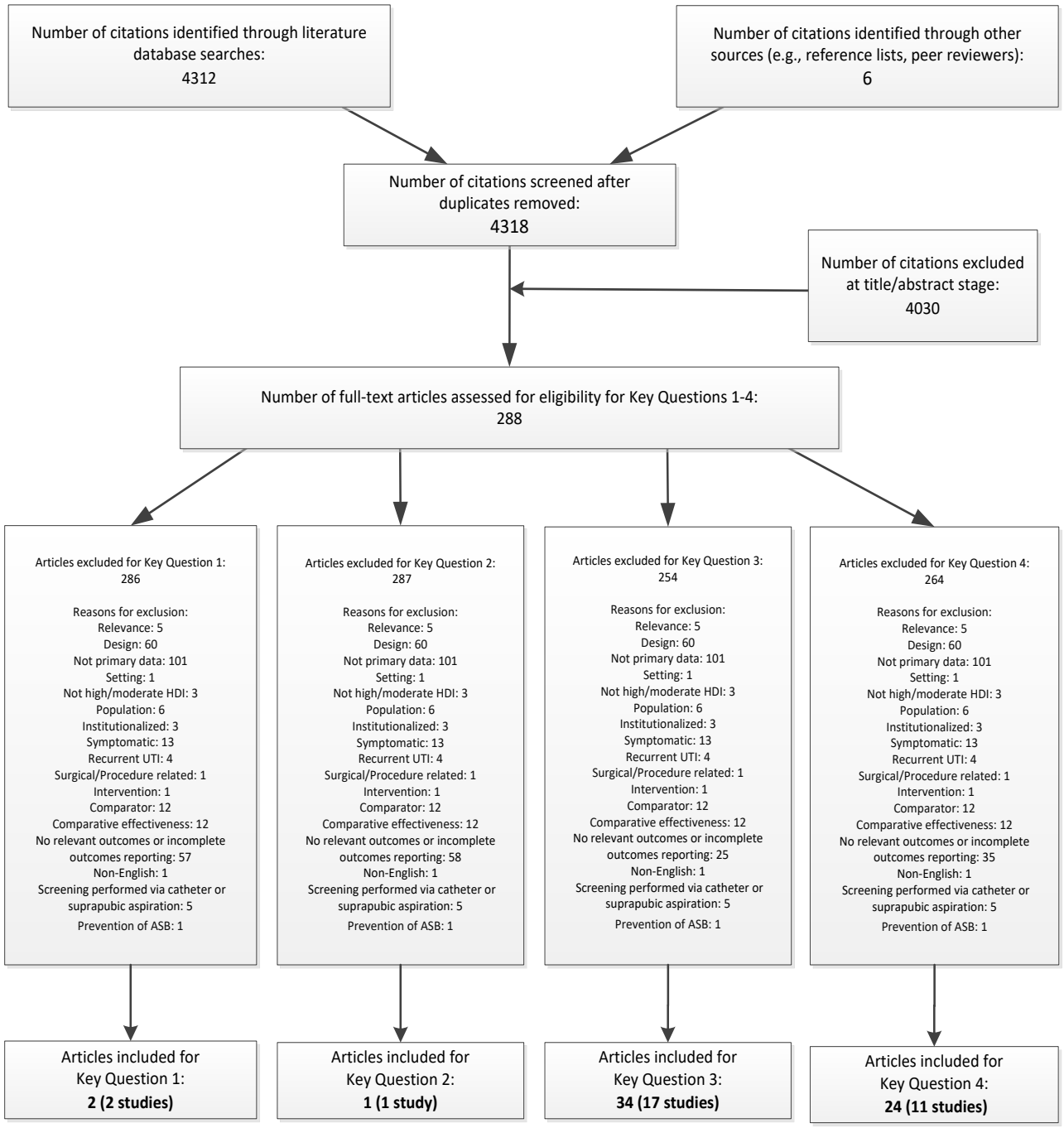
43. pivmecillinam*.mp.
44. sulfadimethoxine*.mp.
45. sulfadiazine*.mp.
46. sulfamethizole*.mp.
47. sulfamethoxazole*.mp.
48. sulfamethoxypyridazine*.mp.
49. sulfonamide*.mp.
50. sulphadimidine*.mp.
51. sulphonamide*.mp.
52. tetracycline*.mp.
53. vancomycin*.mp.
54. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 12 and 54
56. *Bacteriuria/dt, th
57. 55 or 56
58. Mortality/
59. Morbidity/
60. Death/
61. "Drug-Related Side Effects and Adverse Reactions"/
62. safety.ti,ab,kf.
63. harm*.ti,ab,kf.
64. mortality.ti,ab,kf.
65. toxicity.ti,ab,kf.
66. complication*.ti,ab,kf.
67. (death or deaths).ti,ab,kf.
68. (adverse adj2 (interaction* or response* or effect* or event* or reaction* or outcome*)).ti,ab,kf.
69. adverse effects.fs.
70. toxicity.fs.
71. mortality.fs.
72. abnormalities, drug-induced/
73. Congenital abnormalities/
74. exp Pregnancy Complications/
75. exp Infant, Low Birth Weight/
76. exp Infant, Premature/
77. exp Drug Resistance, Bacterial/
78. Drug Resistance/
79. Coinfection/
80. Hypersensitivity/
81. Drug Hypersensitivity/
82. ((birth or fetal or congenital) adj (defect* or anomal* or abnormal*)).ti,ab,kf.
83. (stillbirth* or still birth*).ti,ab,kf.
84. birth weight*.ti,ab,kf.
85. (preterm or pre term).ti,ab,kf.
86. ((drug or antibiotic or antimocrobial or bacteria*) adj resist*).ti,ab,kf.
87. (coinfection* or co infection* or secondary infection*).ti,ab,kf.
88. allergic reaction*.ti,ab,kf.

89. 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88
90. 57 and 89
91. Animals/ not (Humans/ and Animals/)
92. 90 not 91
93. limit 92 to english language
94. remove duplicates from 93

PubMed [publisher-supplied records]

Search	Query
#9	Search ((#8) AND English[Language]) AND publisher[sb]
#8	Search #1 OR #2 OR #6 OR #7
#7	Search (colonization[tiab] or colonization[tiab]) and (bladder*[tiab] or kidney*[tiab] or urin*[tiab] or genitourin*[tiab] or urogenita*[tiab])
#6	Search (#3 OR #4) AND #5
#5	Search asymptomatic[tiab] OR nonsymptomatic[tiab] OR non-symptomatic[tiab] OR absence of symptom*[tiab]
#4	Search (bacteria[tiab] or infection*[tiab]) and (bladder*[tiab] or kidney*[tiab] or urin*[tiab] or genitourin*[tiab] or urogenita*[tiab])
#3	Search urinary tract infection*[tiab] OR UTI[tiab] OR UTIs[tiab]
#2	Search urinary tract infection*[title] OR UTI[title] OR UTIs[title]
#1	Search bacilluria*[tiab] OR bacteriuria*[tiab]

Appendix A Figure 1. Literature Flow Diagram



Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Populations	**KQs 1, 2:** Unselected, asymptomatic, community-dwelling adults age ≥18 years (including those residing in independent living facilities) **KQs 3, 4:** Community-dwelling adults age ≥18 years with asymptomatic bacteriuria (including those residing in independent living facilities); unselected, asymptomatic pregnant women receiving routine prenatal care (any age)	• Persons with symptoms of or suspected urinary tract infection (cystitis or pyelonephritis) or with a history of recurrent urinary tract infection • Persons who have a compromised immune system • Persons who have a catheter, urinary stent, or nephrostomy tube; recipients of a kidney or other organ transplant; patients on kidney dialysis • Pregnant women with sickle cell disease • Persons seen in specialty care for treatment or follow-up of conditions affecting the urinary tract (e.g., prostate cancer) • Persons being tested in preparation for urological procedures • Persons with spinal cord injuries Studies conducted exclusively among persons who are institutionalized or hospitalized
Interventions	**KQs 1, 2:** Screening with urine testing (e.g., urine culture, urinalysis with microscopy, dipstick, dipslide, screening with reflex urine culture) **KQs 3, 4:** Treatment (e.g., antibiotics) or interventions to prevent urinary tract infection in patients with screen-detected, asymptomatic bacteriuria	Interventions to prevent asymptomatic bacteriuria
Comparisons	**KQ 1:** No screening **KQ 3:** No treatment; treatment with placebo	
Outcomes	**KQs 1, 3:** *General health outcomes:* • Urinary tract infection, including cystitis and pyelonephritis • Kidney failure • Quality of life • Mortality *Pregnancy-specific health outcomes:* • Complications of pregnancy associated with maternal or fetal morbidity: preterm birth (before 37 weeks' gestation), low birth weight (<2,500 g), preeclampsia, eclampsia, HELLP syndrome, congenital malformations (birth defects) • Maternal and fetal/infant mortality **KQs 2, 4:** All of the above health outcomes, with a focus on fetal anomalies, stillbirth, and adverse effects of treatment with antibiotics (e.g., recurrent and/or antimicrobial resistant infections, allergic reactions, secondary infections, and longer-term child health outcomes)	

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Setting	Prenatal or primary care settings	Studies conducted exclusively in populations living in special settings outside of the community (e.g., hospital, nursing or care home, rehabilitation center, or other long-term care facility), emergency departments, and other settings not generalizable to primary care
Study Design	**KQs 1, 3:** *Nonpregnant adults:* RCTs *Pregnant women*:* RCTs, observational cohort studies with a comparator of no screening or no treatment **KQs 2, 4:** RCTs, observational cohort studies with and without a comparison group, registry studies	**KQs 1, 3:** *Nonpregnant adults:* Study designs other than RCTs *Pregnant women*:* Study designs other than RCTs or observational cohort studies with a comparator of no screening or no treatment **KQs 2, 4:** Case control studies, case series and case reports, qualitative studies
Countries	*Nonpregnant adults:* Studies conducted in countries categorized as "Very High" on the 2016 Human Development Index (as defined by the United Nations Development Programme) *Pregnant women*:* Studies conducted in countries categorized as "Very High" and "High" on the 2016 Human Development Index	*Nonpregnant adults:* Studies not conducted in countries categorized as "Very High" on the 2016 Human Development Index *Pregnant women*:* Studies not conducted in countries categorized as "Very High" or "High" on the 2016 Human Development Index
Publication Language	English	Languages other than English

*The inclusion criteria for studies of screening for and treatment of asymptomatic bacteriuria in pregnant women are more broad because prior evidence from trials and ensuing recommendations have established a standard practice of screening and treatment.

Appendix A Table 2. Study Design–Specific Quality Rating Criteria

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[1]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer

Appendix B. Included Studies

Below is a list of included studies and their ancillary publications (indented below main results publication):

Key Question 1:

1. Gratacos E, Torres PJ, Vila J, et al. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. Journal of Infectious Diseases. 1994;169(6):1390-2. PMID: 8195624.

Key Question 1 and Key Question 2:

1. Uncu Y, Uncu G, Esmer A, et al. Should asymptomatic bacteriuria be screened in pregnancy? Clin Exp Obstet Gynecol. 2002;29(4):281-5. PMID: 12635746.

Key Question 3:

1. Abrutyn E, Mossey J, Berlin JA, et al. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women?.[Erratum appears in Ann Intern Med 1994 Dec 1;121(11):901]. Annals of Internal Medicine. 1994;120(10):827-33. PMID: 7818631. DOI:10.7326/0003-4819-120-10-199405150-00003
    a. Abrutyn E, Berlin J, Mossey J, et al. Does treatment of asymptomatic bacteriuria in older ambulatory women reduce subsequent symptoms of urinary tract infection? Journal of the American Geriatrics Society. 1996;44(3):293-5. PMID: 8600199. DOI: 10.1111/j.1532-5415.1996.tb00917.x

2. Brumfitt W. The effects of bacteriuria in pregnancy on maternal and fetal health. Kidney international. 1975;8:S113-s9. PMID: 00230726.
    a. Condie A, Williams J, Reeves D, et al. Complications of bacteriuria in pregnancy. Urinary tract infection, proceedings of the first national symposium; 1968 april; london, UK. 1968:148-59. PMID: CN-00231117.
    b. Williams J, Reeves D, Condie A, et al. The treatment of bacteriuria in pregnancy. Urinary tract infection Oxford University Press, London. 1968:160-9. PMID: None.

3. Foley ME, Farquharson R, Stronge JM. Is screening for bacteriuria in pregnancy worthwhile? Br Med J (Clin Res Ed). 1987;295(6592):270. PMID: 3115406.

4. Kincaid-Smith P, Bullen M. Bacteriuria in Pregnancy. Lancet. 1965;1(7382):395-9. PMID: 14238090.
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Key Question 3 and Key Question 4:

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    c. Wren BG. The diagnosis of asymptomatic bacilluria in pregnancy. Medical Journal of Australia. 1969;1(22):1117-21. PMID: 4893255.

Appendix C. Excluded Studies

Exclusion Criteria Code	Exclusion Criteria
1	Relevance
2	Design
3	Not primary data
4	Setting
5	HDI exclusion
6	Population
7	Institutionalized population
8	Symptomatic UTI
9	Recurrent UTI
10	Surgical/procedure related
11	Intervention
12	Comparator
13	Comparative effectiveness
14	No relevant outcomes
15	Non-English publication
16	Screening performed via catheter or suprapubic aspiration
17	Prevention of ASB

Reference	Exclusion Code
Aarnoudse, JG, Meijer-Severs, et al. Do anaerobes cause urinary tract infection? *Lancet*, 1(8164) 368-9. 1980.	6
Abduljabbar, H, Moumena, et al. Urinary tract infection in pregnancy *Ann Saudi Med*, 11(3) 322-4. 1991.	2
Abramson, JH, Sacks, et al. Bacteriuria and hemoglobin levels in pregnancy *JAMA*, 215(10) 1631-7. 1971.	2
Ahmad, S. Asymptomatic group B streptococcal bacteriuria among pregnant women in Saudi Arabia *Br J Biomed Sci*, 72(3) 135-9. 2015.	2
Al-Wali, W. Antibiotics for urinary tract infection in pregnant women *BMJ*, 357() j2934. 2017.	3
Alling, B, Brandberg, et al. Aerobic and anaerobic microbial flora in the urinary tract of geriatric patients during long-term care *J Infect Dis*, 127(1) 34-9. 1973.	7
Andelman, MB, Zackler, et al. A "stick test" for detection of asymptomatic bacteriuria *J Urol*, 100(2) 190-4. 1968.	14
Anderson, BL, Simhan, et al. Additional antibiotic use and preterm birth among bacteriuric and nonbacteriuric pregnant women *Int J Gynaecol Obstet*, 102(2) 141-5. 2008.	12
Anderton, KJ, Abbas, et al. High dose, short course amoxycillin in the treatment of bacteriuria in pregnancy *Br J Clin Pract*, 37(6) 212-4. 1983.	13
Andriole, VT. Urinary tract infections in pregnancy *Urol Clin North Am*, 2(3) 485-98. 1975.	3
Andriole, VT. Advances in the treatment of urinary infections *J Antimicrob Chemother*, 9 Suppl A() 163-72. 1982.	3
Anonymous. Treatment of bacteriuria in pregnancy *Br Med J*, 4(5736) 631-2. 1970.	3
Asscher, AW. Screening for urinary tract infection *J R Coll Physicians Lond*, 4(3) 219-26. 1970.	3
Atkinson, SM. Letter: Bacteriuria in pregnancy *Obstet Gynecol*, 43(1) 159-60. 1974.	3
Atlas, E, Clark, et al. Nalidixic acid and oxolinic acid in the treatment of chronic bacteriuria *Ann Intern Med*, 70(4) 713-21. 1969.	13
Avorn, J, Monane, et al. Reduction of bacteriuria and pyria with cranberry beverage: a randomized trial *J Am Geriatr Soc*, 41(10 Suppl) Sa13. 1993.	11
Bailey, RR. Bacteriuria of pregnancy *N Z Med J*, 95(700) 56. 1982.	2
Bailey, RR. Single-dose antibacterial treatment for bacteriuria in pregnancy *Drugs*, 27(2) 183-6. 1984.	3
Bailey, RR. Urinary tract infection revisited *N Z Med J*, 77(489) 69-74. 1973.	3

Appendix C. Excluded Studies

Reference	Exclusion Code
Bailey, RR. Urinary infection in pregnancy *N Z Med J*, 71(455) 216-20. 1970.	16
Bengtsson, C, Bengtsson, et al. Bacteriuria in a population sample of women: 24-year follow-up study. Results from the prospective population-based study of women in Gothenburg, Sweden *Scand J Urol Nephrol*, 32(4) 284-9. 1998.	2
Bilir, F, Akdemir, et al. Increased serum procalcitonin levels in pregnant patients with asymptomatic bacteriuria *Ann Clin Microbiol Antimicrob*, 12() 25. 2013.	2
Billinson, MR, Aubry, et al. A comparative study of a screening test for bacteriuria *Am J Obstet Gynecol*, 108(6) 988-9. 1970.	14
Bobeck, S, Schersten, et al. Detection and diagnosis of bacteriuria in pregnancy. A study from general practice *Practitioner*, 212(1268) 257-62. 1974.	2
Bookallil, M, Chalmers, et al. Challenges in preventing pyelonephritis in pregnant women in Indigenous communities *Rural Remote Health*, 5(3) 395. 2005.	2
Boscia, JA, Abrutyn, et al. Asymptomatic bacteriuria in elderly persons: treat or do not treat? *Ann Intern Med*, 106(5) 764-6. 1987.	3
Boscia, JA, Kaye, et al. Asymptomatic bacteriuria in the elderly *Clin Geriatr Med*, 4(1) 57-70. 1988.	3
Breidahl, P, Hurst, et al. The post-partum investigation of pregnancy bacteriuria *Med J Aust*, 2(21) 1174-7. 1972.	2
Brown, N, Browder, et al. Treatment of persistent bacteriuria with a six-week course of antibiotic therapy *Antimicrob Agents Chemother*, () 324-333. 1961.	10
Brumfitt, W. Asymptomatic Bacteriuria *Practitioner*, 192() 818-9. 1964.	3
Brumfitt, W, Hamilton-Miller, et al. Trimethoprim *Br J Hosp Med*, 23(3) 281, 284-6, 288. 1980.	3
Brumfitt, W, Pursell, et al. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women *J Infect Dis*, 128() Suppl:657-65 p. 1973.	13
Cai, T, Mazzoli, et al. The reduction of Escherichia coli resistance against ciprofloxacin is a microbiological parameter for asymptomatic bacteriuria predicting: results from a cross-sectional study *European urology, supplements. Conference: 32nd annual european association of urology congress, EAU 2017. United kingdom*, 16(3) e235. 2017.	9
Cai, T, Mazzoli, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? *Clin Infect Dis*, 55(6) 771-7. 2012.	9
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Cameron, I. Urinary tract infection in the elderly *Aust Fam Physician*, 17(7) 539-41. 1988.	3
Campbell-Brown, M, McFadyen, et al. Is screening for bacteriuria in pregnancy worth while? *British Medical Journal Clinical Research Ed.*, 294(6587) 1579-82. 1987.	16
Campos-Outcalt, DE, Corta, et al. Screening for asymptomatic bacteriuria in pregnancy *J Fam Pract*, 20(6) 589-91. 1985.	14
Carroll, R, MacDonald, et al. The detection and treatment of bacteriuria in pregnancy. An essential part of antenatal care *J Ir Med Assoc*, 60(358) 115-7. 1967.	14
Carroll, R, MacDonald, et al. Bacteriuria in pregnancy *Obstet Gynecol*, 32(4) 525-7. 1968.	2
Cattell, WR. The management of urinary-tract infection *Practitioner*, 212(267) 27-36. 1974.	3
Cattell, WR. Renal disease. II. Urinary tract infection in women *J R Coll Physicians Lond*, 31(2) 130-3. 1997.	3

Appendix C. Excluded Studies

Reference	Exclusion Code
Chng, PK, Hall, et al. Antenatal prediction of urinary tract infection in pregnancy *Br J Obstet Gynaecol*, 89(1) 8-11. 1982.	12
Christopher, LJ, Thompson, et al. A trial of hippramine in the treatment of bacteriuria of pregnancy *Ir J Med Sci*, 8(7) 331-7. 1969.	13
Cobbs, CG, Strickler, et al. The postpartum renal status of women with untreated asymptomatic bacteriuria during pregnancy *Am J Obstet Gynecol*, 99(2) 221-7. 1967.	2
Cormican, M, Murphy, et al. Interpreting asymptomatic bacteriuria *BMJ*, 343() d4780. 2011.	3
Corriere, Jn, Lipshultz, et al. Bacteriuria in young women. Effect of estrogen, progestogen, and estrogen-progestogen combination *Urology*, 2(5) 539-541. 1973.	1
Coulehan, JL. Screening yield in an urban low income practice *Am J Public Health*, 65(5) 474-9. 1975.	2
Cunningham, FG, Lucas, et al. Urinary tract infections complicating pregnancy *Baillieres Clin Obstet Gynaecol*, 8(2) 353-73. 1994.	3
Czerwinski, AW, Wilkerson, et al. Evaluation of first morning urine to detect significant bacteriuria. I *Am J Obstet Gynecol*, 110(1) 42-5. 1971.	2
Dalal, S, Nicolle, et al. Long-term Escherichia coli asymptomatic bacteriuria among women with diabetes mellitus *Clin Infect Dis*, 49(4) 491-7. 2009.	14
Dawborn, JK, Gurr, et al. The management of urinary infection in women *Med J Aust*, 1(9) 421-7. 1972.	3
Dempsey, C, Harrison, et al. Characteristics of bacteriuria in a homogeneous maternity hospital population *Eur J Obstet Gynecol Reprod Biol*, 44(3) 189-93. 1992.	2
DeShan, PW, Merrill, et al. The Griess test as a screening procedure for bacteriuria during pregnancy *Obstet Gynecol*, 27(2) 202-5. 1966.	14
DeYoung, GR, Ashmead, et al. Screening for and treating asymptomiatic bacteriuria not useful in women with diabetes *J Fam Pract*, 52(2) 98-9. 2003.	3
Dixon, HG, Brant, et al. The significance of bacteriuria in pregnancy *Lancet*, 1(7480) 19-20. 1967.	2
Dodson, MG, Fortunato, et al. Microorganisms and premature labor *J Reprod Med*, 33(1 Suppl) 87-96. 1988.	3
Drinka, P. Treatment of bacteriuria without urinary signs, symptoms, or systemic infectious illness (S/S/S) *J Am Med Dir Assoc*, 10(8) 516-9. 2009.	3
Elder, HA, Santamarina, et al. Use of sulfasymazine in the treatment of bacteriuria of pregnancy *Antimicrob Agents Chemother*, 6() 142-8. 1966.	14
Emmerson, AM. The use of a simple test for hypoglucosuria (uriglox) in the diagnosis of bacteriuria in pregnancy *Journal of Obstetrics & Gynaecology of the British Commonwealth*, 79(9) 828-32. 1972.	14
Enbom, JA. Bacteriuria in pregnancy. Therapeutic considerations *Postgrad Med*, 49(5) 216-20. 1971.	3
Eng, J, Torkildsen, et al. Bacteriuria in the puerperium: an evaluation of methods for collecting urine specimens *Am J Obstet Gynecol*, 131(7) 739-41. 1978.	2
Fairley, KF, Bond, et al. The site of infection in pregnancy bacteriuria *Lancet*, 1(7444) 939-41. 1966.	2
Fairley, KF, Whitworth, et al. Pregnancy bacteriuria: the significance of site of infection *Med J Aust*, 2(9) 424-7. 1973.	16
Fang, LS, Tolkoff-Rubin, et al. Urinary tract infections in women *Compr Ther*, 5(9) 20-5. 1979.	3
Fass, RJ, Klainer, et al. Urinary tract infection. Practical aspects of diagnosis and treatment *JAMA*, 225(12) 1509-13. 1973.	3
Fatkenheuer, G, Jung, et al. Treatment of Asymptomatic Bacteriuria *Clin Infect Dis*, 62(9) 1190. 2016.	3

Appendix C. Excluded Studies

Reference	Exclusion Code
Fihn, SD. Clinical practice. Acute uncomplicated urinary tract infection in women *N Engl J Med*, 349(3) 259-66. 2003.	3
Finch, RM, Finch, et al. Bacteriological counts of urines in general practice *Journal of the Royal College of General Practitioners*, 19(93) 201-10. 1970.	2
Fischbach, F, Loos, et al. Ciprofloxacin (CF) in the treatment of patients with symptomatic and asymptomatic urinary tract infections (UT): a comparative study of single dose application versus three days treatment *Arch Gynecol*, 237 Suppl() 92-93. 1985.	13
Foley, ME, Farquharson, et al. Urinary tract infection in pregnancy *Ir Med J*, 75(6) 188-9. 1982.	2
Ganguli, L. Serological grouping of Escherichia coli in bacteriuria of pregnancy *J Med Microbiol*, 3(2) 201-8. 1970.	2
Gaymans, R, Haverkorn, et al. Aprospective study of urinary-tract infections in a Dutch general practice *Lancet*, 2(7987) 674-7. 1976.	2
Geerlings, SE, Stolk, et al. Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group *Diabetes Care*, 23(6) 744-9. 2000.	2
Gingell, JC. Bacteriuria again *Br Med J*, 2(5756) 278. 1971.	3
Gleckman, R. The controversy of treatment of asymptomatic bacteriuria in non-pregnant women--resolved *J Urol*, 116(6) 776-7. 1976.	3
Gofin, R, Palti, et al. Bacteriuria in pregnancy and growth and development of the infants *Early Hum Dev*, 9(4) 341-6. 1984.	2
Golan, A, Wexler, et al. Asymptomatic bacteriuria in normal and high-risk pregnancy *Eur J Obstet Gynecol Reprod Biol*, 33(2) 101-8. 1989.	12
Gonzalez Ochoa, A. Trimethoprim and sulfamethoxazole in pregnancy *JAMA*, 217(9) 1244. 1971.	2
Goss, LB. Bacteriuria of Pregnancy *Med Rec Ann*, 57() 342-3. 1964.	3
Goss, LB, Franklin, et al. Asymptomatic Bacteriuria of Pregnancy and Detection by a Simple Stain *Am J Obstet Gynecol*, 87() 493-8. 1963.	12
Greenwood, D, Slack, et al. Urinary tract infection *Br J Clin Pharmacol*, 13(5) 619-30. 1982.	2
Gringras, M, Cooper, et al. The treatment of urinary infection in women. A dip-slide comparative study *Practitioner*, 223(1335) 357-62. 1979.	8
Grio, R, Porpiglia, et al. Asymptomatic bacteriuria in pregnancy: maternal and fetal complications *Panminerva Med*, 36(4) 198-200. 1994.	3
Gruneberg, RN. The bacteriology of urinary tract infection: does it matter? *Proc R Soc Med*, 65(6) 514-6. 1972.	3
Gruneberg, RN, Leigh, et al. Relationship of bacteriuria in pregnancy to acute pyelonephritis, prematurity, and fetal mortality *Lancet*, 2(7610) 1-3. 1969.	2
Gruneberg, RN, Reeves, et al. Bacteriuria in pregnancy *Br Med J*, 1(5740) 107-8. 1971.	3
Hall, DR, Theron, et al. Significance and treatment of asymptomatic bacteriuria during pregnancy *Int J Gynaecol Obstet*, 57(2) 179-80. 1997.	2
Hankins, GD, Whalley, et al. Acute urinary tract infections in pregnancy *Clin Obstet Gynecol*, 28(2) 266-78. 1985.	3
Harding, GK, Ronald, et al. Clinical experiences: genitourinary infections. A. Infections of the urinary tract. Efficacy of trimethoprim-sulfamethoxazole in bacteriuria *J Infect Dis*, 128() Suppl:641-6 p. 1973.	8
Hargreaves, J. Investigation of bacteriuria in pregnancy and its treatment with sulphaemathizole *Practitioner*, 218(1307) 718-20. 1977.	2

Appendix C. Excluded Studies

Reference	Exclusion Code
Harris, RE. The significance of eradication of bacteriuria during pregnancy *Obstet Gynecol*, 53(1) 71-3. 1979.	12
Harris, RE. Postpartum urinary retention: role of antimicrobial therapy *Am J Obstet Gynecol*, 133(2) 174-5. 1979.	6
Harris, RE. Antibiotic therapy of antepartum urinary tract infections *J Int Med Res*, 8(Suppl 1) 40-4. 1980.	3
Harris, RE, Gilstrap, et al. Cystitis during pregnancy: a distinct clinical entity *Obstet Gynecol*, 57(5) 578-80. 1981.	2
Harris, RE, Gilstrap, et al. Prevention of recurrent pyelonephritis during pregnancy *Obstet Gynecol*, 44(5) 637-41. 1974.	8
Harris, RE, Gilstrap, et al. Single-dose antimicrobial therapy for asymptomatic bacteriuria during pregnancy *Obstet Gynecol*, 59(5) 546-9. 1982.	13
Harris, RE, Thomas, et al. Asymptomatic bacteriuria in pregnancy: antibody-coated bacteria, renal function, and intrauterine growth retardation *Am J Obstet Gynecol*, 126(1) 20-5. 1976.	12
Hatala, M, Prat, et al. Tetrazolium test (T.T.C.) in the screening of asymptomatic bacteriuria in pregnancy *Rev Czech Med*, 11(3) 198-202. 1965.	14
Hecker, MT, Donskey, et al. Q: Is antibiotic treatment indicated in a patient with a positive urine culture but no symptoms? *Cleve Clin J Med*, 81(12) 721-4. 2014.	3
Heineman, HS. Urinary infection in pregnancy *Mod Treat*, 7(2) 349-54. 1970.	3
Henning, C, Bucht, et al. Results from the routine detection of bacteriuria in antenatal care in Stockholm County *Acta Pathologica et Microbiologica Scandinavica - Section B, Microbiology & Immunology*, 79(3) 446. 1971.	2
Hibbard, L, Thrupp, et al. Treatment of pyelonephritis in pregnancy *Am J Obstet Gynecol*, 98(5) 609-15. 1967.	8
Holland, WW. Taking stock *Lancet*, 2(7895) 1494-7. 1974.	3
House, TE, Williams, et al. Pregnancy complicated by urinary tract infections *Obstet Gynecol*, 34(5) 670-4. 1969.	13
Hutchings, RF, Gordon, et al. The "Uroscreen" test for significant bacteriuria in pregnancy *West Indian Medical Journal*, 19(2) 71-7. 1970.	14
Institute for, Quality, Efficiency in Health, et al. IQWiG Executive Summaries of Final Reports *Screening for Asymptomatic Bacteriuria Within the Framework of the German Maternity Guidelines, Under Special Consideration of Test Methods*, () . 2015.	3
Ives, JA, Abbott, et al. Bacteriuria in pregnancy and infection in amniotic fluid and infant *Arch Dis Child*, 46(245) 82-4. 1971.	14
Jackson, GG. Diagnosis and importance of asymptomatic bacteriuria in adults *Infection*, 3(3) 175-7. 1975.	3
John, P. A study of asymptomatic bacteriuria among the maternal care patients attending the Maternal and Child Health Clinic, Dhahran, Saudi Arabia *Am J Obstet Gynecol*, 111(1) 26-30. 1971.	14
Jones, SR, Smith, et al. Localization of urinary-tract infections by detection of antibody-coated bacteria in urine sediment *N Engl J Med*, 290(11) 591-3. 1974.	2
Juthani-Mehta, M. Changing Clinicians' Behavior: To Order or Not to Order a Urine Culture *JAMA Intern Med*, 175(7) 1127-9. 2015.	3
Kass, EH. Bacteriuria and excess mortality: what should the next steps be? *Rev Infect Dis*, 7 Suppl 4() S762-6. 1985.	3
Kass, EH. Horatio at the orifice: the significance of bacteriuria *J Infect Dis*, 138(4) 546-57. 1978.	3
Kass, EH. Pregnancy, pyelonephritis and prematurity *Clin Obstet Gynecol*, 13(2) 239-54. 1970.	3
Kass, FH. Should bacteriuria be treated? *Med J Aust*, 1(2) Suppl:38-43. 1973.	3

Appendix C. Excluded Studies

Reference	Exclusion Code
Kaye, D, Hurley, et al. Treatment of Urinary Tract Infection with Ampicillin *Arch Intern Med*, 115() 575-9. 1965.	12
Keating, GM. Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria *Drugs*, 73(17) 1951-66. 2013.	3
Kessous, R, Weintraub, et al. Bacteruria with group-B streptococcus: is it a risk factor for adverse pregnancy outcomes? *Journal of Maternal-Fetal & Neonatal Medicine*, 25(10) 1983-6. 2012.	2
Khanna, SD, Puri, et al. Asymptomatic Bacteriuria and Value of Triphenyl Tetrazolium Chloride Test as a Screening Aid *Indian J Med Sci*, 18() 457-60. 1964.	5
Kincaid-Smith, P. Screening Tests for Bacteriuria in Pregnancy *Lancet*, 1(7383) 487. 1965.	3
Kincaid-Smith, P. Screening for bacteriuria in pregnancy *Lancet*, 1(7703) 809-10. 1971.	3
Kincaid-Smith, P, Kalowski, et al. Co-trimoxazole in urinary tract infection *Med J Aust*, 1(2) Suppl:49-51. 1973.	13
Kirby, A, Simpson, et al. Testing for asymptomatic bacteriuria in pregnancy *Eur J Obstet Gynecol Reprod Biol*, 205() 192-4. 2016.	1
Kovar, WR. Routine urinary tract screening *Nebr Med J*, 65(6) 146. 1980.	2
Kozinn, PJ, Goldberg, et al. Bacteriuria: colonization or infection *JAMA*, 253(13) 1878-9. 1985.	6
Krieger, JN. Complications and treatment of urinary tract infections during pregnancy *Urol Clin North Am*, 13(4) 685-93. 1986.	3
Kumazawa, J, Momose, et al. Clinical effectiveness of lividomycin on urinary tract infections: evaluation with double-blind method *Curr Ther Res Clin Exp*, 15(12) 873-901. 1973.	8

Reference	Exclusion Code
Kunin, CM. Use of antimicrobial agents in treating urinary tract infection *Adv Nephrol Necker Hosp*, 14() 39-65. 1985.	3
Lautenbach, E, Babson, et al. Assessment of the use of urine samples to detect colonization with fluoroquinolone-susceptible and fluoroquinolone-resistant Escherichia coli *Infect Control Hosp Epidemiol*, 30(4) 396-7. 2009.	7
Lawson, DH, Miller, et al. Screening for bacteriuria in pregnancy. A critical reappraisal *Arch Intern Med*, 132(6) 904-8. 1973.	3
Lawson, DH, Miller, et al. Screening for bacteriuria in pregnancy *Lancet*, 1(7706) 968-9. 1971.	3
Leblanc, AL, McGanity, et al. The Impact of Bacteriuria in Pregnancy; a Survey of 1300 Pregnant Patients *Tex Rep Biol Med*, 22() 336-47. 1964.	16
Leigh, DA. Bacteriuria again *Br Med J*, 2(5760) 527-8. 1971.	3
Lein, JN, Bulger, et al. Why bacteriuria in pregnancy should be treated *Postgrad Med*, 45(5) 201-5. 1969.	3
Leis, JA, Rebick, et al. Reducing antimicrobial therapy for asymptomatic bacteriuria among noncatheterized inpatients: a proof-of-concept study *Clin Infect Dis*, 58(7) 980-3. 2014.	6
Leveno, KJ, Harris, et al. Bladder versus renal bacteriuria during pregnancy: recurrence after treatment *Am J Obstet Gynecol*, 139(4) 403-6. 1981.	2
Lin, KW, Brown, et al. Screening for asymptomatic bacteriuria in adults *Am Fam Physician*, 81(4) 508. 2010.	3
Little, PJ. Treatment of bacteriuria of pregnancy *Drugs*, 14(5) 390-1. 1977.	3
Lumbiganon, P, Villar, et al. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial *Obstet Gynecol*, 113(2 Pt 1) 339-45. 2009.	13

Appendix C. Excluded Studies

Reference	Exclusion Code
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Appendix C. Excluded Studies

Reference	Exclusion Code
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Reference	Exclusion Code
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Reference	Exclusion Code
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Williams, JD, Brumfitt, et al. The treatment of bacteriuria in pregnant women with sulphamethoxazole and thrimethoprim. A	2

Appendix C. Excluded Studies

Reference	Exclusion Code
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Williams, JD, Brumfitt, et al. Eradication of Bacteriuria in Pregnancy by a Short Course of Chemotherapy *Lancet*, 1(7390) 831-4. 1965.	12
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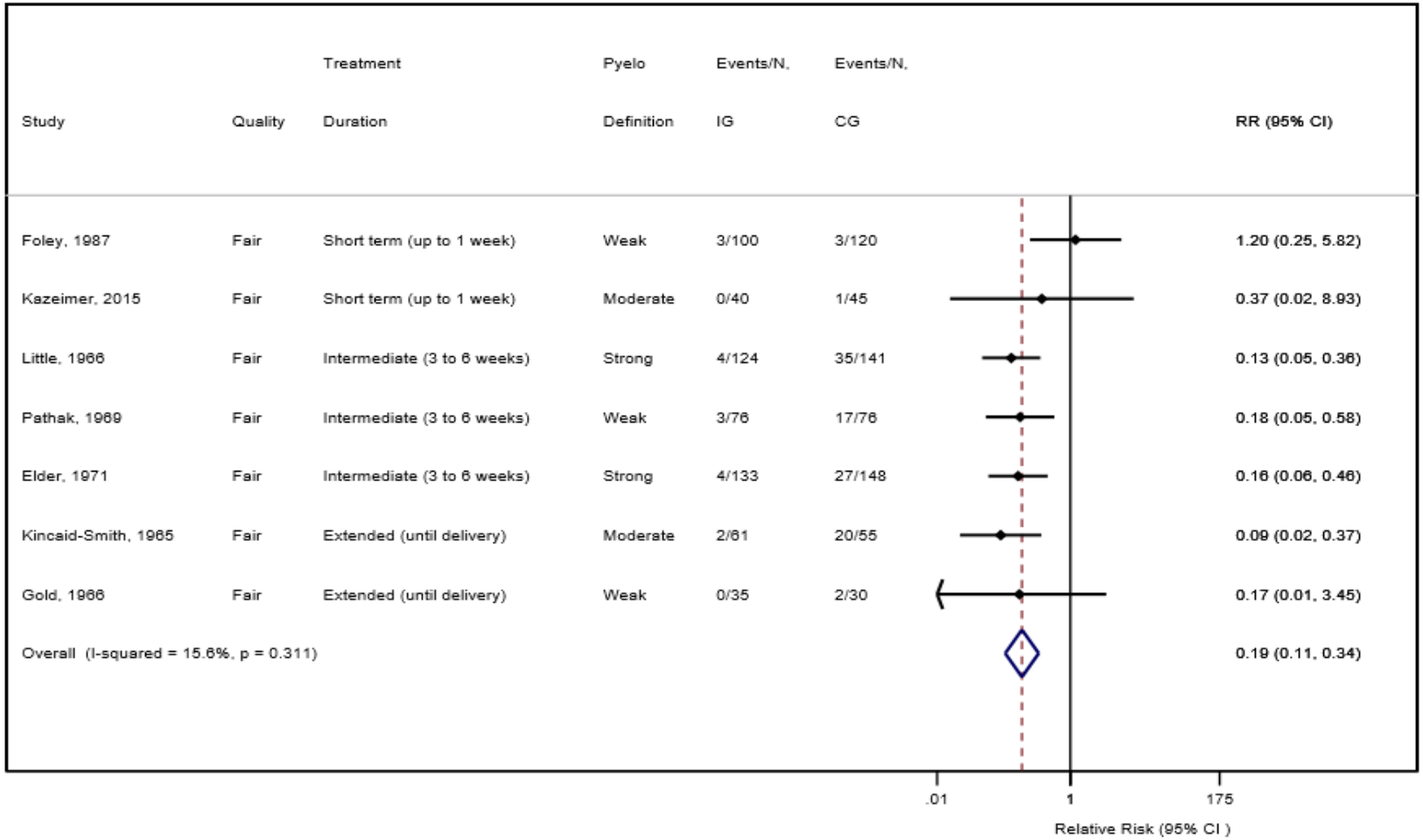
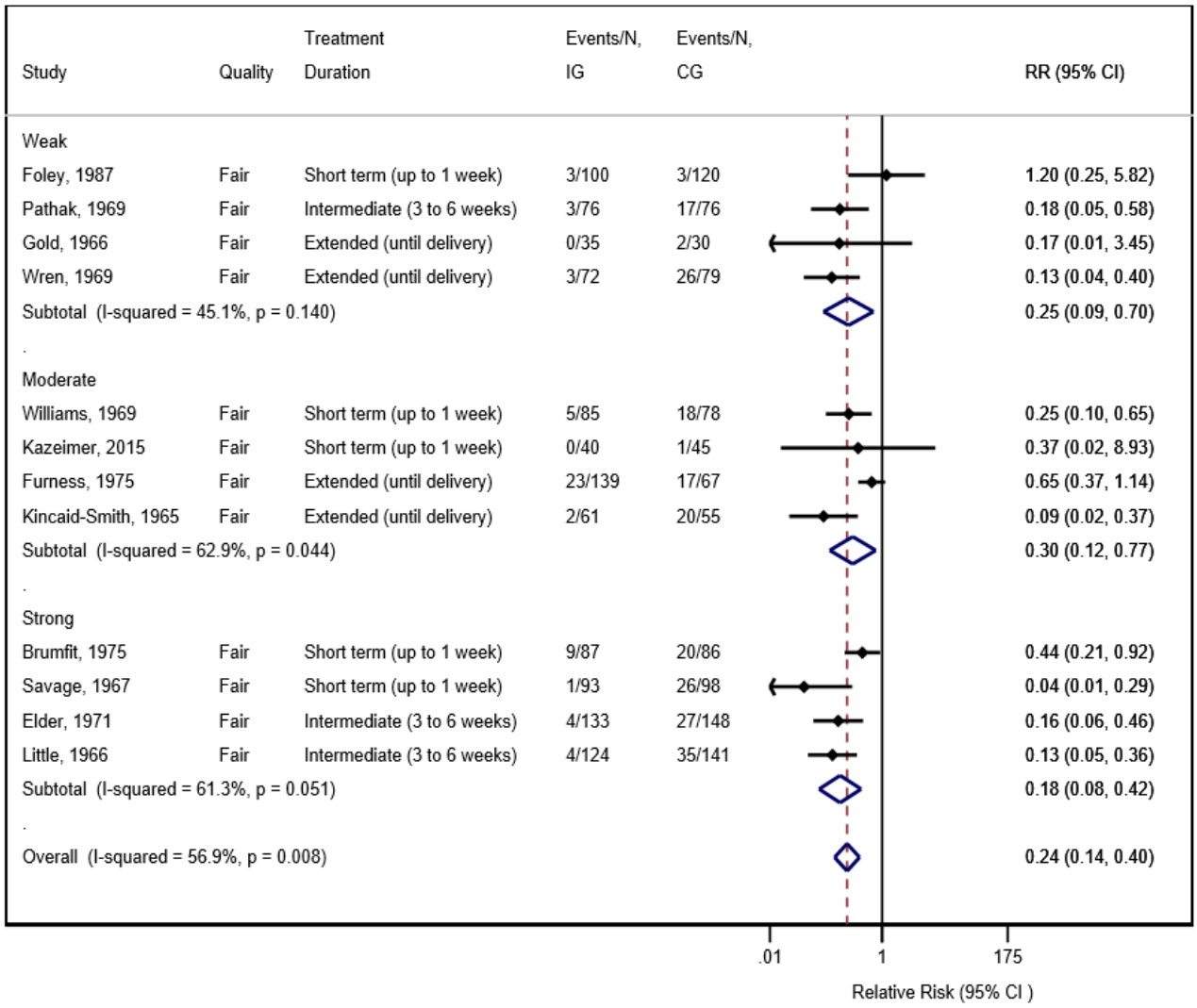
Zilkoski, MW, Smucker, et al. Urinary tract infections in elderly patients *Postgrad Med*, 84(3) 191-4, 197-8. 1988.	3
Zweig, S. Urinary tract infections in the elderly *Am Fam Physician*, 35(5) 123-30. 1987.	3

Appendix D Figure 1. Pooled Analysis of Rates of Pyelonephritis Among Treated Pregnant Women Compared With Controls – Sensitivity Analysis Removing High Risk of Bias Studies



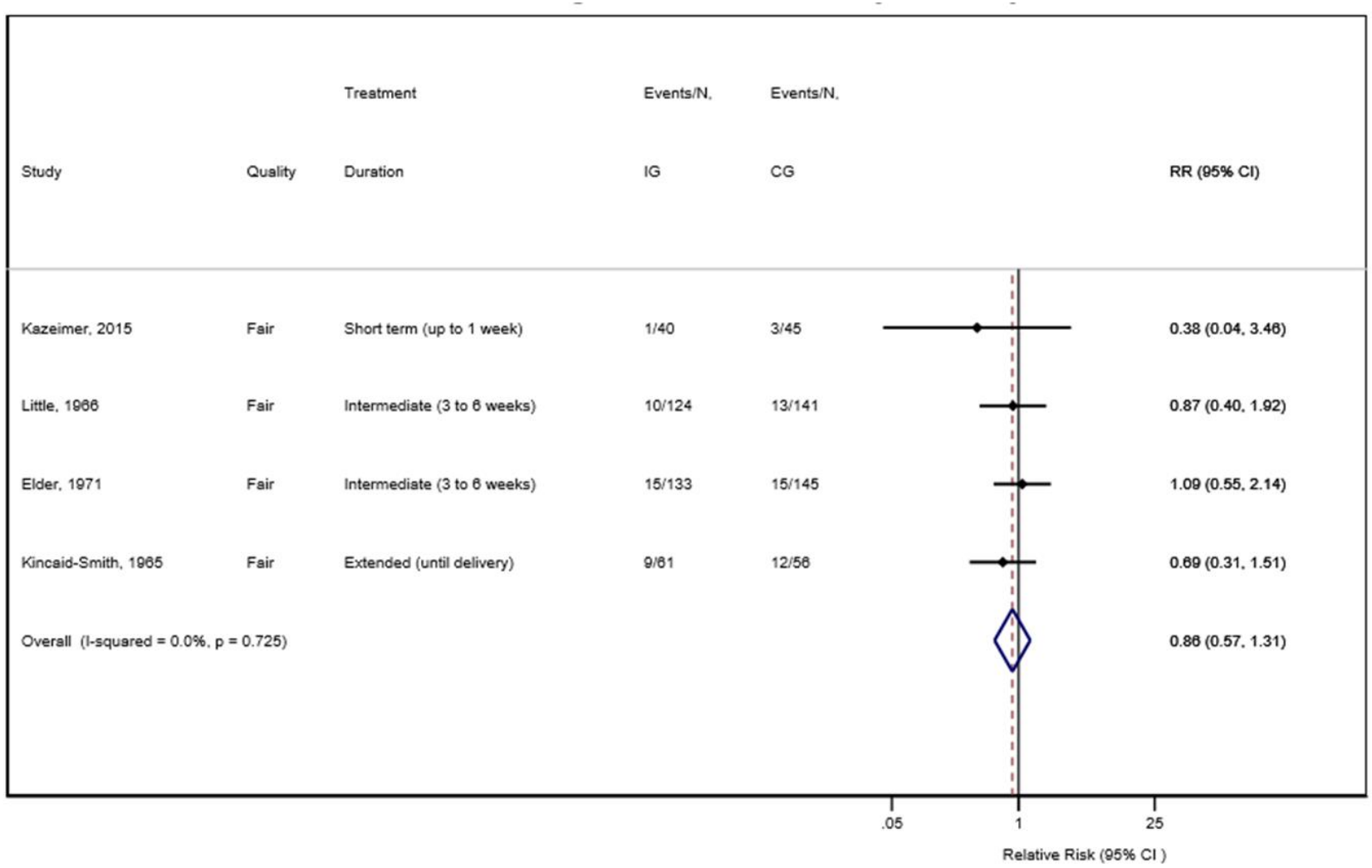
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Appendix D Figure 2. Pooled Analysis of Rates of Pyelonephritis Among Treated Pregnant Women Compared With Controls – By Definition of Pyelonephritis



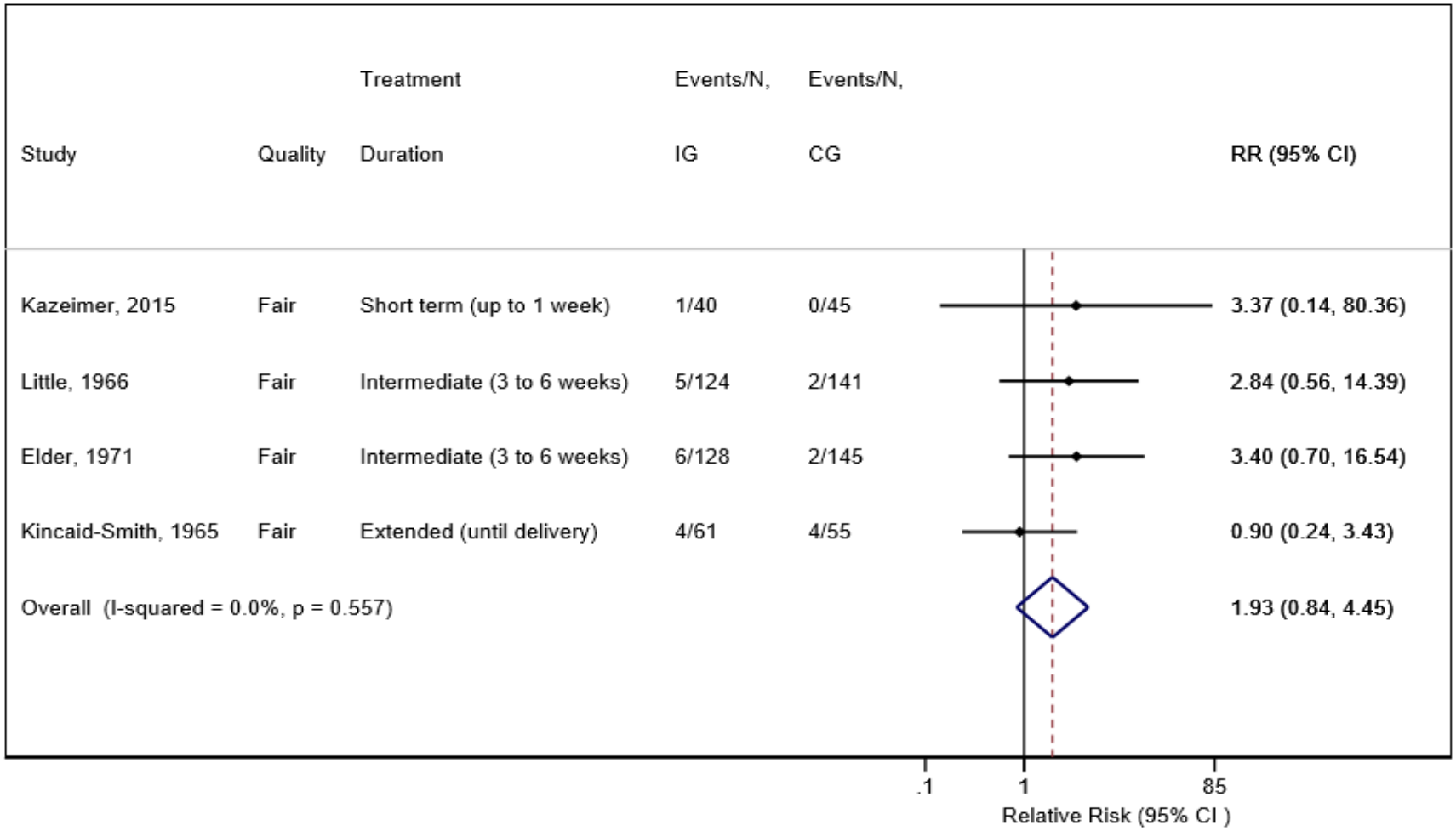
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Appendix D Figure 3. Pooled Analysis of Rates of Low Birth Weight Among Treated Pregnant Women Compared With Controls – Sensitivity Analysis Removing High Risk of Bias Studies



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Appendix D Figure 4. Rates of Perinatal Mortality Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls – Sensitivity Analysis Removing High Risk of Bias Studies



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; N = number of participants; RR = relative risk

Appendix E Table 1. Rates of Symptomatic Infection Among Treated Pregnant Women Compared With Controls

Author, Year	Outcome	Description	Int arm	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Brumfit, 1975[2]	Pyelonephritis	Presence of loin pain and tenderness with a temperature of ≥100 degrees F, positive urine culture*	IG1	9/87 (10.3%)	20/86 (23.3%)	0.44 (0.21 to 0.92)
Elder, 1971[3]	Pyelonephritis	Temperature ≥100 degrees Fahrenheit with signs and symptoms localized to the urinary tract and not otherwise explained†	IG1	4/133 (3.0%)	27/148 (18.2%)	0.16 (0.06 to 0.46)
Foley, 1987[4]	Pyelonephritis	NR	IG1	3/100 (3.0%)	3/120 (2.5%)	1.2 (0.25 to 5.82)
Furness, 1975[5]	Pyelonephritis	Frequency and burning on micturition accompanied by pyrexia or loin tenderness and a subsequent specimen of urine showed the presence of a significant number of bacteriuria	IG1	14/70 (20.0%)	17/67 (25.4%)	0.79 (0.42 to 1.47)
			IG2	9/69 (13.0%)	17/67 (25.4%)	0.51 (0.25 to 1.07)
Gold, 1966[6]	Pyelonephritis	NR‡	IG1	0/35 (0.0%)	2/30 (6.7%)	0.17 (0.01 to 3.45)
Kazemier, 2015[7]	Pyelonephritis	Hospital admission with positive urine culture and ≥2 of the following features: Fever (≥38.0 C), nausea/vomiting, chills, costovertebral tenderness	IG1	0/40 (0.0%)	1/45 (2.2%)	0.37 (0.02 to 8.93)§
Kincaid-Smith, 1965[8]	Pyelonephritis	Loin pain and tenderness, with or without pyrexia, and rigors, with or without symptoms of dysuria and frequency‖	IG1	2/61 (3.3%)	20/55 (36.4%)	0.09 (0.02 to 0.37)
Little, 1966[9]	Pyelonephritis	Loin pain and tenderness, a fever above 100 degrees F, and more than 1o^5per ml. bacteria in urine collected before the start of treatment	IG1	4/124 (3.2%)	35/141 (24.8%)	0.13 (0.05 to 0.36)
Pathak, 1969[10]	Pyelonephritis	NR	IG1	3/76 (3.9%)	17/76 (22.4%)	0.18 (0.05 to 0.58)
Savage, 1967[11]	Pyelonephritis	Dysuria, frequency, flank pain or other localizing evidence of inflammation, with either documented temperature of ≥100 degrees Fahrenheit, or a history of chills and fever	IG1	1/93 (1.1%)	26/98 (26.5%)	0.04 (0.01 to 0.29)
Williams, 1969[12]	Pyelonephritis	Loin pain with tenderness with or without fever at three broad arbitrary levels of osmolality	IG1	5/85 (5.9%)	18/78 (23.1%)	0.25 (0.10 to 0.65)
Wren, 1969[13]	Pyelonephritis	NR	IG1	3/72 (4.2%)	26/79 (32.9%)	0.13 (0.04 to 0.40)
Foley, 1987[4]	Symptomatic UTI	NR	IG1	4/100 (4.0%)	5/120 (4.2%)	0.96 (0.26 to 3.48)
Kazemier, 2015[7]	Symptomatic UTI	UTI treated with antibiotics during pregnancy	IG1	4/40 (10.0%)	8/45 (17.8%)	0.56 (0.02 to 8.93)¶

Appendix E Table 1. Rates of Symptomatic Infection Among Treated Pregnant Women Compared With Controls

* Data only available for a subset of trial participants

† Some participants may have been treated in the emergency ward and not included in study data

‡ Study report of pyelonephritis extends through the postpartum period

§ Study reported risk difference: -2.2 (-23. 4 to 19)

‖ Analysis of IG dropped those with persistent ASB

¶ Study reported risk difference: -7.8 (-28.7 to 13.8)

Abbreviations: CI = confidence interval; IG = intervention group; Int = Intervention; n = number of cases; N = number of participants; NR = not reported; RR = relative risk; UTI = urinary tract infection

Appendix E Table 2. Rates of Low Birth Weight and Preterm Birth Among Treated Pregnant Women Compared With Controls

Outcome Cat	Author, Year	Outcome	Int arm	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Low birthweight	Brumfit, 1975[2]	Birthweight ≤2500 g	IG1	18/235 (7.7%)	21/178 (11.8%)	0.65 (0.36 to 1.18)
	Elder, 1971[3]	Birth weight <2495 g*	IG1	15/133 (11.3%)	15/145 (10.3%)	1.09 (0.55 to 2.14)
	Kazemier, 2015[7]	SGA less than P10	IG1	1/40 (2.5%)	3/45 (6.7%)	0.38 (0.04 to 3.46)†‡
		SGA less than P5	IG1	0/40 (0.0%)	1/45 (2.2%)	0.37 (0.02 to 8.93)§
	Kincaid-Smith, 1965[8]	Birthweight <2500 g	IG1	9/61 (14.8%)	12/56 (21.4%)	0.69 (0.31 to 1.51)
	Little, 1966[9]	Birthweight ≤ 2495 g	IG1	10/124 (8.1%)	13/141 (9.2%)	0.87 (0.40 to 1.92)
	Savage, 1967[11]	Birthweight ≤2500 g	IG1	7/93 (7.5%)	21/98 (21.4%)	0.35 (0.16 to 0.79)
	Wren, 1969[13]	Birth weight Birthweight <2500 g	IG1	4/83 (4.8%)	14/90 (15.6%)	0.31 (0.11 to 0.90)
Preterm birth	Furness, 1975[5]	Preterm birth before 38 weeks	IG1	12/57 (21.1%)	10/52 (19.2%)	1.09 (0.52 to 2.32)
			IG2	12/61 (19.7%)	10/52 (19.2%)	1.02 (0.48 to 2.17)
	Gold, 1966[6]	Preterm birth before 37 weeks‖	IG1	2/35 (5.7%)	0/30 (0.0%)	4.31 (0.21 to 86.32)
	Kazemier, 2015[7]	Preterm birth before 37 weeks	IG1	2/40 (5.0%)	2/45 (4.4%)	1.13 (0.17 to 7.62)¶
		Preterm birth before 34 weeks	IG1	1/40 (2.5%)	0/45 (0.0%)	3.37 (0.14 to 80.36)#
		Preterm birth before 28 weeks	IG1	0/40 (0.0%)	0/45 (0.0%)	NA**
		Preterm birth before 32 weeks	IG1	1/40 (2.5%)	0/45 (0.0%)	3.37 (0.14 to 80.36)††
	Wren, 1969[13]	Preterm birth before 37 weeks	IG1	5/83 (6.0%)	15/90 (16.7%)	0.36 (0.14 to 0.95)

* Excludes induced onset of labor
† Study reported risk difference: -4.2 (-25.3 to 17.1)
‡ Analysis of IG dropped those with persistent ASB
§ Study reported risk difference: -2.2 (-23.4 to 19)
‖ Assumed 37 weeks
¶ Study reported risk difference: .6 (-20.8 to 21.7)
# Study reported risk difference: 2.5 (-18.8 to 23.6)
** Study reported risk difference: 0 (-9.4 to 10.5)
†† Study reported risk difference: NR (-18.8 to 23.6)

Abbreviations: Cat = category; CI = confidence interval; g = grams; IG = intervention group; Int = Intervention; n = number of cases; N = number of participants; NR = not reported; NS = not significant; P5 = 5th percentile; P10 = 10th percentile; RR = relative risk; SGA = small for gestational age

Appendix E Table 3. Mean Birth Weight (Grams) of Infants Born to Treated Pregnant Women Compared With Those Born to Controls

Author, Year	Int arm	IG Mean (SD)	CG Mean (SD)	Between group difference (95% CI); study reported p-value
Brumfit, 1975[2]	IG1	3230 (591)	3169 (613)	61.00 (-56.55, 178.55); p=NS
Elder, 1971[3]	IG1*	3084.4 (526.8)	3122.6 (501.0)	-38.20 (-171.87, 95.47); p=NR
Furness, 1975[5]	IG1	3273.0 (533.0)	3353.0 (532.7)	-64.50 (-238.14, 109.14); p=NS
	IG2	3303.0 (68.2)	3353.0 (73.9)	
Kazemier, 2015[7]	IG1	3453.0 (531.3)	3585.0 (550.1)	-132.00 (-362.09, 98.09); p=NR
Wren, 1969[13]	IG1	3389.0 (560.4)	3142.0 (809.8)	247.00 (40.78, 453.22); p=0.01

***** Excludes induced onset of labor

Abbreviations: Cat = category; CI = confidence interval; g = grams; IG = intervention group; Int = Intervention; NR = not reported; NS = not significant; SD = standard deviation

Appendix E Table 4. Rates of Perinatal Mortality Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls

Author, Year	Outcome	Int arm	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Savage, 1967[11]	Fetal loss after 20 weeks gestation	IG1	0/93 (0.0%)	7/98 (7.1%)	0.07 (0.00 to 1.21)
Kincaid-Smith, 1965[8]	Fetal loss after 28 weeks*	IG1	4/61 (6.6%)	4/55 (7.3%)	0.90 (0.24 to 3.43)
Elder, 1971[3]	Infant death occurring prior to hospital discharge	IG1	6/128 (4.7%)	2/145 (1.4%)	3.4 (0.70 to 16.54)
Wren, 1969[13]	Neonatal death/stillbirth	IG1	0/83 (0.0%)	6/90 (6.7%)	0.08 (0.00 to 1.46)
Kazemier, 2015[7]	Perinatal death	IG1	1/40 (2.5%)	0/45 (0.0%)	3.37 (0.14 to 80.36)†
Little, 1966[9]	Perinatal death	IG1	5/124 (4.0%)	2/141 (1.4%)	2.84 (0.56 to 14.39)

* Analysis of IG dropped those with persistent ASB

† Study reported risk difference: 2.5 (-18.8 to 23.6)

Abbreviations: CI = confidence interval; IG = intervention group; Int = Intervention; n = number of cases; N = number of participants; NR = not reported; RR = relative risk

Appendix E Table 5. Rates of Hypertensive Disorders Among Treated Pregnant Women Compared With Controls

Author, Year	Outcome	Description	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Elder, 1971[3]	Toxemia	Excessive weight gain (i.e., hospitalized for the treatment of edema) and preeclamptic toxemia (i.e., specifically written down by the obstetric staff)	8/127 (6.3%)	6/145 (4.1%)	1.52 (0.54 to 4.27)
Kazemier, 2015[7]	Preeclampsia and HELLP syndrome	Diagnosis of Preeclampsia or HELLP syndrome	4/40 (10.0%)	1/45 (2.2%)	4.50 (0.52 to 38.61)*
Kincaid-Smith, 1965[8]	Toxemia	Proteinuria, hypertension (140/90 mmHg or over), or generalized edema†	8/61 (13.1%)	7/55 (12.7%)	1.03 (0.40 to 2.66)
Little, 1966[9]	Toxemia	"Toxemia " or " pre-eclamptic toxemia " in antenatal notes	10/124 (8.1%)	10/141 (7.1%)	1.14 (0.49 to 2.64)
Wren, 1969[13]	Hypertension	Diastolic pressure above 100 mmHg	6/72 (8.3%)	7/79 (8.9%)	0.94 (0.33 to 2.67)

*Study reported risk difference: 3.9 (-17.5 to 24.9)
†Analysis of IG dropped those with persistent ASB

Abbreviations: CI = confidence interval; HELLP = hemolysis, elevated liver enzymes, low platelet count; IG = intervention group; Int = Intervention; mmHg = millimeters of mercury; n = number of cases; N = number of participants; NR = not reported; NS = not significant; RR = relative risk

Appendix E Table 6. Rates of Congenital Malformations Among Infants Born to Treated Pregnant Women Compared With Those Born to Controls

Author, Year	Outcome	Definition	Events in IG n/N (%)	Events in CG n/N (%)	RR (95% CI)
Kincaid-Smith, 1965[8]	Fetal Loss	Fetal loss after 28 weeks*	4/61 (6.6%)	4/55 (7.3%)	0.90 (0.24 to 3.43)
Elder, 1971[3]	Neonatal death/stillbirth	Infant death occurring prior to hospital discharge.	6/128 (4.7%)	2/145 (1.4%)	3.4 (0.70 to 16.54)
Wren, 1969[13]	Neonatal death/stillbirth	NR	0/83 (0.0%)	6/90 (6.7%)	0.08 (0.00 to 1.46)
Kazemier, 2015[7]	Perinatal death	NR	1/40 (2.5%)	0/45 (0.0%)	3.37 (0.14 to 80.36)†
Little, 1966[9]	Perinatal death	NR	5/124 (4.0%)	2/141 (1.4%)	2.84 (0.56 to 14.39)
Savage, 1967[11]	Perinatal death	Fetal loss after 20 weeks gestation	0/93 (0.0%)	7/98 (7.1%)	0.07 (0.00 to 1.21)

* Analysis of IG dropped those with persistent ASB

† Study reported risk difference: 2.5 (-18.8 to 23.6)

Abbreviations: CG = control group; CI = confidence interval; n = number of events; N = number of participants; NR = not reported; NS = not significant; RR = relative risk

Appendix F. Ongoing Studies

Study reference Trial identifier	Study name	Location	Estimated n	Description	2018 Status
NCT03274960	The Effect of Screening and Treatment of Asymptomatic Bacteriuria Every Trimester During Pregnancy on Incidence of Preterm Birth in Harare, Zimbabwe	Zimbabwe (Low HDI)	480	Women randomized to screening/treatment for ASB or no screening/treatment. For the screening group screening will be repeated in each trimester. Primary outcome is preterm birth.	Ongoing Est. completion date: 11/30/18

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