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Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery: An Updated Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review the evidence about screening for bacterial vaginosis during pregnancy to prevent preterm delivery.

Data Sources: MEDLINE, the Cochrane Library, and trial registries through May 29, 2019; bibliographies from retrieved articles, outside experts, and surveillance of the literature through July 31, 2019.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We selected studies that evaluated the diagnostic accuracy of commercially available tests or tests feasible within primary care settings for bacterial vaginosis. We also selected controlled trials of treatment with metronidazole or clindamycin for bacterial vaginosis during pregnancy that reported preterm delivery or maternal adverse effect outcomes, and we selected observational studies that evaluated harms to children from in utero exposure to the medications. We excluded studies with poor methodological quality and studies conducted in developing countries.

Data Extraction and Analysis: One investigator extracted data and a second checked accuracy. Two reviewers independently rated methodological quality for all included studies using predefined criteria. When at least three similar studies were available, meta-analyses were conducted.

Data Synthesis: We included 44 studies. We did not identify any studies directly evaluating health benefits or harms of screening. Twenty-five studies evaluated the accuracy of screening tests; most were conducted in nonpregnant, symptomatic women. The sensitivity (Sn) and specificity (Sp) varied by test: BD Affirm (pooled Sn, 0.87 [95% confidence interval (CI), 0.80 to 0.92], pooled Sp, 0.81 [95% CI, 0.73 to 0.88]; 5 studies; 2,936 participants), BD Max (Sn, 0.93 [95% CI, 0.91 to 0.94], Sp, 0.92 [95% CI, 0.90 to 0.94]; 1 study; 1,338 participants), BV Blue (Sn range, 0.61 to 0.92; Sp range, 0.86 to 0.99; 3 studies; 864 participants), Amsel's clinical criteria (pooled Sn, 0.76 [95% CI, 0.63 to 0.85]; pooled Sp, 0.95 [95% CI, 0.89 to 0.98]; 14 studies, 5,790 participants), and modified Amsel's clinical criteria (pooled Sn, 0.67 [95% CI, 0.54 to 0.78]; pooled Sp, 0.96 [95% CI, 0.93 to 0.98]; 4 studies; 2,477 participants).

Thirteen randomized, controlled trials (RCT) compared either oral metronidazole or oral or intravaginal clindamycin with either a placebo control or with no treatment for asymptomatic bacterial vaginosis in pregnancy. Among a general obstetric population, six RCTs reported no difference in any delivery before 37 weeks gestation (pooled absolute risk difference [ARD], 0.20% [95% CI, -1.13% to 1.53%]; 6,307 participants), and eight RCTs reported no difference in spontaneous delivery before 37 weeks (pooled ARD, -1.44% [95% CI, -3.31% to 0.43%]). No treatment effects were observed for other pregnancy outcomes including delivery before 32 weeks gestation, low birth weight, premature rupture of membranes, and several others. In the four RCTs reporting preterm delivery before 37 weeks among women with a prior preterm delivery, three reported a significant reduction for treatment compared with control, and one reported no difference. In two RCTs reporting preterm delivery before 34 weeks among women with a prior preterm delivery, both reported no difference between treatment and control groups.

Fourteen studies reported on harms of treatment. Among eight RCTs reporting maternal adverse effects, events were infrequent and minor (e.g., candidiasis, gastrointestinal upset) but were slightly more common for oral clindamycin and metronidazole compared with placebo. Six observational studies reported on adverse effects on children exposed to oral metronidazole in utero. Two meta-analyses of observational studies reported no difference in congenital malformations in exposed children (odds ratio [OR], 0.96 [95% CI, 0.75 to 1.22]; OR, 1.08 [95% CI, 0.90 to 1.29]). Findings from three additional studies published subsequent to these metanalyses observed similar results. One cohort study reported no increased incidence of childhood cancer among exposed children (adjusted relative risk [RR], 0.81 [95% CI, 0.41 to 1.59]).

Limitations: Only English-language studies were included. No direct evidence for the benefits or harms of screening was identified. The evidence on diagnostic accuracy may have limited applicability to pregnant, asymptomatic populations. We did not assess comparative accuracy of tests or comparative effectiveness or harms of treatments. Studies of treatment were generally underpowered for harm outcomes. We did not evaluate treatments other than metronidazole and clindamycin.

Conclusions: We identified no direct evidence that compared screening with no screening and that reported health outcomes. Diagnostic test accuracy studies were mostly conducted in nonpregnant, symptomatic women; the sensitivity of the various tests ranged from 0.61 to 0.93 and the specificity ranged from 0.49 to 0.98. RCTs conducted in general obstetric populations reported no difference in the incidence of preterm delivery and related outcomes for treatment with metronidazole or clindamycin compared with placebo. The evidence is inconclusive for treatment in women with a prior preterm delivery. Maternal adverse events from treatment with metronidazole or clindamycin are infrequent and minor. The observational study evidence about harms to children from in utero exposure to medication is inconclusive because of study limitations and imprecision.

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Abbreviations

AE	Adverse events	N	Number of participants
AHRQ	Agency for Healthcare Research and Quality	NR	Not reported
ARD	Absolute risk difference	OR	Odds ratio
AUC	Area under the curve	PCR	Polymerase chain reaction
BV	Bacterial vaginosis	PPROM	Preterm premature rupture of membranes
BMI	Body mass index	PTD	Preterm delivery
CI	Confidence interval	PTL	Preterm labor
CLIA	Clinical Laboratory Improvement Amendment	RCT	Randomized controlled trial
CQ	Contextual question	RR	Relative risk
EPC	Evidence-based practice Center	SAE	Serious adverse events
FDA	Food and Drug Administration	Sn	Sensitivity
IF	Intermediate Flora	SOE	Strength of evidence
HIV	Human immunodeficiency virus	Sp	Specificity
k	Number of studies	SROC	Summary receive operating characteristics curve
KQ	Key question	STI	Sexually transmitted infections
LR	Likelihood ratio		

Chapter 1. Introduction

Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to update its 2008 recommendation on screening for bacterial vaginosis in pregnancy to prevent preterm delivery.[1] The 2008 recommendation was an update to the 2001 recommendation on this topic and is summarized as follows:

- The USPSTF recommended against screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery (D recommendation).
- The USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery (I statement).

The USPSTF made the 2008 recommendation based on an updated systematic review published in 2008.[2, 3]

Condition Definition

Bacterial Vaginosis

Bacterial vaginosis is a common lower genital tract syndrome defined as a shift from normal hydrogen peroxide–producing lactobacilli to mixed anaerobes, such as *Gardnerella* species, *Prevotella* species, and *Atopobium* species.[4, 5] *Lactobacillus* species comprise between 90 percent and 95 percent of the total bacteria count in the healthy vaginal flora and play a key role in maintaining balance and host defense against pathogens by producing several substances that inhibit the growth of deleterious microorganisms.[6, 7] Symptoms of bacterial vaginosis typically include off-white, thin, homogenous discharge or vaginal "fishy" odor, or both; however, many women with bacterial vaginosis are asymptomatic.

Preterm Delivery

Preterm delivery is defined as birth before 37 completed weeks of gestation.[8] Preterm deliveries can be classified into two broad subtypes: (1) spontaneous preterm delivery following the spontaneous onset of preterm labor or following premature rupture of membranes (PROM) and (2) provider-initiated preterm delivery (i.e., medically indicated or elective inductions of labor or caesarean births). Although the 37-week cutoff is the conventional definition of preterm delivery, adverse outcomes associated with prematurity are inversely related to the gestational age at delivery and may continue until 39 weeks, albeit at lower rates.[9]

Prevalence and Burden of Disease/Illness

Bacterial Vaginosis

Worldwide bacterial vaginosis prevalence estimates range from 12 percent in Australian women and 29 percent in North American women to more than 50 percent in women from Eastern and Southern Africa.[10] The prevalence of bacterial vaginosis in the United States is estimated to be 29.2 percent among all women age 14 to 49 years (some of whom are pregnant), corresponding to 21 million women, according to National Health and Nutrition Examination Survey (NHANES) data from 2001 through 2004, the most recent years for which nationally representative estimates are available.[11] Prevalence varies most notably by race and ethnicity. The NHANES data from 2001 through 2004 showed significantly higher rates among African Americans (52.6%) and Mexican Americans (32%) than among non-Hispanic whites (23%).[11] Among five studies published between 1995 and 2014, a higher prevalence of bacterial vaginosis (range 25% to 50%) was observed among women who have sex with women.[12] In the United States, the prevalence of bacterial vaginosis among pregnant women ranges from 5.8 to 19.3 percent and is influenced by the study population and the diagnostic criteria. The prevalence is higher in some races.[13]

Studies estimate only 25 percent to 50 percent of women with bacterial vaginosis report symptoms.[14-16] Disease recurrence within 12 months of treatment occurs in over half of cases; some suggest this is because bacterial vaginosis results from a disturbance of the vaginal microflora as opposed to definitive infection caused by a single organism.[17] In symptomatic women, studies have shown that recurrent bacterial vaginosis is associated with a significant adverse impact on self-esteem, sexual relationships, and quality of life.[18] Further, women who have bacterial vaginosis are at increased risk for the development of infection with herpes simplex virus type 2, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and human immunodeficiency virus (HIV).[19] Based on epidemiological studies, bacterial vaginosis has been associated with a range of adverse gynecologic and obstetric outcomes including early miscarriage and recurrent pregnancy loss (adjusted relative risk [RR], 2.03 [95% confidence interval [CI], 1.09 to 3.78]),[20] pregnancy loss before 22 weeks (RR range, 3.1 [95% CI, 1.4 to 6.9]),[21] pelvic inflammatory disease (magnitude not well defined),[22] postabortion sepsis (magnitude not well defined),[23] postpartum endometritis (odds ratio [OR], 5.8 [95% CI, 3.0 to 10.9]),[24] and low birth weight (OR, 1.4 [95% CI, 1.1 to 1.8]).[25]

Preterm Delivery

Worldwide, an estimated 11.1 percent (14.9 million) of all live births in 2010 were preterm.[26] In 2018 in the United States, 10.0 percent of live births were preterm, and its complications, such as major intraventricular hemorrhage, acute respiratory illnesses, and sepsis, are the leading causes of death among infants.[27-30] The U.S. National Vital Statistics Reports from 2013 reported that two thirds of all infant deaths in the United States occurred among infants born preterm; the mortality incidence for infants born less than 32 weeks, 32 to 33 weeks, 34 to 36 weeks, and 37 to 38 weeks was 163.7, 16.02, 7.23, and 3.01 per 1,000 live births, respectively, compared with 1.85 for full-term infants.[27] Preterm birth rates vary by race in the United States: the 2018

preterm birth rate was 8.6 percent among Asian women, 11.8 among Native Hawaiian or Other Pacific Islander women, 9.7 percent among Hispanic women, 11.5 percent among American Indians or Alaska Native women, 14.1 percent among black women, and 9.1 percent among white women.[29] In an epidemiologic review of 16 studies reporting on the pattern of preterm delivery, spontaneous preterm labor was reported as the etiology in 27.9 percent to 64.1 percent of preterm deliveries, PPROM was reported as the etiology in 7.1 percent to 51.2 percent of preterm deliveries, and medical indication was reported in 18.7 percent to 35.2 percent of preterm deliveries.[31]

The frequency and severity of adverse outcomes from preterm delivery are higher with earlier gestational age and lower quality of health care during the puerperium. Most babies born at less than 28 weeks of gestational age need neonatal intensive care services to survive, and most babies born at 28 to 32 weeks need special newborn care at a minimum. Babies born before 32 weeks are at especially high risk of cerebral palsy, intellectual impairment, and vision and hearing loss.[32] The vast majority (84%) of all preterm deliveries occur between 32 weeks and 37 weeks.[33] Most babies born between 32 and 37 weeks survive with adequate supportive care but are still at increased risk of neonatal and infant death, cerebral palsy leading to neurodevelopmental delays, and lower school performance. Large economic costs are associated with preterm delivery, including neonatal intensive care and long-term complex health needs and disabilities. In the United States, the costs related to preterm delivery exceeded $26 billion annually in 2006, not including indirect costs.[34]

Etiology and Risk Factors

Bacterial Vaginosis

Bacterial vaginosis is caused by a disruption of the microbiotic environment in the lower genital tract.[35] Mucosal homeostasis is normally maintained in the vaginal canal by an intricate balance between the host mucosal immune response and the microbiota that colonize the mucosal surfaces.[7] *Lactobacillus* species play a key role in maintaining balance and host defense against pathogens by producing several substances that inhibit the growth of deleterious microorganisms.[6, 7] *Lactobacillus* species are thought to inhibit the growth of pathogenic bacteria by generating hydrogen peroxide and other antimicrobials and by maintaining a highly acidic environment (lower pH through lactic acid), which can disrupt bacterial cell membranes and stimulate host immunity.[36] Bacterial vaginosis is characterized by a marked depletion of *Lactobacillus* species and a 1,000-fold increase in the number of anaerobic bacteria.[6, 7] Although it was previously thought that the *Gardnerella* species was the defining organism, multiple anaerobic bacteria, including *Gardnerella*, *Prevotella*, *Atopobium*, *Megasphera,* and others, have been identified.[37, 38] In some women with bacterial vaginosis, up to 35 unique species have been identified.[38] The availability of inexpensive and efficient gene-sequencing assays have allowed for the objective identification of communities of microorganisms and fastidious organisms that were difficult to identify through traditional culture techniques. These laboratory advances have provided data to solidify the concept of bacterial vaginosis as a disbalance in the vaginal microbiome ecosystem.[38] Further research also supports the concept of bacterial vaginosis as a biofilm, which is a community of microorganisms attached to epithelial surfaces and encased in

matrices of polysaccharides, proteins, and nucleic acids.[38-40] Biofilms can persist even in the presence of lactic acid producing bacteria and despite antibiotic usage.

Bacterial vaginosis is sometimes thought of as sexually transmitted. Although several studies have shown the presence of bacterial vaginosis in women who report never having sex,[11, 35, 41] this may be due to varying study definitions of sex (only penetrative or including nonpenetrative sex) and bias surrounding self-reporting.[42-44] Evidence shows that certain sexual behaviors increase the incidence of bacterial vaginosis, including a higher number of partners, lack of condom or contraceptive use, vaginal sex, sex with a female partner, and concurrent sexually transmitted infections (STIs).[45] The RR for incident bacterial vaginosis associated with having a new sexual partner is 1.13 (95% CI, 1.02 to 1.25).[45] The risk for recurrent or persistent bacterial vaginosis over 12 months from sex with the same partner (adjusted RR, 3.1 [95% CI, 1.6 to 6.3]) and any female sexual partner (adjusted RR, 3.6 [95% CI, 1.5 to 8.5]) is also elevated.[17]

Race is also a significant risk for bacterial vaginosis: African American women have the highest prevalence and non-Hispanic white women have the lowest prevalence.[11] Some have postulated this difference could be explained by genetics, socioeconomic status, psychosocial stress, or sexual networks.[7, 46, 47] Research on the relationship between vaginal pH and microbiota also suggests some underlying racial variation in microbiota composition.[48] Women of European ancestry are more likely to have microbiota dominated by *Lactobacilli* species whereas African American women are more likely to exhibit a diverse microbial profile and higher pH.[48] Some investigators have also suggested that nutritional factors may play a role; higher dietary fat intake is associated with bacterial vaginosis, while higher consumption of folate, vitamin E, and calcium have an inverse relationship with bacterial vaginosis.[49] Other factors associated with bacterial vaginosis include poverty, smoking, increased body mass index, vaginal douching, and low educational attainment.[12]

Preterm Delivery

Preterm delivery likely has multiple causes and although several risk factors have been identified as predictive of preterm delivery, it is unclear whether these factors are causal or simply intermediate markers for some other underlying cause(s). A 2007 meta-analysis suggested that the risk of preterm delivery is doubled in the presence of asymptomatic bacterial vaginosis (pooled OR, 2.16 [95% CI, 1.56 to 3.00], 32 studies; 30,518 participants).[50] **Appendix A** (Contextual Questions 1, 2, and 3) provides additional contextual information about the relationship between bacterial vaginosis and preterm delivery and the relationship between bacterial vaginosis and other risks for preterm delivery. An exact causal mechanism is poorly understood, but early hypotheses were that bacterial vaginosis causes infection of the upper genital tract, which may contribute to preterm labor, PPROM, or both.[25, 51] More recent research suggests a more complicated etiology. The mucosal immune response, which is influenced by many factors including genetics, ethnicity, stress, hormones, and the vaginal microbiome, may influence both the risk for acquiring bacterial vaginosis and preterm labor or PPROM.[46] Some experts have also suggested that the risk of preterm delivery may depend less on the type of vaginal flora and more on the type of host immune response to the flora, in particular the presence and response to biofilms.[50, 52]

A significant predictor of preterm delivery is having a prior spontaneous preterm delivery. A secondary analysis of the Preterm Prediction Study dataset reported that women with a history of spontaneous preterm delivery had a 2.5-fold increased risk (95% CI, 1.9 to 3.2) of spontaneous preterm delivery in a subsequent pregnancy compared with women with no history of spontaneous preterm delivery.[53]

Cervical insufficiency, the failure of the cervix to remain closed during pregnancy, is also a risk factor for preterm delivery. Cervical insufficiency is largely assessed with cervical length as measured by digital or ultrasound examinations; the shorter the cervix, the higher the risk for preterm delivery.[54] One study showed that the risk of spontaneous preterm delivery before 35 weeks decreased by 6 percent for each additional millimeter of cervical length (OR, 0.94 [95% CI, 0.92 to 0.95]),[55] and another study found that treatment of women with short cervix using vaginal progesterone was associated with a significant reduction in the risk of preterm birth less than 33 weeks of gestation (RR, 0.62 [95% CI, 0.47 to 0.81]).[56]

Other risk factors for preterm delivery include genitourinary infections, HIV infection, maternal medical conditions, young or advanced maternal age, low maternal body mass index, inadequate prenatal care, short interpregnancy intervals, nonsingleton pregnancies, and maternal race.[34, 51, 52, 57] Other factors that increase the risk of spontaneous preterm delivery include extreme psychosocial stress,[58] excessive physical strain and exhaustion,[59] smoking,[60] and periodontal disease.[61]

In the United States, the rate of preterm delivery among nulliparous African American women is twice as high and the rate of recurrent preterm delivery is four times as high as the rate among white women.[52] Researchers have hypothesized that racial differences in preterm delivery incidence are partly due to commensurate racial differences in bacterial vaginosis prevalence.[62]

Rationale for Screening/Screening Strategies

The rationale for screening asymptomatic pregnant women for bacterial vaginosis is to identify women with bacterial vaginosis early so that they can be offered treatment. Early identification and treatment of bacterial vaginosis may reduce the incidence of preterm delivery and the morbidity and mortality associated with preterm delivery.

The availability of gene sequencing techniques has advanced our understanding of the vaginal microbiome and the dysbiotic and biofilm properties that characterize bacterial vaginosis. However, existing diagnostic techniques largely predate this most current understanding. The epidemiologic and laboratory reference test standard for the diagnosis of bacterial vaginosis is a Gram stain of vaginal secretions, most commonly interpreted using the Nugent scoring system, which scores a specimen from 0 to 10. Scores of 0 to 3 indicate normal flora, scores of 4 to 6 indicate intermediate flora, and scores from 7 to 10 indicate bacterial vaginosis.[63, 64] Additional information about intermediate flora is in **Appendix A** (Contextual Questions 1 and 2). Amsel's clinical criteria are widely used in research and clinical practice. Both the Nugent scoring system and Amsel's clinical criteria are described in detail in **Appendix A Table 1**. A clinical diagnosis is made with Amsel's clinical criteria by fulfilling three of four criteria (we refer to these as

"complete Amsel's criteria" in this report): vaginal pH greater than 4.5, the presence of clue cells (typically at least 20% of vaginal epithelial cells) on wet mount microscopy, thin homogeneous discharge, and an amine (i.e., fishy) odor when potassium hydroxide is added to the vaginal secretions. A modified version of Amsel's test omits the criteria for vaginal discharge. The degree of interobserver and intraobserver variability in the Gram stain interpretation is lower compared with Amsel's clinical criteria and offers the added ability to quantify and classify bacterial load, but scoring of morphotypes can be subjective and interpretation requires specific skills and volume of testing to be proficient.[38, 64]

In recent years, other tests have been approved by the U.S. Food and Drug Administration (FDA) for aiding in the diagnosis of bacterial vaginosis. These include assays based on nucleic acids from a single swab of secretions to detect vaginosis-associated bacterial species; these tests can also detect nonvaginosis-associated organisms such as *Trichomonas vaginalis* and *Candida* species. The BD Affirm Vaginal Panel III uses a nonamplified DNA probe specific to *Gardnerella vaginalis*, while the BD MAX Vaginal Panel is a multiplex polymerase chain reaction (PCR) assay that tests for five vaginosis-associated organisms: *Lactobacillus* species, *Gardnerella vaginalis*, *Atopobium vaginae*, Bacterial Vaginosis Associated Bacteria-2 (BVAB-2), and *Megasphaera*-1.[65] Several other multiplex PCR assays are commercially available (NuSwab, SureSwab) but evaluate slightly different panels of vaginosis-associated bacteria. These assays are offered by large, national laboratories and are considered laboratory developed tests within the Clinical Laboratory Improvement Amendment (CLIA) program and are not required to be approved by the FDA. AmplisensFlorocenosis-BV is approved for use in the European Union but is not FDA approved.[66, 67] Assays that detect elevated vaginal fluid sialidase activity (BV Blue, FDA approved) associated with vaginosis and pH paper-coated vaginal swabs (VS-Sense-Pro, FDA approved) to detect alterations in vaginal pH commonly seen with bacterial vaginosis are also available.[65, 68-72]

Interventions/Treatment

Bacterial vaginosis is typically treated with medications that provide broad-spectrum anaerobic coverage, most commonly, metronidazole or clindamycin (see **Appendix A Table 2** for commonly recommended doses, routes, and frequencies). Vaginal Cleocin (clindamycin) cream is the only medication with an FDA-label indication for the treatment of bacterial vaginosis in pregnant women (second trimester only). However, the Centers for Disease Control and Prevention recommend either clindamycin or metronidazole in oral or vaginal preparations for the treatment of bacterial vaginosis in pregnant women.[15]

Although short-term cure rates following first-line recommended regimens (i.e., clindamycin and metronidazole) are equivalent and approach 80 percent, studies with extended followup report recurrence rates in excess of 50 percent within 6 to 12 months.[17, 73] Recurrence may be due to partner reinfection or the persistence of the biofilm—the bacteria within a slimy extracellular matrix adherent to the vaginal surface that can be difficult to eradicate and that has been documented by vaginal biopsy after therapy with metronidazole.[17, 74] Other drugs, such as tinidazole and secnidazole, have FDA indications for the treatment of bacterial vaginosis, but data are limited regarding their use in pregnancy. Rifaximin is FDA approved but does not have

a label indication for bacterial vaginosis and dequalinium chloride is not FDA approved for any indication in the United States. Nutriceuticals and probiotic agents are marketed with claims of "preserving vaginal health," but none have been FDA approved for the treatment of bacterial vaginosis.

Treatment of bacterial vaginosis in nonpregnant women is typically limited to symptomatic cases. For context, we summarized the harms of treatment of bacterial vaginosis in nonpregnant women in **Appendix A** (Contextual Question 5).

Current Clinical Practice

Appendix A Table 3 summarizes recommendations of professional organizations related to screening asymptomatic women in pregnancy for bacterial vaginosis. For organizations with recommendations on this topic, all either do not recommend routine screening for women at low risk for preterm birth or state the evidence is insufficient to support routine screening. However, the recommendations conflict with respect to screening among women at high risk for preterm birth. One recommends screening and/or treatment among women at increased risk for preterm birth, one recommends against, while others do not specifically address a higher risk population. A limited amount of research is available that describes current practice patterns among physicians with regard to screening for bacterial vaginosis; this information is summarized in **Appendix A** (Contextual Question 4).

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions (KQs) for this review. The analytic framework illustrates the KQs that guided the review (**Figure 1**). The KQs were as follows:

1. Does screening for bacterial vaginosis in asymptomatic pregnant adolescents and women reduce preterm delivery and related morbidity and mortality?
   a) Does the effect of screening vary by baseline risk (e.g., low- vs. high-risk) for preterm delivery?
   b) Does the effect of screening vary by race or ethnicity?
   c) Does the effect of screening vary by maternal age?
   d) Does the effect of screening vary by gestational age?
   e) Does the effect of screening vary by other risks for preterm delivery (e.g., coinfection with sexually transmitted infections, HIV status)?
2. What is the diagnostic accuracy of tests used to screen for bacterial vaginosis?
   a) Does diagnostic accuracy vary based on whether an individual is pregnant?
3. What are the harms of screening for bacterial vaginosis in asymptomatic pregnant adolescents and women?
4. Does treatment of bacterial vaginosis during pregnancy reduce preterm delivery and related morbidity and mortality?
   a) Does the effect of treatment vary by baseline risk (e.g., low- vs. high-risk) for preterm delivery?
   b) Does the effect of treatment vary by race or ethnicity?
   c) Does the effect of treatment vary by maternal age?
   d) Does the effect of treatment vary by gestational age?
   e) Does the effect of treatment vary by other risks for preterm delivery (e.g., coinfection with sexually transmitted infections, HIV status)?
5. What are the harms of treatment of bacterial vaginosis in pregnant adolescents and women?
   a) What are harms to pregnant adolescents and women?
   b) What are harms to the fetus or newborn?

In addition to our KQs, we looked for evidence related to five contextual questions (CQs).

1. What is the association between bacterial vaginosis, intermediate flora, or abnormal vaginal flora and preterm delivery in U.S. populations or in similar populations if no U.S. data are available or are limited?
2. Is treatment of intermediate flora and abnormal flora associated with reduced preterm delivery?
3. What is the association between bacterial vaginosis and other known risks for preterm delivery?

4. What is the uptake or use of various diagnostic tests for bacterial vaginosis in clinical practice?
5. What are the adverse drug events related to metronidazole or clindamycin when used to treat bacterial vaginosis in nonpregnant women and adolescents?

We do not show these CQs in the analytic framework because they were not analyzed using the same systematic review process as the KQs. Findings related to the CQs are summarized in **Appendix A**.

Data Sources and Searches

We searched MEDLINE (via PubMed), Embase, and the Cochrane Library for English-language articles from January 1, 2006, through May 29, 2019, building on the literature included in the prior 2008 evidence review for the USPSTF.[2, 3] For KQ 2 (diagnostic test accuracy), we conducted a PubMed search from inception through December 31, 2005, because both prior reviews on this topic did not include a systematic search for this KQ. We used Medical Subject Headings (MeSH) terms when available and keywords to describe relevant screening tests, treatment interventions, populations, and study designs. The complete search terms and limits are detailed in **Appendix B Tables B1** and **B2**. We also searched the clinicaltrials.gov registry and the World Health Organization International Clinical Trials Registry Platform. To supplement the electronic database searches, we screened relevant systematic reviews and reference lists of included articles. We conducted surveillance of the literature through July 31, 2019.

Study Selection

We developed inclusion and exclusion criteria for selecting studies based on populations, interventions, comparators, outcomes, timing, settings, and study designs; these are described in detail in **Appendix B3**. Briefly, for KQs 1, 3, 4, and 5, we selected controlled trials (randomized or nonrandomized) conducted in pregnant women or adolescents; for KQs 1 and 3, we also required participants to be asymptomatic with respect to vaginal symptoms. For KQs 1 and 3, we selected studies that compared screening with no screening and reported health outcome benefits (e.g., preterm delivery) or harms (e.g., anxiety). For KQs 4 and 5, we selected trials that compared treatment with metronidazole or clindamycin with placebo or no treatment in symptomatic or asymptomatic pregnant women with bacterial vaginosis and that reported health outcomes related to preterm delivery, other adverse pregnancy outcomes, or adverse maternal effects of treatment. For KQ 5, we also selected observational studies that reported on adverse maternal effects or outcomes related to fetal exposure to metronidazole or clindamycin, such as carcinogenesis or congenital malformations. For KQ 2, we selected studies that reported on diagnostic test accuracy for Amsel's clinical criteria or laboratory-based tests in commercial use or feasible for use in primary care settings. We did not require participants to be pregnant in studies selected for KQ 2. Systematic reviews similar in scope to our review were also eligible for study selection for all KQs. Two independent reviewers screened titles and abstracts and then full-text articles for selection; disagreements were resolved by discussion or by a third reviewer. We included English-language studies that met all study selection criteria, that were fair or good

methodological quality, and that were conducted in the 58 countries categorized as very highly developed by the 2017 Human Development Index.[75] We reassessed studies from the prior 2008 review against the study selection and methodological quality criteria for this update.

Quality Assessment and Data Abstraction

For each included study, one reviewer abstracted relevant study characteristics (i.e., population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy, and the lead investigator reviewed all abstracted information for consistency across included studies. We contacted some study authors to clarify some data. We did not use data included in the previous review that we could not verify from the original source publication or from study authors.

Two senior reviewers independently assessed each study's methodological quality. Disagreements in study quality ratings were resolved through discussion or with an independent assessment from a third senior investigator. For randomized, controlled trials (RCTs), we used a risk of bias instrument (RoB 2.0) from the Cochrane Collaboration, which assesses the following risk of bias domains: bias arising from selection or randomization, bias due to missing outcome data, bias due to departures from intended interventions, bias from measurement of outcomes, and bias from selective reporting of results.[76] For controlled cohort studies, we used the ROBINS-I instrument, which includes similar domains as the RoB 2.0 instrument, but includes additional domains related to confounding and measurement of the exposure.[77]

For case-control studies, we used a methodology checklist from the Scottish Intercollegiate Guidelines Network.[78] For systematic reviews and meta-analyses, we used the ROBIS instrument to assess methodological quality.[79] For studies of diagnostic test accuracy, we used the QUADAS-2 instrument.[80] We translated our risk of bias assessments using these instruments into an overall study quality rating using the predefined criteria developed by the USPSTF (**Appendix B3**), which uses study methodological quality ratings of poor, fair, and good. Studies reporting multiple outcomes may have been assigned different quality ratings for different outcomes.

Data Synthesis and Analysis

For diagnostic test accuracy (KQ 2), we synthesized data related to sensitivity, specificity, and likelihood ratios in tabular and narrative formats. When at least three studies using the same index test and test threshold were available, we performed a quantitative synthesis by fitting the bivariate model described by Reitsma et al[81] with the metandi package in Stata (version 15) to generate a summary receiver operating characteristics curve (SROC) and a pooled summary point estimate of sensitivity and specificity. We generated a 95 percent confidence region around the pooled summary point on the SROC curve, which represents a measure of sampling variation (i.e., chance) and can be used to assess precision of the pooled summary estimate. We also generated a 95 percent prediction region around the pooled summary estimate on the SROC curve. The prediction region provides a visual estimate of between-study variability and is used

to determine whether there is more variability in results than can be expected due to sampling variability (i.e., chance) alone. For diagnostic test accuracy studies, the use of prediction regions is preferred to the I^2 statistic for assessing heterogeneity because prediction regions take into account the correlation between sensitivity and specificity and account for variation in test thresholds used.[82] Unlike the confidence region, which identifies the region where we expect the "true" summary pooled estimate to lie, the prediction region represents the region where we expect an estimate from a future single study to lie. We assessed the heterogeneity of pooled findings by visual inspection of the forest plots and by the size and shape of the 95 percent prediction region in the ROC space. A prediction region that is much larger than the 95 percent confidence region indicates a high degree of between-study variability that cannot be explained by chance alone.[82, 83] Further, we assessed the symmetry of both the confidence and prediction regions; regions that cover more space in the vertical direction relative to the horizontal direction indicate less precision (confidence region) and more heterogeneity (prediction region) in the estimate of sensitivity compared with the estimate for specificity.

For benefits of treatment (KQ 4), we synthesized findings using both absolute risk differences (ARD) and RR ratios. For harms of treatment (KQ 5), we also used ORs to synthesize findings. We assessed whether a quantitative synthesis was appropriate for KQs 4 and 5 by evaluating the number of studies available and the clinical and methodological heterogeneity present among available studies based on established guidance,[84] which includes evaluating the similarities in study population, medication, dose, and frequency and similarities in timing and specification of outcomes. When a quantitative synthesis was possible, we used random-effects models with the inverse-variance weighted method of DerSimonian and Laird with the metafor package in R (version 2.0-0).[85] We assessed statistical heterogeneity of findings with the I^2 statistic; an I^2 between 0 and 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, and 50 to 90 percent may represent substantial heterogeneity.[76] We assessed the potential for publication bias through visual inspection of a funnel plot when at least 10 studies were included in an analysis.

We assessed the strength of evidence (SOE) based on AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest.[86] Two senior reviewers independently developed initial SOE assessments for each relevant outcome and comparison across the KQs; discrepancies were resolved through discussion and the independent assessment of a third senior reviewer.

For diagnostic test accuracy (KQ 2), we made a single SOE assessment for the outcome of test accuracy for each test evaluated relying on AHRQ's *Methods Guide* and additional guidance specific to assessing SOE for diagnostic test accuracy.[83, 86] We based our SOE assessment on sensitivity and specificity measures that are more clinically useful than global measures of test accuracy (e.g., area under the curve [AUC], diagnostic OR) because they distinguish between the two dimensions of test accuracy (false positives and false negatives).[82] For these SOE assessments, we started all ratings at a "high."[87] Because test accuracy was explicitly identified as an outcome of interest for KQ 2, we considered all test accuracy outcomes as direct with respect to the directness domain of SOE assessment even though diagnostic accuracy is part of the indirect evidence path on the analytic framework. We evaluated the consistency domain

using the 95 percent prediction region for outcomes that were quantitatively synthesized or by evaluating the range of sensitivity and specificity estimates for outcomes where a quantitative synthesis was not possible and considered whether any inconsistency could be explained by differences in population, test threshold, or other study characteristics. We evaluated the precision domain by assessing the size of the 95 percent confidence regions for pooled estimates and the confidence interval range around individual study estimates where a quantitative synthesis was not possible.

For the benefits of treatment (KQ 4), we conducted SOE assessments for each pooled outcome, and conducted separate assessments for the general obstetric population and for the population with a prior preterm delivery. Because preterm delivery outcomes were explicitly identified as an outcome of interest for KQ 4 we considered them to be direct. We evaluated the consistency domain by visual inspection of the forest plot and with the I^2 statistic and by whether any inconsistency could be explained by study population or design characteristics. We evaluated the precision domain by calculating the optimal information size (i.e., sample size needed in a single adequately powered trial) required to generate a precise estimate and by evaluating whether the confidence intervals around pooled estimates crossed clinically meaningful thresholds of benefit (or harm).

For the harms of treatment (KQ 5), we assessed the SOE separately for maternal harms and harms in children exposed to medication in utero. For maternal harms, we aggregated comparisons and outcomes to generate a single SOE rating when possible. For harms in children exposed to medication in utero, we evaluated the SOE for the outcome of congenital malformations separately from the outcome of incident childhood cancer. Because each of these harms was explicitly identified as an outcome of interest for KQ 5, we considered them all to be direct. We evaluated consistency and precision similar to KQ 4 outcomes.

Expert Review and Public Comment

In response to comments received by expert peer reviewers, we updated and clarified some of the prevalence data and risk factor information in the introduction, and we added text to the introduction and discussion for contextual information about the current understanding of the etiology of bacterial vaginosis and its relationship to preterm delivery and implications for diagnosis and treatment. We also revised the risk of bias assessment for one study, added additional limitations to the discussion related to diagnostic test accuracy and applicability of findings related to harms. Finally, we revised the future research needs section to emphasize research in women with a prior preterm delivery.

U.S. Preventive Services Task Force Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

We screened 2,495 titles and abstracts and 368 full-text articles and identified 44 studies from 48 articles for inclusion (**Figure 2**). The list of articles excluded during full-text review is in **Appendix C**. We did not identify any direct evidence for benefits (KQ 1) or harms (KQ 3) of screening. We identified 25 studies of test accuracy (KQ 2) and 13 RCTs evaluating the benefits of treatment with respect to preterm delivery and related pregnancy outcomes (KQ 4). We identified 14 studies evaluating the harms of treatment in pregnancy (KQ 5).

Diagnostic Test Accuracy (Key Question 2)

Twenty-five cross-sectional diagnostic test accuracy studies reported test accuracy for BD Affirm, BD Max, BV Blue, and Amsel's clinical criteria (complete, modified, or individual components). Two of these studies (Gratacos et al[88] and Mastrobattista et al[89]) were discussed in the previous update as part of a contextual question; the rest are new to this update. **Table 1** provides study characteristics and **Tables 2 through 6** provide results organized by test. **Appendix E Tables 1 through 6** provide our assessment of individual study methodological quality. We assessed six studies as good methodological quality;[88, 90-94] the others were assessed as fair quality generally because of unclear enrollment procedures and unclear information regarding blinding of index and reference test results. More than half of studies in this evidence base did not disclose source of funding. Of those studies disclosing funding sources, a mix of industry, government, and internal hospital/clinic support was identified. The rest of this section describes study characteristics and test accuracy findings organized by test and by pregnancy status when possible.

BD Affirm

Five cross-sectional diagnostic test accuracy studies conducted among 2,936 participants evaluated the BD Affirm VP III microbial identification test, which is a nonamplified nucleic acid probe-based test specific to *Gardnerella vaginalis* and *Trichomonas vaginalis*.[90, 95-98] One study (Witt et al) was performed exclusively in a population of pregnant women.[98] Four studies (Briselden et al,[96] Cartwright et al,[95] Lowe et al,[97] and Witt et al[98]) exclusively enrolled symptomatic women, and 76 percent of the study population in the fifth study (Byun et al[90]) was symptomatic. Briselden et al[96] and Cartwright et al[95] recruited participants from STI clinics in the United States. Lowe et al recruited participants from U.S. military health clinics.[97] Byun et al[90] recruited participants from a hospital-based outpatient gynecology clinic in South Korea, and Witt et al[98] recruited participants from an academic obstetrics clinic in Austria. Race/ethnicity of participants was reported by only two studies; 93 percent of participants were African American in Briselden et al,[96] and 43 percent were African American in Lowe et al. HIV status of participants was not reported by any study. The reference test in four studies was a Gram stain of vaginal secretions interpreted according to the criteria of Nugent et al (i.e., score of 7 or higher was positive for bacterial vaginosis), while Lowe et al[97] used complete Amsel's clinical criteria as the reference test. The prevalence of bacterial vaginosis in the enrolled study populations according to the reference standards used in each study ranged from 9.9 percent to 64.6 percent.

We assessed Byun et al[90] as having good methodological quality and assessed the other four studies as having fair methodological quality.

Table 2 provides results from individual studies. **Appendix F Figure 1** depicts the SROC curve comparing BD Affirm with the reference test, and **Appendix F Figure 2** displays a forest plot with individual study characteristics and sensitivity and specificity estimates. The pooled sensitivity based on five studies (2,936 participants) was 0.87 (95% CI, 0.80 to 0.92) and the pooled specificity was 0.81 (95% CI, 0.73 to 0.88). The pooled positive likelihood ratio was 4.6 (95% CI, 3.1 to 6.8), and the pooled negative likelihood ratio was 0.16 (95% CI, 0.11 to 0.26). The AUC associated with the SROC curve was 0.91 (95% CI, 0.87 to 0.94). The 95 percent prediction region covered nearly one third of the ROC space suggesting moderate heterogeneity in the pooled estimates beyond what would be expected because of chance variation. We were unable to qualitatively identify any specific study or population characteristics (e.g., country, mean age of enrolled participants, percentage with symptoms, prevalence of bacterial vaginosis in enrolled population, setting of enrollment, pregnancy status, reference test used) that could explain this heterogeneity.

BD Max

One cross-sectional diagnostic test accuracy study among 1,338 participants evaluated the BD Max Vaginal panel, which is a multiplex PCR assay that uses nucleic acid amplification to identify up to five species associated with bacterial vaginosis.[65, 99] In this study, reported in Schwebke et al[99] and Gaydos et al,[65] participants were recruited from 10 U.S. academic or community-based gynecology clinics and had symptomatic vaginitis. The authors did not report the race/ethnicity, pregnancy, or HIV status of women in this analysis. The reference test used in this study was a Gram stain of vaginal secretions interpreted according to the criteria of Nugent et al. Notably, participants with Nugent scores between 4 and 6 were excluded from the analysis. We assessed this study as fair methodological quality. The prevalence of bacterial vaginosis in the study population according to the reference test was 50.5 percent. **Table 3** provides results for this study. Authors reported the sensitivity of BD Max as 0.93 (95% CI, 0.91 to 0.94) and the specificity as 0.92 (95% CI, 0.90 to 0.94). We calculated the positive likelihood ratio as 10.9 and the negative likelihood ratio as 0.08.

BV Blue

Three cross-sectional diagnostic test accuracy studies conducted among 864 participants reported test accuracy characteristics for the BV Blue test, which is an assay of vaginal secretions for sialidase enzyme activity.[100-102] Two studies (Bradshaw et al,[100] Hillier et al[101]) specifically excluded pregnant women; one study (Myziuk et al[102]) did not report the pregnancy status of enrolled women. Bradshaw et al[100] recruited women from sexual health clinics in Australia and exclusively enrolled symptomatic women. About half of the women in the other two studies were symptomatic; Hillier et al[101] recruited participants from a U.S. academic gynecology clinic and a local health department clinic, and Myziuk et al[102] recruited participants from a single STI clinic in Canada. Race/ethnicity was not reported by any study, and the HIV prevalence was 0 percent in Bradshaw et al,[100] 3.5 percent in Myziuk et al,[102] and not reported by Hillier et al.[101]

All studies used a Gram stain interpreted using Nugent et al criteria as the reference test. The prevalence of bacterial vaginosis based on the refence test used was 38 percent and 21.1 percent in two studies and was not reported in Hillier et al.[101] We assessed all three studies as fair methodological quality. We were unable to generate pooled estimates of test accuracy because of incomplete data provided in Hillier et al.[101]

Table 4 provides results from individual studies. Bradshaw et al reported test accuracy characteristics of the BV Blue test with respect to two different reference tests. Using the reference test of a Gram stain interpreted according to the criteria of Nugent et al, the sensitivity was 0.88 (95% CI, 0.81 to 0.93) and the specificity was 0.86 (95% CI, 0.80 to 0.91).[100] Using the reference test of Amsel's clinical criteria (positive findings on three of the four criteria), the sensitivity was the same, but the specificity was slightly higher (0.91 [95% CI, 0.85 to 0.94]). Hillier et al reported a sensitivity of 0.61 (95% CI, 0.51 to 0.71) and a specificity of 0.99 (95% CI, 0.96 to 1.0); estimates were higher when limited to only symptomatic individuals.[101] Myziuk et al reported a sensitivity of 0.92 (95% CI, 0.65 to 0.996) and a specificity of 0.98 (95% CI, 0.90 to 0.999).

Complete Amsel's Clinical Criteria

Fifteen cross-sectional diagnostic test accuracy studies conducted among 7,171 participants reported test accuracy characteristics of complete Amsel's clinical criteria.[88, 91, 92, 99-110] One study (Gratacos et al,[88] N=492) exclusively enrolled asymptomatic pregnant women, and one study (Gutman et al,[109] N=269) included pregnant women but they represented only 13 percent of the study population. The rest of the studies either excluded pregnant women or did not report on the pregnancy status of enrolled participants. Studies differed in the percentage of included women who were reported as being symptomatic. The study populations in two studies (Gratacos et al[88] and Hay et al[91]) were nearly all asymptomatic. Six studies did not report the symptom status of enrolled participants, and the rest of the studies either exclusively enrolled symptomatic participants or nearly third to half of the enrolled populations were symptomatic. The settings used to enroll participants varied from single-center STI clinics to multicenter academic or hospital-based gynecology clinics. Eight studies were conducted in the United States. Two of the U.S. studies recruited participants enrolled in longitudinal prospective cohort studies of participants with HIV or at risk for HIV.[103, 106] The prevalence of HIV among participants in these studies was 67 percent in Gallo et al and 74 percent in Sha et al. Results for these studies were stratified by HIV status. The rest of the studies either excluded HIV-positive participants or did not report the HIV status of enrolled participants.

Two studies (Platz-Christensen et al[92] and Hay et al[91]) used a Gram stain of vaginal secretions interpreted according to the criteria of Spiegel et al as the reference test; the rest of the studies used a Gram stain interpreted according to the criteria of Nugent et al. The prevalence of bacterial vaginosis based on the refence test used ranged from 4.5 percent to 63.5 percent across studies. We assessed three studies (Gratacos et al,[88] Hay et al,[91] and Platz-Christensen et al[92]) as good methodological quality and assessed the rest as fair methodological quality.

Table 5 provides results from individual studies. **Appendix F Figure 3** depicts the SROC curve for complete Amsel's clinical criteria compared with the reference test, and **Appendix F Figure**

4 displays a forest plot with individual study characteristics and sensitivity and specificity estimates. The pooled sensitivity based on 14 studies (5,790 participants) was 0.76 (95% CI, 0.63 to 0.85), and the pooled specificity was 0.95 (95% CI, 0.89 to 0.98). The pooled positive likelihood ratio was 14.1 (95% CI, 6.8 to 29.2), the pooled negative likelihood ratio was 0.26 (95% CI, 0.17 to 0.39), and the AUC was 0.93 (95% CI, 0.89 to 0.95). The 95 percent prediction region covered more than one third of the SROC space indicating substantial heterogeneity with respect to the estimate of sensitivity and specificity that cannot be explained by chance variation. We explored several potential sources of heterogeneity including how participants with intermediate flora were handled in the analysis (included or excluded), the number of Amsel's clinical criteria required for a "positive" test (three vs. four), the threshold used for the clue cell criteria (unspecified vs. 20% or more clue cells), different Gram stain interpretation criteria (Spiegel vs. Nugent), whether participants were symptomatic or asymptomatic, and use of different units of analysis (person vs. visits). We note that the only study conducted exclusively among pregnant women (Gratacos et al) reported the lowest sensitivity among all studies (0.36 [95% CI, 0.20 to 0.57]); its specificity was 0.99 (95% CI, 0.98 to 1.0).[88] The women in this study were all asymptomatic. None of the studies that enrolled both symptomatic and asymptomatic women reported findings stratified by symptom status. Further, among the four studies that enrolled exclusively symptomatic women, the sensitivity ranged from 0.72 to 0.92 and the specificity ranged from 0.77 to 0.94. Thus, we could not explain heterogeneity of findings based on symptom status of enrolled participants or any other characteristics that we evaluated.

Hillier et al did not report complete data, so we could not include it in our quantitative synthesis. The reported sensitivity and specificity in this study were 0.67 (95% CI, 0.57 to 0.76) and 1.0 (95% CI, 0.98 to 1.0), respectively.[101] When limited to the subgroup of symptomatic women, the estimate of sensitivity was higher (0.82) and specificity was lower (0.94) in this study.[101]

Modified Amsel's Clinical Criteria

Five cross-sectional diagnostic test accuracy studies conducted among 2,674 participants reported on test accuracy characteristics of modified Amsel's clinical criteria.[88, 89, 99, 107, 108] Study authors modified Amsel's clinical criteria by not including the criteria for the presence of vaginal discharge.; all but one study[108] required two of three criteria to be present for a positive test. Two studies (Gratacos et al[88] and Mastrobattista et al[89]) exclusively enrolled asymptomatic pregnant women, and two studies (Singh et al[107] and Schwebke et al[99]) exclusively enrolled symptomatic women. All but one study[88] was conducted in the United States. Two studies enrolled participants from obstetric clinics;[88, 89] one study enrolled participants from a single STI clinic;[107] one study enrolled participants from academic and community-based STI, HIV, family planning, and generally gynecology clinics;[65, 99] and one study enrolled participants from STI and hospital-based gynecology clinics.[108] No studies reported the HIV status of enrolled participants and only one study reported race/ethnicity (Mastrobattista et al,[89] 41% African American). All studies used a Gram stain of vaginal secretions interpreted according to the criteria of Nugent et al as the reference test. The prevalence of bacterial vaginosis based on the study's reference test ranged from 4.5 percent to 63.5 percent across studies. We assessed the Gratacos et al[88] study as good methodological quality and the rest as fair methodological quality.

Table 6 provides results from individual studies. **Appendix F Figure 5** depicts the SROC curve

comparing the modified Amsel's clinical criteria with the reference test, and **Appendix F Figure 6** displays the forest plot with individual study characteristics and sensitivity and specificity estimates. The pooled sensitivity based on four studies (2,477 participants) was 0.67 (95% CI, 0.54 to 0.78), and the pooled specificity was 0.96 (95% CI, 0.93 to 0.98). The pooled positive likelihood ratio was 17.3 (95% CI, 10.4 to 28.8), and the pooled negative likelihood ratio was 0.34 (95% CI, 0.24 to 0.48). The 95 percent prediction region covers about one fifth of the SROC space, but its shape suggests at least moderate heterogeneity. Potential sources of heterogeneity include how participants with intermediate flora were handled (included or excluded), the threshold used for the clue cell criteria (unspecified vs. 20% or more clue cells), the number of Amsel's clinical criteria required for a positive test (two vs. three), and symptom status of participants. Sensitivity was the highest and specificity the lowest among the only study conducted exclusively among symptomatic participants (Schwebke et al[99]); the pregnancy status of participants in this study was not reported. Among the two studies conducted exclusively in asymptomatic pregnant women, the sensitivity was 0.56 in one study[89] and 0.64 in the other.[88] The specificities were similar (0.96 and 0.98, respectively).

Singh et al,[107] which was conducted in symptomatic, nonpregnant women, did not report complete data, so we could not include it in our quantitative synthesis. We calculated a sensitivity of 0.54 and were unable to calculate the specificity for this study.

A number of included studies also reported test accuracy for the individual components that comprise Amsel's clinical criteria (i.e., positive whiff test, pH>4.5, presence of clue cells, vaginal discharge) compared with a Gram stain reference test or compared with complete Amsel's clinical criteria. These findings are available in **Appendix D Tables 1 through 4**.

Benefits of Treatment (Key Question 4)

Thirteen RCTs reported findings related to preterm delivery, other pregnancy outcomes, or clearance of bacterial vaginosis.[111-123] Data from two of these studies are new to this update; one study was published in 2018,[119] and one study was previously included only for harms but has eligible data for benefits that we have now included.[120] We excluded two studies previously included for this KQ because they did not meet the inclusion criterion for geographic setting of very high human development index established for this update; one was conducted in South Africa[124] and the other in Indonesia.[125] In addition, we determined that one previously included study[126] was a companion article to another previously included study;[113] thus, we did not count the companion article as a separate study for this update. Seven trials were funded by nonprofit and government agencies,[111, 114, 116, 117, 120, 121, 123] two were funded by hospitals,[118, 122] one was funded by a pharmaceutical manufacturer,[115] one was funded by various government and commercial entities,[113] and the funding source was not reported by two studies.[112, 119] **Appendix E Tables 7 through 12** provide our assessment of individual study methodological quality. The rest of this section describes study characteristics and findings organized by outcome and population, including results for subgroups specified in the KQ when possible.

Study Characteristics

Table 7 provides study characteristics with additional characteristics provided in **Appendix D Table 5**. Four studies were conducted in the United States;[111, 118, 121, 122] the others were conducted in Australia[117] and Europe.[112-116, 119, 120, 123]

Ten studies were conducted among general obstetric populations, meaning that participants were enrolled without regard to their risk for preterm delivery. The percentage of participants with a prior preterm delivery in these studies ranged from 0 percent to 10.9 percent.[111-120] Two of these studies also reported findings among subgroups considered high risk for preterm delivery, which was defined as having a prior preterm delivery.[111, 117] Three studies were conducted solely among participants considered high risk for preterm delivery.[121-123] All three defined high risk as a previous preterm delivery; however, one study also considered women with a prepregnancy weight less than 50 kilogram and no previous preterm delivery as high risk.[121] In this study, 68.6 percent of the analyzed population with bacterial vaginosis were high risk based on a prior preterm delivery, and the study reported outcomes for both the overall study population and the subgroup of women with prior preterm delivery.

Most studies identified asymptomatic patients during routine prenatal visits and enrolled participants during the second trimester though criteria for enrollment varied. Eight RCTs screened potential participants and then enrolled those who met diagnostic criteria for bacterial vaginosis, although the diagnostic criteria varied by study.[111-113, 116-119, 122] Five of these eight studies used Gram stain for diagnosis; four studies[111, 116, 118, 119] interpreted using Nugent's criteria, and one study interpreted using Spiegel's criteria.[113] One of these eight studies used complete Amsel's clinical criteria,[122] and the remaining two studies used other methods (morphotype screening on vaginal smear,[112] combination of culture for *Gardernella* in conjunction with gram stain[117]). The prevalence of bacterial vaginosis among the women tested for study entry ranged from 5.9 percent to 33.6 percent in these eight studies. Two studies enrolled women who met diagnostic criteria for bacterial vaginosis or intermediate flora based on Gram stain interpreted using Nugent's criteria,[115, 120] and one of these reported findings from the subgroup of participants with bacterial vaginosis not including intermediate flora.[120] Three studies enrolled participants without regard to bacterial vaginosis status but reported findings for the subgroup of participants testing positive for bacterial vaginosis at study entry (two based on Gram stain interpreted using Nugent's criteria[114, 123] and one using both Amsel's criteria and Gram stain). We report findings only from the subgroups with bacterial vaginosis for these studies.[114, 121, 123]

Three studies evaluated the use of oral metronidazole,[111, 117, 122] two studies evaluated oral clindamycin,[119, 120] one study evaluated oral metronidazole and erythromycin,[121] and seven evaluated intravaginal clindamycin.[112-116, 118, 123] The dosages and duration of treatment varied across studies, and most, but not all, used a placebo control. Two studies repeated treatment if a test of cure demonstrated persistent bacterial vaginosis,[114, 117] and three studies repeated dosing at a later followup point in time without regard to results from a test of cure for some or all participants.[111, 119, 123]

Studies within this body of evidence reported a variety of outcomes. Some studies reported all-

cause preterm delivery, defined as delivery prior to 37 weeks completed gestation regardless of whether delivery was induced for medical indications or a result of spontaneous preterm labor or PROM. Some studies reported only spontaneous preterm deliveries, and some studies reported both spontaneous and all-cause deliveries. In one study, spontaneous abortions occurring at 16 weeks or later were included as part of this outcome.[116] Other outcomes reported included preterm delivery prior to 35, 34, or 32 completed weeks gestation, maternal peripartum infections, low birth weight, very low birth weight, premature rupture of membranes, and neonatal infection or mortality.

We assessed nine RCTs[111-113, 115, 117-120, 123] as good methodological quality and four RCTs[114, 116, 121, 122] as fair methodological quality, primarily because of concerns related to lack of information on allocation concealment and lack of data to assess adequacy of randomization,[116] lack of treatment blinding,[114, 116] post hoc subgroup analyses,[114, 121] or lack of intent to treat analyses.[122]

Preterm Delivery

Twelve of the 13 RCTs[111-122] reported findings related to preterm delivery prior to 37 weeks gestational age; one RCT[123] only reported preterm delivery defined as delivery prior to 34 weeks. Results are provided in **Table 8**.

Preterm Delivery in General Obstetric Populations

Ten RCTs conducted among general obstetric populations (i.e., participants enrolled without regard to risk for preterm delivery) reported preterm delivery outcomes, and most either designated preterm delivery as the primary outcome or were powered based on this outcome. The absolute risk of delivery prior to 37 weeks gestational age in the control groups ranged from 3.1 percent to 15.7 percent. Some studies reported all-cause preterm delivery and others reported spontaneous preterm delivery; initial forest plots clearly depicted differences in point estimates based on the outcome used (**Appendix G Figures 1 and 2**), and the statistical tests for heterogeneity were significant. Thus, we stratified the analysis by outcome (**Figures 3 and 4**). Among the six studies reporting all-cause preterm delivery, the pooled ARD comparing active treatment with control was 0.20 percent (95% CI, -1.13% to 1.53%; 6,307 participants, I^2=0%), and the pooled RR was 1.02 (95% CI, 0.86 to 1.20).[111, 112, 116-119] No individual studies reported a significant difference between active treatment and control. Among the eight studies reporting spontaneous preterm deliveries, the pooled ARD comparing active treatment with control was -1.44 percent (95% CI, -3.31% to 0.43%; 7,571 participants, I^2=61.9%), and the pooled RR was 0.78 (95% CI, 0.56 to 1.07).[111, 113-117, 119, 120] Two of the eight studies reported statistically significant reductions in spontaneous preterm delivery for active treatment compared with control,[115, 120] while the other six reported no significant differences between active treatment and control. One of the studies that reported a significant association enrolled participants with either bacterial vaginosis or intermediate flora; other than this difference, we could not identify other study, population, or intervention (e.g., medication) characteristics that might explain this inconsistency.

Three RCTs reported the incidence of preterm delivery prior to 32 weeks completed gestation

among a general obstetric population (**Appendix G Figures 3 and 4**).[111, 116, 119] The pooled ARD was -0.30 percent (95% CI, -0.97% to 0.38%; 5,564 participants; I^2=15.4%), and the pooled RR was 0.87 (95% CI, 0.54 to 1.42). Two of these studies reported spontaneous preterm delivery,[116, 119] and one reported all-cause preterm delivery.[111] All three studies observed no significant differences between active treatment and control. One RCT also reported no difference in preterm delivery at less than 34 weeks gestation (ARD -0.04% [95% CI, -2.0% to 1.92%]; RR 1.0 [95% CI, 0.7 to 1.5]).[111]

Preterm Delivery in Women With Prior Preterm Delivery

Consistent with the previous report, we did not pool findings for this subgroup because of the observed heterogeneity in findings. Five RCTs reported this outcome; four reported the incidence of preterm delivery less than 37 weeks,[111, 117, 121, 122] and one reported the incidence of preterm delivery at less than 34 weeks.[123]

In the four RCTs conducted among participants with a previous preterm delivery or that reported subgroup findings for such women, the incidence of preterm delivery at less than 37 weeks gestation in control groups ranged from 22.5 percent to 57.1 percent (**Figures 5 and 6**).[111, 117, 121, 122] Carey et al[111] and Hauth et al[121] reported all-cause preterm delivery, and Morales et al[122] and McDonald et al[117] reported spontaneous preterm delivery. Three of the four RCTs reported a statistically significant favorable treatment effect (ARDs ranging from -18.3% to -29.4%), while Carey et al[111] observed no significant treatment effect (ARD 7.50% [95% CI, -6.09% to 21.09%]).

We were not able to definitively explain the inconsistency in findings based on study or population characteristics. All studies used oral metronidazole; two used similar doses of 750 mg or 800 mg daily for 7 days. However, Hauth et al also included erythromycin for 14 days as part of its treatment regimen.[121] McDonald et al used 800 mg daily for 2 days and repeated dosing at 28 weeks gestation if a test of cure remained positive.[117] Carey et al used 1,000 mg doses repeated four times (day of randomization and 48 hours later, and two doses administered 48 hours apart between 24 and 30 weeks gestation and at least 14 days after the very first dose).[111] All studies enrolled participants during the second trimester. Carey et al[111] enrolled participants based on a Gram stain interpreted according to Nugent et al criteria, while the other studies used other criteria (Amsel's clinical criteria alone,[122] Amsel's clinical criteria plus mixed flora using Spiegel criteria on Gram stain,[121] or heavy growth of *G. vaginalis* or Gram stain with *G. vaginalis* and absence of lactobacilli[117]). Carey et al[111] enrolled the highest percentage of nonwhite participants (approximately 85%), but this percentage was reasonably similar to the percentage enrolled by Hauth et al[121] and Morales et al.[122] We could also not explain the inconsistency in findings based on study methodological quality, and all studies were conducted over the same decade (1989 to 1998). The incidence of preterm delivery in the control group was 22.5 percent in Carey et al,[111] which was lower than in the other three studies (35.3%, 44.4%, and 57.1%), suggesting some heterogeneity in the underlying study populations.

Two RCTs reported the incidence of preterm delivery at less than 34 weeks gestation among participants with a prior preterm delivery (**Figures 5** and **6**).[122, 123] In Morales et al, four (11.1%) and two (4.6%) participants in the placebo and oral metronidazole group, respectively, had a

spontaneous preterm delivery at less than 34 weeks (calculated ARD, -6.57% [95% CI, -18.5% to 5.40%]).[122] Vermeulen et al reported the incidence of all-cause preterm delivery at less than 34 weeks gestation among a subgroup of 22 participants with bacterial vaginosis and observed one event in both the vaginal clindamycin and placebo groups.[123]

Preterm Delivery Based on Bacterial Vaginosis Clearance Status

Some studies reported preterm delivery outcomes for subgroups of participants who had documented clearance or persistence of bacterial vaginosis following treatment. Among a subgroup of participants who had followup Gram staining after initial testing and treatment, Carey et al reported no difference in preterm delivery among women with clearance of bacterial vaginosis (incidence 10.6%) versus those with persistence of bacterial vaginosis (incidence 10.7%).[111] Kekki et al also reported no difference in preterm delivery between active treatment and control among a subgroup of women with documented clearance of bacterial vaginosis 1 week posttreatment (calculated ARD, 2.30% [95% CI, -1.45% to 6.06%]).[113]

Other Subgroups

Andrews et al (a companion article to the Carey et al RCT) reported no difference in preterm delivery less than 35 or 37 weeks among women who received treatment for a positive chlamydia test at study entry compared with women who tested negative for chlamydia.[111, 127] No studies reported subgroup findings by maternal or gestational age, race or ethnicity, HIV status, or other population characteristics specified by our KQs.

Other Pregnancy-Related Outcomes

Appendix G Figures 3 and 4 depict other pregnancy-related outcomes for which we were able to calculate pooled summary estimates for the general obstetric population. The pooled ARD for the effect of active treatment compared with control on birth weight less than 2,500 grams was 0.39 percent (95% CI, -1.74% to 2.53%; 5 studies; 5,377 participants, I^2=24.2%) and was 0.06 percent (95% CI, -0.99% to 1.12%; 3 RCTs; 5,149 participants; I^2=45.3%) for birth weight less than 1,500 grams. The pooled ARD for PROM was 0.10 percent (-1.32% to 1.52%; 4 RCTs; 3,568 participants, I^2=9.4%) comparing treatment with control.

Within the body of evidence for the general obstetric population, studies reported outcomes for which we could not generate pooled summary estimates and for which authors observed no significant difference between active treatment and control. These outcomes include maternal peripartum infection,[113] stillborn fetus,[114] preterm labor,[118] and neonatal mortality.[119]

Within the body of evidence for participants with a previous preterm delivery, Morales et al reported a significant treatment effect on preterm labor (calculated ARD, -50.51% [95% CI, -69.41% to -31.60%]), PROM (calculated ARD, -28.79% [95% CI, -45.37% to -12.21%]), and birth weight less than 2,500 grams (calculated ARD, -19.7% [95% CI, -38.13% to -1.26%]).[122] Vermeulen et al reported no significant treatment effect on neonatal sepsis.[123]

Clearance of Bacterial Vaginosis

Six RCTs that reported preterm delivery outcomes also reported outcomes related to the clearance of bacterial vaginosis; however, differences in outcome measurement and timing precluded a quantitative synthesis (**Appendix D Table 6**). Some studies conducted followup testing on all participants; in other studies, followup testing was optional. Across this body of evidence, active treatment was more effective in producing short-term clearance of bacterial vaginosis than control treatment; findings were mixed for longer term clearance and persistence of clearance throughout pregnancy.

In the largest RCT (Carey et al), 657 (77.8%) participants had clearance of vaginosis at the first followup visit after the first course of treatment with oral metronidazole compared with 321 (37.4%) of participants who received placebo.[111] By design, the study protocol included initial dosing on day 0 and day 2, followed by a repeat dose between 24 and 30 weeks gestation and at least 14 days after the very first dose. Thus, the outcome reported provides the incidence of clearance after receiving only the initial portion of the protocol dose.

In Guaschino et al, authors reported clearance in 25 (75.8%) participants treated with intravaginal clindamycin daily for 7 days compared with 26 (70.3%) in the no treatment group.[112] These findings were reported among participants who had an optional vaginal smear at 28 to 30 weeks gestation.

In Morales et al, an RCT conducted among women with a prior preterm delivery, the authors reported on clearance at the time of delivery. Significantly more participants who received oral metronidazole had clearance (88.6%) compared with participants who received placebo (13.9%); we calculated the ARD as 74.8 percent (95% CI, 60.1% to 89.4%).[122]

Several RCTs reported both short-term and long-term clearance incidence. Kekki et al reported significantly higher short-term (within 1 week) and long-term (at 30 to 36 weeks gestation) clearance among participants who received intravaginal clindamycin daily for 7 days compared with placebo.[113] Lamont et al compared multiple clearance outcomes between participants receiving intravaginal clindamycin daily for 3 days and those receiving placebo, including short-term clearance (within 20 to 24 days posttreatment), sustained clearance (at 40 to 48 days posttreatment), and clearance after failing initial treatment.[115] Significantly more participants who received intravaginal clindamycin had clearance or improvement, defined as a Nugent Gram stain score of four or less, at 20 to 24 days compared with placebo; we calculated the ARD as 58.7 percent (95% CI, 50.5% to 67.0%). Sustained clearance or improvement at 40 to 48 days and 30 to 36 weeks did not differ significantly between groups. For those who failed initial treatment and were retreated with a 7-day course of intravaginal clindamycin or placebo, significantly more participants who received intravaginal clindamycin had clearance or improvement at 40 to 48 days (calculated ARD, 17.1% [95% CI, 2.32% to 31.9%]) and 30 to 36 weeks (calculated ARD, 24.8% [95% CI, 7.75% to 41.8%]) compared with placebo.[115] McGregor et al reported a higher incidence of clearance at multiple timepoints after treatment with intravaginal clindamycin compared with placebo, although significance testing was not performed and the actual numeric values were not provided (values were depicted on a figure at 1, 4, and 8 weeks posttreatment and at greater than 36 weeks gestation).[118]

Harms of Treatment (Key Question 5)

We included a total of 14 studies reporting on the harms of treatment. We excluded four previously included studies because they reported on comparative harms of alternative active treatments,[128] reported on harms in women without bacterial vaginosis,[121, 127] or reported a single adverse event but did not attribute it to a specific group.[112] We first present the studies that report maternal adverse effects and then those that present adverse outcomes in children exposed to medication in utero. Eight RCTs reported on maternal adverse effects;[111, 113, 114, 116, 117, 119, 120, 123] four of these studies are new to this update. One was published in 2018;[119] and three were previously included only for benefits but have eligible data for harms that we have now included.[116, 117] Six studies reported on adverse outcomes in children exposed to medication in utero; all were included in the previous update, and we identified no new studies.[129-134] **Appendix E Tables 13 through 29** provide our assessment of individual study methodological quality.

Maternal Adverse Effects

Study Characteristics

Among the 13 RCTs reporting on the benefits of treatment for bacterial vaginosis during pregnancy (KQ 4), eight reported on maternal adverse effects, including vaginal itching or yeast infection and gastrointestinal symptoms. These eight RCTs included four trials of intravaginal clindamycin,[113, 114, 116, 123] two trials of oral clindamycin,[119, 120] and two trials of oral metronidazole.[111, 117] Study characteristics for the RCTs reporting maternal adverse effects are described in the previous section (KQ 4 benefits of treatment) and in **Table 7**.

Findings

Results from individual studies are presented in **Table 9**. Across this body of evidence, maternal adverse effects from treatment with oral clindamycin or oral metronidazole occurred at a higher incidence compared with control treatment but were not severe in nature. Adverse events (AEs) from intravaginal clindamycin were infrequent and mild in nature. The rest of this section presents findings by medication and route of administration.

Intravaginal Clindamycin

Four RCTs evaluating intravaginal clindamycin reported on maternal adverse effects.[113, 114, 116, 123] Vermeulen et al[123] reported no withdrawals because of serious AEs, and Larsson et al[116] reported that no serious treatment-related maternal AEs in the treatment group. Kiss et al reported no AEs observed during the treatment period.[114] Kekki et al[113] reported an incidence of vulvovaginal itching of 3.2 percent in both the treatment and placebo groups, and in Larsson et al,[116] three women withdrew from treatment because of persistent itching (study group unknown). Other side effects reported in Vermeulen et al, a study that included both women with and without bacterial vaginosis, were two cases of candida vaginitis (1 in each study group) and three cases of troublesome discharge (all in the clindamycin group).[123]

Oral Clindamycin

Two RCTs reported maternal AEs from oral clindamycin;[119, 120] one was new to this update.[119] Subtil et al reported no serious AEs but a significantly higher incidence of any side effects in the treatment group compared with the placebo group (3.1% vs. 1.3%, calculated p=0.0035).[119] Incidence of treatment discontinuation was also significantly higher in the treatment group (19.6% vs. 16.3%, calculated p=0.031); reasons for discontinuation were not reported. Ugwumadu et al observed no significant difference in side effects resulting in discontinuation of treatment between clindamycin and placebo groups (7% vs. 3%, p=0.10).[120] Both studies also reported on gastrointestinal side effects. In Subtil et al, participants in the treatment group had a significantly higher incidence of diarrhea (1.6% vs. 0.4%, calculated p=0.0071) but not abdominal pain (0.5% vs. 0%, p=0.062) compared with the placebo group.[119] In Ugwumadu et al, the frequency of gastrointestinal upset was not significantly higher in the placebo group compared with the clindamycin group (4.2% compared with 2.1%, calculated p=0.18).[120] Other reported side effects in Ugwumadu et al include rash (1 in each group), vulvovaginal candidiasis (2 in clindamycin and 1 in placebo group), throat irritation (1 in placebo group), and headache (4 in clindamycin and 1 in placebo group).

Oral Metronidazole

Two RCTs reported maternal AEs from oral metronidazole.[111, 117] Women randomized to oral metronidazole were more likely to experience one or more side effects compared with those randomized to placebo in both studies.[111, 117] In Carey et al, 21.6 percent in the metronidazole group experienced one or more side effects compared with 9.1 percent in the placebo group (calculated p<0.001).[111] Participants treated with metronidazole had a significantly higher incidence of gastrointestinal symptoms (19.7% vs. 7.5%, calculated p>0.001) and vomiting (9.7% vs. 2.8%, calculated p<0.001), as well as a higher incidence of treatment for vaginal yeast infections (12% vs. 4.9%; calculated p<0.001) compared with placebo. In McDonald et al, 27 (6.3%) participants in the treatment group reported AEs compared with 16 (3.7%) participants in the placebo group (calculated p=0.09). Further, 19 (4.4%) and 14 (3.3%) participants discontinued treatment in the metronidazole and placebo groups, respectively (calculated p=0.38), although the reasons for discontinuation were not reported.[117]

Adverse Childhood Outcomes From In Utero Exposure to Medication

Study Characteristics

We included six studies reporting adverse childhood outcomes from in utero exposure to metronidazole;[129-134] all studies were included in the prior review. We provide a summary of study characteristics and results in **Table 10**. **Appendix D Tables 7 through 12** provide additional study characteristics and detailed outcomes**.** Three observational studies[129-131] and two meta-analyses[133, 134] reported on outcomes related to congenital abnormalities and malformations, and one observational study[132] reported on incidence of childhood cancer. We assessed one study as poor methodological quality because of confounding and because of a large amount of missing data;[129] however, we retained it in our synthesis for continuity with the previous review. We assessed all other studies as fair methodological quality.

One case-control study in Hungary (Czeizel et al, N=47,963) identified congenital anomaly cases from the Hungarian Congenital Abnormality Registry and matched them with controls from the national birth registry. Authors obtained data on metronidazole use from physician log books, self-report during interview, and a mailed questionnaire.[131] Diav-Citrin et al conducted a prospective controlled cohort study in Israel comparing participants who contacted the Teratogen Information Service because of an exposure to metronidazole (N=228) with women contacting the service for exposure to nonteratogenic agents (N=629).[129] Outcomes were self-reported by participants and then verified by medical records or the participant's clinician; we assessed this study as poor quality. Sorensen et al conducted a population-based retrospective cohort study in Denmark that compared an exposed group identified from the Pharmaco-Epidemiological Prescription Database of North Jutland (N=124) with a pregnancy cohort (N=13,327); outcome data were obtained from the Danish Medical Birth Registry and the Danish Hospital Discharge Summary.[130] Lastly, Thapa et al conducted a retrospective cohort study of pregnant participants in Tennessee that compared Medicaid claims files with the state's childhood cancer database (N=328,846 participants, 1,172,696 person-years follow up).[132]

We included two meta-analyses of observational studies of in utero exposure to metronidazole;[133, 134] three studies overlapped between the meta-analyses. The 1995 Burtin et al meta-analysis[133] included seven cohort studies (total N not reported), four of which were excluded from the subsequent 1997 Caro-Paton et al meta-analysis[134] because they used participants exposed to metronidazole in the third trimester rather than unexposed participants as the control group. Caro-Paton et al included five studies (total N=199,451), including four cohort studies and one unpublished case-control study.[134]

The studies we included for this KQ do not provide information about the indication for metronidazole treatment; the setting of treatment (i.e., inpatient vs. outpatient); or the dose, duration, and route of treatment. Further, the populations evaluated were not focused on pregnant women exposed to metronidazole specifically for the treatment of bacterial vaginosis, which may limit applicability; however, we retained these studies in this update for continuity with the previous update.

Findings

Congenital Anomalies

The two included meta-analyses found no evidence of an association between metronidazole and congenital malformations (OR, 0.96 [95% CI, 0.75 to 1.22][133] and OR, 1.08 [95% CI, 0.90 to 1.29][134]). Similarly, with one exception, the three observational studies (one poor quality, two fair quality) found no association between metronidazole and congenital abnormalities.[129-131] The exception was reported by Czeizel et al.[131] In this fair-quality study, a significant association between congenital anomalies and exposure to metronidazole during the first month of gestation (OR, 2.24 [95% CI, 1.30 to 3.85]) but not for the second through third or fourth through ninth months.[131] The authors note that because the first month of gestation is counted from the first day of the last menstrual period, several of these weeks of exposure may be before conception or during the all or none phase of fetal development; thus, this finding may be spurious or the result of recall bias or uncontrolled confounding.[131]

Cancer

One fair-quality cohort study among women enrolled in Tennessee Medicaid did not find an association between metronidazole exposure during pregnancy and diagnosis of first cancer before age 5 among exposed children (adjusted RR, 0.81 [95% CI, 0.41 to 1.59]).[132]

Chapter 4. Discussion

Summary of Evidence

Table 11 summarizes the evidence synthesized in this report by KQ and provides our EPC's assessment of the SOE. We identified no direct evidence evaluating the benefits (KQ 1) or harms (KQ 3) of screening, and evidence to address variation in effectiveness of treatment in subpopulations (KQ 4) was only available for women with a prior preterm delivery. Evidence for variation in effectiveness of treatment in subpopulations characterized by race, HIV status, or other characteristics was not identified.

Diagnostic Test Accuracy (Key Question 2)

For diagnostic accuracy of available tests for bacterial vaginosis (KQ 2), we assessed the SOE as low for adequate accuracy for all tests evaluated (BD Affirm, BD Max, BV Blue, complete Amsel's clinical criteria, and modified Amsel's clinical criteria). Across all tests, we downgraded the SOE because this body of evidence largely comprised studies of only fair methodological quality. We further downgraded the SOE because of inconsistency. A low SOE means we have limited confidence in the estimates of test accuracy and that results might not be stable with the addition of future studies.[135]

Most studies were conducted among symptomatic, nonpregnant women; thus, the applicability to asymptomatic pregnant women is not entirely clear. For complete Amsel's and modified Amsel's clinical criteria, the sensitivities observed in the two studies[88, 89] conducted exclusively among pregnant women were lower than the pooled summary estimates, suggesting that the physiologic changes that occur in the vaginal environment during pregnancy may affect the sensitivity of one or more of the clinical criteria used to identify bacterial vaginosis. A lower sensitivity was not observed for the BD Affirm test in the one study conducted exclusively in pregnant women.[98] The BD Affirm test, which is based on a nucleic acid probe for *Gardnerella vaginalis*, may not be affected by the physiologic changes associated with pregnancy.

Although we did not formally conduct a comparative assessment of test accuracy, the tests do vary somewhat in accuracy. However, we do not think any specific test falls below a threshold of accuracy that would not be clinically useful. All tests have reasonably sufficient specificity; the laboratory-based tests (BD Affirm, BD Max, BV Blue) have higher sensitivities than those based on Amsel's clinical criteria but lower specificity. Assuming treatment is effective and harms of treatment are minimal, one might select a test with higher sensitivity to minimize false negatives. In other contexts (e.g., when harms of false positives are more than minimal), a test with higher specificity might be preferred to minimize the harms of unnecessary treatment.

Some researchers have suggested applying likelihood ratios to pretest probabilities to assess how well a positive or negative test would influence the post-test probability of disease as an alternative way to evaluate test accuracy and to assess consistency and precision domains within SOE assessment.[83] We illustrate this approach in **Appendix H**. In this example, we assumed a

pretest probability of bacterial vaginosis of 17.2 percent, which was the average prevalence of bacterial vaginosis among asymptomatic women evaluated for study entry into the RCTs evaluating the benefits of treatment (KQ 4). A positive BD Affirm test increases the post-test probability of bacterial vaginosis to 48.9 percent, a positive BD Max increases the post-test probability to 69.4 percent, and a positive Amsel's test (complete criteria) increases the post-test probability to 61.0 percent. The post-test probability after a negative test is 3.2 percent (BD Affirm), 1.6 percent (BD Max), and 2.8 percent (complete Amsel's clinical criteria). Depending on the clinical treatment threshold one uses to decide to treat, any of these tests might have acceptable accuracy, although some might be considered more accurate based on their larger influence on the post-test probability after a positive test. After a negative test, all would likely decrease the post-test probability of bacterial vaginosis below a threshold for which treatment would likely not be indicated.

Benefits of Treatment (Key Question 4)

Among a general obstetric population, we assessed the evidence as moderate for no benefit of treatment on all-cause preterm delivery and low for no benefit of treatment on spontaneous preterm delivery. The funnel plot (**Appendix G Figure 5**) of studies reporting preterm delivery does not suggest publication bias. We downgraded the SOE for both outcomes because of imprecision and in the case of spontaneous delivery also for inconsistency. With respect to precision, although preterm delivery was a primary outcome for most studies and most were powered based on this outcome, either a lower control group risk was observed than expected or the treatment effect observed was smaller than expected resulting in imprecise estimates, particularly for RR estimates. This evidence is applicable to asymptomatic women and for use of oral metronidazole and oral or intravaginal clindamycin. Compared with the 2008 review, we added two RCTs and excluded two RCTs that were conducted in countries not categorized as very highly developed on the United Nations Human Development Index. Despite this change in the body of evidence, the overall conclusions about no benefit in a general obstetric population remain unchanged from the prior report.

Among women with a prior preterm delivery, we assessed the evidence as insufficient. We downgraded this evidence for both inconsistency and imprecision and note its applicability is largely for treatment with oral metronidazole. Three of four studies reported a statistically significant reduction, while one (Carey et al[111]) reported a nonstatistically significant increase in preterm delivery at less than 37 weeks. We are not able to explain the inconsistency in findings as previously discussed in the results section. We also note that findings from three of these four studies were based on subgroup analyses, some of which were post hoc. The two studies reporting preterm delivery at less than 34 weeks did not observe any significant differences between groups, but results were very imprecise.

We did not identify any new studies for the population of women with a prior preterm delivery, but we note that the 2008 review included a study with a subgroup analysis for this population that was conducted in South Africa and that observed a statistically significant increase in preterm delivery for oral metronidazole compared with placebo for this population.[124] As a result of the inconsistent body of evidence in 2008 review, the report authors were unable to draw a conclusion about benefits, and the USPSTF concluded in 2008 that the evidence was insufficient

to make a recommendation in this population. We excluded the study from South Africa in the current body of evidence, and although this results in less inconsistency in findings than the 2008 report, we are still left with a serious unexplained inconsistency that limits our ability to conclude with even low certainty an effect or no effect of treatment in this population.

Harms of Treatment (Key Question 5)

We assessed the SOE for serious maternal AEs related to treatment as moderate for no difference for oral metronidazole and both oral and intravaginal clindamycin. We assessed the SOE for minor AEs as moderate for no difference for intravaginal clindamycin and as moderate for an increase in minor events for both oral metronidazole and oral clindamycin. We downgraded these bodies of evidence for imprecision because of relatively infrequent events.
We assessed the SOE for congenital malformations and incidence of cancer among children exposed to metronidazole in utero as insufficient. This body of evidence is comprised of observational studies with no more than fair methodological study quality, and despite large sample sizes, the incidence of these types of events was rare, resulting in imprecise estimates. This evidence applies to metronidazole exposure during pregnancy across a range of medical indications and is not specific to treatment for bacterial vaginosis.

Limitations

This review was limited to English-language studies only. Further, we found no available evidence that directly evaluated the health benefits and harms of screening (KQs 1 and 3); thus, we assessed evidence from the indirect pathway on the analytic framework to link screening to health outcomes (KQs 2, 4, and 5).

For diagnostic test accuracy (KQ 2), limited evidence was available for pregnant, asymptomatic populations. We identified no publicly available studies for laboratory-developed multiplex PCR tests that are now available for commercial use from several national labs and only one study for the only FDA-approved multiplex PCR assay. Most studies were of only fair methodological quality, and for most tests, we observed moderate to substantial heterogeneity in estimates. Most studies used Gram stain as a reference standard; however, in light of the advances in the molecular and microbiological understanding of bacterial vaginosis, this may be an imperfect standard. We note that the current SOE assessment framework was not originally designed for evaluating diagnostic test accuracy bodies of evidence; such bodies of evidence typically include more inconsistency than bodies of evidence on interventions. Further, limited guidance exists to gauge consistency and precision domains for diagnostic test accuracy; thus, we tried to limit the subjectivity and increase transparency by providing a detailed rationale for each assessment. We did not formally assess the comparative accuracy of available tests. Lastly, we did not assess tests still in development for amine detection and some PCR assays because these tests are not commercially available or feasible for use in a primary care setting at this time.

For benefits of treatment (KQ 4) and adverse maternal events (KQ 5), studies varied with respect to dose and duration of treatment, use of a test of cure, and methodological quality. Despite this variation, we were able to draw conclusions about treatment effects in a general obstetric

population for delivery less than 37 weeks, though some uncertainty remains because some studies only reported spontaneous preterm delivery and not all-cause delivery outcomes. The consequences related to preterm delivery generally do not differ for medically indicated deliveries versus spontaneous deliveries; however, biased estimates of the treatment effect could be observed depending on how the outcomes were defined and ascertained. Because an indicated preterm delivery is a competing risk to a spontaneous preterm delivery, the use of spontaneous delivery outcomes could introduce informative censoring. Further, some studies may have only measured outcomes occurring after a specific gestational age (e.g., 22 weeks or later) and not all outcomes that occurred after the point of randomization. For example, treatment could result in a medical complication that results in an indicated or spontaneous abortion or delivery that occurs after randomization but before the reporting window begins.

The findings in women with a prior preterm delivery are inconsistent, and we were unable to identify sources for this inconsistency. With respect to harms, trials were underpowered for maternal adverse events and we did not assess the comparative harms of treatment. This review was limited to only metronidazole and clindamycin, although other treatments for bacterial vaginosis are available but either have not been studied in pregnant women or are not considered first-line treatments in pregnant women.

Only observational studies were available to assess the harms to children related to in utero exposure to medications (KQ5), and all of these studies included women exposed to metronidazole for any indication, including but not limited to bacterial vaginosis. We included them for continuity with the previous review and also included one study of harms from in utero exposure to medication that was included in the 2008 review but that we rated as poor methodological quality for this update. We note that the current SOE assessment approaches were designed for treatment interventions and favor RCT designs; most SOE approaches are not well suited for assessing harms from exposures, particularly when the evidence base is observational and when outcomes may be rare. Given the infeasibility of conducting randomized studies large enough and over a long enough duration to provide definitive evidence on in utero exposure, it is unlikely that this body of evidence could ever rise above an insufficient rating. However, we note the widespread and longstanding use of these medications in clinical practice.

Future Research Needs

The most pressing future research need is for an adequately powered, definitive randomized trial of treatment for bacterial vaginosis in women with a previous preterm birth. Further, because bacterial vaginosis is only one of several possible risks that contribute to preterm delivery, future trials should ensure adequate measurement of other preterm delivery risks (e.g., short cervix, genitourinary infections, race, and ethnicity) and report using all-cause preterm delivery outcomes. For the general obstetric population, future research may need to focus on screening or interventions for preterm delivery risks other than bacterial vaginosis or alternative treatments beyond a single-antibiotic approach, because existing treatment approaches in this population do not appear to be effective strategies.

Other needs include research on the performance of diagnostic tests for bacterial vaginosis in

asymptomatic pregnant women to provide estimates of accuracy applicable to this specific population. Research is also needed to better understand the role of PCR and new molecular sequencing tests with respect to the current biological understanding of bacterial vaginosis and existing methods for clinical diagnosis and laboratory reference standards. Further, the development of new tests or treatments for bacterial vaginosis should ensure testing in pregnant populations to understand the impact on both mother and child.

Conclusions

We identified no direct evidence that compared screening with no screening and that reported health outcomes. Diagnostic test accuracy studies were mostly conducted in nonpregnant, sympotmatic women; the sensitivity of the various tests ranged from 0.61 to 0.93 and the specificity ranged from 0.49 to 0.98. RCTs conducted in general obstetric populations reported no difference in the incidence of preterm delivery and related outcomes for treatment with metronidazole or clindamycin compared with placebo. The evidence is inconclusive for treatment in women with a prior preterm delivery. Maternal adverse events from treatment with metronidazole or clindamycin are infrequent and minor. The observational study evidence about harms to children from in utero exposure to medication is inconclusive because of study limitations and imprecision.

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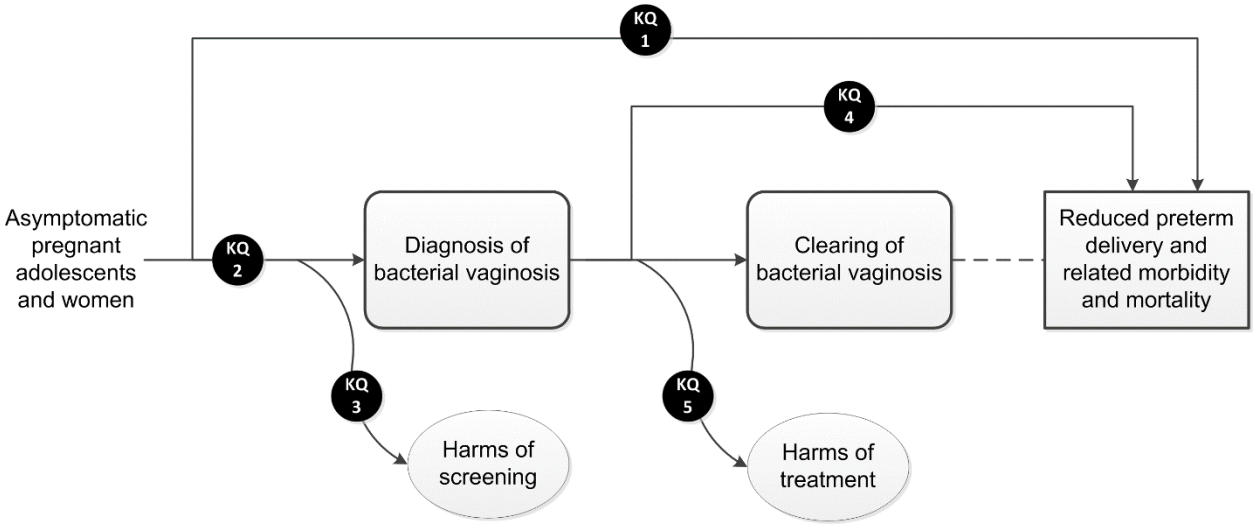
Figure 1. Analytic Framework for Systematic Review of Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery



Abbreviation: KQ=key question.

Figure 2. Literature Flow Diagram for Systematic Review of Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

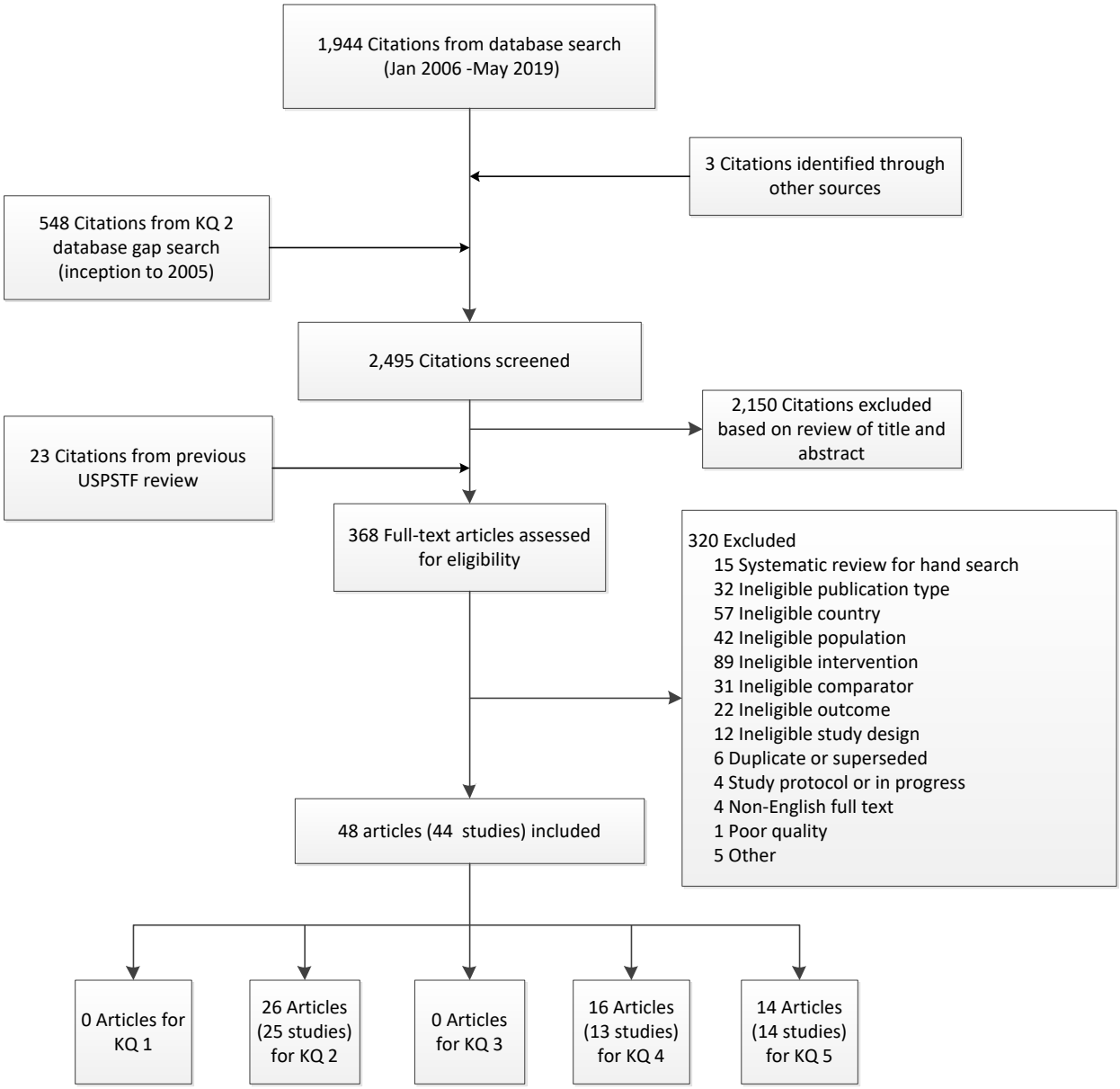


Figure 3. Absolute Risk Difference for Delivery at Less Than 37 Weeks Gestation From Treatment of Bacterial Vaginosis Among a General Obstetric Population

Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Difference [95% CI]
All-Cause Preterm Delivery							
Carey (2000)	Good	1919	10.9	OM	All-cause delivery <37 weeks	12.5	-0.35 [-3.30, 2.59]
Guaschino (2003)	Good	100	7.1	VC	All-cause delivery <37 weeks	15.7	-3.44 [-17.00, 10.12]
Larsson (2006)	Fair	819	7.6	VC	All-cause delivery <37 weeks	6.1	-0.94 [-4.09, 2.22]
McDonald (1997)	Good	480	5.2	OM	All-cause delivery <37 weeks	7.6	-0.95 [-5.54, 3.64]
McGregor (1994)	Good	129	10.9	VC	All-cause delivery <37 weeks	7.3	7.75 [-3.16, 18.66]
Subtil (2018)	Good	2860	1.6	OC	All-cause delivery from 22 to 37 weeks	5.9	0.86 [-1.00, 2.73]
RE Model for All Studies (Q = 3.48, df = 5, p = 0.63; I^2 = 0.0%)							0.20 [-1.13, 1.53]
Spontaneous Preterm Delivery							
Carey (2000)	Good	1919	10.9	OM	Spontaneous delivery <37 weeks	9.4	-0.08 [-2.69, 2.53]
Kekki (2001)	Good	375	0	VC	Spontaneous delivery <37 weeks	3.7	1.09 [-3.00, 5.18]
Kiss (2004)	Fair	351	3.3	VC	Spontaneous delivery <37 weeks	5.7	-2.25 [-6.61, 2.10]
Lamont (2003)	Good	391	7.20	VC	Spontaneous delivery <37 weeks	9.8	-5.80 [-10.82, -0.79]
Larsson (2006)	Fair	785	7.6	VC	Spontaneous delivery <37 weeks	3.1	-0.29 [-2.65, 2.07]
McDonald (1997)	Good	480	5.2	OM	Spontaneous delivery <37 weeks*	6.3	-1.76 [-5.81, 2.29]
Subtil (2018)	Good	2860	1.6	OC	Spontaneous delivery from 22 to 37 weeks	4.1	0.70 [-0.88, 2.28]
Ugwumadu (2003)	Good	410	9.3	OC	Spontaneous delivery from 24 to 37 weeks	15.3	-9.96 [-15.77, -4.14]
RE Model for All Studies (Q = 18.37, df = 7, p = 0.01; I^2 = 61.9%)							-1.44 [-3.31, 0.43]

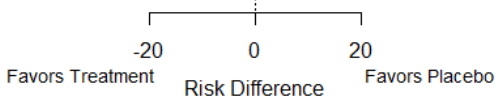


Figure Note: Mixed-methods test of moderators for all-cause versus spontaneous preterm delivery: QM(df=1)=3.7044, p=0.0543.
* Includes spontaneous late abortion (≥16 weeks).

Abbreviations: CI=confidence interval; OC=oral clindamycin; OM=oral metronidazole; N=number of participants; PTD=preterm delivery; RE=random effects; VC=intravaginal clindamycin.

Figure 4. Risk Ratio for Delivery at Less Than 37 Weeks Gestation From Treatment of Bacterial Vaginosis Among a General Obstetric Population

Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Ratio [95% CI]
All-Cause Preterm Delivery							
Carey (2000)	Good	1919	10.9	OM	All-cause delivery <37 weeks	12.5	0.97 [0.77, 1.23]
Guaschino (2003)	Good	100	7.1	VC	All-cause delivery <37 weeks	15.7	0.78 [0.29, 2.09]
Larsson (2006)	Fair	819	7.6	VC	All-cause delivery <37 weeks	6.1	0.85 [0.48, 1.49]
McDonald (1997)	Good	480	5.2	OM	All-cause delivery <37 weeks	7.6	0.87 [0.46, 1.67]
McGregor (1994)	Good	129	10.9	VC	All-cause delivery <37 weeks	7.3	2.07 [0.73, 5.84]
Subtil (2018)	Good	2860	1.6	OC	All-cause delivery from 22 to 37 weeks	5.9	1.15 [0.85, 1.56]
RE Model for All Studies (Q = 3.45, df = 5, p = 0.63; I^2 = 0.0%)							1.02 [0.86, 1.20]
Spontaneous Preterm Delivery							
Carey (2000)	Good	1919	10.9	OM	Spontaneous delivery <37 weeks	9.4	0.99 [0.75, 1.31]
Kekki (2001)	Good	375	0	VC	Spontaneous delivery <37 weeks	3.7	1.29 [0.49, 3.40]
Kiss (2004)	Fair	351	3.3	VC	Spontaneous delivery <37 weeks	5.7	0.60 [0.22, 1.62]
Lamont (2003)	Good	391	7.20	VC	Spontaneous delivery <37 weeks	9.8	0.41 [0.18, 0.92]
Larsson (2006)	Fair	785	7.6	VC	Spontaneous delivery <37 weeks	3.1	0.91 [0.40, 2.03]
McDonald (1997)	Good	480	5.2	OM	Spontaneous delivery <37 weeks*	6.3	0.72 [0.34, 1.54]
Subtil (2018)	Good	2860	1.6	OC	Spontaneous delivery from 22 to 37 weeks	4.1	1.17 [0.81, 1.69]
Ugwumadu (2003)	Good	410	9.3	OC	Spontaneous delivery from 24 to 37 weeks	15.3	0.35 [0.18, 0.67]
RE Model for All Studies (Q = 15.54, df = 7, p = 0.03; I^2 = 55.0%)							0.78 [0.56, 1.07]

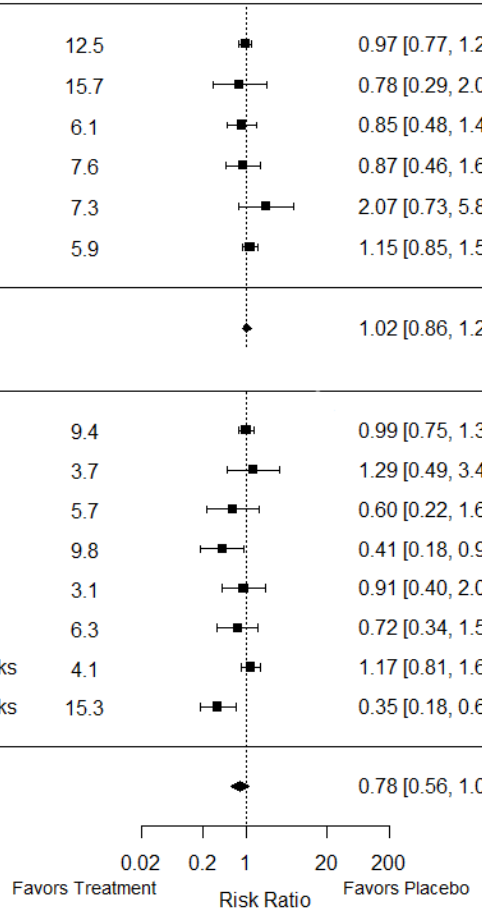


Figure Notes: Mixed-methods test of moderators for all-cause versus spontaneous preterm delivery: p=0.0020.
* Includes spontaneous late abortion (≥16 weeks).

Abbreviations: CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; RE=random effects; VC=intravaginal clindamycin.

Figure 5. Absolute Risk Difference for Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among Participants With a Prior Preterm Delivery

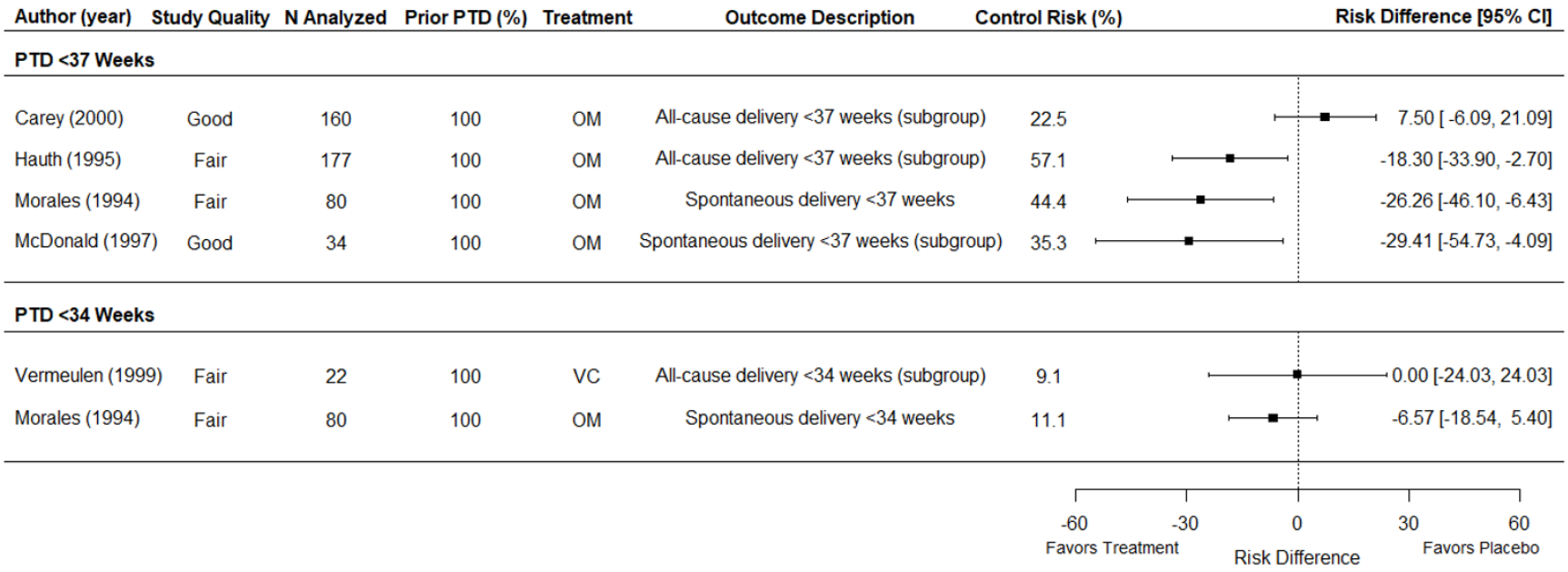


Figure Note: Mixed-methods test of moderators for all-cause versus spontaneous preterm delivery at less than 37 weeks gestation p=0.1362. For Hauth et al,[121] we used data from the subgroup of participants with bacterial vaginosis and history of prior PTD. For Carey et al,[111], we used data from the subgroup of participants with a history of prior PTD. For McDonald et al,[117] we used data from the subgroup of participants with bacterial vaginosis and history of prior PTD. For Vermeulen et al,[123] we used data from the subgroup of participants with bacterial vaginosis.

Abbreviations: CI=confidence interval; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; VC=intravaginal clindamycin.

Figure 6. Risk Ratio for Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among Participants With a Prior Preterm Delivery

Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Ratio [95% CI]
PTD <37 Weeks							
Carey (2000)	Good	160	100	OM	All-cause delivery <37 weeks (subgroup)	22.5	1.33 [0.79, 2.26]
Hauth (1995)	Fair	177	100	OM	All-cause delivery <37 weeks (subgroup)	57.1	0.68 [0.49, 0.93]
Morales (1994)	Fair	80	100	OM	Spontaneous delivery <37 weeks	44.4	0.41 [0.20, 0.85]
McDonald (1997)	Good	34	100	OM	Spontaneous delivery <37 weeks (subgroup)	35.3	0.17 [0.02, 1.24]
PTD <34 Weeks							
Vermeulen (1999)	Fair	22	100	VC	All-cause delivery <34 weeks (subgroup)	9.1	1.00 [0.07, 14.05]
Morales (1994)	Fair	80	100	OM	Spontaneous delivery <34 weeks	11.1	0.41 [0.08, 2.11]

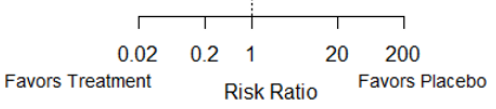


Figure Note: Mixed-methods test of moderators for all-cause versus spontaneous preterm delivery at less than 37 weeks gestation: p=0.0892.

Abbreviations: CI=confidence interval; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; VC = intravaginal clindamycin.

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Bradshaw et al[100]; 2005; Australia; BV Blue, complete Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; fair	Women who presented with symptoms of abnormal vaginal discharge or odor at a single-center sexual health clinic, excluding women who were pregnant, postmenopausal, HIV infected, menstruating, or who had used lubricant or topical vaginal medication within 72 hours	288 enrolled and 288 analyzed for BV Blue and complete Amsel, 252 analyzed for clue cells and vaginal discharge, 251 analyzed for whiff test, 250 analyzed for pH	29 (8)	NR	288 (100) (presumably based on study entry criteria) Abnormal vaginal discharge or odor	0 (0) (presumably based on study entry criteria)	0 (0) (presumably based on study entry criteria)
Briselden et al[96]; 1994; United States; BD Affirm	Cross-sectional; fair	Women at a single center being seen for new genital complaints at a hospital-based sexually transmitted disease clinic	176 enrolled and analyzed	NR	300 (93%) African American 23 (7%) non-Hispanic white	176 (100) (presumably based on study entry criteria) New genital complaints	NR	NR
Byun et al[90]; 2016; South Korea; BD Affirm	Cross-sectional; good	Women at a single-center outpatient hospital gynecology clinic, excluded menstruating women, coitus within 24 hours, recent antibiotic or antifungal treatment	200 enrolled, 195 analyzed	41.7 (10.2)	NR	152 (76) Odorous vaginal discharge, vaginal itching, dyspareunia, dysuria, vaginal burning	NR	3 (1.53*)

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Cartwright et al[95]; 2013; United States; BD Affirm	Cross-sectional; fair	Women presenting with clinically documented vaginitis syndrome at one of two sexually transmitted infection clinics (one at a local health department and one at a university hospital); no antibiotics or vaginal medication use within previous 14 days	NR enrolled, 305 analyzed	Median 24 (range 19 to 60)	NR	323 (100) (presumably based on study entry criteria) presenting with clinically documented vaginitis	NR	NR
Chen et al[110]; 2018; Taiwan; Complete Amsel's clinical criteria	Cross-sectional; fair	Nonpregnant women with a history of sexual activity who had not taken antibiotics or vaginal antimicrobials within 2 months, recruited from hospital-based department of obstetrics and gynecology.	77 enrolled, 77 analyzed	Median 41 (NR)	NR	NR	NR	0 (0)
Gallo et al[103]; 2011; United States; Complete Amsel's clinical criteria	Cross-sectional; fair	Women age 16 to 55 who do not have an AIDS-defining clinical diagnosis and are either injection-drug users or had high-risk sexual behaviors visiting one of four sites	1,310 enrolled, 6,135 HIV positive and 3,005 HIV negative; visits analyzed from 1,283 participants	Median 35 (NR)	744* (58%) black 308* (24%) white 218* (17%) Hispanic 13* (1%) other	NR	862 (67.2*) participants, 6,135 (67.1*) visits	NR

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Gratacos et al[88]; 2005; Spain; Complete Amsel's clinical criteria, modified Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; good	Asymptomatic women with singleton pregnancies starting their antenatal care before 28 weeks at low risk pregnancy clinics	NR enrolled, 492 analyzed	27.5 (5.5)	NR	0 (0) (presumably based on study entry criteria)	NR	492 (100) (presumably based on study entry criteria)
Gutman et al[109]; 2005; United States; Complete Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; fair	Women at a single center hospital outpatient clinic: primary care, colposcopy, or division of research	NR enrolled, 269 analyzed	NR overall Positive for BV: 25.4 (7.7) Negative for BV: 23.3 (6.5)	NR	NR overall Positive for BV: 47 (45) Negative for BV: 41 (25) Vaginal discharge, foul smelling odor, vaginal itching, or vaginal burning	1 (0.4)	35 (13)
Hay et al[91]; 1992; United Kingdom; Complete Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; good	Women at a single center, hospital-based gynecology clinic.	118 enrolled, 114 analyzed	36.2 (range 16 to 65)	NR	3 (2.6) Vaginal discharge	NR	NR
Hellberg et al[93]; 2001; Sweden; Individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; good	Women with certain, predetermined positions on the outpatients list attending a family planning clinic for contraceptive advice	1011 enrolled, 956 analyzed	NR overall Positive for BV: 26.6 (NR) Negative for BV: 25.7 (NR)	NR	NR	NR	NR

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Hillier et al[101]; 2011; United States; BV Blue, complete Amsel's clinical criteria	Cross-sectional; fair	Nonmenstruating and nonpregnant women between the ages of 18 and 60, with or without symptoms of vaginitis, recruited from Magee-Womens Hospital of University of Pittsburgh Medical Center and Allegheny County Health Department	519 enrolled, 519 analyzed	27.6 (8.6)	NR	251 (48.4) Abnormal vaginal odor, abnormal vaginal discharge, pruritis, vaginal burning or pain, vaginal irritation, or lower abdominal pain	NR	0 (0) (presumably based on study entry criteria)
Hilmarsdottir et al[104]; 2006; Iceland; Complete Amsel's clinical criteria	Cross-sectional; fair	Women at a single-center hospital-based sexually transmitted infection clinic	NR enrolled, 327 analyzed	22 (range 14 to 58)	NR	NR	NR	NR
Landers et al[105]; 2004; United States; Complete Amsel's clinical criteria	Cross-sectional; fair	Nonpregnant women between 18 and 45 years with one or more untreated genital complaints at three sites associated with an academic medical center	598 enrolled, 548 analyzed	NR	363 (60%) African American 190 (32%) white 4 (0.6%) Asian 3 (0.5%) Hispanic 6 (1%) other 32 (5%) multiethnic or biracial	598 (100) (presumably based on study entry criteria) Untreated genital complaint	NR	0 (0) (presumably based on study entry criteria)

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Lowe et al[97]; 2009; United States; BD Affirm	Cross-sectional; fair	Active-duty military women who presented for health care with vulvovaginal symptoms at one of four troop medical clinics in the United States Army or Navy; excluded for menstruation or had coitus within previous 24 hours	547 enrolled, 535 analyzed	25.7 (5.8)	230 (43.0%) African American 97 (18.1%) Hispanic 168 (31.4%) White 40 (7.5%) other	547 (100) (presumably based on study entry criteria) Vulvovaginal symptoms such as abnormal discharge, itching/irritation, malodor, vulvar burning, vulvar pain, vaginal discomfort, and others	NR	NR
Mastrobattista et al[89]; 2000; United States; Modified Amsel's clinical criteria, individual criteria (pH, clue cells, whiff test)	Cross-sectional; fair	Asymptomatic pregnant women initiating prenatal care in academic obstetric clinics, excluding women with antimicrobial use within 2 weeks, cervical cerclage, vaginal bleeding, placenta previa, spermicide use, recent douching, or sexual intercourse within 8 hours	69 enrolled, 67 analyzed	27.3 (6.6)	28 (41%) African American 23 (38%) white 15 (22%) Hispanic 3 (4%) Asian	0 (0) (presumably based on study entry criteria)	NR	69 (100) (presumably based on study entry criteria)
Myziuk et al[102]; 2003; Canada; BV Blue, complete Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; fair	Nonmenstruating women 16 years of age and older who presented for a pelvic examination, regardless of the reason at a single-center sexually transmitted disease clinic and an infectious disease referral practice	57 enrolled, 57 analyzed	30.7 (NR)	NR	31 (54) Abnormal discharge	2 (3.5)	NR

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Platz-Christensen et al[92]; 1995; Sweden; Complete Amsel's clinical criteria, individual criteria (clue cells)	Cross-sectional; good	Nonpregnant women of childbearing age without vaginal bleeding and antibiotic treatment within the last month at one university-based hospital outpatient clinic	NR enrolled, 107 analyzed	NR	NR	NR	NR	0 (0) (presumably based on study entry criteria)
Rouse et al[136]; 2009; United States; Individual criteria (pH, clue cells)	Cross-sectional; fair for pH and clue cells, poor for whiff test and complete Amsel	Pregnant patients presenting for emergency care who were not bleeding but required a speculum examination at a community hospital	220 enrolled, 193 analyzed for clue cell, 189 analyzed for with pH	NR	NR	220 (100) self-reported discharge, pruritis, burning, and odor	NR	193 (100)
Schmidt et al[94]; 1994; Denmark; Individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; good	Nonpregnant, nonmenstruating women who did or did not complain of vaginal discharge and were gynecologically examined at a general practice	NR enrolled, 188 with complaint of discharge analyzed, 407 without complaint of discharge analyzed	Median 31	NR	188 (31.6) complained of vaginal discharge	NR	0 (0)
Schwebke et al[108]; 1996; United States; Complete Amsel's clinical criteria, modified Amsel's clinical criteria, individual criteria (pH, clue cells)	Cross-sectional; fair	Women undergoing pelvic examination for evaluation of a new complaint at STD clinics and hospital-based gynecology clinics	617 enrolled, 617 analyzed	30.2 (NR)	NR	NR	NR	NR

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States; BD Max, complete Amsel's clinical criteria, modified Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test)	Cross-sectional; fair	Women at least 14 or 18 years of age (depending on clinic) reporting symptoms of vaginitis at a routine clinical visit at an academic medical center or community clinic identified as a STD, HIV, family planning, and/or gynecology clinic	1,740 enrolled, 1,301 analyzed for complete and modified Amsel, 1,338 analyzed for BD Max	NR for BV test subgroup Parent study (N=1,667): 29.3 (9.4)	NR	1,760 (100) (presumably based on study entry criteria) Abnormal discharge; painful or frequent urination; vaginal itching, burning, or irritation; painful or uncomfortable intercourse; vaginal odor	NR for BV test subgroup. Parent study (N=1,667): 17 (1.0) positive, 257 (15.3) unknown	NR
Sha et al[106]; 2007; United States; Complete Amsel's clinical criteria	Cross-sectional; fair	HIV-infected women and HIV-negative women who were at risk women at 6 sites	3,784 enrolled, 16,263 HIV positive and 4,325 HIV negative visits analyzed from 3,784 participants	NR	NR	NR	2,808 (74.2*) participants, 16,263 (80.0*) visits	NR
Singh et al[107]; 2013; United States; Complete Amsel's clinical criteria, modified Amsel's clinical criteria	Cross-sectional; fair	Nonpregnant women age 18 to 45 years with symptoms of abnormal vaginal discharge but no abnormal vaginal bleeding at a single STI clinic	200 enrolled, 197 analyzed	28.1 (7.6)	NR	197 (100) (presumably based on study entry criteria) Symptoms of vaginal discharge	NR	0 (0) (presumably based on study entry criteria)
Sonnex et al[137]; 1995; United Kingdom; Individual criteria (whiff test)	Cross-sectional; fair	Women attending three general practices or a hospital-based genitourinary clinic in the Cambridge area	297 recruited and analyzed from general practices; 164 from genitourinary clinic	35 (NR) general practice; 24 (NR) genitourinary clinic	NR	135 (45.5) had vaginal discharge; 46 (15.5) had vaginal discharge and malodor from general practice; 54 (32.9 had vaginal discharge from genitourinary clinic	NR	NR

Table 1. Study Characteristics of Diagnostic Accuracy Studies (Key Question 2)

Author; Year; Country; Tests Evaluated	Study Design and Quality	Study Population and Setting	Sample Size	Mean Age (SD)	Race/ Ethnicity	No. (%) Symptomatic and Definition of Symptomatic (if Provided)	No. (%) With HIV	No. (%) Pregnant
Witt et al[98]; 2002; Austria; BD Affirm	Cross-sectional; fair	Pregnant women seen at academic outpatient obstetrics clinic between 12 and 36 weeks gestation	1,725 enrolled and analyzed	NR	NR	1,725 (100) (presumably based on study entry criteria) Clinical signs of vaginal infection including increased vaginal discharge, pruritus, burning, cervical incompetence, lower abdominal pain, preterm labor, or preterm rupture of membranes	NR	1,725 (100) (presumably based on study entry criteria)

Abbreviations: AIDS=acquired immune deficiency syndrome; BV=bacterial vaginosis; HIV=human immunodeficiency virus; KQ=key question; No.=number of participants; NR=not reported; pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution; SD=standard deviation; STD=sexually transmitted disease; STI=sexually transmitted infection.

Table 2. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—BD Affirm VPIII (Key Question 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Briselden et al[96] 1994 United States	Gram stain (Nugent score ≥7)	79 (45.0)	0.94 (NR)	0.81 (NR)	5.1* (3.3* to 7.7*)	0.08* (0.03* to 0.18*)	None
Byun et al[90] 2016 South Korea	Gram stain (Nugent score ≥7)	68 (34.9)	0.75 (NR)	0.89 (NR)	6.8* (4.1* 11.4*)	0.28* (0.19* to 0.43*)	None
Cartwright et al[95]; 2013 United States	Gram stain (Nugent score ≥7) or Gram stain (Nugent score 4 to 6 plus positive for BV based on Amsel's clinical criteria)	197 (64.6)	0.90 (0.86 to 0.94)	0.68 (0.63 to 0.72)	2.8* (2.1* to 3.7*)	0.14* (0.09* to 0.21*)	If intermediate flora (Nugent score 4 to 6) excluded, then specificity increases to 0.76
Lowe et al[97]; 2009 United States	Complete Amsel's clinical criteria (number of criteria NR)	319 (59.6)	0.79* (0.74* to 0.83*)	0.72*(0.66* to 0.78*)	2.8* (2.3* to 3.6*)	0.29* (0.23* to 0.37*)	None
Witt et al[98]; 2002 Austria	Gram stain (Nugent score ≥7)	171 (9.9)	0.89* (0.84* to 0.93*)	0.88* (0.87* to 0.90*)	7.6* (6.6* to 8.8*)	0.12* (0.08* to 0.19*)	When participants with Nugent score 4 to 6 are excluded (N=235), the Sn is 0.90 (0.85 to 0.94) and the Sp is 0.97 (0.96 to 0.98). When participant with Nugent score 4 to 6 are included and considered positive for BV, the Sn is 0.73 (0.69 to 0.78) and Sp is 0.97 (0.96 to 0.98)

* Indicates values that we calculated based on data provided in the study.

Abbreviations: BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported; Sn=sensitivity; Sp=specificity.

Table 3. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—BD MAX (Key Question 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.93 (0.91 to 0.94)	0.92 (0.90 to 0.94)	10.9* (8.3* to 14.5*)	0.08* (0.06* to 0.10*)	Analysis excludes participants with missing Amsel's clinical criteria test (N=37). In addition, Gaydos et al[65] includes participants with intermediate Nugent scores and a positive modified Amsel test as positive for BV (N=1,559) and had a sensitivity of 0.905 (95% CI, 0.883 to 0.922) and specificity of 0.858 (95% CI, 0.830 to 0.883)

* Indicates values that we calculated based on data provided in the study.

Abbreviations: BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants.

Table 4. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—BV Blue (Key Question 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥7)	108 (38)	0.88* (0.81* to 0.93*)	0.86* (0.80* to 0.91*)	6.3* (4.4* to 9.2*)	0.14* (0.08* to 0.23*)	Excluding participants with intermediate flora had sensitivity of 0.88 (95% CI, 0.81 to 0.93) and specificity of 0.95 (95% CI, 0.91 to 0.98). Considering participants with intermediate flora as positive had sensitivity of 0.79 (95% CI, 0.72 to 0.85) and a specificity of 0.97 (95% CI, 0.92 to 0.99).
Bradshaw et al[100]; 2005; Australia	Complete Amsel's clinical criteria (at least three of four)	118 (41)	0.88 (0.81 to 0.93)	0.91 (0.85 to 0.94)	10.0* (6.1* to 16.3*)	0.13* (0.08* to 0.21*)	Excluding participants with intermediate flora had sensitivity of 0.92 (95% CI, 0.85 to 0.96) and specificity of 0.93 (95% CI, 0.88 to 0.96).
Hillier et al[101]; 2011; United States	Gram stain (Nugent score ≥7)	NR	0.61 (0.51 to 0.71)	0.99 (0.96 to 1.0)	NR	NR	For symptomatic women (N=251), sensitivity is 0.68 (95% CI, 0.60 to 0.76) and specificity is 1.0 (95% CI, 0.96 to 1.0).
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥7)	12 (21.1*)	0.92 (0.65* to 0.996*)	0.98 (0.90* to 0.999*)	41.3* (5.9* to 288.6*)	0.09* (0.01* to 0.56*)	None

* Indicates values that we calculated based on data provided in the study.

Abbreviations: BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported.

Table 5. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Complete Amsel's Clinical Criteria (Key Question 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥7)	108 (38)	0.91* (0.84* to 0.95*)	0.90* (0.83* to 0.93*)	8.2* (5.4* to 12.4*)	0.10* (0.06* to 0.19*)	Excluding participants with intermediate flora had sensitivity of 0.91 (95% CI, 0.84 to 0.96) and specificity of 0.99 (95% CI, 0.96 to 1.0).
Chen et al[110]; 2018; Taiwan	Gram stain (Nugent score ≥7)	12 (15.6*)	0.92* (0.65* to 0.99*)	0.49* (0.37* to 0.61*)	1.8* (1.4* to 2.4*)	0.17* (0.03* to 1.1*)	None
Gallo et al[103]; 2011; United States	Gram stain (Nugent score ≥7)	HIV positive: 1,046 (34.8) HIV negative: 2,347 (38.3) (from visits, not number of participants)	HIV positive: 0.58 (0.56 to 0.60) HIV negative: 0.63 (0.60 to 0.66)	HIV positive: 0.90 (0.89 to 0.91) HIV negative: 0.91 (0.90 to 0.92)	HIV positive: 5.6* (5.1* to 6.2*) HIV negative: 6.8* (5.9* to 7.9*)	HIV positive: 0.47* (0.45* to 0.49*) HIV negative: 0.41* (0.38* to 0.44*)	Only data from the HIV-negative population was used in our synthesis (i.e., SROC and forest plot)
Gratacos et al[88]; 2005; Spain	Gram stain (Nugent score ≥7)	22 (4.5)	0.36 (0.20* to 0.57*)	0.99 (0.98* to 1.0*)	34.2* (12.2* to 96.0*)	0.64* (0.47* to 0.88*)	None
Gutman et al[109]; 2005; United States	Gram stain (Nugent score ≥7)	104 (38.7)	0.69 (0.59 to 0.78)	0.93 (0.87 to 0.96)	9.5* (5.4* to 16.7*)	0.33* (0.25* to 0.44*)	AUC is 0.8
Hay et al[91]; 1992; U.K.	Gram stain (Spiegel's criteria)	13 (11.4)	1.0* (0.77* to 1.0*)	1.0 (0.96* to 1.0*)	Infinite*	0*	None
Hillier et al[101]; 2011; United States	Gram stain (Nugent score ≥7)	NR	0.67 (0.57 to 0.76)	1.0 (0.98 to 1.0)	NR	NR	For symptomatic women (N=251), sensitivity is 0.82 (95% CI, 0.75 to 0.88) and specificity is 0.94 (95% CI, 0.87 to 0.98)
Hilmarsdottir et al[104]; 2006; Iceland	Gram stain (Nugent score ≥7)	115 (35.2)	0.79 (0.71* to 0.86*)	0.93 (0.89*to 0.96*)	11.2 (6.9 to 18.4)	0.23* (0.16* to 0.32*)	LR+: 11.2 (6.9 to 18.4) Note: The number of false positives was incorrectly reported in the text.
Landers et al[105]; 2004; United States	Gram stain (not described, presumably Nugent score ≥7)	276 (46)	0.92 (0.88* to 0.95*)	0.77 (0.71* to 0.81*)	4.0* (3.2* to 4.9*)	0.11* (0.07* to 0.16*)	None
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥7)	12 (21.1*)	0.50* (0.25* to 0.75*)	1.0* (0.92* to 1.0*)	Infinite*	0.50* (0.28* to 0.88*)	None

Table 5. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Complete Amsel's Clinical Criteria (Key Question 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Platz-Christensen et al[92]; 1995; Sweden	Gram stain (Spiegel's criteria)	36 (33.3*)	0.94* (0.82* to 0.98*)	1.0* (0.95* to 1.0*)	Infinite*	0.06* (0.01* to 0.21*)	Note: The study authors report sensitivity and specificity for Amsel's clinical criteria as the referent test and Gram stain as the index test.
Sha et al[106]; 2007; United States	Gram stain (Nugent score ≥7)	HIV positive: 6,050 (37.2*) HIV negative: 1,880 (43.5*) (from visits, not number of participants)	HIV positive: 0.36 (0.35 to 0.37) HIV negative: 0.39 (0.36 to 0.41)	HIV positive: 0.971 (0.967 to 0.974) HIV negative: 0.978 (0.971 to 0.983)	HIV positive: 12.2* (10.8* to 13.7*) HIV negative: 17.2* (13.2* to 22.5*)	HIV positive: 0.66* (0.65* to 0.68*) HIV negative: 0.63* (0.61* to 0.65*)	Only data from the HIV-negative population were used in our synthesis (i.e., SROC and forest plot).
Schwebke et al[108]; 1996; United States	Gram stain (Nugent score ≥7)	243 (39.4)	0.62 (0.55* to 0.68*)	0.97 (0.94* to 0.98*)	17.8* (10.3* to 30.6*)	0.40* (0.34* to 0.47*)	If "any clue cells" criteria used in place of 20% clue cells, the sensitivity is 0.704 and specificity is 0.944.
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.76 (0.72 to 0.79)	0.94 (0.92 to 0.96)	12.8* (9.2* to 18.0*)	0.26* (0.23* to 0.30*)	None
Singh et al[107]; 2013; United States	Gram stain (Nugent score ≥7)	125 (63.5*)	0.72* (0.64* to 0.79*)	0.79* (0.68*to 0.87*)	3.5* (2.2* to 5.5*)	0.35* (0.26* to 0.48*)	None

* Indicates values that we calculated based on data provided in the study.

Abbreviations: AUC=area under the curve; CI=confidence interval; HIV=human immunodeficiency virus; KQ=key question; LR+= positive likelihood ratio; N=number of participants; SROC=summary receiver operating characteristics.

Table 6. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Modified Amsel's Clinical Criteria (Key Question 2)

Author; Year; Country	Reference Test	N (%) with Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Gratacos et al[88]; 2005; Spain	Gram stain (Nugent score ≥ 7)	22 (4.5)	0.64 (0.43* to 0.80*)	0.98 (0.96* to 0.99*)	33.2* (16.2* to 68.3*)	0.37* (0.21* to 0.64*)	None
Mastrobattista et al[89]; 2000; United States	Gram stain (Nugent score ≥ 7)	18 (26.9*)	0.56 (0.32 to 0.78)	0.96 (0.90 to 1.0)	13.6* (3.3* to 56.2*)	0.46* (0.28* to 0.78*)	None
Schwebke et al[108]; 1996; United States	Gram stain (Nugent score ≥ 7)	243 (39.4)	0.63 (0.57 to 0.69)	0.96 (0.94 to 0.98)	16.8* (10.0* to 28.4*)	0.39* (0.33* to 0.45*)	None
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥ 7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.82 (0.79 to 0.85)	0.91 (0.88 to 0.93)	8.8* (6.7* to 11.4*)	0.20* (0.17* to 0.23*)	None
Singh et al[107]; 2013; United States	Gram stain (Nugent score ≥ 7)	125 (63.5*)	0.54* (NR)	NR	NR	NR	None

* Indicates values that we calculated based on data provided in the study.

Abbreviations: BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported.

Table 7. Study Characteristics of Randomized, Controlled Trials Reporting Benefits or Maternal Harms of Treating Bacterial Vaginosis on Pregnancy Outcomes (Key Questions 4 and 5)

Author Year	Country	Study Quality	Interventions (N randomized)	N (%) with BV Symptoms	N (%) Nulliparous	N (%) Nonwhite	N (%) With Prior PTD	Outcomes Reported
Carey et al[111] Andrews et al[127] 2000	U.S.	Good	G1: Placebo (987) G2: Oral metronidazole 1000 mg dose four times on days 0, 2,14 and 16 (966)	0 (0)	G1: 407 (41.2) G2: 436 (45.1)	G1: 841 (85.2) G2: 822 (85.1)	G1: 110 (11.1) G2: 103 (10.7)	• All-cause and spontaneous PTD <37, 35, and 32 weeks • Birth weight <2,500 and 1,500 grams • Subgroup findings for women with prior PTD; treatment for chlamydia, and BV clearance • Any maternal tolerability-related side effects: GI symptoms; candidiasis
Guaschino et al[112] 2003	Italy	Fair	G1: No treatment (57) G2: Intravaginal clindamycin 2% cream once daily for 7 days (55)	0 (0)	G1: 35 (61.4) G2: 39 (70.9)	NR	G1: 3 (5.3) G2: 5 (9.1)	• All-cause PTD <37 weeks; • Birthweight <2,500 grams • Preterm or term PROM
Hauth et al[121] 1995	U.S.	Fair	G1: Placebo (87)* G2: Oral metronidazole (750 mg daily) for 7 days and erythromycin (999 mg daily) for 14 days (176)	NR	For parent study G1: 30 (16) G2: 84 (19)	For parent study G1: 150 (79) G2: 309 (71)	For subgroup with BV G1: 56 (65.1) G2: 121 (70.3)	• All-cause PTD <37 weeks • Subgroup findings among women with prior PTD
Kekki et al[113] 2001 Kurkinen-Raty et al[126] 2000	Finland	Good	G1: Placebo (188) G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)	0 (0)	Mean parity G1: 1.9 G2: 1.7	NR	0 (0)	• Spontaneous PTD <37 weeks • Maternal peripartum infection • Subgroup findings among participants with clearance of BV and participants with IF • Maternal candidiasis

Table 7. Study Characteristics of Randomized, Controlled Trials Reporting Benefits or Maternal Harms of Treating Bacterial Vaginosis on Pregnancy Outcomes (Key Questions 4 and 5)

Author Year	Country	Study Quality	Interventions (N randomized)	N (%) with BV Symptoms	N (%) Nulliparous	N (%) Nonwhite	N (%) With Prior PTD	Outcomes Reported
Kiss et al[114] 2004	Austria	Fair	G1: No treatment (179)† G2: Intravaginal clindamycin 2% cream once daily for 6 days and treatment with oral clindamycin (300 mg twice a day) if still positive at 24 to 27 weeks gestation (177)	0 (0)	G1: NR (47.8) G2: NR (47.9)	NR (2)	Between 33 and 36 weeks: G1: 45 (2.1) G2: 47 (2.2) Between 23 and 32 weeks: G1: 24 (1.1) G2: 22 (1.1)	• Spontaneous PTD <37 weeks • Any maternal AEs
Lamont et al[115] 2003	U.K.	Good	G1: Placebo (201) G2: Intravaginal clindamycin 2% cream, once daily for 3 days (208)	0 (0)	G1: 112 (56) G2: 111 (53)	G1: 63 (31) G2: 58 (28)	G1: 11 (8) G2: 10 (7)	• Spontaneous PTD <37 weeks; • Birth weight <2,500 and 1,500 grams; • Stillborn fetus
Larsson et al[116] 2006	Sweden	Fair	G1: No treatment (411) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)	0 (0)	G1: 187 (45.5) G2: 186 (45.5)	NR	Among parous women G1: 13/218 (6.0) G2: 20/217 (9.2)	• All-cause PTD <37 weeks • Spontaneous PTD <37 and <32 completed weeks • Any maternal severe AEs • Treatment withdrawal
McDonald et al[117] 1997	Australia	Good	G1: Placebo (440) G2: Oral metronidazole 800 mg daily for 2 days repeated at 28 weeks for women with persistence (439)	0 (0)	G1: 144 (32.7) G2: 139 (31.7)	G1: 53 (12.3) G2: 47 (10.8)	G1: 24 (5.5) G2: 22 (5.0)	• All-cause and spontaneous PTD <37 weeks • Preterm PROM • Subgroup findings for women with prior PTD • Any maternal AEs or tolerability-related side effects: • Treatment withdrawal
McGregor et al[118] 1994	U.S.	Good	G1: Placebo (69 analyzed) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (60 analyzed)	0 (0)	Mean parity 1.0 (range 0 to 6)	87 (61.2)	15 (10.9)	• All-cause PTD <37 weeks • Preterm PROM • Preterm labor • Birthweight <2,500 grams
Morales et al[122]	U.S.	Fair	G1: Placebo (36 analyzed)	NR	Mean parity G1: 2.2 (1.1)	G1: 18 (50) G2: 20 (45)	80 (100)	• Spontaneous PTD <37 and 34 weeks

Table 7. Study Characteristics of Randomized, Controlled Trials Reporting Benefits or Maternal Harms of Treating Bacterial Vaginosis on Pregnancy Outcomes (Key Questions 4 and 5)

Author Year	Country	Study Quality	Interventions (N randomized)	N (%) with BV Symptoms	N (%) Nulliparous	N (%) Nonwhite	N (%) With Prior PTD	Outcomes Reported
1994			G2: Oral metronidazole 750 mg daily for 7 days (44 analyzed)		G2: 2.4 (1.2)			• Preterm labor • PROM • Birthweight <2,500 grams
Subtil et al[119] 2018	France	Good	G1: Placebo (956) G2: Oral clindamycin 600 mg daily for 4 days or 3 courses of 600 mg daily for 4 days, each 1 month apart (1904)	NR	NR	NR	NR	• All-cause and spontaneous PTD <37 weeks • Spontaneous PTD <32 weeks • Neonatal mortality • Any maternal severe AEs; any tolerability-related side effects; GI symptoms • Treatment withdrawal
Ugwumadu et al[120] 2003	U.K.	Good	G1: Placebo (245)‡ G2: Oral clindamycin 600 mg daily for 5 days (249)	NR	Mean parity G1: 0.8 (1.0) G2: 0.8 (1.1)	G1: 93 (39) G2: 86 (36)	G1: 22 (9) G2: 24 (10)	• Spontaneous PTD <37 weeks • Subgroup findings among participants with intermediate flora • Any maternal AEs or tolerability-related side effects: GI symptoms • Treatment withdrawal
Vermeulen et al[123] 1999	The Nether-lands	Good	G1: Placebo (11)§ G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11)	NR	Mean parity G1: 1.4 (0.9) G2: 1.6 (0.9)	NR	G1: 11 (100) G2: 11 (100)	• All-cause PTD <34 weeks • Neonatal sepsis • Maternal candidiasis • Treatment withdrawal

* This study assessed the impact of treatment among a population of women with and without BV. This N represents the number of women with BV who are eligible for this review. The total N of the placebo group was 191, and the total N of the treatment group was 433. Some population characteristics reported here are for the full study population because characteristics were not reported separately for women with BV.

† This study randomized a total of 4,429 participants to vaginal smear screening, but only a subset of participants tested positive for BV and received treatment; we only abstracted data for the BV positive subset of the study population.

‡ Represents the full randomized population; we only reported findings for the subgroup of women with BV, which was 203 participants for the placebo group and 207 participants for the treatment group.

§ This represents the number of women with BV who were allocated to placebo and treatment; the total number of women randomized in the study was 168 (placebo [N=85] and active treatment [N=83]).

Abbreviations: AE=adverse event; BV=bacterial vaginosis; G=group; GI=gastrointestinal; IF=intermediate flora; N=number of participants; NR=not reported; PROM=premature rupture of membranes; PTD=preterm delivery; SD=standard deviation; U.K.=United Kingdom; U.S.=United States.

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Carey et al[111]; 2000; Andrews et al[127]; 2003; G1: Placebo (966) G2: Oral metronidazole 1,000 mg dose four times (953)	**All-cause PTD (primary outcome)** G1: 121 (12.5) G2: 116 (12.2) Calculated ARD, -0.35% (-3.30% to 2.59%) RR, 1.0 (0.8 to 1.2) Calculated RR, 0.97 (0.77 to 1.23) **Spontaneous PTD** G1: 91 (9.4) G2: 89 (9.3) Calculated ARD, -0.08% (-2.69% to 2.53%) Calculated RR, 0.99 (0.75 to 1.31)	**All-cause PTD <35 weeks** G1: 49 (5.1) G2: 48 (5.0) Calculated ARD, -0.04% (-2.00% to 1.92%) RR, 1.0 (0.7 to 1.5) Calculated RR, 0.99 (0.67 to 1.46) **All-cause PTD <32 weeks** G1: 26 (2.7) G2: 22 (2.3) Calculated ARD, -0.38% (-1.78% to 1.01%) RR, 0.9 (0.5 to 1.5) Calculated RR, 0.86 (0.49 to 1.50)	**Birth weight <2,500 g** G1: 109/956 (11.4) G2: 103/943 (10.9) Calculated ARD, -0.48% (-3.31% to 2.35%) RR, 1.0 (0.7 to 1.2) Calculated RR, 0.96 (0.74 to 1.24) **Birth weight <1,500 g** G1: 26/956 (2.7) G2: 19/943 (2.0) Calculated ARD, -0.70% (-2.07% to 0.66%) RR, 0.7 (0.4 to 1.3) Calculated RR, 0.74 (0.41 to 1.33)	Among women with prior PTD: All-cause PTD <37 weeks G1: 18/80 (22.5) G2: 24/80 (30.0) Calculated ARD, 7.50% (-6.09% to 21.09%) RR, 1.3 (0.8 to 2.0) Calculated RR, 1.33 (0.79 to 2.26) No significant difference in PTD <37 weeks or <35 weeks between treatment and placebo for chlamydia positive vs. chlamydia negative participants Among 1,687 women in both groups who had followup Gram staining and for whom information on delivery was available, preterm birth occurred in 77 of 718 women who had BV at followup (10.7%) and 103 of 969 women whose BV remitted (10.6%) (p=0.95), regardless of treatment
Guaschino et al[112]; 2003; G1: no treatment (51) G2: Intravaginal clindamycin 2% daily for 7 days (49)	**All-cause PTD (primary outcome)** G1: 8 (15.7) G2: 6 (12.2) p=0.78 Calculated ARD, -3.44% (-17.00% to 10.12%) Calculated RR, 0.78 (0.29 to 2.09)	NR	**Birth weight <2,500 g** G1: 7 (13.7) G2: 3 (6.1) p=0.32 Calculated ARD, -7.60% (-19.19% to 3.98%) Calculated RR, 0.45 (0.12 to 1.63) **PROM** (preterm or term per study author confirmation) G1: 3 (5.9) G2: 7 (14.3) p=0.19 Calculated ARD, 8.40% (-3.33% to 20.14%) Calculated RR, 2.43 (0.67 to 8.86)	NR

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Hauth et al[121]; 1995; G1: Placebo (190) G2: Oral metronidazole for 7 days with oral erythromycin for 14 days (426)*	**All-cause PTD** (primary outcome; women with prior history of PTD or prepregnancy weight < 50 kg with or without bacterial vaginosis) G1: 68 (36) G2: 110 (26) RR, 1.4 (1.1 to 1.8) for G1 vs. G2	NR	NR	All-cause PTD <37 weeks among women with bacterial vaginosis and prior PTD: G1: 32/56 (57) G2: 47/121 (39) p= 0.02 Calculated ARD, -18.30% (-33.90% to -2.70%) RR, 1.5 (1.1 to 2.0) reported for G1 vs. G2 Calculated RR, 0.68 (0.49 to 0.93) for G2 vs. G1 All-cause PTD <37 weeks among women with BV and prior PTD or prepregnancy weight <50 kg): G1: 42 (48.8) G2: 54 (31.4) Calculated ARD, -18.30% (-33.90% to -2.70%) RR, 1.6 (1.1 to 2.1) reported for G1 vs. G2 Calculated RR, 0.68 (0.49 to 0.93) for G2 vs. G1
Kekki et al[113]; 2001; Kurkinen-Raty et al[126]; 2000 G1: Placebo (188) G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)	**All-cause PTD** NR **Spontaneous PTD** (study powered based on this outcome) G1: 7 (3.7) G2: 9 (4.8) OR, 1.3 (0.5 to 3.5) Calculated ARD, 1.09% (-3.00% to 5.18%) Calculated RR, 1.29 (0.49 to 3.40)	NR	**Maternal peripartum infection** (postpartum endometritis, postpartum sepsis, cesarean wound infection, episiotomy wound infection) G1: 33 (17.6) G2: 21 (11.2) OR, 1.6 (0.9 to 2.8) (study reported, comparing G1 with G2) Calculated ARD, -6.32% (-13.4% to 0.75%) Calculated RR, 0.64 (0.38 to 1.06)	PTD in patients with complete followup who demonstrated clearance of BV 1-week posttreatment: G1: 0/42 (0%) G2: 2/79 (2.5%) Calculated ARD, 2.30% (-1.45% to 6.06%) Calculated RR, 10.66 (0.02 to 6,039) PTD in participants with intermediate Gram stain findings: G1: 4/18 (22%) G2: 5/17 (29%) OR, 1.2 (95% CI, 0.5 to 2.9) Calculated ARD, 7.19% (-21.76% to 36.14%) Calculated RR, 1.32 (0.43 to 4.12)

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Kiss et al[114]; 2004; G1: No treatment (176)† G2: Intravaginal clindamycin 2% cream once daily for 6 days with test of cure and further treatment if positive (175)	**Spontaneous PTD** (primary outcome) G1: 10 (5.7) G2: 6 (3.4) Calculated ARD, -2.25% (-6.61% to 2.10%) Calculated RR, 0.60 (0.22 to 1.62)			
Lamont et al[115]; 2003; Lamont et al[138]; 2012; G1: Placebo (193) G2: Intravaginal clindamycin 2% cream, once daily for 3 days (198)	**Spontaneous PTD** (primary outcome) G1: 19 (9.8) G2: 8 (4.0) OR, 0.38 (0.16 to 0.90 adjusted for gestational age at treatment Calculated ARD, -5.80% (-10.82% to -0.79%) Calculated RR, 0.41 (0.18 to 0.92)	NR	**Birth weight <2,500 g:** G1:15/193 (7.8) G2: 18/204 (8.8) Calculated ARD, 1.05% (-4.37% to 6.48%) Calculated RR, 1.14 (0.59 to 2.19) **Birth weight <1,500 g:** G1: 4/193 (2.1) G2: 3/204 (1.5) Calculated ARD, -0.60% (-3.20% to 2.00%) Calculated RR, 0.71 (0.16 to 3.13) **Stillborn fetus:** G1: 3/140 (2.1) G2: 1/142 (0.7) Calculated ARD, -1.44% (-4.20% to 1.33%) Calculated RR, 0.33 (0.03 to 3.12)	NR

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Larsson et al[116]; 2006; G1: no treatment (411) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)	**All-cause PTD** (primary outcome) G1: 25 (6.1) G2: 21 (5.2) OR, 0.84 (0.48 to 1.47) Calculated ARD, -0.94% (-4.09% to 2.22%) Calculated RR, 0.85 (0.48 to 1.49) **Spontaneous PTD (between 16 and 37 weeks)** G1: 12/390 (3.1) G2: 11/395 (2.8) OR, 0.90 (0.40 to 2.02) Calculated ARD, -0.29% (-2.65% to 2.07%) Calculated RR, 0.91 (0.40 to 2.03)	**Spontaneous PTD (between 16 weeks and <32 completed weeks)** G1: 5/390 (1.3) G2: 1/395 (0.25) Calculated ARD, -1.03% (-2.25% to 0.19%) Calculated RR, 0.20 (0.02 to 1.68)	NR	NR

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
McDonald et al[117]; 1997; G1: Placebo (428) G2: Oral metronidazole 800 mg daily for 2 days and repeated at 28 weeks gestation for positive test of cure (429)	**All-cause PTD** G1: 32 (7.5) G2: 31 (7.2) Calculated ARD, -0.95% (-5.54% to 3.64%) Calculated RR, 0.87 (0.46 to 1.67) **Spontaneous PTD** (primary outcome) G1: 24 (5.6) G2: 20 (4.7) OR, 0.82 (0.43 to 1.57) Calculated ARD, -1.76% (-5.81% to 2.29%) Calculated RR, 0.72 (0.34 to 1.54)	NR	**PPROM** G1: 14 (3.3) G2: 12 (2.8) OR, 0.85 (0.36 to 1.98) Calculated ARD, -1.72% (-4.94% to 1.49%) Calculated RR, 0.59 (0.22 to 1.60)	**All-cause PTD <37 weeks among subgroup of women who were smear positive** (i.e., not including women with heavy growth of *G. vaginalis*) G1: 18/238 (7.6) G2: 16/242 (6.6) OR, 0.87 (0.41 to 1.83) Calculated ARD, -0.95% (-5.54% to 3.64%) Calculated RR, 0.87 (0.46 to 1.67) **Spontaneous PTD <37 weeks among subgroup of women who were smear positive** (i.e., not including women with heavy growth of *G. vaginalis*) G1: 15/238 (6.3) G2: 11/242 (4.5) OR, 0.71 (95% CI, 0.30 to 1.68) Calculated ARD, -1.76% (-5.81% to 2.30%) Calculated RR, 0.72 (0.34 to 1.54) **Spontaneous PTD <37 weeks among subgroup of women with prior PTD** G1: 10/24 (41.7) G2: 2/22 (9.1) OR, 0.14 (0.01 to 0.84) Calculated ARD, -29.41% (-54.73% to -4.09%) Calculated RR, 0.17 (0.02 to 1.24)

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
McGregor et al[118]; 1994; G1: Placebo (69) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (60)	**All-cause PTD** G1: 5 (7.3) G2: 9 (15.0) Calculated ARD, 7.75% (-3.16% to 18.66%) Calculated RR, 2.07 (0.73 to 5.84)	NR	**PPROM** G1: 3/68 (4.4) G2: 3 /60 (5.0) Calculated ARD, 0.59% (-6.78% to 7.95%) Calculated RR, 1.13 (0.24 to 5.41) **Preterm Labor** G1: 10 (14.5) G2: 13 (21.7) Calculated ARD, 7.17% (-6.15% to 20.50%) Calculated RR, 1.50 (0.71 to 3.16) **Birth weight <2,500 g** G1: 3 (4.4) G2: 8 (13.6) Calculated ARD, 9.21% (-0.76% to 19.18%) Calculated RR, 3.12 (0.87 to 11.22)	NR

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Morales et al[122]; 1994; G1: Placebo (36) G2: Oral metronidazole 750 daily (44)	**Spontaneous PTD** (primary outcome) G1: 16 (44.4) G2: 8 (18.2) p<0.05 Calculated ARD, -26.26% (-46.10% to -6.43%) Calculated RR, 0.41 (0.20 to 0.85)	**Spontaneous PTD <34 weeks** G1: 4 (11.1) G2: 2 (4.6) P NS Calculated ARD, -6.57% (-18.53% to 5.40%) Calculated RR, 0.41 (0.08 to 2.11)	**Preterm labor** G1: 28 (77.8) G2: 12 (27.3) p<0.05 Calculated ARD, -50.51% (-69.41% to -31.60%) Calculated RR, 0.35 (0.21 to 0.59) **Birthweight <2,500 g** G1: 12 (33.3) G2: 6 (13.6) p<0.05 Calculated ARD, -19.7% (-38.13% to -1.26%) Calculated RR, 0.41 (0.17 to 0.98) **PROM** G1: 12 (33.3) G2: 2 (4.6) p<0.05 Calculated ARD, -28.79% (-45.37% to -12.21%) Calculated RR, 0.14 (0.03 to 0.57)	

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Subtil et al[119]; 2014; G1: Placebo (956) G2: Oral clindamycin 600 mg daily for 4 days G3: Oral clindamycin 600 mg daily for 4 days repeated twice at 1-month intervals (G2/G3 combined 1,904)	**All-cause PTD:** G1: 56 (5.9) G2/G3: 128 (6.7) RR, 1.15 (0.85 to 1.56; p=0.37) Calculated ARD, 0.86% (-1.00% to 2.73%) **Spontaneous PTD:** G1: 39 (4.1) G2/G3: 91 (4.8) RR, 1.17 (0.81 to 1.69; p=0.40) Calculated ARD, 0.70% (-0.88% to 2.28%)	**Late miscarriage (>16 weeks) or spontaneous PTD <32 completed weeks (**primary outcome)**:** G1: 10 (1.0) G2/G3: 22 (1.2) RR, 1.10 (0.53 to 2.32, p=0.82) Calculated ARD, 0.11% (-0.69% to 0.91%)	**PPROM** G1: 18 (1.9) G2/G3: 42 (2.2) RR, 1.18 (0.65 to 2.13; p=0.57) Calculated ARD, 0.32% (-0.76% to 1.41%) **Neonatal mortality** G1: 2/955 (0.21) G2: 3/1898 (0.16) Calculated ARD, -0.05% (-0.39% to 0.29%) Calculated RR, 0.75 (0.13 to 4.51) **Neonatal sepsis:** G1: 31/955 (3.2) G2/G3: 48/1898 (2.5) RR; 0.77 (0.49 to 1.22; p=0.27) Calculated ARD, -0.72% (-2.05% to 0.61%) **Birth weight <2,500 grams:** G1: 75/955 (7.9) G2/G3: 160/1898 (8.4) Calculated ARD, 0.58% (-1.54% to 2.69%) Calculated RR, 1.07 (0.83 to 1.40) **Birth weight <1,500 grams** G1: 6/955 (0.63) G2/G3: 25/1898 (1.3) Calculated ARD, 0.69% (-0.03% to 1.41%) Calculated RR, 2.10 (0.86 to 5.09)	NR

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Subtil et al[119]; 2014; (continued)			**Maternal need for antibiotic within 24 hours of delivery** G1: 113 (11.8) G2/G3: 220 (11.6) RR, 0.98 (0.79 to 1.21; p=0.83) Calculated ARD, -0.27% (-2.77% to 2.23%) **Fetal death (>22 weeks)** G1: 6/955 (0.63) G2/G3: 9/1898 (0.47) RR, 0.75 (0.27 to 2.11; p=0.59) Calculated ARD, -0.15% (-0.74% to 0.43%)	
Ugwumadu et al[120]; 2003; G1: Placebo (203) G2: Oral clindamycin 600 mg daily (in two divided doses) for 5 days (207)	**Spontaneous PTD (between 24 and 37 weeks)‡** G1: 31 (15.3) G2: 11 (5.3) Calculated ARD, -9.96% (-15.77% to -4.14%) Calculated RR, 0.35 (0.18 to 0.67) **Spontaneous PTD** (delivery between 24 and up to 37 weeks) or late miscarriage (between 13 weeks and up to 24 weeks) (primary outcome) G1: 38/241 (15.7) G2: 13/244 (5.3) ARD 10.4% (95% CI, 5.0 to 15.8)	NR	NR	**Spontaneous PTD for women with intermediate flora or BV:** G1: 28 (11.6%) G2: 11 (4.5%) Calculated ARD, -7.11% (-11.92% to -2.30%) Calculated RR, 0.39 (0.20 to 0.76) **Spontaneous PTD for women with intermediate flora:** G1: 7/38 (18.4) G2: 2/37 (5.4) Calculated ARD, -13.02% (-27.33% to 1.30%) Calculated RR, 0.29 (0.07 to 1.32)

Table 8. Benefit Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	PTD <37 Weeks; N (%) Effect Estimates (95% CI)	Other PTD Outcomes; N (%) Effect Estimates (95% CI)	Other Pregnancy Outcomes; N (%) Effect Estimates (95% CI)	Subgroup Analyses
Vermeulen et al[123]; 1999; G1: Placebo (11)[§] G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11)	NR for women with bacterial vaginosis but was the primary outcome for the overall study	NR	**Neonatal sepsis** G1: 0 (0) G2: (0)	**All-cause PTD <34 weeks among women with bacterial vaginosis** G1: 1 (9.1) G2: 1 (9.1) ARD 0% (95% CI, -24.03% to 24.03%)

* This study assessed the impact of treatment among a population of women with and without BV. This N represents the number of women with BV who are eligible for this review. The total N of placebo group was 191, and the total N of the treatment group was 433.

† This study randomized a total of 4,429 participants to vaginal smear screening, but only a subset of participants tested positive for BV and received treatment; we only abstracted data for the BV positive subset of the study population.

ǂ Although the study included women with either intermediate flora or bacterial vaginosis, the outcome reported here is for the subgroup with bacterial vaginosis (Nugent score ≥7).

§ This represents the number of women with BV who were allocated to placebo and treatment; the total number of women randomized in the study was 168 (placebo [N=85] and active treatment [N=83])

Abbreviations: ARD=absolute risk difference; BV=bacterial vaginosis; CI=confidence interval; G=group; *G. vaginalis*=*Gardnerella vaginalis*; KQ=key question; N=number of participants; NR=not reported; OR=odds ratio; PROM=premature rupture of membranes; PPROM=preterm premature rupture of membranes; PTD=preterm delivery; RR=relative risk.

Table 9. Maternal Harm Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 5)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	Maternal Harms
Carey et al[111]; 2000; G1: Placebo (859) G2: Oral metronidazole 1000 mg dose four times (845)	**Side effects** G1: 88/966 (9.1%) G2: 206/953 (21.6%) Calculated ARD, 12.51% (95% CI, 9.33% to 15.69%) Calculated RR, 2.37 (95% CI, 1.88 to 3.00) **GI symptoms** G1: 72/966 (7.45%) G2: 188/953 (19.73%) Calculated ARD, 12.27% (95% CI, 9.25% to 15.29%) Calculated RR, 2.65 (95% CI, 2.05 to 3.42) **Vomiting** G1: 27/966 (2.80%) G2: 92/953 (9.65%) Calculated ARD, 6.86% (95% CI, 4.72% to 9.00%) Calculated RR, 3.45 (95% CI, 2.27 to 5.25) **Treatment of candida infection** G1: 47/966 (4.87%) G2: 114/953 (11.96%) Calculated ARD, 7.10% (95% CI, 4.63% to 9.56%) Calculated RR, 2.46 (1.78 to 3.41)
Kekki et al[113]; 2001; Kurkinen-Raty et al[126]; 2000; G1: Placebo (188) G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)	**Vulvovaginal itching consistent with yeast infection** G1: 6/188 (3.19%) G2: 6/187 (3.21%) Calculated ARD, 0.02% (95% CI, -3.55% to 3.58%) Calculated RR, 1.01 (95% CI, 0.33 to 3.06)

Table 9. Maternal Harm Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 5)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	Maternal Harms
Kiss et al[114]; 2004 G1: No treatment (176)† G2: Intravaginal clindamycin 2% cream once daily for 6 days with test of cure and further treatment if positive (175)	**AEs** G1: 0 G2: 0
Larsson et al[116]; 2006; G1: No treatment (411) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)	**Withdrew from treatment for persistent itching** 3/353 (0.85%) (group unknown) **Severe treatment-related AEs** G1: NR G2: 0
McDonald et al[117]; 1997; G1: Placebo (428) G2: Oral metronidazole 800 mg daily for 2 days and repeated at 28 weeks gestation for positive test of cure (429)	**Total AEs (includes nausea, vomiting, diarrhea, headache, dizziness, rash, thrush, back pain)** G1: 16/428 (3.74%) G2: 27/429 (6.29%) Calculated ARD, 2.56% (95% CI, -0.36% to 5.47%) Calculated RR, 1.68 (95% CI, 0.92 to 3.08) **Discontinued treatment (unknown whether because of AEs)** G1: 14/428 (3.27%) G2: 19/429 (4.43%) Calculated ARD, 1.16% (95% CI, -1.42% to 3.73%) Calculated RR, 1.35 (95% CI, 0.69 to 2.67)

Table 9. Maternal Harm Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 5)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	Maternal Harms
Subtil et al[119]; 2014; G1: Placebo (956) G2: Oral clindamycin 600 mg daily for 4 days G3: Oral clindamycin 600 mg daily for 4 days repeated twice at 1-month intervals (G2/G3 combined 1,904)	**Any side effects** G1: 12/956 (1.26%) G2/G3: 58/1904 (3.05%) Calculated ARD, 1.79% (95% CI, 0.75% to 2.84%) Calculated RR, 2.43 (95% CI, 1.31 to 4.50) **Any serious AE** G1: 0/956 G2: 0/1904 Stopped taking treatment (unclear whether because of side effects) G1: 156/956 (16.32%) G2: 374/1904 (19.64%) Calculated ARD, 3.33% (95% CI, 0.38% to 6.27%) Calculated RR, 1.20 (95% CI, 1.02 to 1.43) **Diarrhea** G1: 4/956 (0.42%) G2: 30/1904 (1.58%) Calculated ARD, 1.16% (95% CI, 0.46% to 1.85%) Calculated RR, 3.77 (1.33 to 10.66) **Abdominal pain** G1: 0/956 (0%) G2: 9/1904 (0.5%) Calculated ARD, 0.42% (95% CI, 0.08% to 0.76%) Calculated RR, 9.04 (95% CI, 0.52 to 155.8)

Table 9. Maternal Harm Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 5)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	Maternal Harms
Ugwumadu et al[120]; 2003; G1: Placebo (203) G2: Oral clindamycin 600 mg daily (in two divided doses) for 5 days (207)	**Side effects leading to discontinuation of treatment** G1: 8/241 (3.32%) G2: 17/244 (6.97%) Calculated ARD, 3.65% (95% CI, -0.27% to 7.56%) Calculated RR, 2.10 (95% CI, 0.92 to 4.78) **Gastrointestinal upset** G1: 1/241 (4.15%) G2: 5/244 (2.05%) Calculated ARD, -2.1% (95% CI, -5.18% to 0.98%) Calculated RR, 0.49 (95% CI, 0.17 to 1.42) **Rash** G1: 1/241 (0.41%) G2: 1/244 (0.41%) **Vulvovaginal candidiasis** G1: 2/242 (0.83%) G2: 1/244 (0.41%) **Throat irritation** G1: 1/241 (0.41%) G2: 0/244 (0%) **Headache** G1: 1/241 (0.41%) G2: 4/244 (1.64%)
Vermeulen et al[123]; 1999; G1: Placebo (11)[§] G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11)	**Withdrawals because of serious AEs** G1: 0/85* G2: 0/83* **Candida vaginitis** G1: 1/85* G2: 1/83* **Troublesome discharge** G1: 0/85* G2: 3/83*

* Represents the full study population, not just women with BV.

† This study randomized a total of 4,429 participants to vaginal smear screening, but only a subset of participants tested positive for BV and received treatment; we only abstracted data for the BV positive subset of the study population.

Table 9. Maternal Harm Outcomes From Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (Key Question 5)

§ This represents the number of women with BV who were allocated to placebo and treatment; the total number of women randomized in the study was 168 (placebo [N=85] and active treatment [N=83]

Abbreviations: AE=adverse event; ARD=absolute risk difference; CI=confidence interval; G=group; GI=gastrointestinal; KQ=key question; N=number of participants; RR=relative risk.

Table 10. Study Characteristics and Outcomes of Observational Studies and Meta-Analyses Reporting Harms in Children Related to In Utero Metronidazole Exposure (Key Question 5)

Author (Year) Study Quality	Study Design, Years Covered	Number of Participants, Study Population(s)	Exposure Description	Summary of Outcomes
Burtin et al (1995)[133] Fair	Meta-analysis of 7 single or controlled-cohort studies published 1964 to 1987	N not reported Studies that included at least 10 women exposed to metronidazole during pregnancy; further details NR	Exposed to oral or intravaginal metronidazole during the first trimester compared with not exposed or exposed during the third trimester	Incidence of major congenital anomalies Summary OR 0.93 (95% CI, 0.73 to 1.18) Incidence of any congenital anomalies Summary OR, 0.96 (95% CI, 0.75 to 1.22)
Caro-Paton et al (1997)[134] Fair	Meta-analysis of 5 studies (4 cohort and 1 case control) published 1977 to 1994	N=199,451 Studies in women exposed to metronidazole during pregnancy for whatever its indication; further details NR	Exposed to metronidazole during the first trimester compared with not exposed	Incidence of congenital anomalies Summary OR 1.08 (95% CI, 0.90 to 1.29)
Czeizel et al (1998)[131] Fair	Case control, 1980 to 1991	N=47,963 Pregnant women in Hungary identified through registries	Use of oral or intravenous metronidazole during pregnancy based on self-report, physician prenatal care log books, or both	Incidence of congenital abnormalities: Exposure during 1st month OR 2.24 (95% CI, 1.30 to 3.85) Exposure during 2nd or 3rd month OR 1.14 (95% CI, 0.89 to 1.46) Exposure during 5th through 9th month OR 1.07 (95% CI, 0.95 to 1.20)
Diav-Citrin et al (2001)[129] Poor	Prospective cohort, 1989 to 1998	N=857 Pregnant women who contacted the Israeli Teratogen Information Service for information about gestational exposure to metronidazole or to nonteratogenic agents	Self-report of gestational exposure to metronidazole or to nonteratogenic agents	Incidence of major birth defects RR, 1.13 [95% CI, 0.30 to 4.23)
Sorensen et al (1999)[130] Fair	Retrospective cohort, 1991 to 1996	N=13,451 Women in Denmark who gave birth in North Jutland County between 1991 and 1996 identified using the Danish Medical Birth Registry	Pharmaco-Epidemiological Prescription Database of North Jutland capturing prescriptions for metronidazole during pregnancy	Incidence of congenital anomalies Adjusted OR 0.44 (95% CI, 0.11 to 1.81)
Thapa (1998)[132] Fair	Retrospective cohort, 1975 to 1992	Women ages 15 to 44 years enrolled in Tennessee's Medicaid program at any point during their pregnancy	Tennessee Medicaid pharmacy database capturing prescriptions for metronidazole during pregnancy	Incidence of first primary cancer before age 5 Adjusted RR, 0.81 (95% CI, 0.41 to 1.59)

Abbreviations: N=number of participants; NR=not reported.

Table 11. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

Key Question	No. of Studies and Design; No. of Participants	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1. Benefits of screening	No studies identified					
KQ. 2 Diagnostic test accuracy (by Test)						
BD Affirm	5 cross-sectional studies[90, 95-98]; N=2,936	Pooled Sn, 0.87 (95% CI, 0.80 to 0.92) Pooled Sp, 0.81 (95% CI, 0.73 to 0.88) Pooled +LR, 4.6 (95% CI, 3.1 to 6.8) Pooled -LR, 0.16 (95% CI, 0.11 to 0.26)	Inconsistent*/ precise†	4 of 5 studies with fair methodological quality (unclear enrollment procedures, unclear masking of test results, spectrum bias)	LOW for adequate accuracy	Only 1 study conducted in pregnant women, all studies conducted in symptomatic women
BD Max	1 cross-sectional study[65, 99]; N=1,338	Sn, 0.93 (95% CI, 0.91 to 0.94) Sp, 0.92 (95% CI, 0.90 to 0.94) +LR, 10.9 (95% CI 8.3 to 14.5) -LR, 0.08 (95% CI 0.06 to 0.10)	Unknown consistency/ precise‡	Excluded participants with intermediate flora from analysis	LOW§ for adequate accuracy	Symptomatic women
BV Blue	3 cross-sectional studies[100-102]; N=864	Sn, range 0.61 to 0.92 across studies Sp, range 0.86 to 0.99 across studies	Inconsistent‖ (more inconsistent for Sn than Sp)/precise¶ (more precise for Sp than Sn)	All studies with fair methodological quality (unclear enrollment, unclear masking of results, spectrum bias)	LOW for adequate accuracy	Symptomatic, nonpregnant women
Complete Amsel's criteria	15 cross-sectional studies[88, 91, 92, 99-110]; N=7,171	Based on 14 of the 15 studies: Pooled Sn, 0.76 (95% CI, 0.63 to 0.85) Pooled Sp, 0.95 (95% CI, 0.89 to 0.98) Pooled +LR, 14.1 (95% CI, 6.8 to 29.2) Pooled -LR, 0.26 (95% CI, 0.17 to 0.39)	Inconsistent# /precise** (more precise for Sp than Sn)	12 of 15 studies with fair methodological quality (unclear enrollment, unclear masking of test results, spectrum bias), heterogeneity in application of clinical criteria and unit of analysis (patients vs. visits)	LOW for adequate accuracy	Only 1 study conducted exclusively in pregnant women; most studies conducted in symptomatic women
Modified Amsel's criteria	5 cross-sectional studies[88, 89, 99, 107, 108]; N=2,674	Based on 4 of the 5 studies: Pooled Sn, 0.67 (95% CI, 0.54 to 0.78) Pooled Sp, 0.96 (95% CI, 0.93 to 0.98) Pooled +LR, 17.3 (95% CI, 10.4 to 28.8) Pooled -LR, 0.34 (95% CI, 0.24 to 0.48)	Inconsistent†† (more inconsistent for Sn than Sp)/precise‡‡ (more precise for Sp than Sn)	4 of 5 studies with fair methodological quality (unclear enrollment, unclear masking of test results, spectrum bias)	LOW for adequate accuracy	2 studies conducted exclusively in asymptomatic, pregnant women
KQ 3. Harms of screening	No studies identified					

Table 11. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

Key Question	No. of Studies and Design; No. of Participants	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 4. Benefits of treatment	6 RCTs[111, 112, 116-119]; N=6,307	All-cause preterm delivery <37 weeks in general obstetric population: Pooled ARD, 0.20% (95% CI, -1.13% to 1.53%) Pooled RR, 1.02 (95% CI, 0.86 to 1.20)	Consistent/ imprecise[§§]	All but 1 study of good methodological quality; no reporting bias detected	MODERATE for no benefit of treatment	Applies to treatment of asymptomatic patients with oral or vaginal clindamycin or oral metronidazole; history of prior PTD in this population ranged from 1.6% to 10.9%
	8 RCTs[111, 113-117, 119, 120]; N=7,571	Spontaneous preterm delivery <37 weeks in general obstetric population: Pooled ARD, -1.44% (95% CI, -3.31% to 0.43%) Pooled RR, 0.78 (95% CI, 0.56 to 1.07)	Inconsistent[ll]/ imprecise[¶¶]	All but 2 studies of good methodological quality; no reporting bias detected	LOW for no benefit of treatment	Same as previous row
	3 RCTs[111, 116, 119] N=5,564	Preterm delivery <32 weeks in general obstetric population Pooled ARD, -0.30% (-0.97% to 0.38%) Pooled RR, 0.87 (95% CI, 0.54 to 1.42)	Consistent/ precise[##]	1 study of fair methodological quality; outcome was spontaneous PTD in 2 studies and all-cause PTD in the other study; no reporting bias detected	HIGH for no benefit of treatment	Same as previous row
	5 RCTs[111, 112, 115, 118, 119] N=5,377	Birth weight <2,500 grams in general obstetric population Pooled ARD, 0.39% (95% CI, -1.74% to 2.53%) Pooled RR, 1.03 (95% CI, 0.83 to 1.29)	Consistent/ imprecise***	All studies of good methodological quality; no reporting bias detected	MODERATE for no benefit of treatment	Same as previous row
	3 RCTs [111, 115, 119] N=5,149	Birth weight <1,500 grams in general obstetric population Pooled ARD, 0.06% (95% CI, -0.99% to 1.12%) Pooled RR, 1.05 (95% CI, 0.50 to 2.18)	Consistent/ precise†††	All studies of good methodological quality; no reporting bias detected	HIGH for no benefit of treatment	Same as previous row
	4 RCTs[112, 117-119] N=3,568	PPROM or PROM in general obstetric population Pooled ARD, 0.10% (95% CI, -1.32% to 1.52%) Pooled RR, 1.11 (0.72 to 1.72)	Consistent/ imprecise‡‡‡	All studies of good methodological quality; no reporting bias detected; one study reported PROM while others reported PPROM	MODERATE for no benefit of treatment	Same as previous row

Table 11. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

Key Question	No. of Studies and Design; No. of Participants	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
	4 RCTs[111, 117, 121, 122]; N=451	Preterm delivery <37 weeks (all-cause or spontaneous) in women with prior preterm delivery ARDs range from -29.4% to 7.5% RRs range from 0.17 to 1.33 Results statistically significant in 3 of the 4 studies favoring treatment.	Inconsistent§§§/ imprecise¶¶¶	2 studies of fair methodological quality; findings from 3 studies were from subgroup analyses and it is not clear that they were preplanned. Unable to definitively identify source(s) of inconsistency.	INSUFFICIENT	Applies to treatment of asymptomatic patients with a prior PTD with oral metronidazole
	2 RCTs[122, 123] N=102	Preterm delivery <34 weeks in women with prior preterm delivery ARD 0% in one study and -6.57% (95% CI, -18.5% to 5.4%) in the other study.	Consistent/ imprecise¶¶¶	Both studies with fair study quality; results from one were from subgroup analysis.	INSUFFICIENT	Applies to treatment of asymptomatic patients with a prior PTD with vaginal clindamycin or oral metronidazole
KQ 5. Harms of treatment (by Harm)						
Maternal harms of treatment	Intravaginal clindamycin 4 RCTs[113, 114, 116, 123] N=1,718	Heterogenous outcomes reported. No serious AEs observed in 3 studies.[114, 116, 117] Infrequent side effects such as candidal vaginitis, troublesome discharge, withdrawals because of itching were infrequent and similar between groups when reported by groups[113, 116, 123]	Consistent/ imprecise###	Although RCTs were mostly of good methodological quality, adverse event outcome measurement and reporting were not well described and studies were not powered for adverse events	MODERATE for no difference in serious AEs or minor harms (intravaginal clindamycin)	Applies to treatment of asymptomatic pregnant women with BV
	Oral clindamycin 2 RCTs[119, 120]; N=3,345	Serious AEs not observed in either group in 1 study;[119] not reported in the other study[120] Higher incidence of side effects with active treatment in 1 study (ARD, 1.79% [95% CI, 0.75% to 2.84%])[119] Higher incidence of stopping medication with active treatment in both studies, but findings were statistically significant in only 1 study (ARD, 3.33% [95% CI, 0.38% to 6.27%];[119] ARD, 3.65% [95% CI, -0.27% to 7.56%][120])	Consistent/ imprecise****		MODERATE for no difference in serious AEs but more minor harms (oral clindamycin and metronidazole)	Same as previous row

Table 11. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

Key Question	No. of Studies and Design; No. of Participants	Summary of Findings	Consistency/ Precision	Other Limitations	EPC Assessment of Strength of Evidence	Applicability
	Oral metronidazole 2 RCTs[111, 117]; N=2,776	Higher incidence of side effects/AEs with active treatment in both studies, but findings were statistically significant in only 1 study (ARD, 12.51% [95% CI, 9.33% to 15.69%][111]; ARD, 2.56% [95% CI, -0.36% to 5.47%][117])	Consistent/ imprecise††††			Same as previous row
Harms to children from in utero exposure to medication	3 observational studies[129-131]; N=62,271	Congenital malformations among children exposed to metronidazole in utero: ORs and RR, estimates from individual studies range from 0.44 to 2.24, CIs range from 0.11 to 4.23	Consistent/ imprecise‡‡‡‡	Studies of poor to fair methodological quality, did not address confounding, variation in outcome definition, potential for recall bias in case-control study	INSUFFICIENT	Applies to metronidazole exposure across a range of indications (not specific to women with BV)
	2 meta-analyses of observational studies[133, 134]; N>199,541****	Congenital malformations among children exposed to metronidazole in utero: Pooled OR, 0.96 (95% CI, 0.75 to 1.22)[133] Pooled OR, 1.08 (95% CI, 0.90 to 1.29)[134]		Older analyses that did not use current methods for conducting and reporting analyses, included studies were not assessed for risk of bias		
	1 observational study[132]; N=328,846 participants with 1,172,696 person-years	Cancer incidence before age 5 among children exposed to metronidazole: Adjusted RR, 0.81 (95% CI, 0.41 to 1.59).	Consistency unknown/ imprecise§§§§	Fair methodologic quality; baseline imbalances between groups and potential for residual confounding	INSUFFICIENT	Same as previous row

* The 95% prediction region covers nearly one third of the ROC space **(Appendix F Figure 1)**, and visual inspection of the forest plot **(Appendix F Figure 2)** suggests at least moderate inconsistency in estimates across studies that cannot easily be explained by differences in study populations or settings.

† The 95% confidence region is relatively small, and the CI around the AUC is fairly narrow, suggesting precise estimates (**Appendix F Figure 1**).

‡ Based on the upper and lower confidence intervals for sensitivity and specificity, the positive LR would range from 10.67 to 11.11 and the negative LR would range from 0.078 to 0.82, resulting in minimal variation in post-test probabilities, suggesting precise estimates.

§ We downgraded the overall SOE for study limitations and because of a single study body of evidence with unknown consistency.

‖ The range of estimates across the three studies is inconsistent for sensitivity but reasonably consistent for specificity. In particular, one study had markedly lower sensitivity (0.61) than the others, which were 0.88 and 0.917. This study was only reported in clincialtrials.gov, and very little information about the study setting and population was available to understand why this result was inconsistent with the other two studies.

¶ The LR+ and LR- at the upper and lower limits of the Sn and Sp confidence intervals for each study are reasonably similar and result in only small differences in post-test probabilities. See **Appendix H**.

The 95% prediction region covers over one third of the ROC space (**Appendix F Figure 3**), and visual inspection of the forest plot (**Appendix F Figure 4**) identifies moderate inconsistency in estimates of Sn and Sp that cannot easily be explained by differences in study populations or settings..

Table 11. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

** The confidence region is quite small; thus, we judged this estimate as precise, although more precise for Sp than for Sn (**Appendix F Figure 3)**.
†† Although the prediction region covers only one fifth of the SROC space, the shape of the region suggests future studies could lie in the space of relative poor sensitivity and high specificity or equally likely the space of relatively poor specificity and high sensitivity and visual inspection of the forest plot also suggests inconsistency. **(Appendix F Figure 5** and **Figure 6).**
‡ The 95% confidence region suggests reasonable precision for estimates of Sp, but some imprecision in estimates of Sn (**Appendix F Figure 5)**.
§§ OIS criteria not met, a sample size of 7,116 is required to detect a 20% RR reduction based on 9% control group risk, alpha=0.05, power=0.80, two-tailed test. Further, we assessed that the width of the CI around the RR could not exclude a clinically meaningful benefit or harm; despite the narrow range of the CI around the ARD, the population burden from even a small increase or decrease in PTD could be clinically meaningful.
‖ Although confidence intervals are mostly overlapping, there is some inconsistency in both the direction and magnitude of effect because two studies observed a statistically significant effect of -5.80% and -9.96% compared with the other studies that are much closer to a null effect (ARDs ranging from -2.25% to 1.09%); further I-squared statistic is 61.9% for the ARD.
¶ OIS criteria not met; a sample size of 9,920 is required to detect a 20% RR reduction based on 7% control group risk (average risk across studies), alpha=0.05, power=0.80, two-tailed test. Further, the CIs for both the ARD and RR span a range that could be considered a clinically meaningful benefit or no difference.
Low baseline risk (< 5%) and sample sizes > 2,000 in each group, thus OIS is met. Because of infrequent events, we placed more emphasis on ARD than RR when evaluating precision.
*** OIS criteria not met; a sample size of 7,116 required to detect a 20% RR reduction based on a 9% control group risk (average across these studies), alpha=0.05, power=0.8, two-tailed test.
††† Low baseline risk (< 5%) and sample sizes > 2,000 in each group, thus OIS is met. Because of infrequent events, we placed more emphasis on ARD than RR when evaluating precision.
‡‡ OIS criteria not met; sample size of 24,798 required to detect a 20% RR reduction based on a 3% control group risk (average across these studies), alpha=0.05, power=0.8, two-tailed test.
§§§ Three studies have statistically significant moderate treatment effect sizes, while one study shows an increase in preterm delivery from treatment but is not statistically significant; the source of inconsistency is unexplained.
‖‖ OIS criteria not met; a sample size of 1,248 required to detect a 20% RR reduction based on a 38% control group risk, alpha=0.05, power=0.80, two-tailed test.
¶¶ OIS criteria not met; a sample size of 1,874 required to detect a 20% RR reduction based on a 29% control group risk, alpha= 0.05, power-0.80, two-tailed test.
OIS criteria not met; infrequent events reported.
**** OIS criteria not met; a sample size of 45,236 is required to detect a 20% relative risk increase based on a 2% control group risk, alpha=0.05, power=0.8, two-tailed test.
†††† One study included 155,504 participants,[133] and the other study included 199,451 participants;[134] three studies overlapped between the two analyses.
‡‡‡ OIS criteria met. A sample size of 17,128 is required to detect an elevated RR of 1.20 with alpha=0.05, power=0.80, two-sided test. However, the null effect cannot be excluded, and the CIs from both the individual studies and the meta-analyses span a clinically meaningful range of benefit and harms; thus, we consider the estimate to be imprecise.
§§§§ OIS criteria not met; a sample size of more than 6 million would be required to detect a 20% RR increase based on a 0.0142% control group risk, alpha=0.05, power=0.80, two-tailed test.

Abbreviations: AE=adverse event; ARD=absolute risk difference; AUC=area under the curve; BV=bacterial vaginosis; CI=confidence interval; EPC=Evidence-based Practice Center; KQ=key question; LR=likelihood ratio; N=number of participants; No.=number; OIS=optimal information size; OR=odds ratio; PTD=preterm delivery; RCT=randomized, controlled trial; ROC=receiver operating characteristic; RR=relative risk; Sn=sensitivity; SOE=strength of evidence; SROC=summary receiver operating characteristic; Sp=specificity.

Contextual Questions

Contextual questions (CQ) 1, 2 and 3 were designed to provide the USPSTF with additional information about the relationship between bacterial vaginosis, intermediate flora and preterm delivery. CQ 1 sought information about the epidemiologic association between these conditions and preterm delivery outcomes, while CQ 2 was focused specifically on whether treatment of intermediate flora reduces preterm delivery. Lastly CQ 3 was focused on the association between bacterial vaginosis and other known risks for preterm delivery since the mechanisms underlying preterm delivery are complex and challenging to measure and understand in observational studies. CQ 4 was designed to provide information about existing practice patterns related to the diagnosis of bacterial vaginosis in clinical practice and CQ 5 was designed to provide information about adverse events of treatment with metronidazole and clindamycin in nonpregnant women.

CQ 1. What is the association between bacterial vaginosis, intermediate flora, or abnormal vaginal flora, and preterm delivery in U.S. populations, or in similar populations if no U.S. data is available or is limited?

An association between the diagnosis of bacterial vaginosis or intermediate flora and a risk of preterm birth has been reported for over two decades. A 2007 metanalysis[50] of English-language studies published through 2005 pooled 24 cohort studies or control groups from RCTs, representing 24,190 patients. The vast majority of the studies were conducted in very highly developed countries (Europe, U.S. and Canada). In these studies, bacterial vaginosis was diagnosed with either Amsel's clinical criteria, Gram stain interpreted with Nugent's criteria, or both. Asymptomatic women diagnosed with bacterial vaginosis had a pooled odds ratio of delivery at less than 37 weeks of 2.16 (95% CI, 1.56 to 3.00) compared with women who either did not have bacterial vaginosis or had intermediate flora. In this analysis, the odds of early delivery were similarly elevated for women with and without a history of preterm delivery (OR, 2.63 and 2.22, respectively). The elevated risk was not significantly higher for delivery at less than 34 weeks (4 studies, OR, 1.29 [95% CI, 0.92 to 1.82]) or for delivery at less than 32 weeks (4 studies, OR, 1.34 [95% CI, 0.59 to 3.06]). Second trimester miscarriage had the highest association with diagnosis of bacterial vaginosis during pregnancy (OR, 6.32 [95% CI, 3.65 to 10.94]). The association of bacterial vaginosis with preterm birth was somewhat higher when diagnosed before 16 weeks (RR, 2.97 [95% CI, 1.48 to 5.98]) compared with diagnosis at 20 weeks or greater (RR, 1.89 [95% CI, 1.27 to 2.83]), but these findings were not very precise, suggesting that early diagnosis of bacterial vaginosis in pregnancy is not riskier than later diagnosis. The same review calculated the risk of preterm delivery for pregnant women who had intermediate flora compared with those who had normal flora in five studies representing 1,653 participants. Asymptomatic women with intermediate flora did not have a significantly increased risk of preterm birth compared with those with normal flora (pooled OR, for preterm birth less than 37 weeks 2.41 [95% CI, 0.63 to 9.20]).

Despite the strong association between bacterial vaginosis and preterm birth in the 2007 meta-analysis, among United States populations studied since 2005, bacterial vaginosis has not been associated with a higher risk of preterm delivery in the following populations: asymptomatic pregnant women at high risk for preterm birth diagnosed in the first trimester (p=0.36),[139]

asymptomatic pregnant women at average risk for preterm delivery diagnosed in the second trimester at average risk for preterm birth (OR, 1.1 to 1.8, P>=0.35),[140-143] and symptomatic pregnant women diagnosed in the first trimester who were treated for bacterial vaginosis (adjusted OR, 1.07 [95% CI, 0.64 to 1.79]).[144] In some small subgroups of women at high risk of preterm birth, high levels of specific bacterial species detected through polymerase chain reaction tests were associated with preterm delivery including *Gardnerella vaginalis*, *Leptotrichia/Sneathia*, *Mobiluncus*, and BVAB1.[143, 145] Low levels of *Lactobacillus crispatus* were also associated with preterm birth in one study.[145] It is possible that previously described associations between bacterial vaginosis and preterm labor are due to some other underlying factor that predisposes women to both bacterial vaginosis and preterm labor. This might include sociodemographic variables that cannot be sufficiently accounted for in the analysis or varying levels of immune function within the population.[142, 146]

CQ 2. Is treatment of abnormal vaginal flora and intermediate flora associated with reduced preterm delivery?

Some have argued that intermediate flora, indicated by a Nugent score of 4 to 6 on Gram stain, should be treated as a distinct entity in its own right for the following reasons.[7, 147-149] The microbial profile of intermediate flora can vary substantially and may or may not include Lactobacillus strains or anaerobic bacteria.[63, 150, 151] Intermediate flora may be more accurately described as a transitional state between normal flora and a variety of abnormal flora including but not limited to bacterial vaginosis.[151]Intermediate flora may not respond to treatment similarly as bacterial vaginosis. Two studies conducted in the U.K. among pregnant women with either bacterial vaginosis or intermediate flora treated with clindamycin, found higher rates of reversion to normal flora among those with bacterial vaginosis than among those with intermediate flora (91% vs. 53%).[149, 151]

The 2013 Cochrane Review of antibiotics for treating bacterial vaginosis in pregnancy identified two trials out of 21 that included pregnant women with either bacterial vaginosis or intermediate flora. The review did not find a reduction in preterm birth before 37 weeks when pooling results from all eligible trials (RR, 0.88 [95% CI, 0.71 to 1.09]; 13 trials, 6,491 women).[152] On the other hand, when limited to the two trials that included women with bacterial vaginosis or intermediate flora, treatment did reduce the risk of preterm birth before 37 weeks (pooled RR, 0.53 [95% CI, 0.34 to 0.84]; 2 trials, 894 women).[115, 120] However, this benefit is unlikely to be explained by the inclusion of women with intermediate flora because in both trials, a larger benefit of treatment was seen among women with higher Nugent's score (i.e. bacterial vaginosis). Both trials were multicenter trials conducted in the U.K. evaluating asymptomatic, average risk pregnant women in the early second trimester; they are included in the systematic review update portion of our report. In one study, women who screened positive (Nugent's score of 4 or more) were treated with oral clindamycin. Overall, 15 percent (37/244) in the clindamycin group and 16 percent (38/241) in the placebo group had intermediate flora (Nugent score 4 to 6).[120] The study found an overall benefit of treatment. Though not powered to assess treatment by Nugent score, they noted a benefit across all scores but a maximal benefit in those with a Nugent's score of 10 (rate of spontaneous preterm delivery was 5.4% in the treatment group compared with 35.7% in the placebo group). The second trial randomized women who screened positive (Nugent's score of 4 or greater) to vaginal clindamycin or placebo with a second course of treatment for those with

persistently abnormal Nugent's score.[115] For all participants, preterm birth was decreased (adjusted OR, 0.38 [95% CI, 0.16 to 0.90]). In a subgroup analysis of this data, the treatment tended to be more effective at preventing preterm birth in the group with Nugent's score of 7 or more compared to a Nugent's score of 4 to 6.[149]

A subgroup of a study included in the systematic review portion of our report screened low risk asymptomatic women for bacterial vaginosis at their first prenatal visit using Spiegel Gram stain criteria. Among those diagnosed with intermediate flora (N=106), 22 were randomized to vaginal clindamycin or placebo. There were two preterm deliveries; one occurred in the treatment group and one in the placebo group.[126] In a nonrandomized cohort study from Japan, asymptomatic women were screened in the early second trimester and women with a Nugent's score of 4 or greater were treated with vaginal metronidazole. The authors found no reduction in preterm birth or gestational age at delivery (preterm birth rate 3.48% in the intervention group compared with 4.31% in an unscreened comparison group).[153]

In summary, we found little evidence suggesting that treatment of intermediate flora leads to a benefit in preterm birth prevention. However, studies are limited in number and characterized by small sample sizes. It is possible that given the diversity of intermediate flora states, future research will identify specific categories of intermediate flora for which treatment may be beneficial.

CQ 3. What is the association between bacterial vaginosis and other known risk factors for preterm delivery?

Demographic Characteristics

During pregnancy, the presence of bacterial vaginosis and intermediate flora is more prevalent among African American women compared with non-Hispanic white and Hispanic women, relative risks ranging from 1.5 to 2.[141, 154-157] This association has remained strong even after controlling for differences in socioeconomic status, sexual practices, and other demographic variables.[155] Young age, nulliparity, current tobacco use, low educational attainment and lower income have also been consistently associated with bacterial vaginosis (RR, 1.3 to 2.60).[141, 157-161] These characteristics are also all known risk factors for spontaneous preterm birth.[162, 163]

Clinical Characteristics

Many different and varied clinical characteristics have been identified as being associated with preterm birth. The extent to which these clinical characteristics are also associated with bacterial vaginosis varies. Untreated genitourinary infections other than bacterial vaginosis may be associated with preterm birth and bacterial vaginosis tends to be associated with a higher risk of concurrent genitourinary infections.[162] In a study of nonpregnant reproductive age women in the U.S. military, for every additional episode of bacterial vaginosis, the risk of acquiring chlamydia was 13 percent higher and the risk of acquiring gonorrhea was 27 percent higher.[164] However, in a second study of nonpregnant women at high risk for sexually transmitted infections, bacterial vaginosis was associated with prevalent (RR, 2.83 [95% CI, 1.81 to 4.42]) but not incident chlamydial infection (RR, 1.52 [95% CI, 0.74 to 3.13]).[165] In some populations, the risk of

preterm birth appears to be higher if two or more vaginal infections, including bacterial vaginosis, chlamydia, and trichomonas are present concurrently. This suggests that the association between bacterial vaginosis and other vaginal infections may not be causative. It may instead be associated with shared risk factors such as sexual behaviors and concurrent genital tract infections.

The risk of bacterial vaginosis has not been consistently associated with periodontal disease[166, 167] or vaginal douching.[155, 157, 168] Systematic reviews of reproductive age women have shown an association between bacterial vaginosis and herpes simplex, human immunodeficiency, and human papilloma viruses.[169-171] Altered levels of immune function such as TNFα polymorphisms,[142] level of defensins (human neutrophil peptides) in vaginal fluid,[146] and vaginal cytokine concentrations[172] have been associated with bacterial vaginosis and preterm delivery. An association between bacterial vaginosis and short cervix has not been shown.

CQ 4. What is the uptake or use of various diagnostic tests for bacterial vaginosis in clinical practice?

Few studies have investigated the use of specific diagnostic tests for bacterial vaginosis among pregnant women in clinical practice. A handful of studies investigate practices among U.S. outpatient clinics. In a chart review of 150 visits from 52 patients referred to a specialty referral clinic for vulvovaginal disorders, from 1995 to 1997, the number of pregnant patients was not reported. Microscopy of vaginal fluid was performed at 94 (63%) visits, pH measurement at 4 (3%) visits, and whiff test at 5 (3%) visits. Bacterial vaginosis was diagnosed at 13 (17%) visits.[173] Among American College of Obstetricians and Gynecologists fellows surveyed in 1998, 93 percent used clue cells, 78 percent used an amine test, 59 percent used milky discharge, 48 percent used pH, and 18 percent used *Gardnerella vaginalis* culture to diagnose bacterial vaginosis in pregnant patients. Out of around 570 respondents, 57 percent test only those symptomatic and 11 percent did not test for bacterial vaginosis at all in pregnant patients.[174]

Wiesbord et al conducted a survey of Georgia-licensed obstetrician/gynecologists, family practitioners, and nurse-midwives in 1998. Among 565 respondents who provided prenatal care, 257 (46%) used clue cells alone, 152 (27%) used Gram stain alone, and most others used a combination of an amine test and a wet mount to diagnose bacterial vaginosis in pregnant patients. Four-hundred and seventy-seven (84%) respondents tested symptomatic pregnant women and 165 (29%) respondents tested high-risk pregnant patients for bacterial vaginosis.[175] In a survey of 208 physicians providing gynecology or obstetric care in San Diego, California in 1999 wet mount was the most commonly used test in nonpregnant and pregnant patients (73% and 66%) followed by vaginal culture (18% and 20%), Gram stain (4% and 3%), and rapid test (1% and 1%). Respondents who believed bacterial vaginosis causes preterm delivery were more likely to use wet-mount to test for bacterial vaginosis in symptomatic pregnant patients than those who did not (74% vs. 42%). Eight percent always performed wet mount and 19 percent sometimes performed wet mount to diagnose bacterial vaginosis in asymptomatic pregnant patients. Notably these data were all published before the availability of some newer generation tests. It is not understood how frequently such tests are used compared with Amsel's clinical criteria.

CQ 5. What are the adverse drug events related to metronidazole or clindamycin when used to treat bacterial vaginosis in nonpregnant adolescents and women?

Metronidazole Related Adverse Events

Metronidazole, a nitroimidazole antimicrobial agent, is commonly used in the treatment of bacterial vaginosis, amongst other indications. Adverse events (AEs) attributed to metronidazole use include metallic taste, nausea, vomiting, diarrhea, candida infections, itching, and hypersensitivity.[176-179] A Cochrane Review conducted in 2009 reported on the effects of antimicrobial therapy on bacterial vaginosis in nonpregnant women. The review included Randomized, Controlled Trials conducted since 1981 among nonpregnant women with bacterial vaginosis diagnosed by Amsel's clinical criteria or Gram stain who received any antimicrobial agent. Among included studies, adverse events reported included metallic taste, nausea, vomiting, diarrhea, hypersensitivity, pseudomembranous colitis, any unknown adverse event that the participant or clinicians considered serious, and, any event that led to discontinuation of therapy.[180]

A 2011 RCT on the efficacy of tinidazole compared with oral metronidazole 500 mg twice a day for 7 days found that among the metronidazole group incidences of yeast infection (29.3%) and nausea/vomiting (20.2%) were the most common. Other AEs included headache (14.7%), bad taste (11.0%), diarrhea (3.7%), and anorexia (0.8%).[181] A more recent RCT conducted in 2015 on the safety and efficacy of 1.3 percent single-dose metronidazole vaginal gel for bacterial vaginosis treatment (N=581) found that the incidence of AEs was similar between treatment and placebo gel groups (19% vs. 16.1%, respectively).[182] The most frequently reported AEs were vulvovaginal candida infection (5.6%) and headaches (2.2%).[182] Other reported AEs in the metronidazole vaginal gel group were diarrhea (1.2%), nausea (1.6%), dysmenorrhea (1.2%), and vulvovaginal pruritus (1.6%). While the incidence of AEs among the single-dose gel is less than the oral metronidazole dose, it is difficult to compare across studies.

Multiple studies that compared route of metronidazole administration suggest that route affects incidence of AEs. While the Cochrane review does not compare incidence of AEs between vaginal and oral metronidazole, two randomized controlled studies reported that vaginal metronidazole was associated with fewer gastrointestinal complaints.[176, 183] An RCT (N=277) comparing the efficacy of vaginal metronidazole (1,000 mg pessary used daily for 2 days) with oral metronidazole (2 g one-time dose) in acute symptomatic bacterial vaginosis reported that three AEs were experienced significantly more frequently by the group that received oral dosing: nausea (30.4% vs. 10.2%), abdominal pain (31.9% vs. 16.8%), and metallic taste (17.0% vs. 8.8%).[176] Another RCT (N=112) compared metronidazole vaginal 5 grams twice daily for 5 days and oral metronidazole 500 mg twice daily for 7 days and reported that gastrointestinal symptoms were the most common AE reported in both groups, but these symptoms were more common and more severe in the oral group (51.8% vs. 32.7%, p=0.04) compared with the vaginal group. The percentage who experienced candidiasis was comparable (16% vaginal vs. 14% oral).[183]

Clindamycin-Related Adverse Events

Clindamycin, a lincosamide antibiotic, is another common treatment for bacterial vaginosis. Clindamycin can be administrated in multiple forms including orally or vaginally as ovules or creams.[177, 178] The 2009 Cochrane review includes studies comparing clindamycin cream and placebo groups; however, no analyses was conducted on AEs between these two groups. Included in the Cochrane review is a 1993 placebo-controlled RCT (N=215) of treatment with vaginal 2 percent clindamycin that reported that the most common AEs were nonbacterial vaginitis/cervicitis (18.5%), diarrhea (7.4%), headache (4.6%), abdominal pain (2.8%), and vaginal irritation follow medication insertion (2.8%).[184] However, the authors reported that the AEs were similar between the clindamycin and placebo groups except for nonbacterial vaginitis/cervicitis, which was higher among the clindamycin group (18.5% vs. 7.5%, p=0.03).[184] Other RCTs included in the 2009 Cochrane Review corroborate that common AEs related to clindamycin[185, 186] include vaginal irritation, candidiasis, nausea, headache, metallic taste, and diarrhea.[185-188] The Cochrane review did compare overall AEs between clindamycin ovules and cream and found no differences (RR, 1.11 [95% CI, 0.97 to 1.28] based on one study [N=662]). Specifically, rates of candida infection were comparable (RR, 1.69 [95% CI, 0.41 to 7.00], based on one study [N=658]).

Comparison of Adverse Events Between Metronidazole and Clindamycin

The 2009 Cochrane Review conducted a pooled analysis of four trials evaluating the AEs of clindamycin cream and ovules compared with oral metronidazole antimicrobial therapy on bacterial vaginosis in nonpregnant women (N= 927). There was no statistical difference in overall AE rates (RR, 0.75 [95% CI, 0.54 to 1.05]).[180] However, metronidazole was less likely than clindamycin to cause metallic taste (RR, 0.09 [95% CI, 0.01 to 0.68], based on pooled data from two studies [N=204]), and nausea and vomiting (RR, 0.27 [95% CI, 0.11 to 0.69], based on three studies[185-187] [N=611]). Rates of candidiasis (RR, 1.11 [95% CI, 0.78 to 1.58], based on 4 studies[186, 187, 189, 190] [N=986)], diarrhea (RR, 2.99 [95% CI, 0.12 to 72.85], based on 1[187] study [N=407]), and vaginal irritation (RR, 1.59 [95% CI, 0.31 to 8.17], based on 2[186, 187] studies [N=468]) were not significantly different between groups.

Appendix A Table 1. Summary of Reference Tests Available for Diagnosis of Bacterial Vaginosis in the United States

Reference Test	Description

Gram staining of vaginal fluid ("**Nugent's**" criteria)	Based on a scoring system from 0 to 10 of Gram-stained vaginal fluid smear under microscope (x1,000 with oil immersion) scored according to the quantitative appearance of various organisms' morphologies:
	• Large Gram-positive rods
	  ○ 0 score: 4+ morphotypes present
	  ○ 1 score: 3+ morphotypes present
	  ○ 2 score: 2+ morphotypes present
	  ○ 3 score: 1+ morphotypes present
	  ○ 4 score: 0 morphotypes present
	• Small Gram-negative to Gram-variable rods
	  ○ 0 score: 0 morphotypes present
	  ○ 1 score: 1+ morphotypes present
	  ○ 2 score: 2+ morphotypes present
	  ○ 3 score: 3+ morphotypes present
	  ○ 4 score: 4+ morphotypes present
	• Curved Gram-variable rods
	  ○ 0 score: 0 morphotypes present
	  ○ 1 score: 1+ or 2+ morphotypes present
	  ○ 2 score: 3+ or 4+ morphotypes present
	Total score=Gram-positive rods score + small Gram-negative to Gram-variable rods score + curved Gram-variable rods score. Bacterial vaginosis is diagnosed when total score >7.

Gram staining of vaginal fluid ("**Spiegel's**" criteria)	Gram-stained vaginal fluid smears are evaluated under microscope (x1,000 with oil immersion): • Large Gram-positive bacilli morphology are assumed to be *Lactobacillus* • Smaller Gram-variable bacilli morphology are assumed to be *Gardnerella* • Other organisms are categorized by their respective morphology • Presence of these organisms' morphologies are scored as 1+ for <1 per field, 2+ for 1 to 5 per field, 3+ for 6 to 30 per field, and 4+ for >30 per field • BV is diagnosed with 1 to 2+ score for *Lactobacillus* presence (i.e., few or none seen in the field) and >1 or 2+ presence of other morphotypes
Clinical diagnosis ("**Amsel's**" criteria)	3 out of 4 of the following: • Vaginal pH above 4.5 • Presence of thin, homogenous vaginal discharge • Release of "fishy odor" from vaginal discharge on addition of 10% potassium hydroxide (the "amine" test) • Presence of clue cells (typically at least 20% of vaginal epithelial cells) in the discharge on wet mount

Abbreviations: pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution.

Appendix A Table 2. Summary of Treatments Available in the United States for Bacterial Vaginosis[191]

Medication/ Pregnancy Category*	Formulation	Dose, Route, and Frequency	FDA Label	CDC
Clindamycin "B"	Vaginal ovules (100 mg/ovule)	One ovule intravaginally daily, preferably at bedtime, for 3 days	Indication for treatment of bacterial vaginosis in nonpregnant women.	CDC recommends either oral or vaginal preparations of metronidazole or clindamycin in pregnant women.[191]
	Vaginal cream 2%	One applicator (100 mg) intravaginally daily, preferably at bedtime, for 7 days.	Indication for treatment of bacterial vaginosis in nonpregnant women. One manufacturer (Cleocin) has a label indication for treatment of bacterial vaginosis in 2nd trimester of pregnancy.	
	Oral capsules (various doses)	300 mg orally twice a day for 7 days	***No*** indication for treatment of bacterial vaginosis.	
Metronidazole "B"	Vaginal gel 0.75%	One applicator (37.5 g) intravaginally daily for 5 days	Indication for treatment of bacterial vaginosis in nonpregnant women.	
	Vaginal gel 1.3%	One applicator (65 mg) intravaginally once at bedtime		
	Tablets (various doses)	500 mg twice a day or 250 mg three times a day for 7 days	***No*** indication for treatment of bacterial vaginosis.	
	Extended-release tablets (750 mg)	One tablet, once a day for 7 days		
Tinidazole "C"	Tablets (various doses)	2 g once a day for 2 days or 1 g once a day for 5 days	Indication for treatment of bacterial vaginosis in nonpregnant women.	Not addressed.
Secnidazole NA*	Single-dose oral granules	One 2 g packet of granules orally, preferably sprinkled over food and consumed	Indication for treatment of bacterial vaginosis in adult women.	Not available at time of last CDC guideline update.

*FDA is phasing out the use of the pregnancy categories, so new drugs will not be assigned a category.[192]

Abbreviations: ACOG=American College of Obstetricians and Gynecologists; CDC=Centers for Disease Control and Prevention; FDA=Food and Drug Administration.

Appendix A Table 3. Summary of Recommendations for Screening for Bacterial Vaginosis in Pregnant Women

Organization (Year)	Recommendation
American College of Obstetricians and Gynecologists' (ACOG) Practice Bulletin (2012, reaffirmed 2018)[193]	"Other specific tests and monitoring modalities, such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring have been proposed to assess a woman's risk of preterm delivery. However, available interventional studies based on the use of these tests for screening asymptomatic women have not demonstrated improved perinatal outcomes. Thus, these methods are not recommended as screening strategies."
Society of Obstetricians and Gynecologists of Canada (SOGC) (2017)[194]	"Asymptomatic women and women without identified risk factors for preterm birth should not undergo routine screening for or treatment of bacterial vaginosis. Women at increased risk for preterm birth may benefit from routine screening for and treatment of bacterial vaginosis."
CDC's Sexually Transmitted Disease (STD) Treatment Guidelines (2015)[191]	"Evidence does not support routine screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery. Symptomatic women should be evaluated and treated."
Association of Reproductive Health Professionals (2013)[195]	"Screening for BV is not recommended in asymptomatic women, even in pregnancy."
British Association for Sexual Health and HIVs (BASHH) (2012)[196]	"There is insufficient evidence to recommend routine treatment of asymptomatic pregnant women who attend a genitourinary clinic and are found to have BV. Women with additional risk factors for preterm birth may benefit from treatment before 20 weeks gestation."
National Institute of Clinical Excellence (NICE)* (2011)[197]	"Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk of preterm delivery and other adverse reproductive outcomes."
American Academy of Family Physicians (2008)[198]	Same as current USPSTF recommendation.

* This guideline is undergoing an update expected to be published in July 2020.[199]

Abbreviations: ACOG=American College of Obstetricians and Gynecologists; BASHH=British Association for Sexual Health and HIVs; BV=bacterial vaginosis; NICE= National Institute of Clinical Excellence; SOGC=Society of Obstetricians and Gynecologists of Canada; STD=sexually transmitted disease; USPSTF = United States Preventive Services Task Force.

Appendix B1. Detailed Search Strategy

PubMed Search Strategy

Combined KQs PubMed (January 1, 2006 through May 29, 2019)

	Terms	Results
#1	Search ((Vaginosis, Bacterial[MeSH Terms]) OR Vaginosis, Bacterial[Title/Abstract]) OR "intermediate flora"[Title/Abstract Sort by: Best Match	5311
#6	Search ((((((((((Mass Screening[MeSH Terms]) OR Sensitivity[MeSH Terms]) OR Specificity[MeSH Terms]) OR Sensitivity[Title/Abstract]) OR specificity[Title/Abstract]) OR diagnosis[Title/Abstract]) OR diagnosis[MeSH Terms]) OR screening[Title/Abstract])) OR ((((((("Diagnostic Test Approval"[Mesh]) OR "Clinical Laboratory Techniques"[Mesh]) OR "Vaginal Smears"[Mesh]) OR "Reproducibility of Results"[Mesh]) OR "Point-of-Care Testing"[Mesh]) OR "Vaginosis, Bacterial/diagnosis"[Mesh]) Sort by: Best Match	9861252
#7	Search (#1 AND #6) Sort by: Best Match	2782
#8	Search ("News" [Publication Type]) OR "Editorial" [Publication Type] OR (((case reports[Publication Type]) OR letter[Publication Type]) OR patient education handout[Publication Type]) Sort by: Best Match	3535965
#9	Search (("Africa"[Mesh]) OR "India"[Mesh] OR "Developing Countries"[Mesh])) Sort by: Best Match	393336
#10	Search (#8 OR #9) Sort by: Best Match	3883500
#11	Search (#7 NOT #10) Sort by: Best Match	2397
#12	Search (#7 NOT #10) Sort by: Best Match Filters: English	2077
#13	Search (#7 NOT #10) Sort by: Best Match Filters: Publication date from 2006/01/01; English	1097
#14	Search ((((Pregnancy Outcome[MeSH Terms]) OR Pregnancy[MeSH Terms])) OR ((("Embryonic Structures"[Mesh]) OR "Pregnancy Complications"[Mesh]))) OR pregnan* Sort by: Best Match	1261898
#15	Search (#1 AND #14) Sort by: Best Match	1861
#16	Search ("Mutagenesis"[Mesh]) OR "Carcinogenesis"[Mesh] OR (("adverse effects" [Subheading]) OR "Patient Harm"[Mesh]) OR "Congenital Abnormalities"[Mesh] OR harm[tw] OR defect[tw] OR malform[tw] Sort by: Best Match	3076028
#17	Search (("Clindamycin"[Mesh]) OR "Metronidazole"[Mesh]) OR "secnidazole" [Supplementary Concept] OR secnidazole[tw] OR Metronidazole[tw] OR clindamycin[tw] Sort by: Best Match	29131
#18	Search (#14 AND #16 AND #17) Sort by: Best Match	323
#19	Search (#1 AND #18) Sort by: Best Match	44
#20	Search ("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action]) OR "Bacterial Infections"[Mesh] Sort by: Best Match	1355452
#21	Search (#1 AND #20) Sort by: Best Match	3729
#22	Search (#14 AND #16 AND #21) Sort by: Best Match	121
#23	Search (#15 OR #19 OR #22) Sort by: Best Match	1861
#24	Search (#15 OR #19 OR #22) Sort by: Best Match Filters: English	1624
#25	Search (#15 OR #19 OR #22) Sort by: Best Match Filters: Publication date from 2006/01/01; English	828
#26	Search (#13 OR #25) Sort by: Best Match Filters: Publication date from 2006/01/01; English	1550

Appendix B1. Detailed Search Strategy

Other Data Sources

Cochrane=199 total; 123 unique

- Cochrane Reviews =9 total; 7 unique
- DARE=11 total; 8 unique
- Cochrane Controlled Clinical Trials Registry=184 total; 108 unique

Embase =313 total; 121 unique
ClinicalTrials.gov=141 total;139 unique
Health Services Research Projects in Process (HSRProj) =5 total; 4 unique
World Health Organization International Clinical Trials Registry Platform=30 total; 7 unique

KQ 2 Gap Search PubMed (Inception through December 31, 2005)

	Terms	Results
#71	Search Vaginosis, Bacterial[MeSH Terms] OR Vaginosis, Bacterial[Title] Sort by: PublicationDate	2747
#73	Search (Gram Stain[Title/Abstract] OR Nugent[Title/Abstract])	5593
#77	Search ((BV Blue[Title/Abstract] OR BD Max[Title/Abstract] OR BD Affirm[Title/Abstract] OR VS-Sense Pro[Title/Abstract] OR Amsel[Title/Abstract]))	252
#82	Search ((#73) OR (#77)) AND (#71)	514
#83	Search Mass Screening[MeSH Terms] OR Sensitivity[MeSH Terms] OR Specificity[MeSH Terms] OR Sensitivity[Title/Abstract] OR specificity[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnosis[MeSH Terms] OR screening[Title] OR "Diagnostic Test Approval"[Mesh] OR "Clinical Laboratory Techniques"[Mesh] OR "Vaginal Smears"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Point-of-Care Testing"[Mesh] OR "Vaginosis, Bacterial/diagnosis"[Mesh] Sort by: PublicationDate	9301603
#84	Search (#83) AND (#71)	1595
#87	Search (HIV[MeSH Terms] OR HIV Infections[MeSH Terms] OR HIV Seronegativity[MeSH Terms]) Sort by: PublicationDate	295552
#88	Search Case Reports[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR Patient Education Handout[Publication Type] OR News[Publication Type] Sort by: PublicationDate	3324702
#90	Search (#87) OR (#88)	3562041
#91	Search (#84) NOT (#90)	1508
#92	Search (#91) Filters: English	1292
#99	Search meta-analysis[Publication Type] OR systematic review[Title/Abstract] Sort by: PublicationDate	169048
#100	Search (#92) AND (#99)	7
#93	Search (#92) Filters: Publication date from 1966/01/01 to 2005/12/31; English	613
#102	Search Treatment Outcome[MeSH Terms] Filters: Publication date from 1966/01/01 to 2005/12/31; English	227133
#103	Search (#93) NOT (#102) Filters: Publication date from 1966/01/01 to 2005/12/31; English Sort	548

Appendix B2. Study Selection Criteria

Study Selection Criteria Based on Population, Interventions, Comparators, Outcomes, Timing, and Study Design

	Include	Exclude
Population	KQs 1, 3: Asymptomatic pregnant adolescents and women; studies that include mixed populations of symptomatic and asymptomatic participants will be included if the results for asymptomatic participants are reported separately or if less than 20% of the study population is characterized as symptomatic for bacterial vaginosis KQ 2: Reproductive-age adolescents and women, including pregnant or nonpregnant study participants KQs 4, 5: Pregnant adolescents and women diagnosed with bacterial vaginosis	KQs 1, 3, 4, 5: Nonpregnant adolescents and women KQs 1, 3: Adolescents and women with symptomatic bacterial vaginosis
Intervention	KQ 1, 3: Routine screening for bacterial vaginosis using Gram stain (Nugent criteria) or any tests listed under KQ 2. KQ 2: Screening interventions: Clinical assessment using complete or partial Amsel's clinical criteria BD MAX™ Vaginal Panel BD Affirm™ VPIII Microbial Identification Test Colorimetric assessment of pH VS-SENSE PRO™ (pH indicator vaginal swab) OSOM® BVBLUE® (detects sialidase activity) Other tests* KQs 4, 5: Treatment interventions (oral or vaginal): Metronidazole Clindamycin	KQ 1: Screening for multiple organisms or infections if the impact of screening specifically for bacterial vaginosis cannot be isolated. KQ 2: Screening interventions: Tests for diagnosis of bacterial vaginosis that are obsolete or no longer being marketed KQs 4, 5: Treatment interventions: Treatments not evaluated in pregnant women Interventions that are not FDA approved for treatment of BV: Rifamixin Dequalinium chloride Oral or vaginal probiotics Topical antiseptics Treatment of partner (as sole strategy)
Comparison	KQ 1: No screening, usual care KQ 2: Screening reference standards: Gram stain (based on Nugent criteria) Clinical assessment using complete Amsel's clinical criteria KQs 4, 5: Treatment interventions: Placebo, delayed treatment, or no treatment	KQ 1: Studies with an active comparator group KQ 2: Screening interventions that do not use an included reference standard KQs 4, 5: Studies with an active comparator group (i.e., pharmacologic or nonpharmacologic treatment)
Outcomes	KQs 1, 4: *Health Outcomes* All-cause preterm delivery (spontaneous and indicated deliveries prior to 37 weeks gestation) Spontaneous preterm delivery Indicated preterm delivery Low birth weight Preterm labor Preterm premature rupture of membranes 2nd trimester fetal loss Spontaneous abortion Intrauterine fetal demise Neonatal sepsis Neonatal death *Intermediate Outcome* Clearing of bacterial vaginosis after treatment	KQs 1, 2, 4: Outcomes not specifically listed as included

Appendix B2. Study Selection Criteria

	Include	Exclude
Outcomes (cont'd)	KQ 2: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, normalized frequencies (e.g., x of y tests are true positives or false positives) KQ 3: Anxiety, distress KQ 5: Harms related to fetal exposure to medication: Teratogenesis (e.g., congenital anomalies) Carcinogenesis Maternal AEs, such as: Tolerability Vaginal candidiasis Serious AEs (e.g., those resulting in the need for medical attention)	
Timing	*Intervention timing:* Treatment provided after diagnosis *Outcome timing:* KQs 1, 3, 4, 5: Outcomes measured during current pregnancy at any point after screening or treatment, up to 30 days postdelivery; for outcomes related to harms of fetal exposure, outcomes measured at any time point will be included KQ 2: Screening test and reference standard assessed at same encounter	*Outcome timing:* KQs 1, 3, 4, 5: Outcomes not measured during current pregnancy or within 30 days of delivery, except for harms related to fetal exposure KQ 2: Screening test and reference standard not assessed at same encounter
Setting	Any clinical care settings providing prenatal care, including general obstetrics practices, family medicine practices, and public health clinics Studies conducted in countries categorized as "very high" on the Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries not categorized as "very high" on the Human Development Index
Study design	KQs 1, 4: RCTs, controlled trials, or systematic reviews of RCTs or controlled trials that use study selection criteria similar to this review† KQ 2: Diagnostic test accuracy studies or systematic reviews of diagnostic test accuracy that use study selection criteria similar to this review† KQs 3, 5: RCTs, controlled trials, cohort studies, case-control studies, or systematic reviews that use study selection criteria similar to this review†	Editorials, narrative reviews, letters to the editor, and study designs not listed as specifically included (e.g., case reports, case series, studies without a comparison group); publications not reporting original research
Language	English language	Languages other than English
Study quality	Good- and fair-quality studies	Poor-quality studies will be excluded from the main analyses but will be synthesized in sensitivity analyses if no good- or fair-quality studies are available for a KQ.

* Other diagnostic tests will be included if the following criteria are met: 1) test is feasible for use in primary care settings, 2) test is evaluated in a separate cohort from the one in which the test was initially developed and validated, and 3) test is evaluated with a priori defined test thresholds.

† Only the most recent systematic review will be included if there are multiple reviews from the same group of investigators using the same review protocol. When there are several systematic reviews on the same topic and similar included primary studies, the review with a low risk of bias and the latest cutoff date for the literature search will be selected.

Abbreviations: BV=bacterial vaginosis; FDA=Food and Drug Administration; KQ=key question; pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution; RCT=randomized, controlled trial.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria

Good:	Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair:	Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.
Poor:	Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:

Good:	Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair:	Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor:	Has a fatal flaw, such as using inappropriate reference standard, improperly administering screening test, using biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VI
https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes
Harris et al, 2001[200]

Appendix C. Excluded Studies

List of Exclusion Codes:
X1: Systematic review for hand search
X2: Ineligible publication type
X3: Ineligible country
X4: Ineligible population
X5: Ineligible intervention
X6: Ineligible comparator
X7: Ineligible outcome
X8: Ineligible study design
X9: Duplicate or superseded
X10: Study protocol or in progress
X11: Abstract only
X12: Non-English full text
X13: Other

1. Screening for bacterial vaginosis in pregnancy: recommendations and rationale. Am J Prev Med. 2001 Apr;20(3 Suppl):59-61. PMID: 11306233. Exclusion Code: X2.
2. Screening for bacterial vaginosis in pregnancy: recommendations and rationale. Am J Nurs. 2002 Aug;102(8):91-3. PMID: 12394045. Exclusion Code: X2.
3. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008 Feb 5;148(3):214-9. PMID: 19046169. Exclusion Code: X2.
4. Abdali K, Jahed L, Amooee S, et al. Comparison of the effect of vaginal zataria multiflora cream and oral metronidazole pill on results of treatments for vaginal infections including trichomoniasis and bacterial vaginosis in women of reproductive age. Biomed Res Int. 2015;2015:683640. doi: 10.1155/2015/683640. PMID: 26385347. Exclusion Code: X3.
5. Africa CW. Efficacy of methods used for the diagnosis of bacterial vaginosis. Expert Opin Med Diagn. 2013 Mar;7(2):189-200. doi: 10.1517/17530059.2013.753876. PMID: 23585843. Exclusion Code: X2.
6. Allergan Sales LLC. Safety and tolerability of metronidazole gel 1.3%. March 18, 2015. In ClinicalTrials.gov. [cited December 2, 2018]. Bethesda, MD: National Library of Medicine. 2016. Available from: https://ClinicalTrials.gov/show/NCT02392026. NCT02392026. Exclusion Code: X4.
7. American International. Diagnosing bacterial vaginosis/vaginitis (BV) using the gynecologene test method. September 23, 2015. In ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT02558179. NCT02558179. Exclusion Code: X10.
8. Anderson B, Zhao Y, Andrews W, et al. Effect of antibiotic exposure on Nugent score among pregnant women with and without bacterial vaginosis. Obstet Gynecol. 2011;117(4):844-9. doi: 10.1097/AOG.0b013e318209dd57. PMID: CN-00812284. Exclusion Code: X4.
9. Andrews WW, Goldenberg RL. What we have learned from an antibiotic trial in fetal fibronectin positive women. Semin Perinatol. 2003 Jun;27(3):231-8. PMID: 12889590. Exclusion Code: X4.
10. Assistance Publique Hopitaux De Marseille. Identification and impact of vaginal flora anomalies among pregnant woman. June 11, 2007. In ClinicalTrials.gov. [cited December 2, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT00484653. NCT00484653. Exclusion Code: X9.
11. Assistance Publique Hopitaux De Marseille. Medico-economic impact of screening atopobium vaginae and gardnerella vaginalis in molecular biology by "point-of-care" during pregnancy. November 11, 2014. In ClinicalTrials.gov. [cited December 2, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT02288832. Exclusion Code: X10.
12. August Wolff GmbH & Co, Arzneimittel KG. Safety, tolerability and efficacy of vaginal suppository WO3191 in the post-treatment of bacterial vaginosis. February 22, 2016. In ClinicalTrials.gov. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT02687789. NCT02687789. Exclusion Code: X4.

13. Balashov SV, Mordechai E, Adelson ME, et al. Identification, quantification and subtyping of Gardnerella vaginalis in noncultured clinical vaginal samples by quantitative PCR. J Med Microbiol. 2014 Feb;63(Pt 2):162-75. doi: 10.1099/jmm.0.066407-0. PMID: 24200640. Exclusion Code: X7.
14. Balashov SV, Mordechai E, Adelson ME, et al. Multiplex quantitative polymerase chain reaction assay for the identification and quantitation of major vaginal lactobacilli. Diagn Microbiol Infect Dis. 2014 Apr;78(4):321-7. doi: 10.1016/j.diagmicrobio.2013.08.004. PMID: 24445159. Exclusion Code: X5.
15. Beck D, Foster JA. Machine learning techniques accurately classify microbial communities by bacterial vaginosis characteristics. PLoS One. 2014;9(2):e87830. doi: 10.1371/journal.pone.0087830. PMID: 26023904. Exclusion Code: X5.
16. Belgian Contract Research O. Therapeutic Equivalence (non-inferiority), Randomized, Observer-blind, two Parallel Group, Clinical Trial for Comparing the Efficacy and Tolerability of a Generic Formulation of Vaginal Ovule containing Clindamycin 100 mg/ovule versus Dalacin® 100 mg Vaginal Ovules (Pfizer©) in patients with Bacterial Vaginosis - Therapeutic equivalence trial between two formulations of clindamycin 100mg vaginal ovules. Verisfield (UK) Ltd., Greek branch. Athens Greece: 2017. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004292-41. Exclusion Code: X10.
17. Bharti R, Sainia P, Kapoor G, et al. Evaluation of vaginal pH as a screening tool for bacterial vaginosis and impact of screening and treating for bacterial vaginosis on preterm births. Indian J Public Health Res Dev. 2017;8(4):214-9. doi: 10.5958/0976-5506.2017.00342.4. PMID: CN-01440663. Exclusion Code: X3.
18. Bitzer EM, Schneider A, Wenzlaff P, et al. Self-testing of vaginal pH to prevent preterm delivery: a controlled trial. Dtsch Arztebl Int. 2011 Feb;108(6):81-6. doi: 10.3238/arztebl.2011.0081. PMID: 20852454. Exclusion Code: X8.
19. Blankenstein T, Lytton SD, Leidl B, et al. Point-of-care (POC) diagnosis of bacterial vaginosis (BV) using VGTest ion mobility spectrometry (IMS) in a routine ambulatory care gynecology clinic. Arch Gynecol Obstet. 2015 Aug;292(2):355-62. doi: 10.1007/s00404-014-3613-x. PMID: 26078959. Exclusion Code: X5.
20. Boggess KA, Trevett TN, Madianos PN, et al. Use of DNA hybridization to detect vaginal pathogens associated with bacterial vaginosis among asymptomatic pregnant women. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 1):752-6. doi: 10.1016/j.ajog.2005.01.068. PMID: 16150270. Exclusion Code: X5.
21. Bothuyne-Queste É, Hannebicque-Montaigne K, Canis F, et al. Is the bacterial vaginosis risk factor of prematurity? Study of a cohort of 1336 patients in the hospital of Arras. Journal de Gynécologie Obstétrique et Biologie de la Reproduction. 2012 2012/05/01/;41(3):262-70. doi: 10.1016/j.jgyn.2012.01.007. Exclusion Code: X12.
22. Bradshaw C, Pirotta M, Hocking J, et al. Double-blind randomised placebo controlled trial of oral metronidazole in combination with either vaginal clindamycin or an oestrogen-containing vaginal probiotic for the treatment of bacterial vaginosis. Sex Transm Infect. 2011;87:A80-a1. doi: 10.1136/sextrans-2011-050109.132. PMID: CN-01033602. Exclusion Code: X4.
23. Bravo AB, Miranda LS, Lima OF, et al. Validation of an immunologic diagnostic kit for infectious vaginitis by Trichomonas vaginalis, Candida spp., and Gardnerella vaginalis. Diagn Microbiol Infect Dis. 2009 Mar;63(3):257-60. doi: 10.1016/j.diagmicrobio.2008.11.010. PMID: 19216938. Exclusion Code: X3.
24. Bretelle F, Fenollar F, Baumstarck K, et al. Screen-and-treat program by point-of-care of Atopobium vaginae and Gardnerella vaginalis in preventing preterm birth (AuTop trial): study protocol for a randomized controlled trial. Trials. 2015 Oct 19;16:470. doi: 10.1186/s13063-015-1000-y. PMID: 26482128. Exclusion Code: X10.
25. Bretelle F, Rozenberg P, Pascal A, et al. High Atopobium vaginae and Gardnerella vaginalis vaginal loads are associated with preterm birth. Clin Infect Dis. 2015 Mar 15;60(6):860-7. doi: 10.1093/cid/ciu966. PMID: 25452591. Exclusion Code: X5.
26. Briery CM, Chauhan SP, Magann EF, et al. Treatment of bacterial vaginosis does not reduce preterm birth among high-risk asymptomatic women in fetal fibronectin positive patients. J Miss State Med Assoc. 2011 Mar;52(3):72-5. PMID: 20012637. Exclusion Code: X6.
27. Brocklehurst P, Gordon A, Heatley E, et al. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev. 2013(1). doi: 10.1002/14651858.CD000262.pub4. PMID: CD000262. Exclusion Code: X1.

28. Brown HL, Fuller DA, Davis TE, et al. Evaluation of the Affirm Ambient Temperature Transport System for the detection and identification of Trichomonas vaginalis, Gardnerella vaginalis, and Candida species from vaginal fluid specimens. J Clin Microbiol. 2001 Sep;39(9):3197-9. PMID: 11526150. Exclusion Code: X6.
29. Brown HL, Fuller DD, Jasper LT, et al. Clinical evaluation of affirm VPIII in the detection and identification of Trichomonas vaginalis, Gardnerella vaginalis, and Candida species in vaginitis/vaginosis. Infect Dis Obstet Gynecol. 2004;12(1):17-21. doi: 10.1080/1064744042000210375. PMID: 15460191. Exclusion Code: X6.
30. Cakiroglu Y, Caliskan S, Doger E, et al. Do the interactions between coital frequency, cervical length, and urogenital infection affect obstetric outcomes? Turk J Obstet Gynecol. 2015 Jun;12(2):66-70. doi: 10.4274/tjod.89106. PMID: 28913045. Exclusion Code: X3.
31. Carter J, Beck D, Williams H, et al. GA-based selection of vaginal microbiome features associated with bacterial vaginosis. Genet Evol Comput Conf. 2014;2014:265-8. doi: 10.1145/2576768.2598378. PMID: 25541628. Exclusion Code: X5.
32. Cartwright CP, Lembke BD, Ramachandran K, et al. Development and validation of a semiquantitative, multitarget PCR assay for diagnosis of bacterial vaginosis. J Clin Microbiol. 2012 Jul;50(7):2321-9. doi: 10.1128/jcm.00506-12. PMID: 23320114. Exclusion Code: X5.
33. Cartwright CP, Pherson AJ, Harris AB, et al. Multicenter study establishing the clinical validity of a nucleic-acid amplification-based assay for the diagnosis of bacterial vaginosis. Diagn Microbiol Infect Dis. 2018 Nov;92(3):173-8. doi: 10.1016/j.diagmicrobio.2018.05.022. Exclusion Code: X5.
34. Castell S, Krause G, Schmitt M, et al. Feasibility and acceptance of cervicovaginal self-sampling within the German National Cohort (Pretest 2). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2014 Nov;57(11):1270-6. doi: 10.1007/s00103-014-2054-9. PMID: 25303829. Exclusion Code: X5.
35. Cauci S, Culhane JF. High sialidase levels increase preterm birth risk among women who are bacterial vaginosis-positive in early gestation. Am J Obstet Gynecol. 2011 Feb;204(2):142.e1-9. doi: 10.1016/j.ajog.2010.08.061. PMID: 21261445. Exclusion Code: X5.
36. CDA Research Group, Inc. GoldenCareTM for the treatment of bacterial vaginosis. January 8, 2013. In ClinicalTrials.gov. [cited December 2, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT01762670. NCT01762670. Exclusion Code: X14.
37. CDA Research Group, Inc. LUXSOL(TM) topical cream for the treatment of symptomatic bacterial vaginosis; a proof of concept study. July 22, 2014. In ClinicalTrials.gov. [cited December 2, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT02197182. NCT02197182. Exclusion Code: X4.
38. Centers for Disease Control and Prevention. Maternal effects of bacterial vaginosis (BV) treatment in pregnancy. September 12, 2005. In ClinicalTrials.gov. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000+. Available from: https://ClinicalTrials.gov/show/NCT00153517. NCT00153517. Exclusion Code: X6.
39. Chaijareenont K, Sirimai K, Boriboonhirunsarn D, et al. Accuracy of Nugent's score and each Amsel's criteria in the diagnosis of bacterial vaginosis. J Med Assoc Thai. 2004 Nov;87(11):1270-4. PMID: 15825698. Exclusion Code: X3.
40. Chaim W, Karpas Z, Lorber A. New technology for diagnosis of bacterial vaginosis. Eur J Obstet Gynecol Reprod Biol. 2003 Nov 10;111(1):83-7. PMID: 14557018. Exclusion Code: X5.
41. Chandiok S, Crawley BA, Oppenheim BA, et al. Screening for bacterial vaginosis: a novel application of artificial nose technology. J Clin Pathol. 1997 Sep;50(9):790-1. PMID: 9389983. Exclusion Code: X5.
42. Charonis G, Larsson PG. Use of pH/whiff test or QuickVue Advanced pH and Amines test for the diagnosis of bacterial vaginosis and prevention of postabortion pelvic inflammatory disease. Acta Obstet Gynecol Scand. 2006;85(7):837-43. doi: 10.1080/00016340600589776. PMID: 16817083. Exclusion Code: X5.

43. Chaudry AN, Travers PJ, Yuenger J, et al. Analysis of vaginal acetic acid in patients undergoing treatment for bacterial vaginosis. J Clin Microbiol. 2004 Nov;42(11):5170-5. doi: 10.1128/jcm.42.11.5170-5175.2004. PMID: 15528711. Exclusion Code: X5.
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46. Cohrssen A, Anderson M, Merrill A, et al. Reliability of the whiff test in clinical practice. J Am Board Fam Pract. 2005 Nov-Dec;18(6):561-2. PMID: 16322419. Exclusion Code: X7.
47. Common Sense. Va-sense - bacterial vaginosis once a week screening and treatment to reduce infective complications, abortion and preterm delivery in pregnant women with previous preterm delivery. June 29, 2010. In ClinicalTrials.gov. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: https://ClinicalTrials.gov/show/NCT01152528. NCT01152528. Exclusion Code: X14.
48. Cox C, McKenna JP, Watt AP, et al. New assay for Gardnerella vaginalis loads correlates with Nugent scores and has potential in the diagnosis of bacterial vaginosis. J Med Microbiol. 2015 Sep;64(9):978-84. doi: 10.1099/jmm.0.000118. PMID: 25316066. Exclusion Code: X5.
49. Crist Jr AE, Bankert D, Mallory RV, et al. Comparison of the BD affirm VPIII test to primary care and clinical laboratory methods for the diagnosis of bacterial vaginosis and yeast vaginitis. Infectious Diseases in Clinical Practice. 2011;19(4):273-5. doi: 10.1097/IPC.0b013e318210fdc0. Exclusion Code: X6.
50. Cristiano L, Rampello S, Noris C, et al. Bacterial vaginosis: prevalence in an Italian population of asymptomatic pregnant women and diagnostic aspects. Eur J Epidemiol. 1996 Aug;12(4):383-90. PMID: 8891543. Exclusion Code: X6.
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Appendix D Table 1. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—pH (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥7); participants with intermediate flora were excluded (N=36)	108 (38)	0.96 (0.91 to 0.99)	0.78 (0.71 to 0.84)	4.41*	0.05*	None
Gratacos et al[88]; 2005; Spain	Gram stain (Nugent score ≥7)	22 (4.5)	0.75 (NR)	0.78 (NR)	NR	NR	None
Gutman et al[109];† 2005; United States	Gram stain (Nugent score ≥7)	104 (38.7)	0.89 (0.82 to 0.95)	0.74 (0.66 to 0.80)	NR	NR	AUC is 0.82.
Hay et al[91]; 1992; U.K.	Gram stain (Spiegel's criteria)	13 (11.4)	1.00* (0.77* to 1.0*)	0.77* (0.86* to 0.84*)	4.39*	0.00*	None
Hellberg et al[93]; 2001; Sweden	Complete Amsel's clinical criteria	131 (13.7)	0.97 (NR)	0.86 (NR)	NR	NR	None
Mastrobattista et al[89]; 2000; United States	Gram stain (Nugent score ≥7)	18 (26.9*)	0.61 (0.39* to 0.80*)	0.80 (0.66* to 0.89*)	2.99*	0.49*	None
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥7)	12 (21.1*)	0.67 (0.39* to 0.86*)	0.91 (0.79* to 0.97*)	7.50*	0.37*	None
Rouse et al[136]; 2009; United States	Gram stain (Nugent's criteria)‡	32 (16.6)	0.66 (0.47 to 0.81)	0.85 (0.78 to 0.90)	4.29*	0.41*	Switching from a pH cutoff of >4.5 to ≥4.5 results in sensitivity of 0.81 (95% CI, 0.63 to 0.92) and specificity of 0.68 (95% CI, 0.60 to 0.75).

Appendix D Table 1. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—pH (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Schmidt et al[94]; 1994; Denmark	Complete Amsel's clinical criteria	77 (41.0) of those with discharge complaint; 53 (13.0) of those without discharge complaint	1.00 (0.95* to 1.0*) for those with discharge complaint; 1.00 (0.93* to 1.0*) for those without discharge complaint	0.76 (0.67* to 0.83*) for those with discharge complaint; 0.81 (0.77* to 0.85*) for those without discharge complaint	4.11* for those with discharge complaint; 5.28* for those without discharge complaint	0.00* for those with discharge complaint; 0.00* for those without discharge complaint	None
Schwebke et al[108]; 1996; United States	Gram stain (Nugent score ≥ 7)	243 (39.4)	0.89 (0.85* to 0.93*)	0.73 (0.69* to 0.78*)	3.34*	0.15*	None
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.90 (0.88 to 0.92)	0.73 (0.69 to 0.76)	3.31*	0.14*	None

* Indicates values that we calculated based on data provided in the study.
† Study used ≥ 4.5 instead of > 4.5 pH for positive diagnosis.
‡ Scoring system is not explicitly stated but assumed to be Nugent.

Abbreviations: AUC=area under the curve; BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported; pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution; U.K.=United Kingdom.

Appendix D Table 2. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Vaginal Discharge (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥ 7); participants with intermediate flora were excluded (N=36)	108 (38)	0.84 (0.77 to 0.90)	0.46 (0.38 to 0.54)	1.56*	0.34*	None
Gratacos et al[88]; 2005; Spain	Gram stain (Nugent score ≥ 7)	22 (4.5)	0.14 (NR)	0.97 (NR)	NR	NR	None
Gutman et al[109]; 2005; United States	Gram stain (Nugent score ≥ 7)	104 (38.7)	0.79 (0.69 to 0.87)	0.54 (0.46 to 0.62)	NR	NR	AUC is 0.77.
Hay et al[91]; 1992; U.K.	Gram stain (Spiegel's criteria)	13 (11.4)	0.85* (0.58* to 0.96*)	0.67* (0.58* to 0.76*)	2.59*	0.23*	None
Hellberg et al[93]; 2001; Sweden	Complete Amsel's clinical criteria	131 (13.7)	0.52 (NR)	0.95 (NR)	NR	NR	None
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥ 7)	12 (21.1*)	0.58 (0.32* to 0.81*)	0.47 (0.33* to 0.61*)	1.09*	0.89*	None
Schmidt et al[94]; 1994; Denmark	Complete Amsel's clinical criteria	77 (41.0) of those with discharge complaint; 53 (13.0) of those without discharge complaint	0.90 (0.81* to 0.95*) for those with discharge complaint; 0.93 (0.82* to 0.97*) for those without discharge complaint	0.80 (0.72* to 0.87*) for those with discharge complaint; 0.89 (0.85* to 0.92*) for those without discharge complaint	4.52* for those with discharge complaint; 8.39* for those without discharge complaint	0.13* for those with discharge complaint; 0.08* for those without discharge complaint	None
Schwebke et al[99]; Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥ 7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.59 (0.55 to 0.62)	0.90 (0.87 to 0.92)	5.95*	0.46*	None

* Indicates values that we calculated based on data provided in the study.

Abbreviations: AUC=area under the curve; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported; U.K.=United Kingdom.

Appendix D Table 3. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Whiff Test (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥7); participants with intermediate flora were excluded (N=36)	108 (38)	0.69 (0.60 to 0.78)	1.00 (0.98 to 1.00)	Infinite*	0.31*	None
Gratacos et al[88]; 2005; Spain	Gram stain (Nugent score ≥7)	22 (4.5)	0.27 (NR)	0.99 (NR)	NR	NR	None
Gutman et al[109]; 2005; United States	Gram stain (Nugent score ≥7)	104 (38.7)	0.67 (0.57 to 0.76)	0.93 (0.88 to 0.97)	NR	NR	AUC is 0.80.
Hay et al[91]; 1992; U.K.	Gram stain (Spiegel's criteria)	13 (11.4)	0.85* (0.58* to 0.96*)	0.99* (0.95* to 1.0*)	85.46*	0.16*	None
Hellberg et al[93]; 2001; Sweden	Complete Amsel's clinical criteria	131 (13.7)	0.99 (NR)	0.93 (NR)	NR	NR	None
Mastrobattista et al[89]; 2000; United States	Gram stain (Nugent score ≥7)	18 (26.9*)	0.28 (0.13* to 0.51*)	0.96 (0.86* to 0.99*)	6.81*	0.75*	None
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥7)	12 (21.1*)	0.50 (0.25* to 0.75*)	0.98 (0.88* to 1.0*)	22.50*	0.51*	None
Schmidt et al[94]; 1994; Denmark	Complete Amsel's clinical criteria	77 (41.0) of those with discharge complaint; 53 (13.0) of those without discharge complaint	0.78 (0.68* to 0.86*) for those with discharge complaint; 0.76 (0.62* to 0.85*) for those without discharge complaint	0.99 (0.95* to 1.0*) for those with discharge complaint; 1.00 (0.99* to 1.0*) for those without discharge complaint	86.49* for those with discharge complaint; Infinite* for those without discharge complaint	0.22* for those with discharge complaint; 0.25* for those without discharge complaint	None

Appendix D Table 3. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Whiff Test (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV on Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.77 (0.74 to 0.80)	0.94 (0.92 to 0.96)	13.53*	0.24*	None
Sonnex et al[137]; 1995; U.K.	Gram stain (Nugent score ≥7)	50 (16.8)	0.82 (0.69* to 0.90*)	0.95 (0.92* to 0.97*)	16.88*	0.19*	The results here are for the general practice population. The sensitivity and specificity were 0.87 (95% CI, 0.71* to 0.95*) and 0.98 (95% CI, 0.95* to 1.0*), respectively, among 164 women at a hospital-based genitourinary medicine clinic (23.3% of whom had confirmed BV).

* Indicates values that we calculated based on data provided in the study.

Abbreviations: AUC=area under the curve; BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported; U.K.=United Kingdom.

Appendix D Table 4. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Clue Cells (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV On Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Bradshaw et al[100]; 2005; Australia	Gram stain (Nugent score ≥7); participants with intermediate flora were excluded (N=36)	108 (38)	0.96 (0.91 to 0.99)	0.99 (0.96 to 1.00)	138.67*	0.04*	None
Gratacos et al[88];† 2005; Spain	Gram stain (Nugent score ≥7)	22 (4.5)	0.59 (NR)	0.94 (NR)	NR	NR	None
Gutman et al[109]; 2005; United States	Gram stain (Nugent score ≥7)	104 (38.7)	0.74 (0.65 to 0.82)	0.86 (0.80 to 0.91)	NR	NR	AUC is 0.80.
Hay et al[91]; 1992; U.K.	Gram stain (Spiegel's criteria)	13 (11.4)	1.00* (0.77* to 1.0*)	1.00* (0.96* to 1.0*)	Infinite*	0.00*	None
Hellberg et al[93]; 2001; Sweden	Complete Amsel's clinical criteria	131 (13.7)	1.0 (NR)	0.92 (NR)	NR	NR	None
Mastrobattista et al[89];‡ 2000; United States	Gram stain (Nugent score ≥7)	18 (26.9*)	0.50 (0.29* to 0.71*)	0.94 (0.84* to 0.98*)	8.17*	0.53*	None
Myziuk et al[102]; 2003; Canada	Gram stain (Nugent score ≥7)	12 (21.1*)	0.92 (0.65* to 0.99*)	1.00 (0.92* to 1.0*)	Infinite*	0.08*	None
Platz-Christensen et al[92];§ 1995; Sweden	Gram stain (Spiegel's criteria)	36 (33.3*)	0.92* (0.78* to 0.97*)	1.00* (0.95* to 1.0*)	Infinite*	0.08*	None
Rouse et al[136]; 2009; United States	Gram stain (Nugent's criteria)‖	32 (16.6)	0.38 (0.22 to 0.56)	0.91 (0.86 to 0.95)	4.31*	0.68*	None

Appendix D Table 4. Accuracy of Diagnostic Tests From Studies of Diagnostic Test Accuracy—Clue Cells (KQ 2)

Author; Year Country	Reference Test	N (%) With Confirmed BV On Referent Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Other Comments
Schmidt et al[94]; 1994; Denmark	Complete Amsel's clinical criteria	77 (41.0) of those with discharge complaint; 53 (13.0) of those without discharge complaint	0.97 (0.91* to 0.99*) for those with discharge complaint; 1.00 (0.93* to 1.0*) for those without discharge complaint	0.93 (0.86* to 0.96*) for those with discharge complaint; 0.92 (0.89* to 0.95*) for those without discharge complaint	13.51* for those with discharge complaint; 12.64* for those without discharge complaint	0.03* for those with discharge complaint; 0.00* for those without discharge complaint	None
Schwebke et al[108]; 1996; United States	Gram stain (Nugent score ≥7)	243 (39.4)	0.60 (0.54 to 0.66)	0.94 (0.92* to 0.96*)	10.70*	0.42*	Switching from a clue cell threshold of >20% to "any clue cells" results in sensitivity of 0.80 (95% CI, NR) and specificity of 0.79 (95% CI, NR).
Schwebke et al[99] Gaydos et al[65]; 2018/2017; United States	Gram stain (Nugent score ≥7); participants with Nugent score 4 to 6 were excluded (N=213)	783 (50.5*)	0.79 (0.76 to 0.81)	0.86 (0.83 to 0.89)	5.78*	0.25*	None

* Indicates values that we calculated based on data provided in the study.
† Study used any clue cells for positive diagnosis.
‡ Study used any clue cells for positive diagnosis.
§ Study authors report sensitivity and specificity for clue cells as the referent test and Gram Stain as the index test.
‖ Scoring system is not explicitly stated but assumed to be Nugent.

Abbreviations: AUC=area under the curve; BV=bacterial vaginosis; CI=confidence interval; KQ=key question; N=number of participants; NR=not reported; U.K.=United Kingdom.

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Carey et al[111]; 2000; Andrews et al[127]; 2003; United States; National Institute of Child Health and Human Development and National Institute of Allergy and Infectious Disease; Good	G1: Placebo (987) G2: Oral metronidazole 1,000 mg dose four times (966) Dose given on day 0 (day of randomization) and again on day 2, followed by a repeated two-dose regimen 48 hours apart between 24 and 30 weeks gestation and at least 14 days after the first dose	*Key inclusion criteria:* Asymptomatic, pregnancy between 16 weeks 0 days and 23 weeks 6 days of gestation, tested positive for BV and negative for *T. vaginalis* *Key exclusion criteria:* Symptomatic or received antibiotics since study screening, antenatal care or delivery planned at a location outside of study field, planned antibiotic therapy before delivery, current or planned cervical cerclage and/or tocolytic-drug therapy, preterm labor before screening, fetal death or known life-threatening fetal anomaly, multifetal gestation, or medical illnesses, positive tests for syphilis or gonorrhea	Mean (SD) maternal age, yrs: G1: 23 (5) G2: 23 (6) N (%) nonwhite G1: 841 (85.2) G2: 822 (85.1) Mean (SD) gestational age wks: G1: 19.8 (2.6) G2: 19.5 (2.5) N (%) nulliparous: G1: 407 (41.2) G2: 436 (45.1) Prior PTD: G1: 110 (11.1) G2: 103 (10.7) N (%) with symptoms of BV G1: 0 (0) G2: 0 (0)	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7) combined with pH of vaginal sample >4.4 BV prevalence among women tested for study entry: 33.6%
Guaschino et al[112]; 2003; Italy; NR; Good	G1: No treatment (57) G2: Intravaginal clindamycin 2% cream once daily for 7 days (55)	*Key inclusion criteria:* Women between 14 and 25 weeks gestation with diagnosis of asymptomatic bacterial vaginosis without clinical symptoms of vaginosis who visited outpatient obstetric services of participating centers *Key exclusion criteria:* Multiple gestation, symptomatic vaginal or urinary tract infection, antibiotic therapy in the previous 15 days, or contraindications to the use of clindamycin.	Mean (SD) maternal age, yrs: G1: 29.1 (4.4) G2: 29.2 (4.6) N (%) no-white NR Mean (SD) gestational age wks: G1: 19.2 (3.9) G2: 19.2 (3.9) N (%) nulliparous: G1: 35 (61.4) G2: 39 (70.9) Prior PTD: G1: 3 (5.3) G2: 5 (9.1) N (%) with symptoms of BV G1: 0 (0) G2: 0 (0)	*Gardnerella*, *Bacteroides*, and *Mobiluncus* morphotype screening on vaginal smear using Hillier et al methodology. BV prevalence among women tested for study entry: 5.9%

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Hauth et al[121]; 1995; United States; March of Dimes Birth Defects Foundation and an Agency for Health Care Policy Research; Fair	G1: Placebo (87)* G2: Oral metronidazole (750 mg in 3 divided doses daily) for 7 days and 999 mg erythromycin (in 3 divided doses daily) for 14 days (176)	*Key inclusion criteria:* Women between 22 and 24 weeks of gestation who receive antepartum care at public health clinics with either a previous spontaneous preterm delivery or who weighed less than 50 kg before pregnancy. *Key exclusion criteria:* Known allergies to metronidazole or erythromycin, uncertain length of gestation, multiple gestation, prior vaginal bleeding, or medical complication of pregnancy such as diabetes or chronic renal disease.	Mean (SD) maternal age, yrs. (from parent study): G1: 23.6 (4.8) G2: 23.7 (4.9) N (%) nonwhite (from parent study): G1: 150 (79) G2: 309 (71) Mean (SD) gestational age wks. (from parent study): G1: 22.9 (2.5) G2: 23.0 (2.3) N (%) nulliparous (from parent study): G1: 30 (16) G2: 84 (19) N (%) with prior PTD (from subgroup with BV): G1: 56 (65.1) G2: 121 (70.3) N (%) with symptoms of BV: NR	Three of four Amsel's clinical criteria plus few white blood cells and mixed flora on Gram stain of vaginal fluid based on Spiegel et al and Thomason et al criteria. BV prevalence among women tested for study entry: 42.1%
Kekki et al[113]; 2001; Kurkinen-Raty et al[126]; 2000; Finland; Helsinki University Central Hospital Research Funds, Pharmacia-Upjohn and Paulo Foundation; Good	G1: Placebo (188) G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)	*Key inclusion criteria:* Gravid women who were patients at antenatal clinics who screened positive for BV at their 10- to 17-week gestation antenatal clinical visit *Key exclusion criteria:* Multiple pregnancies or history of preterm delivery	Mean (range) maternal age yrs: 28.8 (17 to 43) N (%) nonwhite: NR Mean (SD) gestational age wks: NR; participants were randomized to treatment between 12 and 19 weeks N (%) nulliparous: NR but mean parity in G1 1.9 and mean parity in G2 1.7 N (%) with prior PTD: 0 (0) N (%) with symptoms of BV: 0 (0)	Gram stain of vaginal smear interpreted using Spiegel et al criteria, interpreted as normal, intermediate flora, or BV BV prevalence among women tested for study entry: 10.4%

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Kiss et al[114]; 2004; Austria; Health Austria and Federal Ministry of Education, Science and Culture; Fair	G1: No treatment (179)† G2: Intravaginal clindamycin 2% cream once daily for 6 days with test of cure and treatment with oral clindamycin (300 mg twice a day) if still positive at 24 to 27 weeks gestation (177)	*Key inclusion criteria:* Women presenting for routine prenatal visits between 15 weeks plus 0 days and 19 weeks plus 6 days of gestation as confirmed by last menstrual period and an ultrasound before 18 weeks *Key exclusion criteria:* Multiple gestations, women with subjective complaints (contractions, vaginal bleeding, or symptoms suggestive of vaginal infection)	Mean (SD) maternal age, yrs: 28.9 (5.6) N (%) nonwhite: NR (2) Mean (SD) gestational age wks: 17 (1.6) N (%) nulliparous: G1: NR (47.8) G2: NR (47.9) N (%) with prior PTD between 33 and 36 weeks: G1 45 (2.1) G2: 47 (2.2) N (%) with prior PTD between 23 and 32 weeks: G1: 24 (1.1) G2: 22 (1.1) N (%) with symptoms of BV: 0 (0)	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7) BV prevalence among women tested for study entry: 8.6%
Lamont et al[115]; 2003; Lamont et al[138]; 2012; United Kingdom; Pharmacia/Upjohn; Good	G1: Placebo (201) G2: Intravaginal clindamycin 2% cream, once daily for 3 days (208)	*Key inclusion criteria:* Asymptomatic women age 16 to 40 years between 13 and 20 weeks gestation at their first antenatal visit with Gram stain positive for bacterial vaginosis or intermediate flora *Key exclusion criteria:* Known sensitivity to clindamycin, a history of antibiotic-related colitis, inflammatory bowel disease, or frequent periodic diarrhea	Mean (SD) maternal age, yrs: G1: 27 (5) G2: 27 (5) N (%) nonwhite: G1: 63 (31) G2: 58 (28) N (%) at 13-16 weeks gestation 245 (60) N (%) at 20 weeks gestation or later G1: 4 (2) G2: 6 (3) N (%) nulliparous G1: 112 (56) G2: 111 (53) N (%) with prior PTD G1: 11 (8) G2: 10 (7) N (%) with symptoms of BV: 0 (0)	Gram stain of vaginal smear scored according to Nugent et al criteria; women with intermediate flora (scores 4 to 6) and women with bacterial vaginosis (scores ≥7) were randomized) BV prevalence among women tested for study entry: NR

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Larsson et al[116]; 2006; Sweden; Medical Research Council of Southeast Sweden and Linkoping University; Fair	G1: No treatment (411) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)	*Key inclusion criteria:* Women, age 18 years or older, registered at an antenatal clinic who screened positive for BV at their initial antenatal visit *Key exclusion criteria:* Antibiotic treatment in early pregnancy, symptomatic vaginal infection, therapeutic termination of pregnancy, early spontaneous miscarriage (<16 weeks) or missed miscarriage (no fetus at 16- to 18-week ultrasound), postinclusion need for cervical cerclage, postinclusion treatment with either metronidazole or clindamycin outside the study, and multiple pregnancy (twins or triplets)	Mean (SD) maternal age, yrs: G1: 28.6 (4.97) G2: 28.5 (4.83) N (%) nonwhite: NR Mean (SD) gestational age: 13 weeks, 6 days (18 days) N (%) nulliparous: G1: 187 (45.5) G2: 186 (45.5) N (%) prior PTD (among parous women) G1: 13/218 (6.0) G2: 20/217 (9.2) N (%) with symptoms of BV: 0 (0)	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7) BV prevalence among women tested for study entry: 9.3%
McDonald et al[117]; 1997; Australia; National Health and Medical Research Council of Australia; Government Employees Medical Research Fund; Queen Victoria Hospital Foundation; Queen Victoria Hospital Special Purposes Pathology Fund; and the Queen Victoria Hospital Special Purposes Research, Education and Training Fund; Good	G1: Placebo (440) G2: Oral metronidazole 800 mg in 2 divided doses daily for 2 days and repeated at 28 weeks gestation for women with positive test of cure (439)	*Key inclusion criteria:* Singleton, asymptomatic women attending their 18-week antenatal visit who subsequently screened positive for BV *Key exclusion criteria:* Multiple pregnancy, age <17 years, in vitro fertilization, allergy to metronidazole, symptomatic BV requiring antibiotic treatment, ruptured membranes, cervical cerclage, insulin-dependent diabetes, placenta previa, antibiotic therapy for vaginitis within the 2 weeks preceding enrollment, language difficulties not resolved by an interpreter or inability to attend again before 28 weeks	Mean (SD) maternal age, yrs: G1: 25.9 (5.6) G2: 26.6 (5.5) N (%) nonwhite: G1: 53 (12.3) G2: 47 (10.8) Mean (SD) gestational age wks. (at randomization/treatment): G1: 24.1 (1.49) G2: 24.0 (1.59) N (%) nulliparous: G1: 144 (32.7) G2: 139 (31.7) N (%) with prior PTD: G1: 24 (5.5) G2: 22 (5.0) N (%) with symptoms of BV: 0 (0%)	Vaginal swab for "heavy growth" of *G. vaginalis* or Gram stain interpreted as having numerous small gram variable bacilli resembling *G. vaginalis* and anaerobes; absence or reduction of lactobacilli, plus or minus the presence of clue cells BV prevalence among women tested for study entry: 26.5%

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
McGregor et al[118]; 1994; United States; University of Colorado Health Sciences Center and the Children's Hospital, Kempe Research Center; Good	G1: Placebo (N randomized NR; 69 analyzed) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (N randomized NR; 60 analyzed)	*Key inclusion criteria:* Women initiating prenatal care between 16 and 27 weeks gestation who tested positive for BV *Key exclusion criteria:* History of allergy or antibiotic-associated colitis; diabetes, liver, kidney, or heart-related medical problems; known obstetric complications (e.g., cerclage, placenta previa), multiple gestation; use of antibiotics in prior 2 weeks	Mean (range) maternal age, yrs: 23.8 (17 to 47) N (%) nonwhite: 87 (61.2) Mean (SD) gestational age wks: NR Mean parity (range): 1.0 (0 to 6) N (%) with prior PTD: 15 (10.9) N (%) with symptoms of BV: 0 (0)	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7) and presence of ≥20% clue cells, plus two of the following three criteria: pH >4.5, positive whiff test, presence of discharge BV prevalence among women tested for study entry: NR
Morales et al[122]; 1994; United States; Department of Obstetrics and Gynecology, Orlando Regional Medical Center; Fair	G1: Placebo (N randomized NR, 36 analyzed) G2: Oral metronidazole 750 mg in three divided doses daily for 7 days (N randomized NR, 44 analyzed)	*Key inclusion criteria:* Women in the high-risk obstetric clinic with a singleton gestation between 13 and 20 weeks with a preterm delivery in preceding pregnancy from either idiopathic preterm labor or premature rupture of membranes who screened positive for bacterial vaginosis *Key exclusion criteria:* Significant maternal medical complication including cardiac, respiratory, renal, liver, endocrine, or rheumatic disease; cocaine documented in prior or index pregnancy; previous pregnancy resulted in preterm birth with documented intraamniotic or urinary tract infection or incompetent cervix; antibiotics used 2 weeks before enrollment; fetal anomalies; second-trimester bleeding; and asymptomatic bacteriuria on initial screen	Mean (SD) maternal age, yrs: G1: 25.1 (4.4) G2: 24.4 (3.7) N (%) black: G1: 18 (50) G2: 20 (45) Mean (SD) gestational age wks: NR Mean parity (SD): G1: 2.2 (1.1) G2: 2.4 (1.2) N (%) with prior PTD: 80 (100) N (%) with symptoms of BV: NR	Based on clinical criteria (homogeneous discharge, vaginal pH >4.5, presence of clue cells in wet-mount preparation, and fish-like amine odor when mixed with 10% potassium hydroxide solution) and no evidence of *Trichomonas* BV prevalence among women tested for study entry: NR

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Subtil et al[119]; 2014; France; NR; Good	G1: Placebo (958) G2: Oral clindamycin 600 mg daily for 4 days (943)‡ G3: Oral clindamycin 600 mg daily for 4 days, repeated twice at 1-month intervals (968)	*Key inclusion criteria:* Pregnant women before 15 weeks gestation with bacterial vaginosis, no previous late miscarriage (>16 weeks gestation) or PTD *Key exclusion criteria:* Gestation >15 weeks, allergy to clindamycin, vaginal bleeding in the week prior to enrollment, planning to give birth in a different region of the country	Mean (SD) maternal age, yrs: G1: 27.7 (5.5) G2/G3: 28.0 (5.4) N (%) nonwhite: NR Mean (SD) gestational age wks: G1: 12.4 (2.1) G2/G3: 12.3 (2.2) N (%) nulliparous: G1: 521 (54.3) G2/G3: 969 (50.7) N (%) with prior induced PTD: G1: 14 (1.5) G2/G3: 33 (1.7) N (%) with symptoms of BV: NR	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7) BV prevalence among women tested for study entry: 6.7%
Ugwumadu et al[120]; 2003; United Kingdom; Research and Development Programme, NHS Executive London; Good	G1: Placebo (245)§ G2: Oral clindamycin 600 mg daily (in two divided doses) for 5 days (249)	*Key inclusion criteria:* Women 16 years or older and 12 to 22 weeks pregnant seeking antenatal care who tested positive for abnormal vaginal flora or bacterial vaginosis *Key exclusion criteria:* Women were excluded if they had multiple pregnancies; needed or had cervical cerclage; history of cone biopsy; uterine, cervical, or fetal anomaly; disorders including diabetes, renal disease, collagen disease, lupus, antiphospholipid syndrome, essential hypertension; known allergy to clindamycin	Mean (SD) maternal age, yrs: G1: 28.5 (5.4) G2: 28.8 (5.6) N (%) nonwhite: G1: 93 (39) G2: 86 (36) Mean (SD) gestational age wks: G1: 15.7 (2.6) G2: 15.6 (2.6) Mean parity (SD) G1: 0.8 (1.0) G2: 0.8 (1.1) N (%) with prior spontaneous PTD: G1: 22 (9) G2: 24 (10) N (%) with symptoms of BV:	Gram stain with Nugent score of 4 to 10 (results reported separately for BV only [i.e., Nugent score ≥7] subgroup) BV or intermediate flora prevalence among women tested for study entry: 12.1%

Appendix D Table 5. Additional Study Characteristics of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQs 4 and 5)

Author; Publication Year; Country; Sponsor; Study Quality	Interventions (N Randomized)	Key Inclusion and Exclusion Criteria	Sample Characteristics	Method of BV Diagnosis and Prevalence of BV
Vermeulen et al[123]; 1999; The Netherlands; Praeventiefonds; the Hague, the Netherlands; Good	G1: Placebo (11)[‖] G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11)	*Key inclusion criteria:* Women with a viable singleton pregnancy without major fetal congenital anomalies, at <26 weeks of gestation and a history of spontaneous preterm delivery *Key exclusion criteria:* Previous preterm births associated with intrauterine growth retardation, hypertension, or pre-eclampsia, placental disorders, congenital urine anomalies, maternal diseases, or a known allergy to clindamycin	Mean (SD) maternal age, yrs: G1: 30.9 (3.8) G2: 31.4 (4.0) N (%) nonwhite: NR Mean (SD) gestational age wks: G1: 20.4 (3.2) G2: 19.6 (3.9) Mean parity (SD) G1: 1.4 (0.9) G2: 1.6 (0.9) N (%) with prior PTD: G1: 11 (100) G2: 11 (100) N (%) with symptoms of BV: NR	Gram stain of vaginal smear interpreted according to criteria of Nugent et al (i.e., score ≥7)

*This study assessed the impact of treatment among a population of women with and without BV. This N represents the number of women with BV who are eligible for this review. The total N of placebo group was 191, and the total N of the treatment group was 433. The population characteristics reported here are for the full study population because characteristics were not reported separately for women with BV.

†This study randomized a total of 4,429 participants to vaginal smear screening, but only a subset of participants tested positive for BV and received treatment; we only abstracted data for the BV positive subset of the study population.

‡ The study authors planned the main analysis to consider the two clindamycin groups together, compared with placebo. Supplemental analysis comparing among the three study groups was planned only if a difference between treatment and placebo was observed in the main analysis.

§ Represents the full randomized population; we only reported findings for the subgroup of women with BV, which was 203 participants for placebo group and 207 participants for the treatment group.

‖ This represents the number of women with BV who were allocated to placebo and treatment; the total number of women randomized in the study was 168 (placebo [N=85] and active treatment [N=83])

Abbreviations: BV=bacterial vaginosis; G=group; N=number of participants; NHS=National Health Service; NR=not reported; pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution; PTD=preterm delivery; SD=standard deviation.

Appendix D Table 6. Intermediate Outcomes Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQ 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	BV Clearance or Recurrence
Carey et al[111]; 2000; G1: Placebo (859) G2: Oral metronidazole 1000 mg dose four times (845)	Clearance of BV defined by Nugent's score ≥7 on Gram stain at followup visit after first course of treatment. G1: 321 (37.4) G2: 657 (77.8) Calculated ARD, 40.38% (95 % CI, 36.1% to 44.66%) Calculated RR, 2.08 (95% CI, 1.89 to 2.29)
Guaschino et al[112]; 2003; G1: No treatment (37) G2: Intravaginal clindamycin 2% daily for 7 days (33)	Clearance of BV defined by optional vaginal smear test at 28 to 30 weeks gestation during followup visit G1: 26 (70.3) G2: 25 (75.8) Calculated ARD, 5.49% (-15.26% to 26.34%) Calculated RR, 1.08 (0.81 to 1.43)
Kekki et al[113]; 2001; Kurkinen-Raty et al[126]; 2000; G1: Placebo (188) G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)	Short-term clearance (within 1 week of treatment) based on Gram stain (Spiegel et al, criteria) G1: 62/181 (34.3) G2: 119/181 (65.8) OR, 1.9 (1.3 to 2.8) Calculated ARD, 31.49% (21.72% to 41.27%) Calculated RR, 1.92 (1.53 to 2.41) Long-term clearance (mean 34 weeks gestation, range from 30 to 36 weeks); patients with incomplete followup and intermediate flora were excluded G1: 68/125 (54.4) G2: 95/121 (78.5) Calculated ARD, 24.11% (12.72% to 35.50%) Calculated RR, 1.44 (1.20 to 1.74) Recurrence in 3rd trimester (i.e., initial clearing at first test of cure, followed by recurrence during test of cure between 30 and 36 weeks gestation); patients with incomplete followup and intermediate flora were excluded G1: 18/125 (14.4) G2: 8/125 (6.4) Calculated ARD, -8.0% (-15.50% to -0.50%) Calculated RR, 0.44 (0.20 to 0.98) Persistence (i.e., no clearance in short- or long-term followup); patients with incomplete followup and intermediate flora were excluded G1: 49/125 (39.2) G2: 8/121 (6.6) Calculated ARD, -32.59% (-42.22% to -22.95%) Calculated RR, 0.17 (0.08 to 0.34)

Appendix D Table 6. Intermediate Outcomes Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQ 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	BV Clearance or Recurrence
Lamont et al[115]; 2003; Lamont et al[138]; 2012; G1: Placebo (193) G2: Intravaginal clindamycin 2% cream, once daily for 3 days (198)	Short-term clearance defined as Nugent's score <4 on Gram stain and resolution of all Amsel's clinical criteria at 20 to 24 days posttreatment G1: 3/183 (1.6) G2: 31/171 (18.1) Calculated ARD, 16.5% (10.5% to 22.6%) Calculated RR, 11.1 (3.44 to 35.5) Short-term improvement defined as Nugent's score <4 on Gram stain but one or more Amsel's clinical criteria unresolved at 20 to 24 days posttreatment G1: 19/183 (10.4) G2: 90/171 (52.6) Calculated ARD, 42.3% (33.6% to 50.9%) Calculated RR, 5.07 (3.24 to 7.94) Short-term clearance or improvement; defined as Nugent's score <4 on Gram stain at 20 to 24 days posttreatment G1: 22/183 (12.0) G2: 121/171 (70.8) Calculated ARD, 58.7% (50.5% to 67.0%) Calculated RR, 5.89 (3.93 to 8.81) Sustained clearance or improvement, defined as Nugent's score <4 on Gram stain at 40 to 48 days posttreatment G1: 17/20 (85.0) G2: 105/112 (93.8) Calculated ARD, 8.75% (-7.53% to 25.0%) Calculated RR, 1.10 (0.91 to 1.33) Sustained clearance or improvement, defined as Nugent's score <4 at 30 to 36 weeks gestation G1: 16/21 (76.2) G2: 96/107 (89.7) Calculated ARD, 13.5% (-5.57% to 32.6%) Calculated RR, 1.18 (0.92 to 1.51) Clearance or improvement, defined as Nugent's score <4 on Gram stain after failing initial treatment and being retreated with 7-day course of clindamycin or placebo after 40 to 48 days post-initial treatment G1: 22/142 (15.5) G2: 15/46 (32.6) Calculated ARD, 17.1% (2.32% to 31.9%) Calculated RR, 2.11 (1.20 to 3.71)

Appendix D Table 6. Intermediate Outcomes Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQ 4)

Author et al; Publication Year; Intervention (N Analyzed) Comparator (N Analyzed)	BV Clearance or Recurrence
Lamont et al[115]; 2003; Lamont et al[138]; 2012; (continued)	Clearance or improvement, defined as Nugent's score <4 on Gram stain after failing initial treatment and being retreated with 7-day course of clindamycin or placebo at 30 to 36 weeks gestation G1: 36/136 (26.5) G2: 21/41 (51.2) Calculated ARD, 24.8% (7.75% to 41.8%) Calculated RR, 1.94 (1.29 to 2.91)
McGregor et al[118]; 1994; G1: Placebo (69) G2: Intravaginal clindamycin 2% cream, once daily for 7 days (60)	Clearance 1 week after treatment based on Gram stain and clinical criteria used at enrollment G1: actual values NR, depicted on a figure G2: actual values NR, depicted on a figure G2 > G1 on figure Clearance 4 weeks after treatment based on Gram stain and clinical criteria used at enrollment G1: actual values NR, depicted on a figure G2: actual values NR, depicted on a figure G2 > G1 on figure Clearance 8 weeks after treatment based on Gram stain and clinical criteria used at enrollment G1: actual values NR, depicted on a figure G2: actual values NR, depicted on a figure G2 > G1 on figure Clearance at 36 weeks gestation based on Gram stain and clinical criteria used at enrollment G1: actual values NR, depicted on a figure G2: actual values NR, depicted on a figure G2 > G1 on figure
Morales et al[122]; 1994; G1: Placebo (36) G2: Oral metronidazole 750 daily (44)	Clearance at the time of delivery (presumably using the same criteria as study entry) G1: 5 (13.9) G2: 39 (88.6) Calculated ARD, 74.8% (60.1% to 89.4%) Calculated RR, 6.38 (2.81 to 14.49)

* This study randomized a total of 4,429 participants to vaginal smear screening, but only a subset of participants tested positive for BV and received treatment; we only abstracted data for the BV positive subset of the study population.

Abbreviations: ARD=absolute risk difference; BV=bacterial vaginosis; CI=confidence interval; G=group; KQ=key question; N=number of participants; NR=not reported; RR=relative risk.

Appendix D Table 7. Additional Study Characteristics of Cohort Studies of Harms of In Utero Exposure to Metronidazole (KQ5)

Author; Year; Study Design; Study Quality	Country; Years Covered; Study Sponsor	Study Population; Total N	Exposed Group	Comparison Group
Diav-Citrin et al[129]; 2001; Prospective cohort; Poor	Israel; 1989 to 1998; NR	N=857 Women who contacted the Israeli Teratogen Information Service during pregnancy	228 women contacting the Information Service and who reported exposure to metronidazole Mean maternal age: 20.7 (SD, 5.2) Mean gestational age: 8 weeks (IQR, 6 to 10) Mean daily dose: 973 mg (SD, 483.2) Mean duration of exposure: 7.9 days (SD 3.8)	629 women contacting the Information Service and who reported exposure to nonteratogenic agents; women in this group were significantly more likely to be nulliparas than the exposed group Mean maternal age: 30.2 (SD, 5.0) Mean gestational age: 10 weeks (IQR, 7 to 17)
Sorensen et al[130]; 1999; Retrospective cohort; Fair	Denmark; 1991 to 1996; European Union BIO-MED programme, Danish Medical Research Council, North Jutland Research Council, Aarhus University Foundation, Helsefonden	N=13,451 Women in Denmark who gave birth in North Jutland County identified using the Danish Medical Birth Registry	124 women identified using the Pharmaco-Epidemiological Prescription Database of North Jutland who received a prescription for metronidazole during pregnancy	13,327 women identified using the Pharmaco-Epidemiological Prescription Database of North Jutland who did not receive a prescription for metronidazole during pregnancy
Thapa et al[132]; 1998; Retrospective cohort; Fair	U.S.; 1975 to 1992; National Cancer Institute	N=328,846 participants; 1,172,696 person-years followup Women ages 15 to 44 years enrolled in Tennessee's Medicaid program at any point during their pregnancy	79,716 person-years of followup of women who had a claim for a metronidazole prescription in Tennessee's Medicaid pharmacy database; dose, formulation, and duration of exposure N	1,092,90 person-years of followup in women who did not have a claim for a metronidazole prescription in Tennessee's Medicaid pharmacy database

Abbreviations: IQR=interquartile range; N=number of participants; NR=not reported; SD=standard deviation; U.S.=United States.

Appendix D Table 8. Detailed Harm Outcomes Reported in Cohort Studies of In Utero Exposure to Metronidazole (KQ5)

Author; Year	Outcome
Diav-Citrin et al[129]; 2001	Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (including elective terminations of pregnancy due to prenatally diagnosed anomalies): Exposed: 5/192 (2.60%) Unexposed: 12/579 (2.07%) RR, 1.13 (95% CI, 0.30 to 4.23; p=0.777) Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (excluding elective terminations of pregnancy due to prenatally diagnosed anomalies) Exposed: 3/190 (1.58%) Unexposed: 8/575 (1.39%) RR, 1.26 (95% CI, 0.45 to 3.52; p=0.739) Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (including elective terminations of pregnancy due to prenatally diagnosed anomalies but excluding chromosomal abnormalities and genetic disorders) Exposed: 4/192 (2.08%) Unexposed: 10/577 (1.73%) RR, 1.20 (95% CI, 0.38 to 3.79) Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences after exposure to metronidazole during organogenesis (including elective termination of pregnancy due to prenatally diagnosed anomalies) Exposed: 4/131 (3.05%) Unexposed: 12/579 (2.07%) RR, 1.47 (95% CI, 0.48 to 4.50) Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences after exposure to metronidazole during organogenesis (excluding elective termination of pregnancy due to prenatally diagnosed anomalies) Exposed: 3/129 (2.33%) Unexposed: 8/575 (1.39%) RR, 1.67 (95% CI, 0.45 to 6.21)
Sorensen et al[130]; 1999	Congenital anomalies (not further defined) Exposed: NR (2.4%) Unexposed: NR (5.2%) Crude OR, 0.44 (95% CI, 0.11 to 1.80) Adjusted OR, 0.44 (95% CI, 0.11 to 1.81); adjusted for maternal and gestational age, birth order, smoking status

Appendix D Table 8. Detailed Harm Outcomes Reported in Cohort Studies of In Utero Exposure to Metronidazole (KQ5)

Author; Year	Outcome
Thapa et al[132]; 1998	Incidence of first primary cancer before age 5 identified from the Tennessee Childhood Cancer Database, assembled from review of records from the four tertiary medical centers in Tennessee Exposed: 9/79,716 person-years (rate 11.3 per 100,000) Unexposed: 166/1,092,980 person-years (rate 14.2 per 100,000) Adjusted RR, 0.81 (95% CI, 0.41 to 1.59); adjusted for maternal age less than 24 years, rural county of residence, white race, unwed status, maternal education less than 12 years, birth order (first born)

Abbreviation: CI=confidence interval; NR=not reported; OR=odds ratio; RR=relative risk.

Appendix D Table 9. Additional Study Characteristics of Case-Control Study of Harms of In Utero Exposure to Metronidazole (KQ5)

Author; Year; Study Quality	Country; Years Covered; Study Sponsor	Number of Participants; Study setting	Cases (N)	Controls (N)	Exposure and Measurement
Czeizel et al[131]; 1998 Fair	Hungary; 1980 to 1991; European Union BIO-MED programme	47,963; Population-based study among pregnant women in Hungary	Children with congenital anomalies identified through national registry of congenital anomalies excluding minor abnormalities such as congenital hip dysplasia identified by Ortolani click and inguinal hernias (17,300)	Children without congenital anomalies identified through national birth registry matched to cases based on sex, date of birth, and district of parental residence; two to three controls were matched per case (30,663)	Oral and vaginal exposure to metronidazole during pregnancy; dose, formulation, and timing of exposure were ascertained Multiple exposure ascertainment methods used: prenatal care logbooks that require physicians to record drugs taken during pregnancy, self-report of drugs taken during pregnancy via mailed questionnaire, and relevant medical documents Confounding factors ascertained: maternal age, birth order, threatened abortion, maternal disorders, family history, use of other drugs

Abbreviations: N=number of participants.

Appendix D Table 10. Detailed Harm Outcomes Reported in Case Control Study of In Utero Exposure to Metronidazole (KQ5)

Author; Year	Outcome
Czeizel et al[131]; 1998	Total congenital abnormalities with exposure to metronidazole during 1st month of gestation, N (%) Cases: 29/17,300 (0.17%) Controls: 24/30,633 (0.08%) OR, 2.24 (95% CI, 1.30 to 3.85) Total congenital abnormalities with exposure to metronidazole during 2nd or 3rd month of gestation, N (%) Cases: 107/17,300 (0.62%) Controls: 162/30,633 (0.53%) OR, 1.14 (95% CI, 0.89 to 1.46) Total congenital abnormalities with exposure to metronidazole during 4th through 9th month of gestation, N (%) Cases: 457/17,300 (2.64%) Controls 742/30,633 (2.42%) OR, 1.07 (95% CI, 0.95 to 1.20)

Abbreviations: CI=confidence interval; N=number of participants; OR=odds ratio.

Appendix D Table 11. Additional Study Characteristics of Meta-Analyses of Harms of In Utero Exposure to Metronidazole (KQ5)

Author; Year; Study Quality	Years Covered by Search; Years Covered by Included Studies; Study Sponsor	Number of Studies; Number of Participants	Inclusion Criteria
Burtin et al[133]; 1995 Fair	1959 to 1999; 1964 to 1987; Association Francaise pour la Recherche Therapeutique	7 cohort studies; NR	Studies of any design that included at least 10 women exposed to metronidazole (oral or intravaginal) during pregnancy Control group of unexposed women or women exposed exclusively during the third trimester
Caro-Paton et al[134]; 1997 Fair	1966 to 1996; 1977 to 1994; NR	5 total; 4 cohort studies and 1 case-control study; 199,451	Studies evaluating exposure to metronidazole during pregnancy for whatever its indication

Abbreviation: NR=not reported.

Appendix D Table 12. Detailed Harm Outcomes Reported in Meta-Analyses of In Utero Exposure to Metronidazole (KQ5)

Author; Year; Study Quality	Outcome
Burtin et al[133]; 1995; Fair	Major congenital malformations observed in live-born infants, excluding spontaneous abortion and stillbirth: Summary OR, 0.93 (95% CI, 0.73 to 1.18); no significant heterogeneity (p=0.636) Any congenital malformations observed in live-born infants, excluding spontaneous abortion and stillbirth: Summary OR, 0.96 (95% CI, 0.75 to 1.22)
Caro-Paton et al[134]; 1997; Fair	Congenital malformations: Summary OR, 1.08 (95% CI, 0.90 to 1.29); no significant heterogeneity (p=0.32)

Abbreviations: CI=confidence interval; OR=odds ratio.

Appendix E Table 1. Study Quality Ratings for Diagnostic Accuracy Studies: Part 1

Study Author (Year)	Overall Study Quality	Comments
Bradshaw et al (2005)[100]	Fair	Unclear whether consecutive or random sample was enrolled, no information about masking of index and referent tests, exclusion of some participants with intermediate flora from analyses
Briselden et al (1994)[96]	Fair	No information about whether a consecutive or random sample was enrolled
Byun et al (2016)[90]	Good	None
Cartwright et al (2013)[95]	Fair	Some concerns for bias due to selection of patients, spectrum bias (all symptomatic), and lack of information about masking of index and referent tests
Chen et al (2018)[110]	Fair	No information about whether consecutive or random enrollment used and whether testers were blinded to results of index and reference tests.
Gallos et al (2011)[103]	Fair	Unclear whether enrollment was consecutive or random; also the analysis was done at the visit level (not participant level) with each participant contributing up to 10 visits; thus, the observations are not independent of each other and the authors have not accounted for this in their analysis
Gratacos et al (1999)[88]	Good	None
Gutman et al (2005)[109]	Fair	Unclear whether patients were consecutively or randomly enrolled and whether referent test was interpreted without knowledge of index test
Hay et al (1992)[91]	Good	None
Hellberg et al (2001)[93]	Good	None
Hillier et al (2011)[101]	Fair	Unclear method of sample enrollment; no information about masking of index and referent test results
Hilmarsdottir et al (2006)[104]	Fair	Unclear whether consecutive or random sample used, does not provide information on scoring of index test, only provides information on number analyzed so do not know how many were eligible or enrolled but had missing data
Landers et al (2004)[105]	Fair	Unclear whether consecutive or random sample enrollment used, masking of test results not reported
Lin et al (2002)[201]	Poor	In addition to high concerns for bias in patient selection and index test performance, the analysis does not use patients as the unit of analysis; it uses "slides," each patient contributed two sets of slides (an original and a duplicate) that were read multiple times by technicians and each "read" contributed a data point to the analysis
Lowe et al (2009)[97]	Fair	Unclear whether consecutive or random sample enrollment used, unclear criteria for positive referent test
Mastrobattista et al (2000)[89]	Fair	Unclear whether consecutive or random sample enrollment used, no reporting of whether referent and index test results were masked
Myziuk et al (2003)[102]	Fair	Unclear risk of bias in patient selection, index test, and reference test domains
Platz-Christensen et al (1995)[92]	Good	Uses Spiegel criteria for referent test on Gram stain

Appendix E Table 1. Study Quality Ratings for Diagnostic Accuracy Studies: Part 1 (continued)

Study Author (Year)	Overall Study Quality	Comments
Rouse et al (2009)[136]	Fair (pH and clue cells) Poor (whiff and modified Amsel's clinical criteria)	Unclear risk of bias in patient selection and reference test domains for pH and clue cells, high level of missing data for whiff and modified Amsel's clinical criteria resulting in high concern for bias for those two tests
Schmidt et al (1994)[94]	Good	None
Schwebke et al (1996)[108]	Fair	Unclear risk of bias in some domains including patient selection and masking of index test results
Schwebke (2018)[99] Gaydos (2017)[65]	Fair	Impact of excluding participants with intermediate Nugent scores from the analysis is unclear
Sha et al (2007)[106]	Fair	Unclear whether used consecutive or random enrollment; no indication that results of index and referent test were masked; also the analysis was done at the visit level (not participant level) with each participant contributing multiple observations; thus, the observations are not independent of each other and the authors have not accounted for this in their analysis
Singh et al (2013)[107]	Fair	Unclear risk of bias due to patient selection and reference test (lack of information about masking)
Sonnex et al (1995)[137]	Fair	No information about method of enrollment and no indication that index and referent tests were masked
Witt et al (2002)[98]	Fair	Unclear whether consecutive or random sample were enrolled, unclear whether results of index and referent test were masked

Abbreviation: pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution.

Appendix E Table 2. Study Quality Ratings for Diagnostic Accuracy Studies: Part 2

Study Author(s) (Year(s))	Consider Patients Evaluated (prior testing, presentation, intended use of index test and setting). Is there concern that the included patients do not match the review question?	Consider Index Test. Is there concern that the index test, its conduct, or interpretation differ from the review question?	Consider Reference Test. Is there concern that the target condition as defined by the reference standard does not match the review question?
Bradshaw et al (2005)[100]	Low	Low	Low
Briselden et al (1994)[96]	Low	Low	Low
Byun et al (2016)[90]	Unclear	Low	Low
Cartwright et al (2013)[95]	Unclear	Low	Low
Chen et al (2018)[110]	Low	Low	Low
Gallos et al (2011)[103]	High	Low	Low
Gratacos et al (1999)[88]	Low	Low	Low
Gutman et al (2005)[109]	Low	Low	Low
Hay et al (1992)[91]	Low	Low	Unclear
Hellberg et al (2001)[93]	Unclear	Unclear	Unclear
Hillier et al (2011)[101]	Low	Low	Low
Hilmarsdottir et al (2006)[104]	Unclear	Low	Low
Landers et al (2004)[105]	Low	Low	Low
Lin et al (2002)[201]	Unclear	Unclear	Low
Lowe et al (2009)[97]	Low	Low	Low
Mastrobattista et al (2000)[89]	Low	Low	Low
Myziuk et al (2003)[102]	Low	Low	Low
Platz-Christensen et al (1995)[92]	Low	Low	Low
Rouse et al (2009)[136]	Low	Low	Low
Schmidt et al (1994)[94]	Low	Low	Low
Schwebke et al (1996)[108]	Low	Low	Low
Schwebke (2018)[99] Gaydos (2017)[65]	Unclear	Low	Low
Sha et al (2007)[106]	Unclear	Low	Low
Singh et al (2013)[107]	Low	Low	Low
Sonnex et al (1995)[137]	Low	Low	Low
Witt et al (2002)[98]	Low	Low	Low

Appendix E Table 3. Study Quality Ratings for Diagnostic Accuracy Studies: Part 3

Study Author(s) Year(s)	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Comments
Bradshaw et al (2005)[100]	Unclear	Yes	Yes	Unclear	Unclear whether a consecutive or random sample was enrolled
Briselden et al (1994)[96]	Unclear	Yes	Yes	Unclear	No information about whether a consecutive or random sample was enrolled
Byun et al (2016)[90]	Unclear	Yes	Yes	Low	None
Cartwright et al (2013)[95]	Unclear	Yes	Yes	Unclear	Study cites another paper for details of the study population, the other paper describes the study population as deidentified samples. This paper describes study population as women with clinically documented vaginitis, but unclear whether a consecutive or random sample was used.
Chen et al (2018)[110]	Unclear	Yes	Yes	Unclear	Unclear whether a consecutive or random sample of patients was enrolled.
Gallos et al (2011)[103]	Unclear	Yes	Yes	Unclear	Unclear whether a consecutive or random sample of patients was enrolled.
Gratacos et al (1999)[88]	Yes	Yes	Yes	Low	None
Gutman et al (2005)[109]	Unclear	Yes	Yes	Unclear	Not clear how many patients were eligible and no mention of consecutive or random sample being enrolled
Hay et al (1992)[91]	Yes	Yes	Yes	Low	None
Hellberg et al (2001)[93]	Yes	Yes	Unclear	Low	Cites another paper for detailed study enrollment criteria; the cited paper verifies that consecutively enrollment was used.
Hillier et al (2011)[101]	Unclear	Yes	Yes	Unclear	Unclear how sample was enrolled
Hilmarsdottir et al (2006)[104]	Unclear	Yes	Unclear	Unclear	No information about study inclusion/exclusion criteria or method of recruitment/enrollment
Landers et al (2004)[105]	Unclear	Yes	Yes	Unclear	Unclear whether consecutive or random enrollment used
Lin et al (2002)[201]	No	No	Unclear	High	Study used a case-control design with no information about inclusion/exclusion criteria
Lowe et al (2009)[97]	Unclear	Yes	Yes	Unclear	Unclear whether a consecutive or random sample of women were enrolled
Mastrobattista et al (2000)[89]	Unclear	Yes	Yes	Unclear	Unclear whether consecutive or random sample enrollment was used
Myziuk et al (2003)[102]	Unclear	Yes	Unclear	Unclear	Unclear whether a consecutive or random sample of patients were enrolled
Platz-Christensen et al (1995)[92]	Yes	Yes	Yes	Low	None

Appendix E Table 3. Study Quality Ratings for Observational Studies: Part 3 (continued)

Study Author(s) Year(s)	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Comments
Rouse et al (2009)[136]	Unclear	Yes	Unclear	Unclear	No information about study inclusion/exclusion criteria or how subjects were enrolled (i.e., consecutively or randomly)
Schmidt et al (1994)[94]	Yes	Yes	Yes	Low	None
Schwebke et al (1996)[108]	Unclear	Yes	Unclear	Unclear	No information provided regarding how patients were identified for enrollment or study inclusion/exclusion criteria.
Schwebke (2018)[99] Gaydos (2017)[65]	Yes	Yes	Yes	Low	None
Sha et al (2007)[106]	Unclear	Yes	Unclear	Unclear	Review of cited study confirms enrollment methods.
Singh et al (2013)[107]	Unclear	Yes	Yes	Unclear	No information about whether participants were consecutively or randomly enrolled.
Sonnex et al (1995)[137]	Unclear	Yes	Unclear	Unclear	No information on whether a consecutive or random sample was enrolled, no information about study inclusion or exclusion criteria.
Witt et al (2002)[98]	Unclear	Yes	Unclear	Unclear	Unclear whether consecutive or random sample was enrolled, very little information about participant inclusion and exclusion criteria.

Appendix E Table 4. Study Quality Ratings for Diagnostic Accuracy Studies: Part 4

Study Author(s) Year(s)	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Could the conduct or interpretation of the index test have introduced bias?	Comments
Bradshaw et al (2005)[100]	Unclear	Yes	Unclear	Masking of referent test results NR
Briselden et al (1994)[96]	Yes	Yes	Low	Although not explicitly stated, it appears that separate personnel performed the index and referent tests
Byun et al (2016)[90]	Yes	Yes	Low	None
Cartwright et al (2013)[95]	Unclear	Yes	Unclear	No information as to whether index tests were interpreted without knowledge of referent test
Chen et al (2018)[110]	Unclear	Yes	Unclear	No information provided.
Gallos et al (2011)[103]	Yes	Yes	Low	Although not explicitly stated that clinicians were masked to results of index tests, slides for Gram stains were shipped to a central laboratory so it would not have been possible for them to have been aware of the results at the time that the clinical assessment of BV was made.
Gratacos et al (1999)[88]	Yes	Yes	Low	None
Gutman et al (2005)[109]	Yes	Yes	Low	Because reference tests were sent to outside lab for interpretation, the examiners could not have been aware of the results.
Hay et al (1992)[91]	Yes	Yes	Low	The referent tests were all done in a single batch at the end of the study such that the examiners performing the index test could not have been aware of the results.
Hellberg et al (2001)[93]	No	Yes	Low	The index tests here are components of the referent test that was used; thus, it would be impossible to not have knowledge of both test results at the same time, but the index tests would have to have been conducted first before determining the referent test.
Hillier et al (2011)[101]	Unclear	Yes	Unclear	No information about masking of test results.
Hilmarsdottir et al (2006)[104]	Yes	Unclear	Low	Have to assume that they required 3 of 4 Amsel's clinical criteria to be positive for a positive overall test.
Landers et al (2004)[105]	Unclear	Yes	Unclear	Index text results not reported as masked
Lin et al (2002)[201]	Unclear	Unclear	High	No information is provided regarding how the index test was performed or interpreted.
Lowe et al (2009)[97]	Yes	Yes	Low	None
Mastrobattista et al (2000)[89]	Unclear	Yes	Unclear	Unclear whether index tests were masked

Appendix E Table 4. Study Quality Ratings for Diagnostic Accuracy Studies: Part 4 (continued)

Study Author(s) Year(s)	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Could the conduct or interpretation of the index test have introduced bias?	Comments
Myziuk et al (2003)[102]	Unclear	Yes	Unclear	No information about whether persons performing Amsel's were masked to results of Gram stain, but since Gram stains often go to lab to be performed after clinic visit, it is unlikely the clinicians would have had those results. It is also not clear where BV Blue was performed (in clinic vs. lab) or whether persons performing BV Blue were masked to the other index and referent test results.
Platz-Christensen et al (1995)[92]	Yes	Yes	Low	Not explicitly reported that results were masked but can be inferred by the description of who and where test was performed
Rouse et al (2009)[136]	Yes	Yes	Low	None
Schmidt et al (1994)[94]	Unclear	Yes	Low	Index test is a component of the referent test and would be performed before the referent test score could be calculated.
Schwebke et al (1996)[108]	Yes	Yes	Low	Not explicitly stated, but since Gram stains were sent to central laboratory it is unlikely clinicians would have access to the results
Schwebke (2018)[99] Gaydos (2017)[65]	Yes	Yes	Low	None
Sha et al (2007)[106]	Unclear	Yes	Unclear	No information about masking of results
Singh et al (2013)[107]	Yes	Yes	Low	Gram stain sent to off-site lab for testing so would not have been available to examining clinician performing the index test
Sonnex et al (1995)[137]	Unclear	Yes	Unclear	No information about masking of index test results and seems unlikely given only one study author
Witt et al (2002)[98]	Unclear	Yes	Unclear	Unclear whether results of index test were masked

Abbreviations: BV=bacterial vaginosis; NR=not reported.

Appendix E Table 5. Study Quality Ratings for Diagnostic Accuracy Studies: Part 5

Study Author(s) (Year(s))	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Comments
Bradshaw et al (2005)[100]	Yes	Unclear	Unclear	Masking of index text results NR
Briselden et al (1994)[96]	Yes	Yes	Low	None
Byun et al (2016)[90]	Yes	Yes	Low	None
Cartwright et al (2013)[95]	Yes	Unclear	Unclear	No information as to whether referent tests were interpreted without knowledge of index test; reference standard considers intermediate flora on Nugent's as positive if also had positive Amsel's clinical criteria.
Chen et al (2018)[110]	Yes	Unclear	Unclear	No information provided.
Gallos et al (2011)[103]	Yes	Yes	Low	None
Gratacos et al (1999)[88]	Yes	Yes	Low	None
Gutman et al (2005)[109]	Yes	Unclear	Unclear	Unclear whether referent test was interpreted without knowledge of index test diagnosis
Hay et al (1992)[91]	Yes	Yes	Low	Reference standard is Spiegel criteria
Hellberg et al (2001)[93]	Yes	No	Low	The index tests here are components of the referent test that was used; thus, it would be impossible to not have knowledge of both test results, but the index tests would have to have been conducted first before determining the referent test.
Hillier et al (2011)[101]	Yes	Unclear	Unclear	No information about masking of test results
Hilmarsdottir et al (2006)[104]	Yes	Yes	Low	None
Landers et al (2004)[105]	Yes	Unclear	Unclear	Referent test results not reported as masked
Lin et al (2002)[201]	Yes	Unclear	Unclear	Unclear whether technicians who interpreted the Gram stain slides were masked to results of index test
Lowe et al (2009)[97]	Unclear	Yes	Unclear	The explicit criteria used to make clinical diagnosis are not stated.
Mastrobattista et al (2000)[89]	Yes	Unclear	Unclear	Unclear whether referent tests were masked
Myziuk et al (2003)[102]	Yes	Unclear	Unclear	No information as to whether lab staff were masked to results of either index tests

Appendix E Table 5. Study Quality Ratings for Diagnostic Accuracy Studies: Part 5 (continued)

Study Author(s) (Year(s))	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Comments
Platz-Christensen et al (1995)[92]	Unclear	Yes	Low	Somewhat unclear whether Gram stain based on Spiegel criteria is diagnostic for BV
Rouse et al (2009)[136]	Yes	Unclear	Unclear	Unclear whether microbiology lab had results of index test
Schmidt et al (1994)[94]	Yes	No	Low	Referent test is composed of index test components, so not possible to mask.
Schwebke et al (1996)[108]	Yes	Unclear	Unclear	No explicit mention that the central laboratory was masked to results of index test.
Schwebke (2018)[99] Gaydos (2017)[65]	Yes	Yes	Low	None
Sha et al (2007)[106]	Yes	Unclear	Unclear	No information about masking of results
Singh et al (2013)[107]	Yes	Unclear	Unclear	No information about whether off site lab personnel were masked to results of the index tests
Sonnex et al (1995)[137]	Yes	Unclear	Unclear	No information about masking of referent test results and seems unlikely given only one study author
Witt et al (2002)[98]	Yes	Unclear	Unclear	Unclear whether results of index test were masked

Abbreviations: BV=bacterial vaginosis; NR=not reported.

Appendix E Table 6. Study Quality Ratings for Diagnostic Accuracy Studies: Part 6

Study Author(s) (Year(s))	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions Between Index Test(s) and Reference Standard	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were nearly all patients (>80%) included in the analysis?	Could the patient flow have introduced bias?	Comments
Bradshaw et al (2005)[100]	Study reports data for all 288, although unclear how many were eligible and enrolled but did not have available data. Participants with intermediate flora were excluded from some analyses.	Concurrent collection	Yes	Yes	Yes	Yes	Unclear	Impact of excluding participants with intermediate flora from some analysis unknown
Briselden et al (1994)[96]	Appears that all women who enrolled had data available for the BV analysis.	Concurrent collection	Yes	Yes	Yes	Unclear	Low	None
Byun et al (2016)[90]	5 patients were excluded because of inadequate sample quality.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Cartwright et al (2013)[95]	18/323=5.6% were excluded for missing data (1) or indeterminate results on the BV-PCR (17), which is not a test of interest to this review.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Chen et al (2018)[110]	None mentioned.	Concurrent collection	Yes	Yes	Yes	Unclear	Low	No information about eligible sample and sample analyzed
Gallos et al (2011)[103]	Data were available for 1283/1310=97.9% of participants that were enrolled.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Gratacos et al (1999)[88]	NR	Concurrent collection	Yes	Yes	Yes	Unclear	Low	The number of potentially eligible but not enrolled participants is NR.
Gutman et al (2005)[109]	NR	Concurrent collection	Yes	Yes	Yes	Yes	Low	The number of potential eligible but not enrolled participants is NR.
Hay et al (1992)[91]	4 patients were excluded after enrollment because of heavy bleeding.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None

Appendix E Table 6. Study Quality Ratings for Diagnostic Accuracy Studies: Part 6 (continued)

Study Author(s) (Year(s))	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions Between Index Test(s) and Reference Standard	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were nearly all patients (>80%) included in the analysis?	Could the patient flow have introduced bias?	Comments
Hellberg et al (2001)[93]	55 (5.4%) of patients were excluded for missing records.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Hillier et al (2011)[101]	None	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Hilmarsdottir et al (2006)[104]	NR	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Landers et al (2004)[105]	50 participants were excluded from analysis for reasons not reported.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Lin et al (2002)[201]	NR	Unclear timing, presumably concurrent collection.	Yes	Yes	Yes	Unclear	Low	None
Lowe et al (2009)[97]	12 women were excluded for incomplete data.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Mastrobattista et al (2000)[89]	2 patients were excluded for poor quality specimens.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Myziuk et al (2003)[102]	NR	Concurrent collection	Yes	Yes	Yes	Unclear	Low	Study does not report the number eligible for which data were missing or not available. It only reports number analyzed.
Platz-Christensen et al (1995)[92]	None were reported as excluded, although unclear how many were eligible and tested but were not included in analysis.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Rouse et al (2009)[136]	Missing Gram stain samples for 27/220 (12.2%) participants overall, missing pH test for 4/193 participants with Gram stain, missing whiff test for 83/193 (57%) participants with Gram stain	Concurrent collection	Yes	Yes	Yes for pH and clue cells alone, no for whiff and modified Amsel's clinical criteria	Yes	Low for pH and clue cells, high for whiff and modified Amsel's	High level of missing data for whiff and modified Amsel's clinical criteria

Appendix E Table 6. Study Quality Ratings for Diagnostic Accuracy Studies: Part 6 (continued)

Study Author(s) (Year(s))	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions Between Index Test(s) and Reference Standard	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were nearly all patients (>80%) included in the analysis?	Could the patient flow have introduced bias?	Comments
Schmidt et al (1994)[94]	8 excluded for missing data.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Schwebke et al (1996)[108]	NR	Concurrent collection.	Yes	Yes	Yes	Unclear	Low	The number of enrolled women without data to analyze is not presented so unclear whether the number analyzed is similar to the number enrolled.
Schwebke (2018)[99] Gaydos (2017)[65]	Out of 1,740 eligible participants, 63 were removed due to specimens without evaluable results, 126 were removed due to not compliant reference test or not compliant/indeterminate/ failed BD Max test, and 213 were removed due to intermediate reference test (Gram stain score 4 to 6).	Concurrent	Yes	Yes	Yes	Yes	Unclear	189 (10.9%) participants were excluded from all analyses because they had an intermediate reference test (Gram stain) or not compliant/ indeterminate/failed index test (BD Max).
Sha et al (2007)[106]	Women who seroconverted during the study (N=16) were excluded from the analysis; the analysis was done at the visit level, not patient level.	Concurrent collection	Yes	Yes	Yes	Unclear	Unclear	Because analysis is at the visit level, unclear whether nearly all patients are included over time and patients can contribute more than one visit to the data.
Singh et al (2013)[107]	Three participants excluded for missing data.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None
Sonnex et al (1995)[137]	No information	Concurrent collection	Yes	Yes	Yes	Unclear	Low	Unclear whether study had any women enrolled that were not analyzed

Appendix E Table 6. Study Quality Ratings for Diagnostic Accuracy Studies: Part 6 (continued)

Study Author(s) (Year(s))	Describe Any Patients Who Did Not Receive the Index Test(s) and/or Reference Standard or Who Were Excluded	Describe the Time Interval and Any Interventions Between Index Test(s) and Reference Standard	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were nearly all patients (>80%) included in the analysis?	Could the patient flow have introduced bias?	Comments
Witt et al (2002)[98]	The study authors excluded the participants with intermediate flora from their analysis. Data were provided and we are able to calculate the Sn and Sp with these participants included.	Concurrent collection	Yes	Yes	Yes	Yes	Low	None

Abbreviations: BV=bacterial vaginosis; NA=not applicable; NR=not reported; PCR=polymerase chain reaction; pH=logarithmic scale used to specify the acidity or basicity of an aqueous solution.

Appendix E Table 7. Study Quality Ratings for Randomized, Controlled Trials: Part 1

Study Author (Year)	Overall Study Quality Rating	Overall Rationale for Study Quality Rating
Cary et al (2000)[111]	Good	None
Guaschino et al (2003)[112]	Good	None
Hauth et al (1995)[121]	Fair	Using data from a subgroup analysis that was not prespecified
Kekki et al (2001)[113]	Good	None
Kiss et al (2004)[114]	Fair	Some concerns for bias because of the lack of participant and caregiver masking to treatment assignment and because the subgroup analysis of women with BV was not prespecified
Lamont et al (2003)[115]	Good	None
Larsson et al (2006)[116]	Fair	Some concerns for bias over lack of information regarding allocation concealment; also participants and caregivers in treatment group were not masked to treatment allocation
McDonald et al (1997)[117]	Good	None
McGregor et al (1994)[118]	Fair	Some concerns for bias because of lack of information about allocation concealment and no data to assess baseline characteristics to ensure adequate randomization
Morales et al (1994)[122]	Fair	Some concerns for bias because did not use intent to treat analysis; 6 patients were excluded for failure to complete assigned treatment, and three patients were excluded for receiving antibiotic treatment for other conditions.
Subtil et al (2018)[119]	Good	None
Ugwumadu et al (2003)[120]	Good	Low for the main study results among women with both intermediate flora and bacterial vaginosis; some concerns for the findings in the subgroup of participants with BV
Vermeulen et al (1999)[123]	Good	None

Abbreviations: BV=bacterial vaginosis.

Appendix E Table 8. Study Quality Ratings for Randomized, Controlled Trials: Part 2

Study Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Cary et al (2000)[111]	Yes	No information	No	Some concerns	No information on method of randomization and no information about allocation concealment
Guaschino et al (2003)[112]	Probably yes	Yes	Probably no	Low	None
Hauth et al (1995)[121]	Yes	Yes	No	Low	None
Kekki et al (2001)[113]	Probably yes	Yes	No information	Low	None
Kiss et al (2004)[114]	Yes	Probably yes	No	Low	Participants not selected based on BV status but similar proportion of patients with BV in both the intervention and control groups
Lamont et al (2003)[115]	Yes	Yes	No	Low	None
Larsson et al (2006)[116]	Yes	No information	No	Some concerns	No information about allocation concealment
McDonald et al (1997)[117]	Yes	Yes	Probably no	Low	The placebo group contained 14% of study population < 20 years old compared with only 6% in intervention group
McGregor et al (1994)[118]	Probably yes	No information	No information	Some concerns	Some concerns for bias as no information about allocation concealment and no data on baseline characteristics to assess balance between groups
Morales et al (1994)[122]	Yes	Probably yes	Probably no	Low	Higher proportion of patients with more than 1 prior PTD in Metronidazole group (22/44=50% vs. 14/36=38%) although this difference was reported as NS
Subtil et al (2018)[119]	Yes	Yes	No	Low	None
Ugwumadu et al (2003)[120]	Yes	Yes	No	Low	None.
Vermeulen et al (1999)[123]	Probably yes	Probably yes	No	Low	The article does say that randomization (which was for women with prior preterm deliveries) was stratified by center and by BV status. No further details are given, but this suggests that the subgroup analysis by BV status was preplanned.

Abbreviations: BV=bacterial vaginosis; PTD=preterm delivery; NS=not sufficient.

Appendix E Table 9. Study Quality Ratings for Randomized, Controlled Trials: Part 3

Study Author(s) (Year)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interventions?	Comments
Cary et al (2000)[111]	No	No	NA	NA	No	NA	Low	None
Guaschino et al (2003)[112]	Yes	No information	No information	NA	No	NA	Low	Treatment was not masked, introducing some concerns for bias because of differential awareness for symptoms or care that occurred as a result of knowing treatment assignment, but this would largely only be applicable to intermediate outcomes and not to delivery or birthweight outcomes.
Hauth et al (1995)[121]	No	No	NA	NA	No	NA	Low	None
Kekki et al (2001)[113]	No	No	NA	NA	No	NA	Low	None
Kiss et al (2004)[114]	Yes	Yes	Probably no	NA	No	NA	Some concerns	Control group was not placebo controlled; only the intervention group was aware of their group assignment.
Lamont et al (2003)[115]	No	No	NA	NA	No	NA	Low	None
Larsson et al (2006)[116]	Yes	Yes	Probably no	NA	No	NA	Some concerns	Only participants and clinicians of participants in the treatment group were aware of diagnosis and treatment assignment. Participants in intervention group were not blinded to treatment allocation; control group did not receive placebo.
McDonald et al (1997)[117]	No	No	NA	NA	No	NA	Low	None
McGregor et al (1994)[118]	No	No	NA	NA	No	NA	Low	None
Morales et al (1994)[122]	No	No	NA	NA	No	NA	Low	None
Subtil et al (2018)[119]	No	No	NA	NA	No	NA	Lo	None

Appendix E Table 9. Study Quality Ratings for Randomized, Controlled Trials: Part 3 (continued)

Study Author(s) (Year)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interventions?	Comments
Ugwumadu et al (2003)[120]	No	No	NA	NA	No	NA	Low	None
Vermeulen et al (1999)[123]	No	No	NA	NA	No	NA	Low	None

Abbreviations: NA=not applicable.

Appendix E Table 10. Study Quality Ratings for Randomized, Controlled Trials: Part 4

Study Author(s) (Year)	Were outcome data available for all, or nearly all, participants randomized?	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Cary et al (2000)[111]	Yes	NA	NA	Low	1757/1953=90.0% returned for followup visit and 1919/1953=98.2% had outcome data available
Guaschino et al (2003)[112]	Yes	NA	NA	Low	No treatment group: Data for followup 51/57=89.5% Clindamycin group: Data for followup 49/55= 89.1%
Hauth et al (1995)[121]	Yes	NA	NA	Low	616/624=98.7% had followup data
Kekki et al (2001)[113]	Yes	NA	NA	Low	BV clearance outcome G1: 90.4% followup G2: 90.9% followup Preterm delivery G1: 100% G2: 100%
Kiss et al (2004)[114]	Yes	NA	NA	Low	4,155/,4492= 93.8% completed the study.
Lamont et al (2003)[115]	Yes	NA	NA	Low	Pregnancy outcomes: Placebo: 201/201= 100% Clindamycin: 208/208=100% Visit 2 followup for repeat Gram stain Placebo: 190/201= 95% Clindamycin: 178/208=86%
Larsson et al (2006)[116]	Yes	NA	NA	Low	8,791/9,025=97.4%
McDonald et al (1997)[117]	Yes	NA	NA	Low	429/439= 97.7% in treatment group; 428/440 =97.2% in placebo group
McGregor et al (1994)[118]	Yes	NA	NA	Low	Overall followup available for 129/142=90.8% of participants. Data by group not provided to assess differential attrition.
Morales et al (1994)[122]	No	Unclear	No	Some concerns	Data available for 80/94=85% of participants that were enrolled. Five participants were lost to followup. However, authors also excluded 6 participants who did not complete treatment and 3 participants who received antibiotics for other reasons, and authors do not report to which group these participants were allocated, thus violating the intent to treat principle.
Subtil et al (2018)[119]	Yes	NA	NA	Low	941/943=99.8% in treatment group; 963/968=99.5% in placebo group
Ugwumadu et al (2003)[120]	Yes	NA	NA	Low	244/249=98% in the treatment group and 241/245=98% in the placebo group

Appendix E Table 10. Study Quality Ratings for Randomized, Controlled Trials: Part 4 (continued)

Study Author(s) (Year)	Were outcome data available for all, or nearly all, participants randomized?	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Vermeulen et al (1999)[123]	Yes	NA	NA	Low	Data for all enrolled participants in both groups were available

Abbreviations: BV=bacterial vaginosis; G=group; NA=not applicable.

Appendix E Table 11. Study Quality Ratings for Randomized, Controlled Trials: Part 5

Study Author(s) (Year(s))	Were outcome assessors aware of the intervention received by study participants?	Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	Were the outcomes measured in the same manner for all individuals (equal), in a way that accurately reflects the outcome (valid), and in reproducible manner (reliable)?	Bias arising from measurement of the outcome?	Comments
Cary et al (2000)[111]	No information	Probably no	Yes	Low	None
Guaschino et al (2003)[112]	No information	No	Yes	Low	None
Hauth et al (1995)[121]	No	NA	Yes	Low	None
Kekki et al (2001)[113]	Probably no	NA	Yes	Low	Outcome assessors for BV clearance were masked, but it is unclear whether outcome assessors for preterm delivery were masked
Kiss et al (2004)[114]	No information	Probably no	Yes	Low	None
Lamont et al (2003)[115]	No information	No	Yes	Low	None
Larsson et al (2006)[116]	No information	Probably no	Yes	Low	None
McDonald et al (1997)[117]	No	NA	Yes	Low	None
McGregor et al (1994)[118]	No information	No	Yes	Low	None
Morales et al (1994)[122]	NI	Probably no	Yes	Low	None
Subtil et al (2018)[119]	No	NA	Yes	Low	None.
Ugwumadu et al (2003)[120]	NI	No	Yes	Low	None
Vermeulen et al (1999)[123]	NI	Probably no	Probably yes	Low	None

Abbreviations: BV=bacterial vaginosis; NA=not applicable; NI=no information.

Appendix E Table 12. Study Quality Ratings for Randomized, Controlled Trials: Part 6

Study Author(s) (Year(s))	Are the reported outcome data likely to have been selected on the basis of results from multiple outcome measurements within the outcome domain?	Are the reported outcome data likely to have been selected on the basis of results from multiple analyses of the data?	Bias arising from selection of reported results?	Comments
Cary (2000)[111]	No	No	Low	None
Guaschino (2003)[112]	No	No	Low	None
Hauth (1995)[121]	No	Yes	Some concerns	Data we are using are from a subgroup analysis of results stratified by BV status. This was not a prespecified subgroup, and no information on whether treatment and control groups of women who were BV positive were similar at baseline.
Kekki (2001)[113]	No	No	Low	None
Kiss (2004)[114]	No	Yes	Some concerns	We are using data from a subgroup analysis of women with BV; this was not a prespecified subgroup analysis.
Lamont (2003)[115]	No	No	Low	None
Larsson (2006)[116]	No	No	Low	None
McDonald (1997)[117]	No	No	Low	None
McGregor (1994)[118]	No	No	Low	None
Morales (1994)[122]	Probably no	No	Low	None
Subtil (2018)[119]	Probably no	Probably no	Low	The primary outcome was a composite outcome, but our review is more interested in the individual secondary outcomes.
Ugwumadu (2003)[120]	Probably no	No	Low	The study population included 15.7% of participants with intermediate vaginal flora. However, authors report data in a way that allows us to limit our results to only women with a Nugent score >7; thus, we are technically reporting on a post hoc subgroup analysis.
Vermeulen (1999)[123]	Probably yes	Probably yes	Low	The authors provide outcomes for the entire enrolled population (intention to treat) and also for completers. We are reporting results from the subgroup analysis in women with BV; randomization was stratified by both center and BV status suggesting it was preplanned.

Abbreviation: BV=bacterial vaginosis.

Appendix E Table 13. Study Quality Ratings for Controlled Cohort Studies: Part 1

Study Author(s) (Year(s))	Overall Quality Rating	Overall Rationale for Quality Rating
Diav-Citrin et al (2001)[129]	Poor	Authors did not address potential confounding, high degree of missing data in both the exposed and control groups
Sorensen et al (1999)[130]	Fair	Authors did not fully address confounding; some bias from lack of information about how outcome was defined
Thapa et al (1998)[132]	Fair	Some baseline imbalances between groups and potential for residual confounding

Appendix E Table 14. Study Quality Ratings for Controlled Cohort Studies: Part 2

Study Author(s) (Year(s))	Is there potential for con-founding of the effect of interven-tion?	Was the analysis based on splitting participants' follow up time according to intervention?	Were intervention discon-tinuations or switches likely related to factors prognostic for the outcome?	Did the authors use appropriate analyses method that controlled for all the important con-founding domains?	Were con-founding domains measured validly and reliably by the variables available?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use appropriate analyses that adjusted for all important confounding domains and time varying confounding?	Were con-founding domains adjusted for measured validly and reliably by the variables available?	Overall bias due to con-founding	Comments
Diav-Citrin et al (2001)[129]	Yes	No	NA	No	NA	No	No	No	High	No adjusted analyses performed, no reporting that confounding variables were measured. Exposure to other teratogens not assessed. Larger percentage of women who had abortions in the exposed group.
Sorensen et al (1999)[130]	Yes	No	NA	Probably no	NA	No information	Probably no	Probably yes	Some concerns	Adjusted for smoking, birth order, and maternal age; did not assess exposure to other teratogens in either group.
Thapa et al (1998)[132]	Yes	No	NA	Probably yes	Probably yes	No	No	Probably yes	Some concerns	Analysis adjusted for some demographic variables, but no data presented on carcinogenic exposures between groups; also trimester of enrollment in Medicaid was very different between groups, suggesting differences in access to healthcare and/or difference in socioeconomic characteristics between groups.

Abbreviation: NA=not applicable.

Appendix E Table 15. Study Quality Ratings for Controlled Cohort Studies: Part 3

Study Author(s) (Year(s))	Was selection of participants into the study based on participant characteristics observed after the start of intervention?	Were the post-intervention variables that influenced selection likely associated with the intervention?	Were the post-intervention variables that influenced selection likely influenced by the outcome or a cause of the outcome?	Do start of followup and start of intervention coincide for most participants?	Were adjustment techniques used that likely correct for selection biases?	Overall Bias in Selection of Participants into the Study	Comments
Diav-Citrin et al (2001)[129]	No	NA	NA	Yes	NA	Some concerns	Participants had to be callers to the Teratogen Information Service to be enrolled, and these participants may be more aware of "exposures" than participants who do not call into this service.
Sorensen et al (1999)[130]	No	NA	NA	Yes	NA	Low	Used data sources that were population based for selection into the study
Thapa et al (1998)[132]	No	NA	NA	Yes	NA	Low	Used population-based data sources for selection into the study

Abbreviation: NA=not applicable.

Appendix E Table 16. Study Quality Ratings for Controlled Cohort Studies: Part 4

Study Author(s) (Year(s))	Were intervention groups clearly defined?	Was the information used to define intervention groups recorded at the start of the intervention?	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Overall Bias in Classification of Intervention	Comments
Diav-Citrin et al (2001)[129]	Yes	Yes	No	Low	None
Sorensen et al (1999)[130]	Yes	Yes	No	Low	None
Thapa et al (1998)[132]	Yes	Yes	No	Low	None

Appendix E Table 17. Study Quality Ratings for Controlled Cohort Studies: Part 5

Study Author(s) (Year(s))	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Overall Bias due to Deviation from Intended Intervention	Comments
Diav-Citrin et al (2001)[129]	No	NA	Low	None
Sorensen et al (1999)[130]	No information	No information	Low	None
Thapa et al (1998)[132]	No	NA	Low	None

Abbreviation: NA=not applicable.

Appendix E Table 18. Study Quality Ratings for Controlled Cohort Studies: Part 6

Study Author(s) (Year(s))	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on intervention status?	Were participants excluded due to missing data on other variables needed for the analysis?	Are the proportion of participants and reasons for missing data similar across interventions?	Is there evidence that results were robust to the presence of missing data?	Overall Bias due to Missing Data	Comments
Diav-Citrin et al (2001)[129]	No	No	Yes	No	No information	High	Followup birth outcome data only available for 52.4% of metronidazole-exposed participants and for 37.4% of control participants.
Sorensen et al (1999)[130]	Probably yes	No	No	No information	No information	Some concerns	Used population-level prescription and birth registry databases, but authors did not have data on malformed fetuses detected at prenatal diagnosis and aborted fetuses.
Thapa et al (1998)[132]	Yes	No	No	No information	No information	Uncertain because no information	94.2% of potentially eligible women were able to be linked to a child. Authors discuss the implications of migration on findings in the discussion.

Appendix E Table 19. Study Quality Ratings for Controlled Cohort Studies: Part 7

Study Author(s) (Year(s))	Could the outcome measure have been influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?	Were the methods of outcome assessment comparable across intervention groups?	Were any systematic errors in measurement of the outcome related to intervention received?	Overall Bias in Measurement of Outcomes	Comments
Diav-Citrin et al (2001)[129]	Probably no	No information	Yes	Probably no	Low	Because the outcome was major malformations, it is unlikely that knowledge of the exposure would have influenced the measurement of this outcome.
Sorensen et al (1999)[130]	No	No information	Yes	No information	Some concerns	Outcome definition for malformations not provided by study authors; thus, it is not clear how this was measured using birth registry data.
Thapa et al (1998)[132]	No	No information	Yes	Probably no	Low	Because the outcome was incidence of cancer, it is unlikely that knowledge of the exposure would have influenced the measurement of this outcome.

Appendix E Table 20. Study Quality Ratings for Controlled Cohort Studies: Part 8

Study Author(s) (Year(s))	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Overall Bias in Selection of the Reported Result	Comments
Diav-Citrin et al (2001)[129]	No	No	No	Low	None
Sorensen et al (1999)[130]	No	No	No	Low	None
Thapa et al (1998)[132]	No	No	No	Low	None

Appendix E Table 21. Study Quality Ratings for Case Control Studies: Part 1

Study Author(s) (Year(s))	Overall Study Quality	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Are the results of this study directly applicable to the patient group targeted by this guideline	Notes
Czeizel et al (1998)[131]	Fair	No	Yes	Differential followup, which might be due to the differential methods for outcome ascertainment used between the exposed and unexposed groups. Also, potential for recall bias, particularly among cases.

Appendix E Table 22. Study Quality Ratings for Case Control Studies: Part 2

Study Author(s) (Year(s))	The Study Addresses an Appropriate and Clearly Focused Question	Cases and Controls Taken From Comparable Populations	The Same Exclusion Criteria Are Used for Both Cases and Controls	What percentage of each group (cases and controls) participated in the study?	Comparison Made Between Participants and Nonparticipants to Establish Similarities or Differences
Czeizel et al (1998)[131]	Yes	Yes	Can't say	Cases: 82% Controls: 65%	Yes

Appendix E Table 23. Study Quality Ratings for Case Control Studies: Part 3

Study Author(s) (Year(s))	Cases Are Clearly Defined and Differentiated From Control	It Is Clearly Established That Controls are Noncases	Measures Taken to Prevent Knowledge of Primary Exposure Influencing Case Ascertainment	Exposure Status Is Measured in a Standard, Valid and Reliable Way	Main Potential Confounders Are Identified and Considered in Design and Analysis	Confidence Intervals Are Provided
Czeizel et al (1998)[131]	Yes	Yes	Yes	No	Cannot say	Yes

Appendix E Table 24. Study Quality Ratings for Meta-Analyses: Part 1

Study Author(s) (Year(s))	Overall Study Quality	Rationale for Study Quality
Burtin et al (1995)[133]	Fair	No review protocol, no information about how studies were selected and data abstracted, no risk of bias assessment for included studies; this is an older review and methods for conducting and reporting systematic reviews were not as robust as they are now.
Caro-Paton et al (1997)[134]	Fair	No review protocol, no information about how studies were selected and data abstracted, no risk of bias assessment for included studies; this is an older review and methods for conducting and reporting systematic reviews were not as robust as they are now.

Appendix E Table 25. Study Quality Ratings for Meta-Analyses: Part 2

Study Author(s) (Year(s))	Did the review adhere to predefined objectives and eligibility criteria?	Were the eligibility criteria appropriate for the review question?	Were eligibility criteria unambiguous?	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, sample size, study quality, outcomes measured)?	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Concerns Regarding Specification of Study Eligibility Criteria
Burtin et al (1995)[133]	No information	Yes	Yes	Unclear or some concerns	Very little information to judge	Low
Caro-Paton et al (1997)[134]	No information	Yes	Yes	Unclear or some concerns	Very little information to judge	Low

Appendix E Table 26. Study Quality Ratings for Meta-Analyses: Part 3

Study Author(s) (Year(s))	Did the review search an appropriate range of databases/electronic sources for published and unpublished reports?	Were methods additional to database searching used to identify relevant reports?	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Were restrictions based on date, publication format, or language appropriate?	Were efforts made to minimize error in selection of studies?	Concerns Regarding Methods Used to Identify and/or Select Studies
Burtin et al (1995)[133]	Yes	Yes	Probably no	Probably yes	No information	Unclear or some concerns
Caro-Paton et al (1997)[134]	Yes	Yes	Probably yes	Probably yes	No information	Unclear or some concerns

Appendix E Table 27. Study Quality Ratings for Meta-Analyses: Part 4

Study Author(s) (Year(s))	Were efforts made to minimize error in data collection?	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Were all relevant study results collected for use in the synthesis?	Was risk of bias (or methodological quality) formally assessed using an appropriate tool?	Were efforts made to minimize error in risk of bias assessment?	Concerns Regarding Methods Used to Collect Data and Appraise Studies
Burtin et al (1995)[133]	No information	Probably yes	No information	No	No information	Unclear or some concerns
Caro-Paton et al (1997)[134]	No information	Probably yes	No information	No	No information	Unclear or some concerns

Appendix E Table 28. Study Quality Ratings for Meta-Analyses: Part 5

Study Author(s) (Year(s))	Did the synthesis include all studies that it should?	Were all pre-defined analyses reported or departures explained?	Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Were the findings robust, e.g. as demonstrated through sensitivity analyses?	Were biases in primary studies minimal or addressed in the synthesis?	Concerns Regarding the Synthesis
Burtin et al (1995)[133]	Probably yes	No information	Probably yes	Probably yes	Yes	Yes	Unclear or some concerns
Caro-Paton et al (1997)[134]	Probably yes	No information	Probably yes	Probably yes	No information	Yes	Unclear or some concerns

Appendix E Table 29. Study Quality Ratings for Meta-Analyses: Part 6

Study Author(s) (Year(s))	Did the interpretation of findings address all of the concerns identified in all domains?	Was the relevance of identified studies to the review's research question appropriately considered?	Did the reviewers avoid emphasizing results on the basis of their statistical significance?
Burtin et al (1995)[133]	No information	Yes	Yes
Caro-Paton et al (1997)[134]	No information	Yes	Yes

Appendix F Figure 2. Forest Plot of Diagnostic Test Accuracy Studies Evaluating the BD Affirm VPIII Test

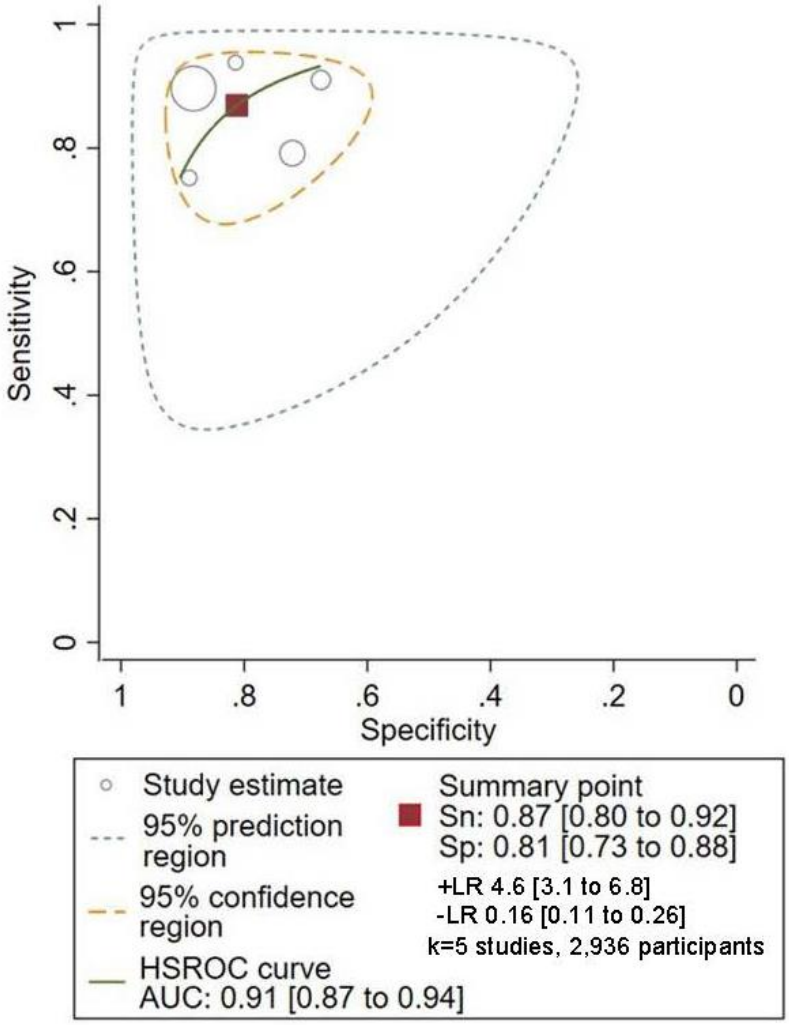
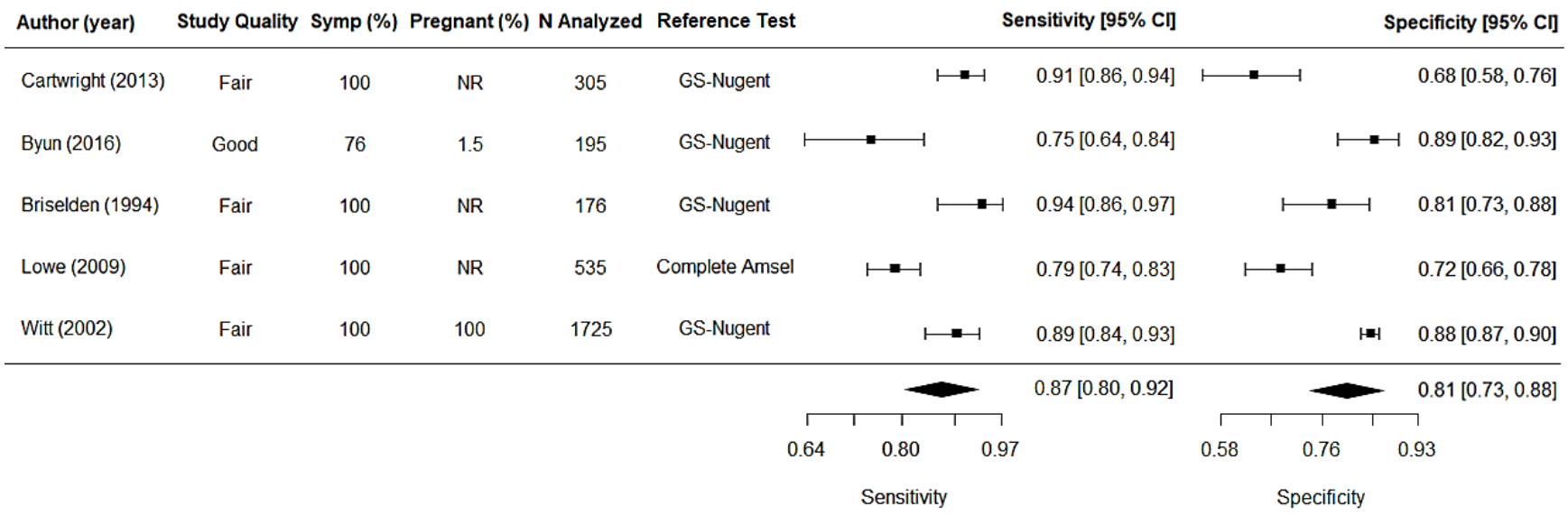


Figure Notes: The 95 percent confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling variation (i.e., chance). It is the region within which we expect the true pooled summary point to lie. It can be used to assess precision of the pooled estimate. The smaller the region, the more precise the estimate. In this figure, precision of the estimates for sensitivity and specificity is similar. The 95 percent prediction region provides a visual estimate of the between-study variability that cannot be attributed to chance. It is the region within which we expect any future individual study estimate to lie. It can be used to assess the consistency of study findings. The larger the prediction region is within the SROC space and relative to the size of the confidence region, the more inconsistency (i.e., heterogeneity) is present. In this example, the prediction region covers nearly one third of the SROC space and is about three times larger relative to the confidence region, suggesting at least moderate heterogeneity beyond what we would expect from chance alone. However, the prediction region is symmetric, suggesting inconsistency in both the sensitivity and specificity estimates.

Abbreviations: AUC=area under the curve; HSROC=hierarchical summary receiver operating characteristic; Sn=sensitivity; Sp=specificity.

Appendix F Figure 2. Forest Plot of Diagnostic Test Accuracy Studies Evaluating the BD Affirm VPIII Test



Abbreviations: CI=confidence interval; GS=Gram stain; NR=not reported; Symp=symptomatic.

Appendix F Figure 3. Summary Receiver Operating Characteristics Curve for Complete Amsel's Clinical Criteria Compared With Gram Stain

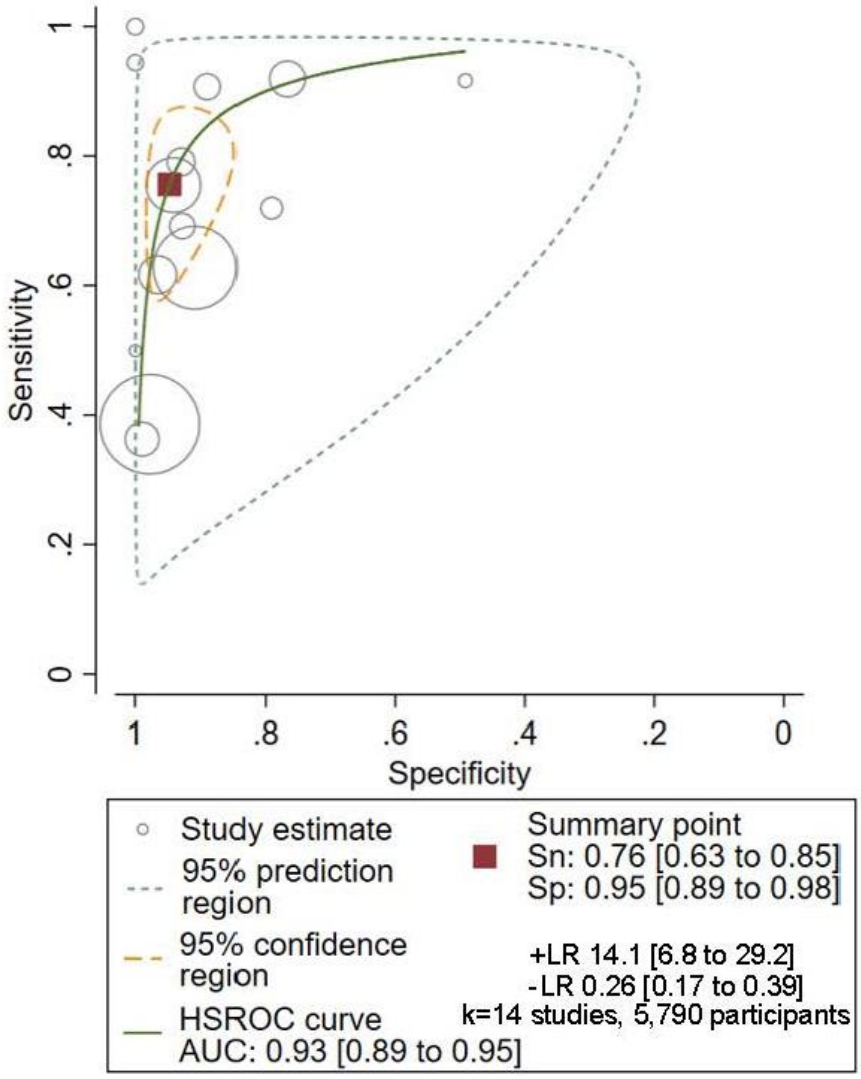


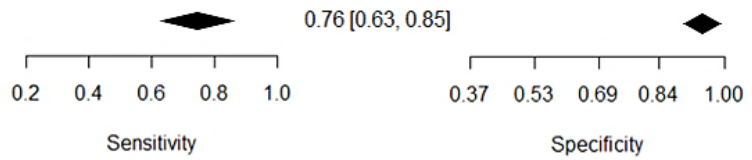
Figure Notes: The 95 percent confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling variation (i.e., chance). It is the region within which we expect the true pooled summary point to lie. It can be used to assess precision of the pooled estimate. The smaller the region, the more precise the estimate. In this figure, the estimate for specificity is more precise than the estimate for sensitivity as indicated by the region being elongated in the vertical direction relative to the horizontal direction.

The 95 percent prediction region provides a visual estimate of the between-study variability that cannot be attributed to chance. It is the region where we expect any future individual study estimate to lie. It can be used to assess the consistency of study findings. The larger the prediction region is within the SROC space and relative to the size of the confidence region, the more inconsistency (i.e., heterogeneity) is present. In this example, the prediction region covers over one third of the SROC space and is substantially larger relative to the confidence region, suggesting moderate to substantial heterogeneity beyond what we would expect from chance alone..

Abbreviations: AUC=area under the curve; HSROC=hierarchical summary receiver operating characteristic; Sn=sensitivity; Sp=specificity.

Appendix F Figure 4. Forest Plot of Diagnostic Test Accuracy Studies Evaluating Complete Amsel's Clinical Criteria Compared With Gram Stain

Author (year)	Study Quality	Symp (%)	Pregnant (%)	N Analyzed	Reference Test	Sensitivity [95% CI]	Specificity [95% CI]
Bradshaw (2005)	Fair	100	0	288	GS-Nugent	0.91 [0.84, 0.95]	0.89 [0.83, 0.93]
Chen (2018)	Fair	NR	0	77	GS-Nugent	0.92 [0.65, 0.99]	0.49 [0.37, 0.61]
Gallo (2011)	Fair	NR	NR	421	GS-Nugent	0.63 [0.60, 0.66]	0.91 [0.89, 0.92]
Gratacos (1999)	Good	0	100	492	GS-Nugent	0.36 [0.20, 0.57]	0.99 [0.98, 1.00]
Gutman (2005)	Fair	45	13	269	GS-Nugent	0.69 [0.60, 0.77]	0.93 [0.88, 0.96]
Hay (1992)	Good	2.6	NR	114	GS-Spiegel	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]
Hilmarsdottir (2006)	Fair	NR	NR	327	GS-Nugent	0.79 [0.71, 0.86]	0.93 [0.89, 0.96]
Landers (2004)	Fair	100	0	548	GS-Nugent	0.92 [0.88, 0.95]	0.77 [0.71, 0.81]
Myziuk (2003)	Fair	54	0	57	GS-Nugent	0.50 [0.25, 0.75]	1.00 [0.92, 1.00]
Platz-Christensen (1995)	Good	NR	0	107	GS-Spiegel	0.94 [0.82, 0.98]	1.00 [0.95, 1.00]
Schwebke (1996)	Fair	NR	NR	617	GS-Nugent	0.62 [0.55, 0.68]	0.97 [0.94, 0.98]
Schwebke (2018)	Fair	100	NR	1301	GS-Nugent	0.76 [0.72, 0.78]	0.94 [0.92, 0.96]
Sha (2007)	Fair	NR	NR	975	GS-Nugent	0.39 [0.36, 0.41]	0.98 [0.97, 0.98]
Singh (2013)	Fair	100	0	197	GS-Nugent	0.72 [0.64, 0.79]	0.79 [0.68, 0.87]
						0.76 [0.63, 0.85]	0.95 [0.89, 0.98]



Abbreviations: CI=confidence interval; GS=Gram stain; N=number of participants; NR=not reported; Symp=symptomatic.

Appendix F Figure 5. Summary Receiver Operating Characteristics Curve for Diagnostic Test Accuracy of Modified Amsel's Clinical Criteria

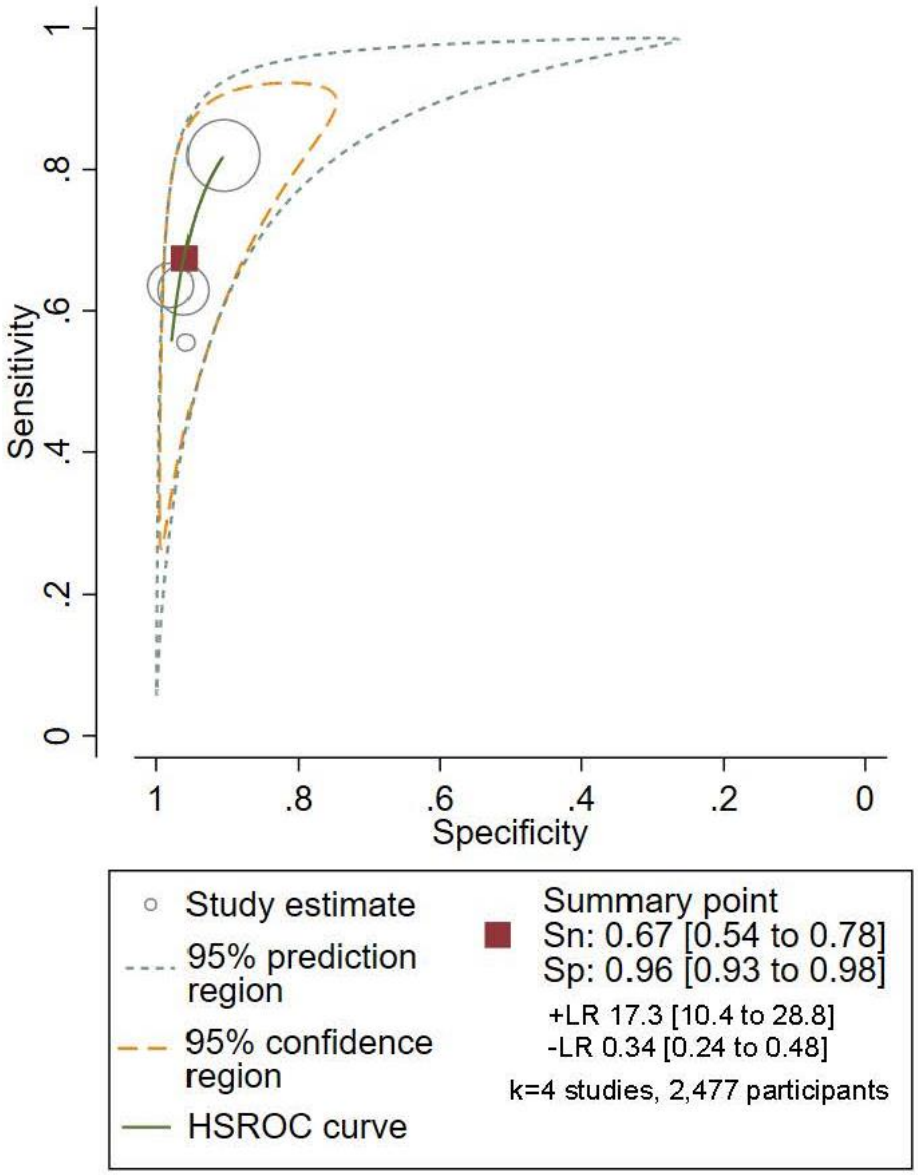
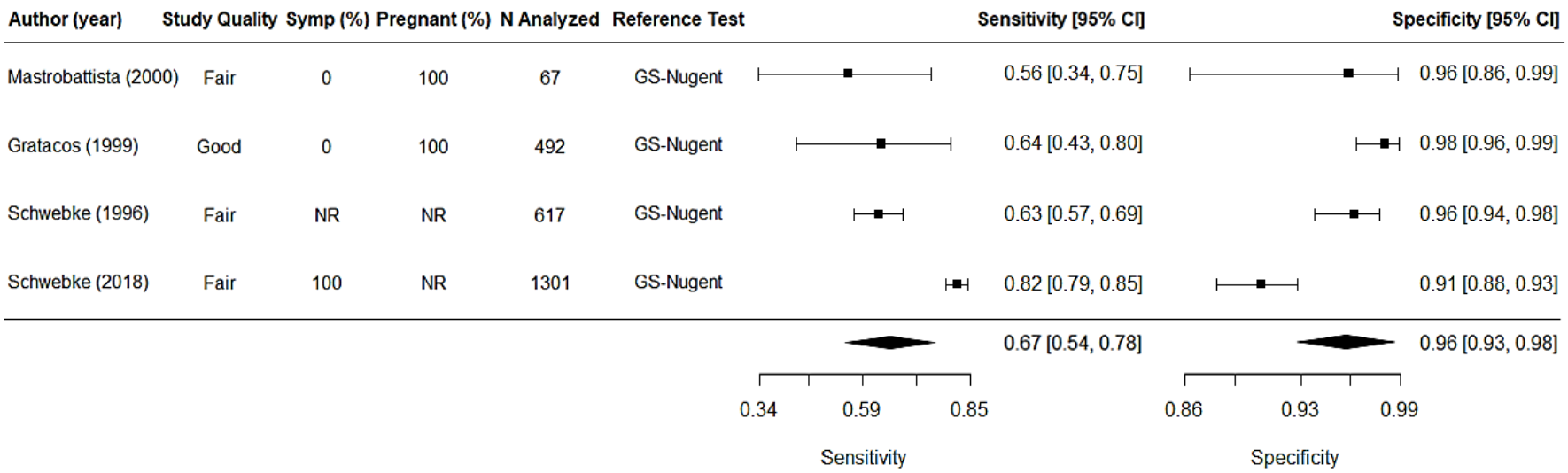


Figure Notes: The 95 percent confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling variation (i.e., chance). It is the region within which we expect the true pooled summary point to lie. It can be used to assess precision of the pooled estimate. The smaller the region, the more precise the estimate. In this figure, precision of the estimates for specificity is higher compared with the precision of the estimates for sensitivity. The 95 percent prediction region provides a visual estimate of the between-study variability that cannot be attributed to chance. It is the region within which we expect any future individual study estimate to lie. It can be used to assess the consistency of study findings. The larger the prediction region is within the SROC space and relative to the size of the confidence region, the more inconsistency (i.e., heterogeneity) is present. In this example, the prediction region covers only about one fifth of the SROC space and is only somewhat larger than the confidence region, suggesting no more than a small amount of heterogeneity beyond what we would expect from chance alone. However, the region it spans implies that a future study with high sensitivity/low specificity is equally likely as a study with low sensitivity/high specificity.

Abbreviations: HSROC=hierarchical summary receiver operating characteristic; Sn=sensitivity; Sp=specificity.

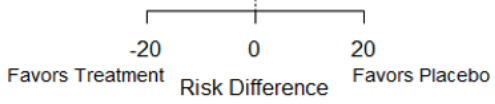
Appendix F Figure 6. Forest Plot of Diagnostic Test Accuracy Studies Evaluating Modified Amsel's Clinical Criteria



Abbreviations: CI=confidence interval; GS=Gram stain; N=Number of participants; NR=not reported; Symp=symptomatic.

Appendix G Figure 1. Initial Analysis of Treatment Effect (Absolute Risk Difference) on Preterm Delivery Unstratified by Outcome in General Obstetric Population

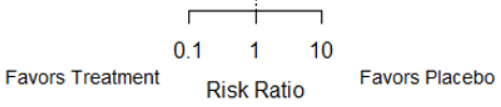
Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Difference [95% CI]
Carey (2000)	Good	1919	10.9	OM	All-cause delivery <37 weeks	12.5	-0.35 [-3.30, 2.59]
Guaschino (2003)	Good	100	7.1	VC	All-cause delivery <37 weeks	15.7	-3.44 [-17.00, 10.12]
Larsson (2006)	Fair	819	7.6	VC	All-cause delivery <37 weeks	6.1	-0.94 [-4.09, 2.22]
McDonald (1997)	Good	480	5.2	OM	All-cause delivery <37 weeks	7.6	-0.95 [-5.54, 3.64]
McGregor (1994)	Good	129	10.9	VC	All-cause delivery <37 weeks	7.3	7.75 [-3.16, 18.66]
Subtil (2018)	Good	2860	1.6	OC	All-cause delivery from 22 to 37 weeks	5.9	0.86 [-1.00, 2.73]
Kekki (2001)	Good	375	0	VC	Spontaneous delivery <37 weeks	3.7	1.09 [-3.00, 5.18]
Kiss (2004)	Fair	351	3.3	VC	Spontaneous delivery <37 weeks	5.7	-2.25 [-6.61, 2.10]
Lamont (2003)	Good	391	7.20	VC	Spontaneous delivery <37 weeks	9.8	-5.80 [-10.82, -0.79]
Ugwumadu (2003)	Good	410	9.3	OC	Spontaneous delivery from 24 to 37 weeks	15.3	-9.96 [-15.77, -4.14]



Abbreviations: CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; VC=intravaginal clindamycin.

Appendix G Figure 2. Initial Analysis of Treatment Effect (Risk Ratio) on Preterm Delivery Unstratified by Outcome in General Obstetric Population

Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Ratio [95% CI]
Carey (2000)	Good	1919	10.9	OM	All-cause delivery <37 weeks	12.5	0.97 [0.77, 1.23]
Guaschino (2003)	Good	100	7.1	VC	All-cause delivery <37 weeks	15.7	0.78 [0.29, 2.09]
Larsson (2006)	Fair	819	7.6	VC	All-cause delivery <37 weeks	6.1	0.85 [0.48, 1.49]
McDonald (1997)	Good	480	5.2	OM	All-cause delivery <37 weeks	7.6	0.87 [0.46, 1.67]
McGregor (1994)	Good	129	10.9	VC	All-cause delivery <37 weeks	7.3	2.07 [0.73, 5.84]
Subtil (2018)	Good	2860	1.6	OC	All-cause delivery from 22 to 37 weeks	5.9	1.15 [0.85, 1.56]
Kekki (2001)	Good	375	0	VC	Spontaneous delivery <37 weeks	3.7	1.29 [0.49, 3.40]
Kiss (2004)	Fair	351	3.3	VC	Spontaneous delivery <37 weeks	5.7	0.60 [0.22, 1.62]
Lamont (2003)	Good	391	7.20	VC	Spontaneous delivery <37 weeks	9.8	0.41 [0.18, 0.92]
Ugwumadu (2003)	Good	410	9.3	OC	Spontaneous delivery from 24 to 37 weeks	15.3	0.35 [0.18, 0.67]



Abbreviations: CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; VC=intravaginal clindamycin.

Appendix G Figure 3. Absolute Risk Difference of Various Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among a General Obstetric Population

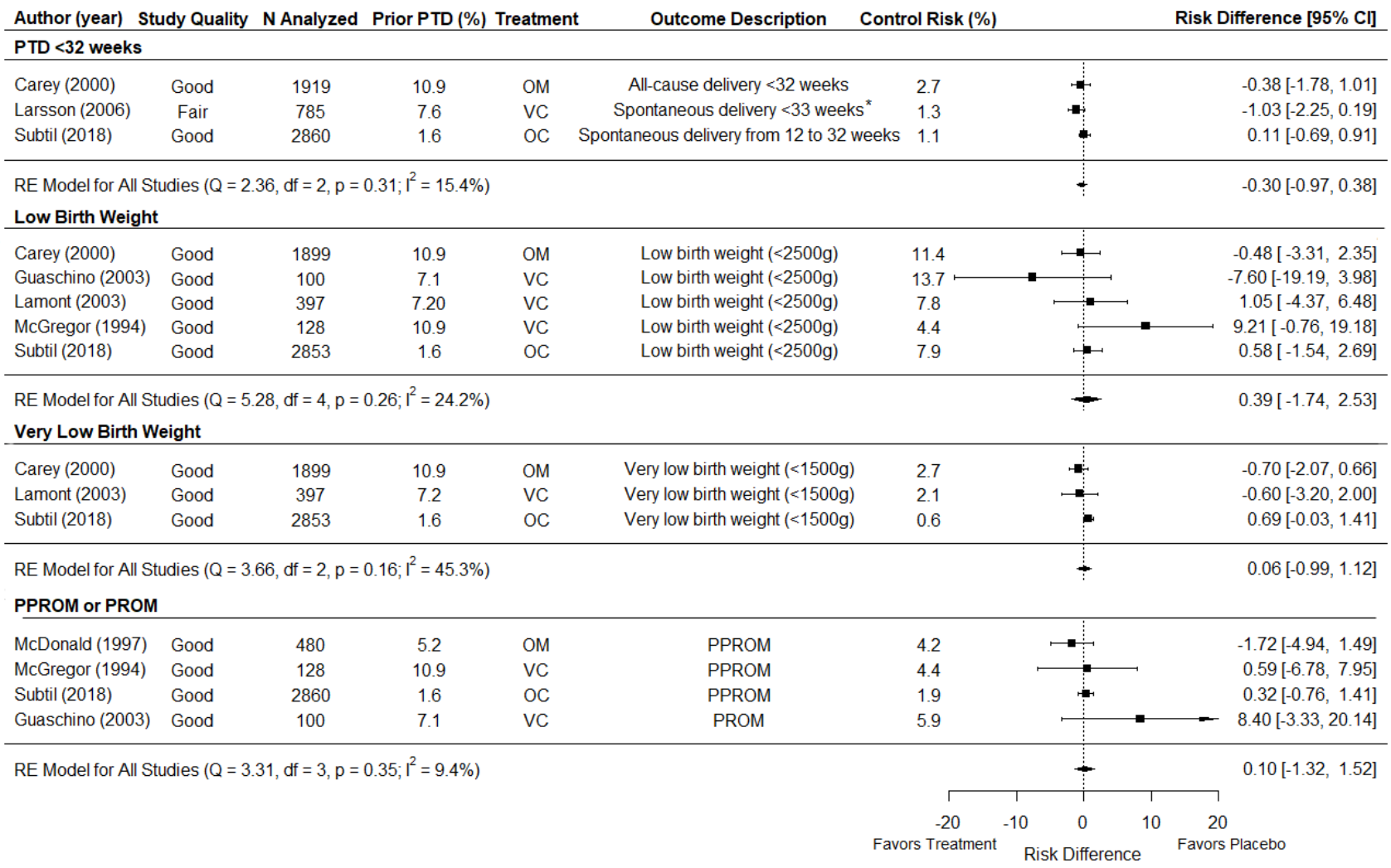


Figure Note * Includes spontaneous late abortion (≥16 weeks).

Abbreviations: CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PPROM=preterm premature rupture of membranes; PROM=premature rupture of membranes; PTD=preterm delivery; RE=random effects; VC=intravaginal clindamycin.

Appendix G Figure 4. Risk Ratio for Various Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among a General Obstetric Population

Author (year)	Study Quality	N Analyzed	Prior PTD (%)	Treatment	Outcome Description	Control Risk (%)	Risk Ratio [95% CI]
PTD <32 weeks							
Carey (2000)	Good	1919	10.9	OM	All-cause delivery <32 weeks	2.7	0.86 [0.49, 1.50]
Larsson (2006)	Fair	785	7.6	VC	Spontaneous delivery <33 weeks*	1.3	0.20 [0.02, 1.68]
Subtil (2018)	Good	2860	1.6	OC	Spontaneous delivery from 12 to 32 weeks	1.1	1.10 [0.53, 2.32]
RE Model for All Studies (Q = 2.24, df = 2, p = 0.33; I^2 = 10.6%)							0.87 [0.54, 1.42]
Low Birth Weight							
Carey (2000)	Good	1899	10.9	OM	Low birth weight (<2500g)	11.4	0.96 [0.74, 1.23]
Guaschino (2003)	Good	100	7.1	VC	Low birth weight (<2500g)	13.7	0.45 [0.12, 1.63]
Lamont (2003)	Good	397	7.20	VC	Low birth weight (<2500g)	7.8	1.14 [0.59, 2.19]
McGregor (1994)	Good	128	10.9	VC	Low birth weight (<2500g)	4.4	3.12 [0.87, 11.22]
Subtil (2018)	Good	2853	1.6	OC	Low birth weight (<2500g)	7.9	1.07 [0.83, 1.40]
RE Model for All Studies (Q = 4.97, df = 4, p = 0.29; I^2 = 19.5%)							1.03 [0.83, 1.29]
Very Low Birth Weight							
Carey (2000)	Good	1899	10.9	OM	Very low birth weight (<1500g)	2.7	0.74 [0.41, 1.33]
Lamont (2003)	Good	397	7.2	VC	Very low birth weight (<1500g)	2.1	0.71 [0.16, 3.13]
Subtil (2018)	Good	2853	1.6	OC	Very low birth weight (<1500g)	0.6	2.10 [0.86, 5.09]
RE Model for All Studies (Q = 3.88, df = 2, p = 0.14; I^2 = 48.5%)							1.05 [0.50, 2.18]
PPROM or PROM							
McDonald (1997)	Good	480	5.2	OM	PPROM	4.2	0.59 [0.22, 1.60]
McGregor (1994)	Good	128	10.9	VC	PPROM	4.4	1.13 [0.24, 5.41]
Subtil (2018)	Good	2860	1.6	OC	PPROM	1.9	1.17 [0.68, 2.02]
Guaschino (2003)	Good	100	7.1	VC	PROM	5.9	2.43 [0.67, 8.86]
RE Model for All Studies (Q = 2.99, df = NA, p = 0.39; I^2 = 0.0%)							1.11 [0.72, 1.72]

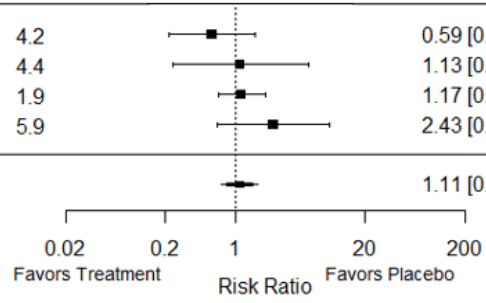
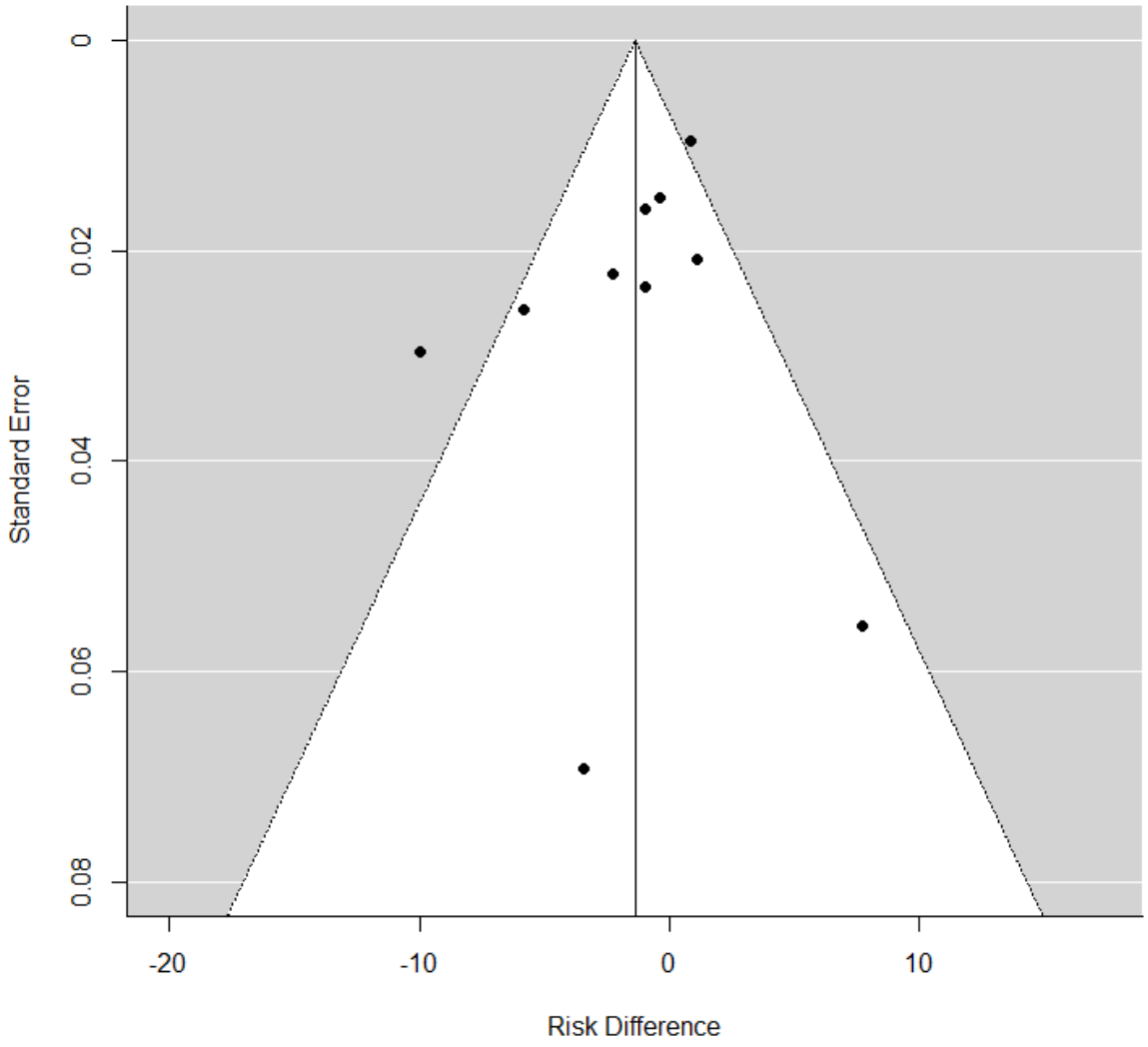


Figure Note: * Includes spontaneous late abortion (≥16 weeks).

Abbreviations: CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PPROM=preterm premature rupture of membranes; PROM=premature rupture of membranes; PTD=preterm delivery; RE=random effects; VC=intravaginal clindamycin.

Appendix G Figure 5. Funnel Plot of Pooled Estimate of Treatment Effect (Absolute Risk Difference) on Preterm Delivery at Unstratified by Outcome in General Obstetric Population



Appendix H Table 1. Likelihood Ratios and Post-Test Probabilities After Positive and Negative Tests

The purpose of this appendix is to provide a more nuanced assessment of test accuracy. We used the likelihood ratios reported by studies or that we calculated based on data reported in the studies to show the influence of a positive and negative test on the post-test probability of bacterial vaginosis. We assumed a pretest probability of 17.2 percent, which was the average prevalence of bacterial vaginosis among asymptomatic women evaluated for study entry into the RCTs evaluating the benefits of treatment (KQ 4).

Test	+LR	Post-test Probability After Positive Test	-LR	Post-test Probability After Negative Text
BD Affirm (pooled)	4.6	48.9%	0.16	3.2%
Lower 95% CL	3.1	39.2%	0.11	2.2%
Upper 95% CL	6.8	58.6%	0.26	5.1%
BD Max (Schwebke et al.)	10.9	69.4%	0.08	1.6%
Lower 95% CL	10.7	68.9%	0.08	1.6%
Upper 95% CL	11.1	69.8%	0.08	1.7%
BD Blue (Bradshaw et al)	6.3	56.6%	0.14	2.8%
Lower 95% CL	5.8	54.6%	0.13	2.7%
Upper 95% CL	6.6	58.0%	0.15	3.0%
BD Blue (Hillier et al)	61	92.7%	0.39	7.6%
Lower 95% CL	51	91.4%	0.39	7.5%
Upper 95% CL	72	93.7%	0.41	7.8%
BD Blue (Myziuk et al)	41.7	89.6%	0.09	1.7%
Lower 95% CL	29.6	86.0%	0.08	1.7%
Upper 95% CL	45.5	90.4%	0.09	1.9%
Complete Amsel's clinical criteria (pooled)	14.1	61.0%	0.26	2.8%
Lower 95% CL	6.8	58.6%	0.17	3.4%
Upper 95% CL	29.2	85.8%	0.39	7.5%
Modified Amsel's clinical criteria (pooled)	17.3	78.2%	0.34	6.6%
Lower 95% CL	10.4	68.4%	0.24	4.7%
Upper 95% CL	28.8	85.7%	0.48	9.1%

Table Notes: Positive likelihood ratios greater than 10 and negative likelihood ratios less than 0.1 have been suggested as thresholds for indicating an accurate test that will result in clinically useful changes to the pretest probability. However, such universally applied thresholds do not take into account differences in pretest probability. A very rare condition may need a positive likelihood ratio much higher than 10 to result in a meaningful increase in the probability of disease after a positive test that would result in a decision to treat, and likewise a very common condition may need a negative likelihood ratio much lower than 0.1 to result in a meaningful decrease in the probability of disease after a negative test that would result in a decision not to treat.[82, 202]

Abbreviations: CL = confidence limit; LR = likelihood ratio.