

## **Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery**

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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 December 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 and specificity varied by test: BD Affirm (pooled sensitivity, 0.87 [95% confidence interval {CI}, 0.80 to 0.92], pooled specificity, 0.81 [95% CI, 0.73 to 0.88]; 5 studies; 2,936 participants), BD Max (sensitivity, 0.93 [95% CI, 0.91 to 0.94]; specificity, 0.92 [95% CI, 0.90 to 0.94]; 1 study; 1,338 participants), BVBLUE (sensitivity range, 0.61 to 0.92; specificity range, 0.86 to 0.99; 3 studies; 864 participants), Amsel's clinical criteria (pooled sensitivity, 0.76 [95% CI, 0.63 to 0.85]; pooled specificity, 0.95 [95% CI, 0.89 to 0.98]; 14 studies; 5,790 participants), and modified Amsel's clinical criteria (pooled sensitivity, 0.67 [95% CI, 0.54 to 0.78]; pooled specificity, 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 meta-analyses observed similar results. One cohort study reported no increased incidence of childhood cancer among exposed children (adjusted relative risk, 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; across individual studies the sensitivity of the various tests ranged from 0.36 to 1.0 and the specificity ranged from 0.49 to 1.0. 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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# 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.<sup>1</sup> 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.<sup>2,3</sup>

## 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.<sup>4,5</sup> *Lactobacillus* species comprise between 90 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.<sup>6,7</sup> 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.<sup>8</sup> 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.<sup>9</sup>



# 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.<sup>10</sup> The prevalence of bacterial vaginosis in the United States is estimated to be 29.2 percent among all women ages 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.<sup>11</sup> Prevalence varies most notably by race/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%).<sup>11</sup> 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.<sup>12</sup> 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/ethnicities.<sup>13</sup>

Studies conducted between 1983 and 2006 estimate that only 25 to 50 percent of women with bacterial vaginosis report symptoms.<sup>14-16</sup> Disease recurrence within 12 months of treatment occurs in more than 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.<sup>17</sup> In symptomatic women, studies have shown that recurrent bacterial vaginosis is associated with a significant adverse effect on self-esteem, sexual relationships, and quality of life.<sup>18</sup> 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).<sup>19</sup> 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]),<sup>20</sup> pregnancy loss before 22 weeks (RR range, 3.1 [95% CI, 1.4 to 6.9]),<sup>21</sup> pelvic inflammatory disease (magnitude not well defined),<sup>22</sup> postabortion sepsis (magnitude not well defined),<sup>23</sup> postpartum endometritis (odds ratio [OR], 5.8 [95% CI, 3.0 to 10.9]),<sup>24</sup> and low birth weight (OR, 1.4 [95% CI, 1.1 to 1.8]).<sup>25</sup>

## Preterm Delivery

Worldwide, an estimated 11.1 percent (14.9 million) of all live births in 2010 were preterm.<sup>26</sup> 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.<sup>27-30</sup> 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.<sup>27</sup> Preterm birth rates vary by race/ethnicity 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 Indian or Alaska Native women, 14.1 percent among black women, and 9.1 percent among white women.<sup>29</sup> 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 to 64.1 percent of preterm deliveries, preterm PROM (PPROM) was reported as the etiology in 7.1 to 51.2 percent of preterm deliveries, and medical indication was reported in 18.7 to 35.2 percent of preterm deliveries.<sup>31</sup>

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.<sup>32</sup> The vast majority (84%) of all preterm deliveries occur between 32 and 37 weeks.<sup>33</sup> 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.<sup>34</sup>

## Etiology and Risk Factors

### Bacterial Vaginosis

Bacterial vaginosis is caused by a disruption of the microbiotic environment in the lower genital tract.<sup>35</sup> 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.<sup>7</sup> *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.<sup>6,7</sup> *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.<sup>36</sup> Bacterial vaginosis is characterized by a marked depletion of *Lactobacillus* species and a 1,000-fold increase in the number of anaerobic bacteria.<sup>6,7</sup> Although it was previously thought that the *Gardnerella* species was the defining organism, multiple anaerobic bacteria, including *Gardnerella*, *Prevotella*, *Atopobium*, *Megasphaera*, and others, have been identified.<sup>37,38</sup> In some women with bacterial vaginosis, up to 35 unique species have been identified.<sup>38</sup> 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.<sup>38</sup> 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.<sup>38-40</sup> 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,<sup>11, 35, 41</sup> this may be due to varying study definitions of sex (only penetrative or including nonpenetrative sex) and bias surrounding self-reporting.<sup>42-44</sup> 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).<sup>45</sup> The RR for incident bacterial vaginosis associated with having a new sexual partner is 1.13 (95% CI, 1.02 to 1.25).<sup>45</sup> 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.<sup>17</sup>

Race/ethnicity is also a significant risk for bacterial vaginosis; African American women have the highest prevalence and non-Hispanic white women have the lowest prevalence.<sup>11</sup> Some have postulated this difference could be explained by genetics, socioeconomic status, psychosocial stress, or sexual networks.<sup>7, 46, 47</sup> Research on the relationship between vaginal pH and microbiota also suggests some underlying racial/ethnic variation in microbiota composition.<sup>48</sup> 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.<sup>48</sup> 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.<sup>49</sup> Other factors associated with bacterial vaginosis include poverty, smoking, increased body mass index, vaginal douching, and low educational attainment.<sup>12</sup>

## 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).<sup>50</sup> **Appendix A** (Contextual Questions [CQs] 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, PPRM, or both.<sup>25, 51</sup> More recent research suggests a more complicated etiology. The mucosal immune response, which is influenced by many factors, including genetics, race/ethnicity, stress, hormones, and the vaginal microbiome, may influence both the risk for acquiring bacterial vaginosis and preterm labor or PPRM.<sup>46</sup> 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.<sup>50, 52</sup>

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.<sup>53</sup>

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.<sup>54</sup> 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]),<sup>55</sup> 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 at less than 33 weeks of gestation (RR, 0.62 [95% CI, 0.47 to 0.81]).<sup>56</sup>

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/ethnicity.<sup>34, 51, 52, 57</sup> Other factors that increase the risk of spontaneous preterm delivery include extreme psychosocial stress,<sup>58</sup> excessive physical strain and exhaustion,<sup>59</sup> smoking,<sup>60</sup> and periodontal disease.<sup>61</sup>

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.<sup>52</sup> Researchers have hypothesized that racial/ethnic differences in preterm delivery incidence are partly due to commensurate racial/ethnic differences in bacterial vaginosis prevalence.<sup>62</sup>

## Rationale for Screening/Screening Strategies

The rationale for screening for bacterial vaginosis in asymptomatic pregnant women 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 of 7 to 10 indicate bacterial vaginosis.<sup>63, 64</sup> Additional information about intermediate flora is in **Appendix A** (CQs 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.<sup>38, 64</sup>

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 *T. vaginalis* and *Candida* species. The BD Affirm Vaginal Panel III (Becton, Dickinson and Co., Franklin Lakes, NJ) 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, *G. vaginalis*, *Atopobium vaginae*, Bacterial Vaginosis Associated Bacteria-2 (BVAB-2), and *Megasphaera*-1.<sup>65</sup> Several other multiplex PCR assays are commercially available (NuSwab [LabCorp, Burlington, NC], SureSwab [Quest Diagnostics, Secaucus, NJ]) 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. AmpliSens Florocenosis-BV (InterLabService, Moscow, Russia) is approved for use in the European Union but is not FDA approved.<sup>66, 67</sup> Assays that detect elevated vaginal fluid sialidase activity (OSOM BVBLUE [Sekisui Diagnostics, Burlington, MA], FDA approved) associated with vaginosis and pH paper-coated vaginal swabs (VS-SENSE Pro [McKesson, Irving, TX], FDA approved) to detect alterations in vaginal pH commonly seen with bacterial vaginosis are also available.<sup>65, 68-72</sup>

## 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.<sup>15</sup>

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.<sup>17, 73</sup> 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.<sup>17, 74</sup> 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. Nutraceuticals 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** (CQ 5).

## Current Clinical Practice

**Appendix A Table 3** summarizes recommendations of professional organizations related to screening for bacterial vaginosis in asymptomatic women in pregnancy. 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 clinicians with regard to screening for bacterial vaginosis; this information is summarized in **Appendix A** (CQ 4).

# Chapter 2. Methods

## Key Questions and Analytic Framework

The Evidence-based Practice Center 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/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 STIs, 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/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 STIs, 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 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.<sup>2,3</sup> Because the previous reviews on this topic for the USPSTF did not include a systematic search for KQ 2 (diagnostic test accuracy), we conducted a separate PubMed search from inception through December 31, 2005, to supplement our main search for this update. 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 December 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.<sup>75</sup> 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.<sup>76</sup> 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.<sup>77</sup>

For case-control studies, we used a methodology checklist from the Scottish Intercollegiate Guidelines Network.<sup>78</sup> For systematic reviews and meta-analyses, we used the ROBIS instrument to assess methodological quality.<sup>79</sup> For studies of diagnostic test accuracy, we used the QUADAS-2 instrument.<sup>80</sup> 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<sup>81</sup> 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.<sup>82</sup> 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.<sup>82, 83</sup> 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 (ARDs) 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,<sup>84</sup> 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).<sup>85</sup> 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.<sup>76</sup> We considered pooled findings statistically significant when the 95% CIs excluded the null value. 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.<sup>86</sup> 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.<sup>83, 86</sup> 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-positive and false-negative results).<sup>82</sup> For these SOE assessments, we started all ratings at a “high.”<sup>87</sup> 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 CI 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 CIs 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.

## **USPSTF Involvement**

This review was funded by AHRQ. AHRQ staff 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.

## **Expert Review and Public Comment**

The draft Research Plan was posted for public comment on the USPSTF Web site from February 22, 2018, to March 21, 2018. In response to public comments, the USPSTF added additional subpopulations for assessing variation in benefits and harms of screening and treatment. In addition, the USPSTF clarified terminology related to populations, screening tests, interventions, and comparators in the Research Plan. A final Research Plan was posted on the USPSTF's Web site on May 17, 2018.

A draft version of this report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate.

A draft version of this evidence report was posted for public comment on the USPSTF Web site from October 8, 2019, to November 4, 2019. A few comments were received, but no changes were made to the evidence or to our conclusions.

## 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 (KQ 2)

Twenty-five cross-sectional diagnostic test accuracy studies reported test accuracy for BD Affirm, BD Max, BVBLUE, and Amsel's clinical criteria (complete, modified, or individual components). Two of these studies (Gratacos et al<sup>88</sup> and Mastrobattista et al<sup>89</sup>) were discussed in the previous update as part of a CQ; the rest are new to this update. **Table 1** provides study characteristics and **Tables 2–6** provide results organized by test. **Appendix E Tables 1–6** provide our assessment of individual study methodological quality. We assessed six studies as good methodological quality,<sup>88, 90-94</sup> 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 VPIII microbial identification test, which is a nonamplified nucleic acid probe-based test specific to *G. vaginalis* and *T. vaginalis*.<sup>90, 95-98</sup> One study (Witt et al) was performed exclusively in a population of pregnant women.<sup>98</sup> Four studies (Briselden et al,<sup>96</sup> Cartwright et al,<sup>95</sup> Lowe et al,<sup>97</sup> and Witt et al<sup>98</sup>) exclusively enrolled symptomatic women, and 76 percent of the study population in the fifth study (Byun et al<sup>90</sup>) was symptomatic. Briselden et al<sup>96</sup> and Cartwright et al<sup>95</sup> recruited participants from STI clinics in the United States. Lowe et al recruited participants from U.S. military health clinics.<sup>97</sup> Byun et al<sup>90</sup> recruited participants from a hospital-based outpatient gynecology clinic in South Korea, and Witt et al<sup>98</sup> 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<sup>96</sup> 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<sup>97</sup> 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 to 64.6 percent. We assessed Byun et al<sup>90</sup>

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 due to 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.<sup>65, 99</sup> In this study, reported in Schwebke et al<sup>99</sup> and Gaydos et al,<sup>65</sup> 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 status, 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.

## BVBLUE

Three cross-sectional diagnostic test accuracy studies conducted among 864 participants reported test accuracy characteristics for the BVBLUE test, which is an assay of vaginal secretions for sialidase enzyme activity.<sup>100-102</sup> Two studies (Bradshaw et al,<sup>100</sup> Hillier et al<sup>101</sup>) specifically excluded pregnant women; one study (Myziuk et al<sup>102</sup>) did not report the pregnancy status of enrolled women. Bradshaw et al<sup>100</sup> 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<sup>101</sup> recruited participants from a U.S. academic gynecology clinic and a local health department clinic, and Myziuk et al<sup>102</sup> 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,<sup>100</sup> 3.5 percent in Myziuk et al,<sup>102</sup> and not reported by Hillier et al.<sup>101</sup>

All studies used a Gram stain interpreted using the criteria of Nugent et al as the reference test. The prevalence of bacterial vaginosis based on the reference test used was 38 and 21.1 percent in two studies and was not reported in Hillier et al.<sup>101</sup> 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.<sup>101</sup>

**Table 4** provides results from individual studies. Bradshaw et al reported test accuracy characteristics of the BVBLUE 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).<sup>100</sup> 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.<sup>101</sup> 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.<sup>88, 91, 92, 99-110</sup> One study (Gratacos et al;<sup>88</sup> N=492) exclusively enrolled asymptomatic pregnant women, and one study (Gutman et al;<sup>109</sup> 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<sup>88</sup> and Hay et al<sup>91</sup>) 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.<sup>103, 106</sup> 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<sup>92</sup> and Hay et al<sup>91</sup>) 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 reference test used ranged from 4.5 to 63.5 percent across studies. We assessed three studies (Gratacos et al,<sup>88</sup> Hay et al,<sup>91</sup> and Platz-Christensen et al<sup>92</sup>) 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).<sup>88</sup> 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.<sup>101</sup> 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.<sup>101</sup>

## 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.<sup>88, 89, 99, 107, 108</sup> Study authors modified Amsel's clinical criteria by not including the criteria for the presence of vaginal discharge; all but one study<sup>108</sup> required two of three criteria to be present for a positive test. Two studies (Gratacos et al<sup>88</sup> and Mastrobattista et al<sup>89</sup>) exclusively enrolled asymptomatic pregnant women, and two studies (Singh et al<sup>107</sup> and Schwebke et al<sup>99</sup>) exclusively enrolled symptomatic women. All but one study<sup>88</sup> was conducted in the United States. Two studies enrolled participants from obstetric clinics;<sup>88, 89</sup> one study enrolled participants from a single STI clinic;<sup>107</sup> one study enrolled participants from academic and community-based STI, HIV, family planning, and generally gynecology clinics;<sup>65, 99</sup> and one study enrolled participants from STI and hospital-based gynecology clinics.<sup>108</sup> No studies reported the HIV status of enrolled participants and only one study reported race/ethnicity (Mastrobattista et al;<sup>89</sup> 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 to 63.5 percent across studies. We assessed the Gratacos et al<sup>88</sup> 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 in the only study conducted exclusively among symptomatic participants (Schwebke et al<sup>99</sup>); 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<sup>89</sup> and 0.64 in the other.<sup>88</sup> The specificities were similar (0.96 and 0.98, respectively).

Singh et al,<sup>107</sup> 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 1–4**.

## Benefits of Treatment (KQ 4)

Thirteen RCTs reported findings related to preterm delivery, other pregnancy outcomes, or clearance of bacterial vaginosis.<sup>111-123</sup> Data from two of these studies are new to this update; one study was published in 2018<sup>119</sup> and one study was previously included only for harms but has eligible data for benefits that we have now included.<sup>120</sup> 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<sup>124</sup> and the other in Indonesia.<sup>125</sup> In addition, we determined that one previously included study<sup>126</sup> was a companion article to another previously included study;<sup>113</sup> thus, we did not count the companion article as a separate study for this update. Seven trials were funded by nonprofit and government agencies,<sup>111, 114, 116, 117, 120, 121, 123</sup> two were funded by hospitals,<sup>118, 122</sup> one was funded by a pharmaceutical manufacturer,<sup>115</sup> one was funded by various government and commercial entities,<sup>113</sup> and the funding source was not reported by two studies.<sup>112, 119</sup> **Appendix E Tables 7–12** 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;<sup>111, 118, 121, 122</sup> the others were conducted in Australia<sup>117</sup> and Europe.<sup>112-116, 119, 120, 123</sup>

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 to 10.9 percent.<sup>111-120</sup> Two of these studies also reported findings among subgroups considered high risk for preterm delivery, which was defined as having a prior preterm delivery.<sup>111, 117</sup> Three studies were conducted solely among participants considered high risk for preterm delivery.<sup>121-123</sup> All three defined high risk as a previous preterm delivery; however, one study also considered women with a prepregnancy weight of less than 50 kg and no previous preterm delivery as high risk.<sup>121</sup> 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, although 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.<sup>111-113, 116-119, 122</sup> Five of these eight studies used Gram stain for diagnosis; four studies<sup>111, 116, 118, 119</sup> interpreted using Nugent's criteria, and one study interpreted using Spiegel's criteria.<sup>113</sup> One of these eight studies used complete Amsel's clinical criteria,<sup>122</sup> and the remaining two studies used other methods (morphotype screening on vaginal smear,<sup>112</sup> combination of culture for *Gardnerella* in conjunction with Gram stain<sup>117</sup>). The prevalence of bacterial vaginosis among the women tested for study entry ranged from 5.9 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,<sup>115, 120</sup> and one of these reported findings from the subgroup of participants with bacterial vaginosis not including intermediate flora.<sup>120</sup> 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<sup>114, 123</sup> and one using both Amsel's criteria and Gram stain). We report findings only from the subgroups with bacterial vaginosis for these studies.<sup>114, 121, 123</sup>

Three studies evaluated the use of oral metronidazole,<sup>111, 117, 122</sup> two studies evaluated oral clindamycin,<sup>119, 120</sup> one study evaluated oral metronidazole and erythromycin,<sup>121</sup> and seven evaluated intravaginal clindamycin.<sup>112-116, 118, 123</sup> 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,<sup>114, 117</sup> 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.<sup>111, 119, 123</sup>

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 preterm deliveries. In one study, spontaneous abortions occurring at 16 weeks or later were included as part of this outcome.<sup>116</sup> 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, PROM, and neonatal infection or mortality.

We assessed nine RCTs<sup>111-113, 115, 117-120, 123</sup> as good methodological quality and four RCTs<sup>114, 116, 121, 122</sup> 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,<sup>116</sup> lack of treatment blinding,<sup>114, 116</sup> post hoc subgroup analyses,<sup>114, 121</sup> or lack of intent to treat analyses.<sup>122</sup>

## Preterm Delivery

Twelve of the 13 RCTs<sup>111-122</sup> reported findings related to preterm delivery prior to 37 weeks gestational age; one RCT<sup>123</sup> 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 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).<sup>111, 112, 116-119</sup> 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).<sup>111, 113-117, 119, 120</sup> Two of the eight studies reported statistically significant reductions in spontaneous preterm delivery for active treatment compared with control,<sup>115, 120</sup> 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**).<sup>111, 116, 119</sup> 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,<sup>116, 119</sup> and one reported all-cause preterm delivery.<sup>111</sup> 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]).<sup>111</sup>

### **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 at less than 37 weeks,<sup>111, 117, 121, 122</sup> and one reported the incidence of preterm delivery at less than 34 weeks.<sup>123</sup>

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 to 57.1 percent (**Figures 5 and 6**).<sup>111, 117, 121, 122</sup> Carey et al<sup>111</sup> and Hauth et al<sup>121</sup> reported all-cause preterm delivery, and Morales et al<sup>122</sup> and McDonald et al<sup>117</sup> 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<sup>111</sup> 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.<sup>121</sup> McDonald et al used 800 mg daily for 2 days and repeated dosing at 28 weeks gestation if a test of cure remained positive.<sup>117</sup> 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).<sup>111</sup> All studies enrolled participants during the second trimester. Carey et al<sup>111</sup> enrolled participants based on a Gram stain interpreted according to the criteria of Nugent et al, while the other studies used other criteria (Amsel's clinical criteria alone,<sup>122</sup> Amsel's clinical criteria plus mixed flora using Spiegel's criteria on Gram stain,<sup>121</sup> or heavy growth of *G. vaginalis* or Gram stain with *G. vaginalis* and absence of lactobacilli<sup>117</sup>). Carey et al<sup>111</sup> enrolled the highest percentage of nonwhite participants (approximately 85%), but this percentage was reasonably similar to the percentage enrolled by Hauth et al<sup>121</sup> and Morales et al.<sup>122</sup> 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,<sup>111</sup> 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**).<sup>122, 123</sup> 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%]).<sup>122</sup> 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.<sup>123</sup>

### **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 a followup Gram stain after initial testing and treatment, Carey et al reported no difference in preterm delivery among women with clearance of bacterial vaginosis (incidence, 10.6%) vs. those with persistence of bacterial vaginosis (incidence, 10.7%).<sup>111</sup> 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%]).<sup>113</sup>

### **Other Subgroups**

Andrews et al (a companion article to the Carey et al RCT) reported no difference in preterm delivery at 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.<sup>111, 127</sup> No studies reported subgroup findings by maternal or gestational age, race/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 g 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 g. The pooled ARD for PROM was 0.10 percent (95% CI, -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,<sup>113</sup> stillborn fetus,<sup>114</sup> preterm labor,<sup>118</sup> and neonatal mortality.<sup>119</sup>

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 g (calculated ARD, -19.7% [95% CI, -38.13% to -1.26%]).<sup>122</sup> Vermeulen et al reported no significant treatment effect on neonatal sepsis.<sup>123</sup>

## 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.<sup>111</sup> 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.<sup>112</sup> 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%).<sup>122</sup>

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.<sup>113</sup> 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.<sup>115</sup> Significantly more participants who received intravaginal clindamycin had clearance or improvement, defined as a Nugent Gram stain score of 4 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.<sup>115</sup> 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).<sup>118</sup>

## Harms of Treatment (KQ 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,<sup>128</sup> reported on harms in women without bacterial vaginosis,<sup>121, 127</sup> or reported a single adverse event (AE) but did not attribute it to a specific group.<sup>112</sup> 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;<sup>111, 113, 114, 116, 117, 119, 120, 123</sup> four of these studies are new to this update. One was published in 2018<sup>119</sup> and three were previously included only for benefits but have eligible data for harms that we have now included.<sup>116, 117</sup> 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.<sup>129-134</sup> **Appendix E Tables 13–29** 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,<sup>113, 114, 116, 123</sup> two trials of oral clindamycin,<sup>119, 120</sup> and two trials of oral metronidazole.<sup>111, 117</sup> 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. 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.<sup>113, 114, 116, 123</sup> Vermeulen et al<sup>123</sup> reported no withdrawals because of serious AEs, and Larsson et al<sup>116</sup> reported no serious treatment-related maternal AEs in the treatment group. Kiss et al reported no AEs observed during the treatment period.<sup>114</sup> Kekki et al<sup>113</sup> reported an incidence of vulvovaginal itching of 3.2 percent in both the treatment and placebo groups, and in Larsson et al,<sup>116</sup> 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).<sup>123</sup>

### *Oral Clindamycin*

Two RCTs reported maternal AEs from oral clindamycin;<sup>119, 120</sup> one was new to this update.<sup>119</sup> 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  $p=0.0035$ ).<sup>119</sup> 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%;  $p=0.10$ ).<sup>120</sup> 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.<sup>119</sup> 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  $p=0.18$ ).<sup>120</sup> 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.<sup>111, 117</sup> Women randomized to oral metronidazole were more likely to experience one or more side effects compared with those randomized to placebo in both studies.<sup>111, 117</sup> 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  $p<0.001$ ).<sup>111</sup> 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.<sup>117</sup>

## **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;<sup>129-134</sup> all studies were included in the prior review. We provide a summary of study characteristics and results in **Table 10. Appendix D Tables 7–12** provide additional study characteristics and detailed outcomes. Three observational studies<sup>129-131</sup> and two meta-analyses<sup>133, 134</sup> reported on outcomes related to congenital abnormalities and malformations, and one observational study<sup>132</sup> 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;<sup>129</sup> 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 clinician log books, self-report during interview, and a mailed questionnaire.<sup>131</sup> 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).<sup>129</sup> 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.<sup>130</sup> 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 followup).<sup>132</sup>

We included two meta-analyses of observational studies of in utero exposure to metronidazole;<sup>133, 134</sup> three studies overlapped between the meta-analyses. The 1995 Burtin et al meta-analysis<sup>133</sup> included seven cohort studies (total N not reported), four of which were excluded from the subsequent 1997 Caro-Paton et al meta-analysis<sup>134</sup> 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.<sup>134</sup>

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]<sup>133</sup> and OR, 1.08 [95% CI, 0.90 to 1.29]<sup>134</sup>). Similarly, with one exception, the three observational studies (one poor quality, two fair quality) found no association between metronidazole and congenital abnormalities.<sup>129-131</sup> The exception was reported by Czeizel et al.<sup>131</sup> 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.<sup>131</sup> 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.<sup>131</sup>

## *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 years among exposed children (adjusted RR, 0.81 [95% CI, 0.41 to 1.59]).<sup>132</sup>

## Chapter 4. Discussion

### Summary of Evidence

**Table 11** summarizes the evidence synthesized in this report by KQ and provides our 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/ethnicity, HIV status, or other characteristics was not identified.

#### Diagnostic Test Accuracy (KQ 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, BVBLUE, 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.<sup>135</sup>

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<sup>88, 89</sup> 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.<sup>98</sup> The BD Affirm test, which is based on a nucleic acid probe for *G. 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, BVBLUE) 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-negative results. In other contexts (e.g., when harms of false-positive results 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 posttest probability of disease as an alternative way to evaluate test accuracy and to assess consistency and precision domains within

SOE assessment.<sup>83</sup> 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 posttest probability of bacterial vaginosis to 48.9 percent, a positive BD Max increases the posttest probability to 69.4 percent, and a positive Amsel's test (complete criteria) increases the posttest probability to 61.0 percent. The posttest 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 posttest probability after a positive test. After a negative test, all would likely decrease the posttest probability of bacterial vaginosis below a threshold for which treatment would likely not be indicated.

## Benefits of Treatment (KQ 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 preterm 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<sup>111</sup>) 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.<sup>124</sup> 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 (KQ 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 laboratories 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 maternal AEs (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 preterm delivery at less than 37 weeks, although some uncertainty remains because some studies only reported spontaneous preterm delivery and not all-cause preterm delivery outcomes. The consequences related to preterm delivery generally do not differ for medically indicated deliveries vs. 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 AEs 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 (KQ 5), 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/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 effect 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, symptomatic women; across individual studies the sensitivity of the various tests ranged from 0.36 to 1.0 and the specificity ranged from 0.49 to 1.0. 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 AEs 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.

## References

1. Calonge N, Petitti DB, DeWitt TG, et al. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: US Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2008;148(3):214-9.
2. Nygren P, Fu R, Freeman M, et al. Screening and treatment for bacterial vaginosis in pregnancy: systematic review to update the 2001 US Preventive Services Task Force recommendation. *Ann Intern Med.* 2008 January;148(3):214-9. PMID: 18252683.
3. Nygren P, Fu R, Freeman M, et al. Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an update review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008 Feb 5;148(3):220-33. doi: 10.7326/0003-4819-148-3-200802050-00008. PMID: 18758800.
4. Srinivasan S, Fredricks DN. The human vaginal bacterial biota and bacterial vaginosis. *Interdiscip Perspect Infect Dis.* 2008;2008: 750479.
5. Livengood CH. Bacterial vaginosis: an overview for 2009. *Rev Obstet Gynecol.* 2009 Winter;2(1):28-37. PMID: 19399292.
6. Martin DH. The microbiota of the vagina and its influence on women's health and disease. *Am J Med Sci.* 2012 Jan;343(1):2-9. doi: 10.1097/MAJ.0b013e31823ea228. PMID: 22143133.
7. Lamont RF, Sobel JD, Akins RA, et al. The vaginal microbiome: new information about genital tract flora using molecular based techniques. *BJOG.* 2011 Apr;118(5):533-49. doi: 10.1111/j.1471-0528.2010.02840.x. PMID: 21251190.
8. Quinn J-A, Munoz FM, Gonik B, et al. Preterm birth: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine.* 2016;34(49):6047-56. doi: 10.1016/j.vaccine.2016.03.045. PMID: PMC5139808.
9. Marlow N. Full term; an artificial concept. *Arch Dis Child Fetal Neonatal Ed.* 2012 May;97(3):F158-9. doi: 10.1136/fetalneonatal-2011-301507. PMID: 22262663.
10. Bradshaw CS, Sobel JD. Current treatment of bacterial vaginosis-limitations and need for innovation. *J Infect Dis.* 2016 Aug 15;214 Suppl 1:S14-20. doi: 10.1093/infdis/jiw159. PMID: 27449869.
11. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001-2004 National Health and Nutrition Examination Survey data. *Obstet Gynecol.* 2007 Jan;109(1):114-20. doi: 10.1097/01.AOG.0000247627.84791.91. PMID: 17197596.
12. Vodstrcil LA, Walker SM, Hocking JS, et al. Incident bacterial vaginosis (BV) in women who have sex with women is associated with behaviors that suggest sexual transmission of BV. *Clin Infect Dis.* 2015 Apr 01;60(7):1042-53. doi: 10.1093/cid/ciu1130. PMID: 25516188.
13. Kenyon C, Colebunders R, Crucitti T. The global epidemiology of bacterial vaginosis: a systematic review. *Am J Obstet Gynecol.* 2013 Dec;209(6):505-23. doi: 10.1016/j.ajog.2013.05.006. PMID: 23659989.
14. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. *Am J Med.* 1983;74(1):14-22.
15. American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: vaginitis (Reaffirmed 2017). *Obstet Gynecol.* 2006 May;107(5):1195-206. PMID: 16648432.



16. Klebanoff MA, Schwebke JR, Zhang J, et al. Vulvovaginal symptoms in women with bacterial vaginosis. *Obstet Gynecol*. 2004 Aug;104(2):267-72. doi: 10.1097/01.AOG.0000134783.98382.b0. PMID: 15291998.
17. Bradshaw CS, Morton AN, Hocking J, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. *J Infect Dis*. 2006 Jun 01;193(11):1478-86. doi: 10.1086/503780. PMID: 16652274.
18. Bilardi JE, Walker S, Temple-Smith M, et al. The burden of bacterial vaginosis: women's experience of the physical, emotional, sexual and social impact of living with recurrent bacterial vaginosis. *PLoS One*. 2013;8(9):e74378. doi: 10.1371/journal.pone.0074378. PMID: 24040236.
19. Verstraelen H, Verhelst R, Vaneechoutte M, et al. The epidemiology of bacterial vaginosis in relation to sexual behaviour. *BMC Infect Dis*. 2010 Mar 30;10:81. doi: 10.1186/1471-2334-10-81. PMID: 20353563.
20. Ralph SG, Rutherford AJ, Wilson JD. Influence of bacterial vaginosis on conception and miscarriage in the first trimester: cohort study. *BMJ*. 1999 Jul 24;319(7204):220-3. PMID: 10417083.
21. McGregor JA, French JI, Parker R, et al. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation. *Am J Obstet Gynecol*. 1995 Jul;173(1):157-67. PMID: 7631673.
22. Taylor BD, Darville T, Haggerty CL. Does bacterial vaginosis cause pelvic inflammatory disease? *Sex Transm Dis*. 2013 Feb;40(2):117-22. doi: 10.1097/OLQ.0b013e31827c5a5b. PMID: 23324974.
23. Achilles SL, Reeves MF. Prevention of infection after induced abortion: release date October 2010: SFP guideline 20102. *Contraception*. 2011 Apr;83(4):295-309. doi: 10.1016/j.contraception.2010.11.006. PMID: 21397086.
24. Watts DH, Krohn MA, Hillier SL, et al. Bacterial vaginosis as a risk factor for post-cesarean endometritis. *Obstet Gynecol*. 1990 Jan;75(1):52-8. PMID: 2296423.
25. Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. *N Engl J Med*. 1995;333(26):1737-42.
26. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012 2012/06/09;379(9832):2162-72. doi: 10.1016/S0140-6736(12)60820-4.
27. Mathews T, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. 2015.
28. Schindler T, Koller-Smith L, Lui K, et al. Causes of death in very preterm infants cared for in neonatal intensive care units: a population-based retrospective cohort study. *BMC Pediatr*. 2017;17(1):59.
29. Hamilton BE, Martin JA, Osterman MJK, et al. Births: provisional data for 2018. Vital Statistics Rapid Release; no 7. Hyattsville, MD: National Center for Health Statistics; 2019. <https://www.cdc.gov/nchs/data/vsrr/vsrr-007-508.pdf>.
30. McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. *Obstet Gynecol*. 2008;111(1):35-41.
31. Savitz DA, Blackmore CA, Thorp JM. Epidemiologic characteristics of preterm delivery: etiologic heterogeneity. *Am J Obstet Gynecol*. 1991 Feb;164(2):467-71. PMID: 1992685.

32. Allen MC. Neurodevelopmental outcomes of preterm infants. *Curr Opin Neurol*. 2008 Apr;21(2):123-8. doi: 10.1097/WCO.0b013e3282f88bb4. PMID: 18317268.
33. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health*. 2013;10(Suppl 1):S2. doi: 10.1186/1742-4755-10-s1-s2. PMID: 24625129.
34. Behrman R, Butler A. Preterm birth: causes consequences and prevention. Committee on Understanding Premature Birth and Assuring Health Outcomes, Institute of Medicine of the National Academies. Washington DC: National Academies Press; 2006.
35. Martin DH, Marrazzo JM. The vaginal microbiome: current understanding and future directions. *J Infect Dis*. 2016 Aug 15;214 Suppl 1:S36-41. doi: 10.1093/infdis/jiw184. PMID: 27449871.
36. Lewis FM, Bernstein KT, Aral SO. Vaginal microbiome and its relationship to behavior, sexual health, and sexually transmitted diseases. *Obstet Gynecol*. 2017 Apr;129(4):643-54. doi: 10.1097/aog.0000000000001932. PMID: 28277350.
37. Turovskiy Y, Sutyak Noll K, Chikindas ML. The aetiology of bacterial vaginosis. *J Appl Microbiol*. 2011 May;110(5):1105-28. doi: 10.1111/j.1365-2672.2011.04977.x. PMID: 21332897.
38. Coleman JS, Gaydos CA. Molecular diagnosis of bacterial vaginosis: an update. *J Clin Microbiol*. 2018 Sep;56(9)doi: 10.1128/jcm.00342-18. PMID: 29769280.
39. Machado A, Cerca N. Influence of biofilm formation by *Gardnerella vaginalis* and other anaerobes on bacterial vaginosis. *J Infect Dis*. 2015 Dec 15;212(12):1856-61. doi: 10.1093/infdis/jiv338. PMID: 26080369.
40. Swidsinski A, Mendling W, Loening-Baucke V, et al. Adherent biofilms in bacterial vaginosis. *Obstet Gynecol*. 2005 Nov;106(5 Pt 1):1013-23. doi: 10.1097/01.AOG.0000183594.45524.d2. PMID: 16260520.
41. Muzny CA, Schwebke JR. Pathogenesis of bacterial vaginosis: discussion of current hypotheses. *J Infect Dis*. 2016 Aug 15;214 Suppl 1:S1-5. doi: 10.1093/infdis/jiw121. PMID: 27449868.
42. Unemo M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: challenges ahead. *Lancet Infect Dis*. 2017 Aug;17(8):e235-e79. doi: 10.1016/s1473-3099(17)30310-9. PMID: 28701272.
43. Tabrizi SN, Fairley CK, Bradshaw CS, et al. Prevalence of *Gardnerella vaginalis* and *Atopobium vaginae* in virginal women. *Sex Transm Dis*. 2006 Nov;33(11):663-5. doi: 10.1097/01.olq.0000216161.42272.be. PMID: 17374511.
44. Fethers KA, Fairley CK, Morton A, et al. Early sexual experiences and risk factors for bacterial vaginosis. *J Infect Dis*. 2009 Dec 1;200(11):1662-70. doi: 10.1086/648092. PMID: 19863439.
45. Schwebke JR, Desmond R. Risk factors for bacterial vaginosis in women at high risk for sexually transmitted diseases. *Sex Transm Dis*. 2005;32(11):654-8.
46. Murphy K, Mitchell CM. The interplay of host immunity, environment and the risk of bacterial vaginosis and associated reproductive health outcomes. *J Infect Dis*. 2016 Aug 15;214 Suppl 1:S29-35. doi: 10.1093/infdis/jiw140. PMID: 27056955.
47. Kenyon CR, Delva W, Brotman RM. Differential sexual network connectivity offers a parsimonious explanation for population-level variations in the prevalence of bacterial vaginosis: a data-driven, model-supported hypothesis. *BMC Womens Health*. 2019 Jan 10;19(1):8. doi: 10.1186/s12905-018-0703-0. PMID: 30630481.

48. Godha K, Tucker KM, Biehl C, et al. Human vaginal pH and microbiota: an update. *Gynecol Endocrinol*. 2017 Dec 22;1-5. doi: 10.1080/09513590.2017.1407753. PMID: 29271266.
49. Neggers YH, Nansel TR, Andrews WW, et al. Dietary intake of selected nutrients affects bacterial vaginosis in women. *J Nutr*. 2007 Sep;137(9):2128-33. PMID: 17709453.
50. Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol*. 2007 Jun;21(3):375-90. doi: 10.1016/j.bpobgyn.2006.12.005. PMID: WOS:000247462000004.
51. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *Lancet*. 2008 2008/01/05/;371(9606):75-84. doi: 10.1016/S0140-6736(08)60074-4.
52. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. *N Engl J Med*. 2010 Feb 11;362(6):529-35. doi: 10.1056/NEJMra0904308. PMID: 20147718.
53. Mercer BM, Goldenberg RL, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*. 1999 Nov;181(5 Pt 1):1216-21. PMID: 10561648.
54. To MS, Skentou CA, Royston P, et al. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. *Ultrasound Obstet Gynecol*. 2006 Apr;27(4):362-7. doi: 10.1002/uog.2773. PMID: 16565989.
55. Berghella V, Roman A, Daskalakis C, et al. Gestational age at cervical length measurement and incidence of preterm birth. *Obstet Gynecol*. 2007;110(2, Part 1):311-7.
56. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol*. doi: 10.1016/j.ajog.2017.11.576.
57. Slyker JA, Patterson J, Ambler G, et al. Correlates and outcomes of preterm birth, low birth weight, and small for gestational age in HIV-exposed uninfected infants. *BMC Pregnancy Childbirth*. 2014 Jan 8;14:7. doi: 10.1186/1471-2393-14-7. PMID: 24397463.
58. Shapiro GD, Fraser WD, Frasci MG, et al. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. *J Perinat Med*. 2013 Nov;41(6):631-45. doi: 10.1515/jpm-2012-0295. PMID: 24216160.
59. Kajeepeta S, Sanchez SE, Gelaye B, et al. Sleep duration, vital exhaustion, and odds of spontaneous preterm birth: a case-control study. *BMC Pregnancy Childbirth*. 2014 Sep 27;14:337. doi: 10.1186/1471-2393-14-337. PMID: 25261975.
60. Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. *Am J Obstet Gynecol*. 2000 Feb;182(2):465-72. PMID: 10694353.
61. Ide M, Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes--systematic review. *J Periodontol*. 2013 Apr;84(4 Suppl):S181-94. doi: 10.1902/jop.2013.134009. PMID: 23631578.
62. Fiscella K. Racial disparities in preterm births. The role of urogenital infections. *Public Health Rep*. 1996 Mar-Apr;111(2):104-13. PMID: 8606905.
63. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol*. 1991;29(2):297-301.

64. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for use in genitourinary medicine clinics. *Sex Transm Infect.* 2002;78(6):413-5. doi: 10.1136/sti.78.6.413.
65. Gaydos CA, Beqaj S, Schwebke JR, et al. Clinical validation of a test for the diagnosis of vaginitis. *Obstet Gynecol.* 2017 Jul;130(1):181-9. doi: 10.1097/aog.0000000000002090. PMID: 28594779.
66. Plummer EL, Garland SM, Bradshaw CS, et al. Molecular diagnosis of bacterial vaginosis: does adjustment for total bacterial load or human cellular content improve diagnostic performance? *J Microbiol Methods.* 2017 Feb;133:66-8. doi: 10.1016/j.mimet.2016.12.024. PMID: 28042056.
67. Rumyantseva T, Shipitsyna E, Guschin A, et al. Evaluation and subsequent optimizations of the quantitative AmpliSens Florocenosis/Bacterial vaginosis-FRT multiplex real-time PCR assay for diagnosis of bacterial vaginosis. *APMIS.* 2016 Dec;124(12):1099-108. doi: 10.1111/apm.12608. PMID: 27714844.
68. Hoffman MK, Bellad MB, Charantimath US, et al. A comparison of colorimetric assessment of vaginal pH with Nugent score for the detection of bacterial vaginosis. *Infect Dis Obstet Gynecol.* 2017;2017:1040984. doi: 10.1155/2017/1040984. PMID: 28293099.
69. Hay P, Tummon A, Ogunfile M, et al. Evaluation of a novel diagnostic test for bacterial vaginosis: 'the electronic nose'. *Int J STD AIDS.* 2003 Feb;14(2):114-8. doi: 10.1258/095646203321156881. PMID: 12662390.
70. Scherf U. Letter to Dr. Patricia Dionne, GeneOhm Sciences Canada, Inc. (BD Diagnostics). Silver Spring, MD: Department of Health & Human Services, Food and Drug Administration; 2016. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf16/den160001.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf16/den160001.pdf). Accessed November 20, 2017.
71. Harper CC. Letter to Natasha Leskovsek, Common Sense Ltd. Silver Spring, MD: Department of Health and Human Services, Food and Drug Administration; 2009. Accessed November 20, 2017.
72. Cooper JM. Letter to Mr. Thomas M. Tsakeris, Gryphus Diagnostids, LLC. Rockville, MD: Department of Health and Human Services, Food and Drug Administration; 2005. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf5/k050755.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf5/k050755.pdf). Accessed November 20, 2017.
73. Klebanoff MA, Hauth JC, MacPherson CA, et al. Time course of the regression of asymptomatic bacterial vaginosis in pregnancy with and without treatment. *Am J Obstet Gynecol.* 2004;190(2):363-70.
74. Swidsinski A, Mendling W, Loening-Baucke V, et al. An adherent *Gardnerella vaginalis* biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. *Am J Obstet Gynecol.* 2008 Jan;198(1):97.e1-6. doi: 10.1016/j.ajog.2007.06.039. PMID: 18005928.
75. United Nations Development Programme. Human Development Index. Website. New York City, NY: United Nations Development Programme; 2016. <http://hdr.undp.org/en/composite/HDI>. Accessed October 15,, 2017.
76. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011. [www.handbook.cochrane.org](http://www.handbook.cochrane.org). Accessed Aug 24, 2016.

77. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
78. Sleith C. Methodology checklist 4: case control studies. *Edinburgh (UK): Scottish Intercollegiate Guidelines Network*. 2012.
79. Whiting P, Savović J, Higgins JP, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 2016;69:225-34.
80. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.
81. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005 Oct;58(10):982-90. doi: 10.1016/j.jclinepi.2005.02.022. PMID: 16168343.
82. Bossuyt P, Davenport C, Deeks J, et al. Chapter 11: Interpreting results and drawing conclusions. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane handbook for systematic reviews of diagnostic test accuracy*. Version 9. London, The United Kingdom: The Cochrane Collaboration; 2013.
83. Singh S, Chang SM, Matchar DB, et al. Grading a body of evidence on diagnostic tests. *J Gen Intern Med*. 2012;27(1):47-55.
84. West SL, Gartlehner G, Mansfield AJ, et al. Comparative effectiveness review methods: clinical heterogeneity Methods Research Paper. AHRQ Publication No. 10-EHC070-EF. Rockville MD: Agency for Healthcare Research and Quality; September 2010. PMID: 21433337. <http://effectivehealthcare.ahrq.gov/>
85. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986 Sep;7(3):177-88. PMID: 3802833.
86. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. <http://effectivehealthcare.ahrq.gov/>
87. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008 May 17;336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE. PMID: 18483053.
88. Gratacos E, Figueras F, Barranco M, et al. Prevalence of bacterial vaginosis and correlation of clinical to Gram stain diagnostic criteria in low risk pregnant women. *Eur J Epidemiol*. 1999 Nov;15(10):913-6. PMID: 10669125.
89. Mastrobattista JM, Bishop KD, Newton ER. Wet smear compared with gram stain diagnosis of bacterial vaginosis in asymptomatic pregnant women. *Obstet Gynecol*. 2000 Oct;96(4):504-6. PMID: 11004348.
90. Byun SW, Park YJ, Hur SY. Affirm VPIII microbial identification test can be used to detect gardnerella vaginalis, Candida albicans and trichomonas vaginalis microbial infections in Korean women. *J Obstet Gynaecol Res*. 2016 Apr;42(4):422-6. doi: 10.1111/jog.12913. PMID: 26787446.
91. Hay PE, Taylor-Robinson D, Lamont RF. Diagnosis of bacterial vaginosis in a gynaecology clinic. *Br J Obstet Gynaecol*. 1992 Jan;99(1):63-6. PMID: 1547176.

92. Platz-Christensen JJ, Larsson PG, Sundstrom E, et al. Detection of bacterial vaginosis in wet mount, Papanicolaou stained vaginal smears and in gram stained smears. *Acta Obstet Gynecol Scand*. 1995 Jan;74(1):67-70. PMID: 7856436.
93. Hellberg D, Nilsson S, Mardh PA. The diagnosis of bacterial vaginosis and vaginal flora changes. *Arch Gynecol Obstet*. 2001 Mar;265(1):11-5. PMID: 11327086.
94. Schmidt H, Hansen JG. A wet smear criterion for bacterial vaginosis. *Scand J Prim Health Care*. 1994 Dec;12(4):233-8. PMID: 7863139.
95. Cartwright CP, Lembke BD, Ramachandran K, et al. Comparison of nucleic acid amplification assays with BD affirm VPIII for diagnosis of vaginitis in symptomatic women. *J Clin Microbiol*. 2013 Nov;51(11):3694-9. doi: 10.1128/jcm.01537-13. PMID: 23985917.
96. Briselden AM, Hillier SL. Evaluation of affirm VP Microbial Identification Test for *Gardnerella vaginalis* and *Trichomonas vaginalis*. *J Clin Microbiol*. 1994 Jan;32(1):148-52. PMID: 8126171.
97. Lowe NK, Neal JL, Ryan-Wenger NA. Accuracy of the clinical diagnosis of vaginitis compared with a DNA probe laboratory standard. *Obstet Gynecol*. 2009 Jan;113(1):89-95. doi: 10.1097/AOG.0b013e3181909f63. PMID: 18931272.
98. Witt A, Petricevic L, Kaufmann U, et al. DNA hybridization test: rapid diagnostic tool for excluding bacterial vaginosis in pregnant women with symptoms suggestive of infection. *J Clin Microbiol*. 2002 Aug;40(8):3057-9. PMID: 12149379.
99. Schwebke JR, Gaydos CA, Nyirjesy P, et al. Diagnostic performance of a molecular test versus clinician assessment of vaginitis. *J Clin Microbiol*. 2018 Apr 11doi: 10.1128/jcm.00252-18. PMID: 29643195.
100. Bradshaw CS, Morton AN, Garland SM, et al. Evaluation of a point-of-care test, BVBlue, and clinical and laboratory criteria for diagnosis of bacterial vaginosis. *J Clin Microbiol*. 2005 Mar;43(3):1304-8. doi: 10.1128/jcm.43.3.1304-1308.2005. PMID: 15750100.
101. University of Pittsburgh. A validation study of genzyme diagnostics OSOM *Trichomonas* rapid test and BVBlue test. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine; 2000-.
102. Myziuk L, Romanowski B, Johnson SC. BVBlue test for diagnosis of bacterial vaginosis. *J Clin Microbiol*. 2003;41(5):1925-8.
103. Gallo MF, Jamieson DJ, Cu-Uvin S, et al. Accuracy of clinical diagnosis of bacterial vaginosis by human immunodeficiency virus infection status. *Sex Transm Dis*. 2011 Apr;38(4):270-4. doi: 10.1097/OLQ.0b013e3181f6e4eb. PMID: 21515758.
104. Hilmarsdottir I, Hauksdottir GS, Johannesdottir JD, et al. Evaluation of a rapid Gram stain interpretation method for diagnosis of bacterial vaginosis. *J Clin Microbiol*. 2006 Mar;44(3):1139-40. doi: 10.1128/jcm.44.3.1139-1140.2006. PMID: 16427240.
105. Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. *Am J Obstet Gynecol*. 2004 Apr;190(4):1004-10. doi: 10.1016/j.ajog.2004.02.015. PMID: 15118630.
106. Sha BE, Gawel SH, Hershov RC, et al. Analysis of standard methods for diagnosing vaginitis: HIV infection does not complicate the diagnosis of vaginitis. *J Low Genit Tract Dis*. 2007 Oct;11(4):240-50. doi: 10.1097/LGT.0b013e318033dfed. PMID: 17666604.

107. Singh RH, Zenilman JM, Brown KM, et al. The role of physical examination in diagnosing common causes of vaginitis: a prospective study. *Sex Transm Infect.* 2013 May;89(3):185-90. doi: 10.1136/sextrans-2012-050550. PMID: 23631602.
108. Schwebke JR, Hillier SL, Sobel JD, et al. Validity of the vaginal gram stain for the diagnosis of bacterial vaginosis. *Obstet Gynecol.* 1996 Oct;88(4 Pt 1):573-6. PMID: 8841221.
109. Gutman RE, Peipert JF, Weitzen S, et al. Evaluation of clinical methods for diagnosing bacterial vaginosis. *Obstet Gynecol.* 2005 Mar;105(3):551-6. doi: 10.1097/01.Aog.0000145752.97999.67. PMID: 15738023.
110. Chen HM, Chang TH, Lin FM, et al. Vaginal microbiome variances in sample groups categorized by clinical criteria of bacterial vaginosis. *BMC Genomics.* 2018 Dec 31;19(Suppl 10):876. doi: 10.1186/s12864-018-5284-7. PMID: 30598080.
111. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 2000 Feb 24;342(8):534-40. doi: 10.1056/NEJM200002243420802. PMID: 10684911.
112. Guaschino S, Ricci E, Franchi M, et al. Treatment of asymptomatic bacterial vaginosis to prevent pre-term delivery: a randomised trial. *Eur J Obstet Gynecol Reprod Biol.* 2003 Oct 10;110(2):149-52. PMID: 12969574.
113. Kekki M, Kurki T, Pelkonen J, et al. Vaginal clindamycin in preventing preterm birth and peripartur infections in asymptomatic women with bacterial vaginosis: a randomized, controlled trial. *Obstet Gynecol.* 2001 May;97(5 Pt 1):643-8. PMID: 11339909.
114. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ.* 2004 Aug 14;329(7462):371. doi: 10.1136/bmj.38169.519653.EB. PMID: 15294856.
115. Lamont RF, Duncan SL, Mandal D, et al. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol.* 2003 Mar;101(3):516-22. PMID: 12636956.
116. Larsson PG, Fahraeus L, Carlsson B, et al. Late miscarriage and preterm birth after treatment with clindamycin: a randomised consent design study according to Zelen. *BJOG.* 2006 Jun;113(6):629-37. doi: 10.1111/j.1471-0528.2006.00946.x. PMID: 16709205.
117. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (*Gardnerella vaginalis*): a randomised, placebo controlled trial. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1391-7. PMID: 9422018.
118. McGregor JA, French JI, Jones W, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase - results of a controlled trial of topical clindamycin cream. *Am J Obstet Gynecol.* 1994 Apr;170(4):1048-60. doi: 10.1016/S0002-9378(94)70098-2. PMID: WOS:A1994NG74200011.
119. Subtil D, Brabant G, Tilloy E, et al. Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial. *Lancet.* 2018 Oct 12doi: 10.1016/S0140-6736(18)31617-9. PMID: 30322724.
120. Ugwumadu A, Manyonda I, Reid F, et al. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora

- and bacterial vaginosis: a randomised controlled trial. *Lancet*. 2003 Mar 22;361(9362):983-8. doi: 10.1016/S0140-6736(03)12823-1. PMID: 12660054.
121. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med*. 1995 Dec 28;333(26):1732-6. doi: 10.1056/NEJM199512283332603. PMID: 7491136.
  122. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. *Am J Obstet Gynecol*. 1994 Aug;171(2):345-7; discussion 8-9. PMID: 8059811.
  123. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. *Br J Obstet Gynaecol*. 1999 Jul;106(7):652-7. PMID: 10428520.
  124. Odendaal HJ, Popov I, Schoeman J, et al. Preterm labour-is bacterial vaginosis involved? *S Afr Med J*. 2002;92(3):231-4.
  125. Joesoef MR, Hillier SL, Wiknjosastro G, et al. Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight. *Am J Obstet Gynecol*. 1995;173(5):1527-31.
  126. Kurkinen-Raty M, Vuopala S, Koskela M, et al. A randomised controlled trial of vaginal clindamycin for early pregnancy bacterial vaginosis. *Br J Obstet Gynaecol*. 2000 Nov;107(11):1427-32. doi: 10.1111/j.1471-0528.2000.tb11660.x. PMID: WOS:000165812500017.
  127. Andrews WW, Hauth JC, Cliver SP, et al. Association of asymptomatic bacterial vaginosis with endometrial microbial colonization and plasma cell endometritis in nonpregnant women. *Am J Obstet Gynecol*. 2006 Dec;195(6):1611-6. doi: 10.1016/j.ajog.2006.04.010. PMID: 16769017.
  128. Yudin MH, Landers DV, Meyn L, et al. Clinical and cervical cytokine response to treatment with oral or vaginal metronidazole for bacterial vaginosis during pregnancy: a randomized trial. *Obstet Gynecol*. 2003 Sep;102(3):527-34. PMID: 12962937.
  129. Diav-Citrin O, Shechtman S, Gotteiner T, et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. *Teratology*. 2001 May;63(5):186-92. doi: 10.1002/tera.1033. PMID: 11320529.
  130. Sorensen HT, Larsen H, Jensen ES, et al. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. *J Antimicrob Chemother*. 1999 Dec;44(6):854-6. PMID: 10590296.
  131. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol*. 1998 Mar;105(3):322-7. PMID: 9532994.
  132. Thapa PB, Whitlock JA, Brockman Worrell KG, et al. Prenatal exposure to metronidazole and risk of childhood cancer: a retrospective cohort study of children younger than 5 years. *Cancer*. 1998 Oct 1;83(7):1461-8. PMID: 9762949.
  133. Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol*. 1995 1995/02/01;172(2, Part 1):525-9. doi: 10.1016/0002-9378(95)90567-7.
  134. Caro-Paton T, Carvajal A, Martin de Diego I, et al. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol*. 1997 Aug;44(2):179-82. PMID: 9278206.



135. Wilson JD, Ralph SG, Rutherford AJ. Rates of bacterial vaginosis in women undergoing in vitro fertilisation for different types of infertility. *BJOG*. 2002 Jun;109(6):714-7. PMID: 12118653.
136. Rouse AG, Gil KM, Davis K. Diagnosis of bacterial vaginosis in the pregnant patient in an acute care setting. *Arch Gynecol Obstet*. 2009 Apr;279(4):545-9. doi: 10.1007/s00404-008-0766-5. PMID: 19246753.
137. Sonnex C. The amine test: a simple, rapid, inexpensive method for diagnosing bacterial vaginosis. *Br J Obstet Gynaecol*. 1995 Feb;102(2):160-1. PMID: 7756209.
138. Lamont RF, Taylor-Robinson D, Bassett P. Rescreening for abnormal vaginal flora in pregnancy and re-treating with clindamycin vaginal cream significantly increases cure and improvement rates. *Int J STD AIDS*. 2012 Aug;23(8):565-9. doi: 10.1258/ijsa.2011.011229. PMID: WOS:000309297400007.
139. Figueroa D, Mancuso MS, Szychowski JM, et al. Does midtrimester Nugent score or high vaginal pH predict gestational age at delivery in women at risk for recurrent preterm birth? *Am J Obstet Gynecol*. 2011 Jan;204(1):46.e1-4. doi: 10.1016/j.ajog.2010.08.029. PMID: 20885970.
140. French JI, McGregor JA, Parker R. Readily treatable reproductive tract infections and preterm birth among black women. *Am J Obstet Gynecol*. 2006 Jun;194(6):1717-26; discussion 26-7. doi: 10.1016/j.ajog.2006.03.004. PMID: 16709205.
141. Hitti J, Nugent R, Boutain D, et al. Racial disparity in risk of preterm birth associated with lower genital tract infection. *Paediatr Perinat Epidemiol*. 2007 Jul;21(4):330-7. doi: 10.1111/j.1365-3016.2007.00807.x. PMID: 16648432.
142. Jones NM, Holzman C, Friderici KH, et al. Interplay of cytokine polymorphisms and bacterial vaginosis in the etiology of preterm delivery. *J Reprod Immunol*. 2010 Dec;87(1-2):82-9. doi: 10.1016/j.jri.2010.06.158. PMID: 20573348.
143. Nelson DB, Hanlon A, Nachamkin I, et al. Early pregnancy changes in bacterial vaginosis-associated bacteria and preterm delivery. *Paediatr Perinat Epidemiol*. 2014 Mar;28(2):88-96. doi: 10.1111/ppe.12106. PMID: 25518272.
144. Johnson HL, Ghanem KG, Zenilman JM, et al. Sexually transmitted infections and adverse pregnancy outcomes among women attending inner city public sexually transmitted diseases clinics. *Sex Transm Dis*. 2011 Mar;38(3):167-71. doi: 10.1097/OLQ.0b013e3181f2e85f. PMID: 21275914.
145. Nelson DB, Hanlon A, Hassan S, et al. Preterm labor and bacterial vaginosis-associated bacteria among urban women. *J Perinat Med*. 2009;37(2):130-4. doi: 10.1515/jpm.2009.026. PMID: 18591634.
146. Xu J, Holzman CB, Arvidson CG, et al. Midpregnancy vaginal fluid defensins, bacterial vaginosis, and risk of preterm delivery. *Obstet Gynecol*. 2008 Sep;112(3):524-31. doi: 10.1097/AOG.0b013e318184209b. PMID: 17986357.
147. Donders GGG. Definition and classification of abnormal vaginal flora. *Best Pract Res Clin Obstet Gynaecol*. 2007 2007/06/01/;21(3):355-73. doi: 10.1016/j.bpobgyn.2007.01.002.
148. Taylor-Robinson D, Morgan DJ, Sheehan M, et al. Relation between Gram-stain and clinical criteria for diagnosing bacterial vaginosis with special reference to Gram grade II evaluation. *Int J STD AIDS*. 2003;14(1):6.

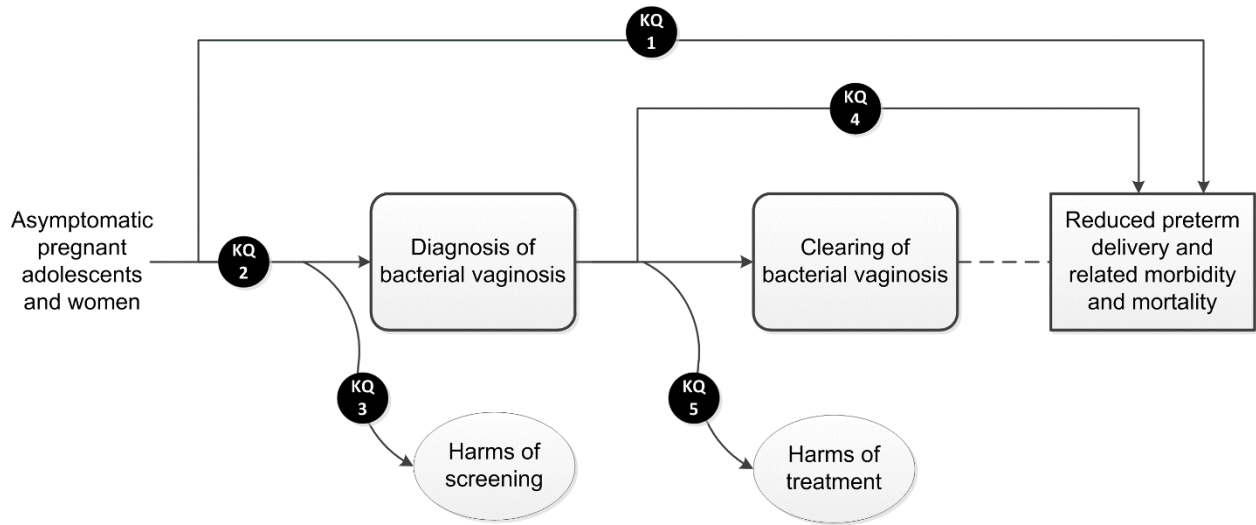
149. Rosenstein IJ, Morgan DJ, Lamont RF, et al. Effect of intravaginal clindamycin cream on pregnancy outcome and on abnormal vaginal microbial flora of pregnant women. *Infect Dis Obstet Gynecol.* 2000;8(3-4):158-65.
150. Hillier SL, Krohn MA, Nugent RP, et al. Characteristics of three vaginal flora patterns assessed by Gram stain among pregnant women. *International Journal of Gynecology & Obstetrics.* 1992 1992/11/01/;39(3):249-50. doi: 10.1016/0020-7292(92)90677-B.
151. Farr A, Kiss H, Hagmann M, et al. Role of Lactobacillus species in the intermediate vaginal flora in early pregnancy: a retrospective cohort study. *PLoS One.* 2015;10(12):e0144181.
152. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev.* 2007;1(1).
153. Honda H, Yokoyama T, Akimoto Y, et al. The frequent shift to intermediate flora in preterm delivery cases after abnormal vaginal flora screening. *Sci Rep.* 2014 Apr 25;4:4799. doi: 10.1038/srep04799. PMID: 24762852.
154. Jesse DE, Swanson MS, Newton ER, et al. Racial disparities in biopsychosocial factors and spontaneous preterm birth among rural low-income women. *J Midwifery Womens Health.* 2009 Jan-Feb;54(1):35-42. doi: 10.1016/j.jmwh.2008.08.009. PMID: 19114237.
155. Ness RB, Hillier S, Richter HE, et al. Can known risk factors explain racial differences in the occurrence of bacterial vaginosis? *J Natl Med Assoc.* 2003 Mar;95(3):201-12. PMID: 12749680.
156. Mancuso MS, Figueroa D, Szychowski JM, et al. Midtrimester bacterial vaginosis and cervical length in women at risk for preterm birth. *Am J Obstet Gynecol.* 2011;204(4):342.e1-5. doi: 10.1016/j.ajog.2010.11.003. PMID: 21183154.
157. Nelson DB, Bellamy S, Odibo A, et al. Vaginal symptoms and bacterial vaginosis (BV): how useful is self-report? Development of a screening tool for predicting BV status. *Epidemiol Infect.* 2007 Nov;135(8):1369-75. doi: 10.1017/s095026880700787x. PMID: 17532736.
158. Koumans EH, Lane SD, Aubry R, et al. Evaluation of Syracuse Healthy Start's program for abnormal flora management to reduce preterm birth among pregnant women. *Matern Child Health J.* 2011 Oct;15(7):1020-8. doi: 10.1007/s10995-010-0661-0. PMID: 19795485.
159. Dingens AS, Fairfortune TS, Reed S, et al. Bacterial vaginosis and adverse outcomes among full-term infants: a cohort study. *BMC Pregnancy Childbirth.* 2016 Sep 22;16(1):278. doi: 10.1186/s12884-016-1073-y. PMID: 27658456.
160. Desseauve D, Chantrel J, Fruchart A, et al. Prevalence and risk factors of bacterial vaginosis during the first trimester of pregnancy in a large French population-based study. *Eur J Obstet Gynecol Reprod Biol;* 2012. p. 30-4.
161. Larsson PG, Fahraeus L, Carlsson B, et al. Predisposing factors for bacterial vaginosis, treatment efficacy and pregnancy outcome among term deliveries; results from a preterm delivery study. *BMC Womens Health.* 2007 Oct 22;7:20. doi: 10.1186/1472-6874-7-20. PMID: 17510259.
162. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. *Obstet Gynecol.* 2008;112(2):359-72.
163. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2016. *Natl Vital Stat Rep.* 2018 January 31;67(1):1-55.

164. Bautista C, Wurapa E, Sateren W, et al. Association of Bacterial Vaginosis With Chlamydia and Gonorrhea Among Women in the U.S. Army. *Am J Prev Med*; 2016.
165. Ness RB, Kip KE, Soper DE, et al. Bacterial vaginosis (BV) and the risk of incident gonococcal or chlamydial genital infection in a predominantly black population. *Sex Transm Dis*. 2005 Jul;32(7):413-7. PMID: 15976598.
166. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. *J Perinat Med*. 2007;35(2):93-9. doi: 10.1515/jpm.2007.039. PMID: 16643824.
167. Harper L, Parry S, Stamilio D, et al. The interaction effect of bacterial vaginosis and periodontal disease on the risk of preterm delivery. *Am J Perinatol*; 2012. p. 347-52.
168. Luong ML, Libman M, Dahhou M, et al. Vaginal douching, bacterial vaginosis, and spontaneous preterm birth. *J Obstet Gynaecol Can*. 2010 Apr;32(4):313-20. doi: 10.1016/s1701-2163(16)34474-7. PMID: 21325838.
169. Gillet E, Meys JFA, Verstraelen H, et al. Bacterial vaginosis is associated with uterine cervical human papillomavirus infection: a meta-analysis. *BMC Infect Dis*. 2011;11doi: 10.1186/1471-2334-11-10.
170. Esber A, Vicetti Miguel RD, Cherpes TL, et al. Risk of bacterial vaginosis among women with herpes simplex virus type 2 infection: a systematic review and meta-analysis. *J Infect Dis*. 2015;212(1):8-17. doi: 10.1093/infdis/jiv017.
171. Atashili J, Poole C, Ndumbe PM, et al. Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *AIDS (London, England)*. 2008;22(12):1493-501. doi: 10.1097/QAD.0b013e3283021a37. PMID: PMC2788489.
172. Genc MR, Witkin SS, Delaney ML, et al. A disproportionate increase in IL-1beta over IL-1ra in the cervicovaginal secretions of pregnant women with altered vaginal microflora correlates with preterm birth. *Am J Obstet Gynecol*. 2004 May;190(5):1191-7. doi: 10.1016/j.ajog.2003.11.007. PMID: 15167817.
173. Wiesenfeld HC, Macio I. The infrequent use of office-based diagnostic tests for vaginitis. *Am J Obstet Gynecol*. 1999 1999/07/01;181(1):39-41. doi: 10.1016/S0002-9378(99)70433-3.
174. McGregor JA, Hager WD, Gibbs RS, et al. Assessment of office-based care of sexually transmitted diseases and vaginitis and antibiotic decision-making by obstetrician-gynecologists. *Infect Dis Obstet Gynecol*. 1998;6(6):247-51. doi: 10.1155/s1064744998000519. PMID: 9972486.
175. Weisbord JS, Koumans EH, Toomey KE, et al. Sexually transmitted diseases during pregnancy: screening, diagnostic, and treatment practices among prenatal care providers in Georgia. *South Med J*. 2001 Jan;94(1):47-53. PMID: 11213942.
176. Brandt M, Abels C, May T, et al. Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2008;141(2):158-62. doi: 10.1016/j.ejogrb.2008.07.022.
177. Menard J-P. Antibacterial treatment of bacterial vaginosis: current and emerging therapies. *Int J Women Health*. 2011;3:295-305. doi: 10.2147/IJWH.S23814.
178. Donders GGG, Zodzika J, Rezeberga D. Treatment of bacterial vaginosis: what we have and what we miss. *Expert Opin Pharmacother*. 2014;15(5):645-57. doi: 10.1517/14656566.2014.881800.

179. Schwebke JR. Asymptomatic bacterial vaginosis: response to therapy. *Am J Obstet Gynecol.* 2000 Dec;183(6):1434-9. doi: 10.1067/mob.2000.107735. PMID: 11120507.
180. Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. *Cochrane Database Syst Rev.* 2009 Jul 8(3):CD006055. doi: 10.1002/14651858.CD006055.pub2. PMID: 19588379.
181. Schwebke JR, Desmond RA. Tinidazole vs metronidazole for the treatment of bacterial vaginosis. *Am J Obstet Gynecol.* 2011;204(3):211.e1-.e6. doi: 10.1016/j.ajog.2010.10.898.
182. Schwebke JR, Marrazzo J, Beelen AP, et al. A Phase 3, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Evaluating the Safety and Efficacy of Metronidazole Vaginal Gel 1.3% in the Treatment of Bacterial Vaginosis. *Sex Transm Dis.* 2015;42(7):376-81. doi: 10.1097/OLQ.0000000000000300.
183. Hanson JM, McGregor JA, Hillier SL, et al. Metronidazole for bacterial vaginosis. A comparison of vaginal gel vs. oral therapy. *J Reprod Med.* 2000 Nov;45(11):889-96. PMID: 11127100.
184. Stein GE, Christensen SL, Mummaw NL, et al. Placebo-controlled trial of intravaginal clindamycin 2% cream for the treatment of bacterial vaginosis. *Ann Pharmacother.* 1993 Nov;27(11):1343-5. doi: 10.1177/106002809302701106. PMID: 8286805.
185. Greaves W, Chungafun J, Morris B, et al. Clindamycin versus metronidazole in the treatment of bacterial vaginosis. *Obstet Gynecol.* 1988;72(5):799-802. doi: 10.1016/S0196-0644(89)80433-0.
186. Schmitt C, Sobel JD, Meriwether C. Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. *Obstet Gynecol.* 1992;79(6):1020-3.
187. Fischbach F, Petersen E, Weissenbacher E, et al. Efficacy of Clindamycin Vaginal Cream Versus Oral Metronidazole in the Treatment of Bacterial Vaginosis. *Obstet Gynecol.* 1993;82(3):405-10.
188. Bradshaw CS, Pirota M, De Guingand D, et al. Efficacy of oral metronidazole with vaginal clindamycin or vaginal probiotic for bacterial vaginosis: randomised placebo-controlled double-blind trial. *PLoS One.* 2012;7(4):e34540. doi: 10.1371/journal.pone.0034540. PMID: 22782818.
189. Beigi RH, Yudin MH, Cosentino L, et al. Cytokines, pregnancy, and bacterial vaginosis: comparison of levels of cervical cytokines in pregnant and nonpregnant women with bacterial vaginosis. *J Infect Dis.* 2007 Nov 1;196(9):1355-60. doi: 10.1086/521628. PMID: 18251229.
190. Paavonen J. Pelvic inflammatory disease. From diagnosis to prevention. *Dermatol Clin.* 1998 Oct;16(4):747-56, xii. PMID: 9891675.
191. Workowski KA, Bolan GA, Centers for Disease C, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015 Jun 05;64(RR-03):1-137. PMID: 26042815.
192. U. S. Food & Drug Administration. Pregnancy and Lactation Labeling (Drugs) Final Rule. Silver Spring, MD; 2018.  
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>. Accessed 05/01/2018.
193. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol.* 2012 Oct;120(4):964-73. doi: 10.1097/AOG.0b013e3182723b1b. PMID: 22996126.

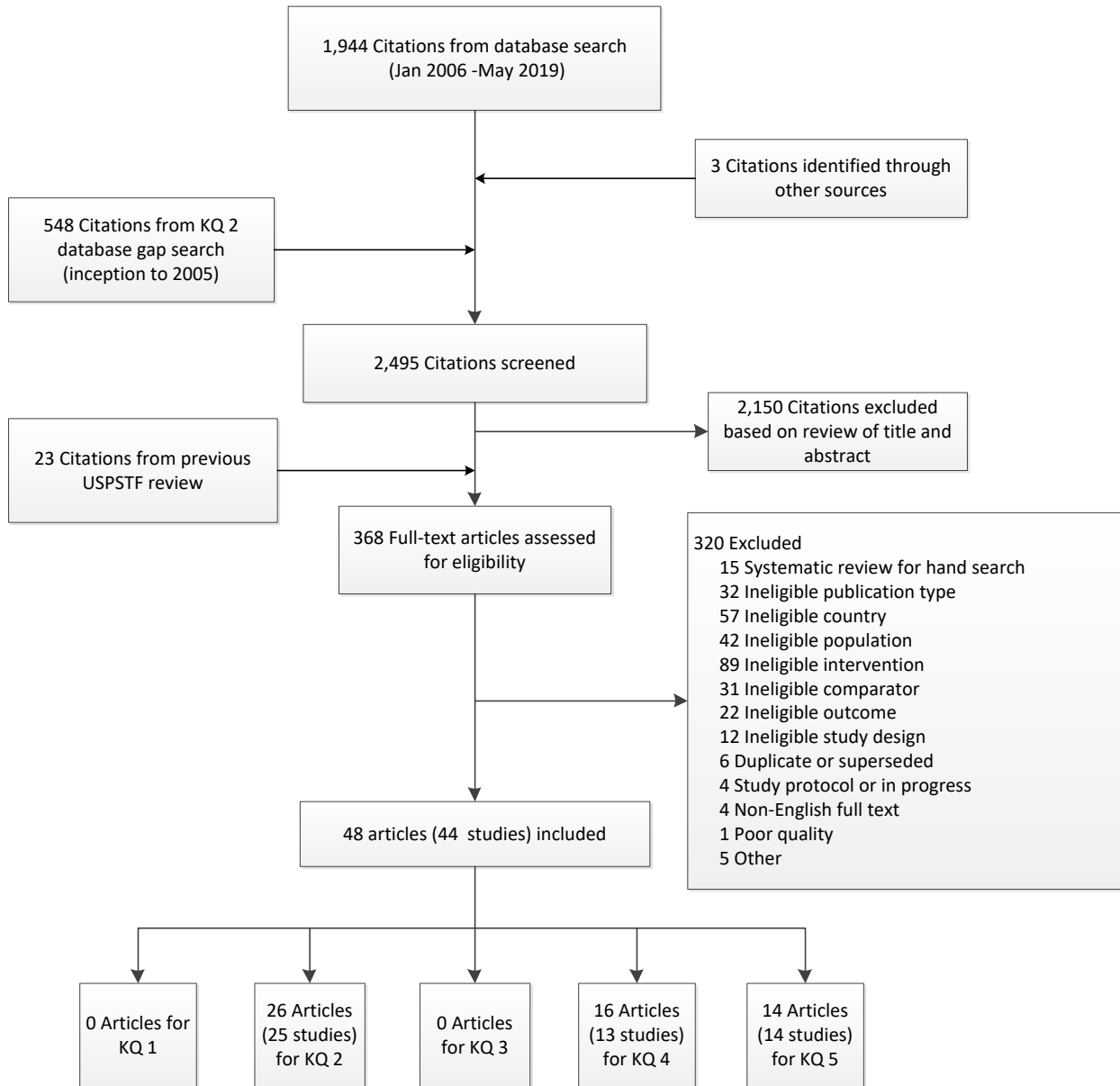
194. Yudin MH, Money DM, Boucher M, et al. Screening and Management of Bacterial Vaginosis in Pregnancy. *J Obstet Gynaecol Can.* 2008;30(8):702-8. doi: 10.1016/s1701-2163(16)32919-x.
195. Association of Reproductive Health Professionals. Hot topics in sexually transmitted infections and associated conditions. Washington, DC: Association of Reproductive Health Professionals; 2013. <http://www.arhp.org/Publications-and-Resources/Quick-Reference-Guide-for-Clinicians/Sexually-Transmitted-Infections-and-Associated-Conditions/Bacterial-Vaginosis>. Accessed December 6, 2017.
196. Hay P, Patel S, Daniels D. UK National Guideline for the management of Bacterial Vaginosis 2012. UK: Clinical Effectiveness Group, British Association for Sexual Health & HIV; 2012. <https://www.bashh.org/documents/4413.pdf>. Accessed November 20, 2017.
197. National Institute for Health and Care Excellence. Antenatal care for uncomplicated pregnancies. *NICE clinical guidelines. Updated edition. London.* 2008.
198. American Academy of Family P. Bacterial Vaginosis. Leawood, KS: American Academy of Family Physicians; 2008.
199. National Institute of Health and Care Excellence. Antenatal care for uncomplicated pregnancies update. London: National Institute of Health and Care Excellence; n.d. <https://www.nice.org.uk/guidance/indevelopment/gid-ng10096>. Accessed December 4, 2018.
200. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
201. Lin DP, Pan BJ, Fuh JC, et al. Improving Gram-stained reproducible result by further adding clue cells in diagnosing bacterial vaginosis. *Kaohsiung J Med Sci.* 2002 Apr;18(4):164-70. PMID: 12164009.
202. Jaeschke R, Guyatt G, Lijmer J. Diagnostic tests. In: Guyatt G, Rennie D, eds. *Users' guide to the medical literature.* Chicago: AMA Press; 2002:121-40.

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



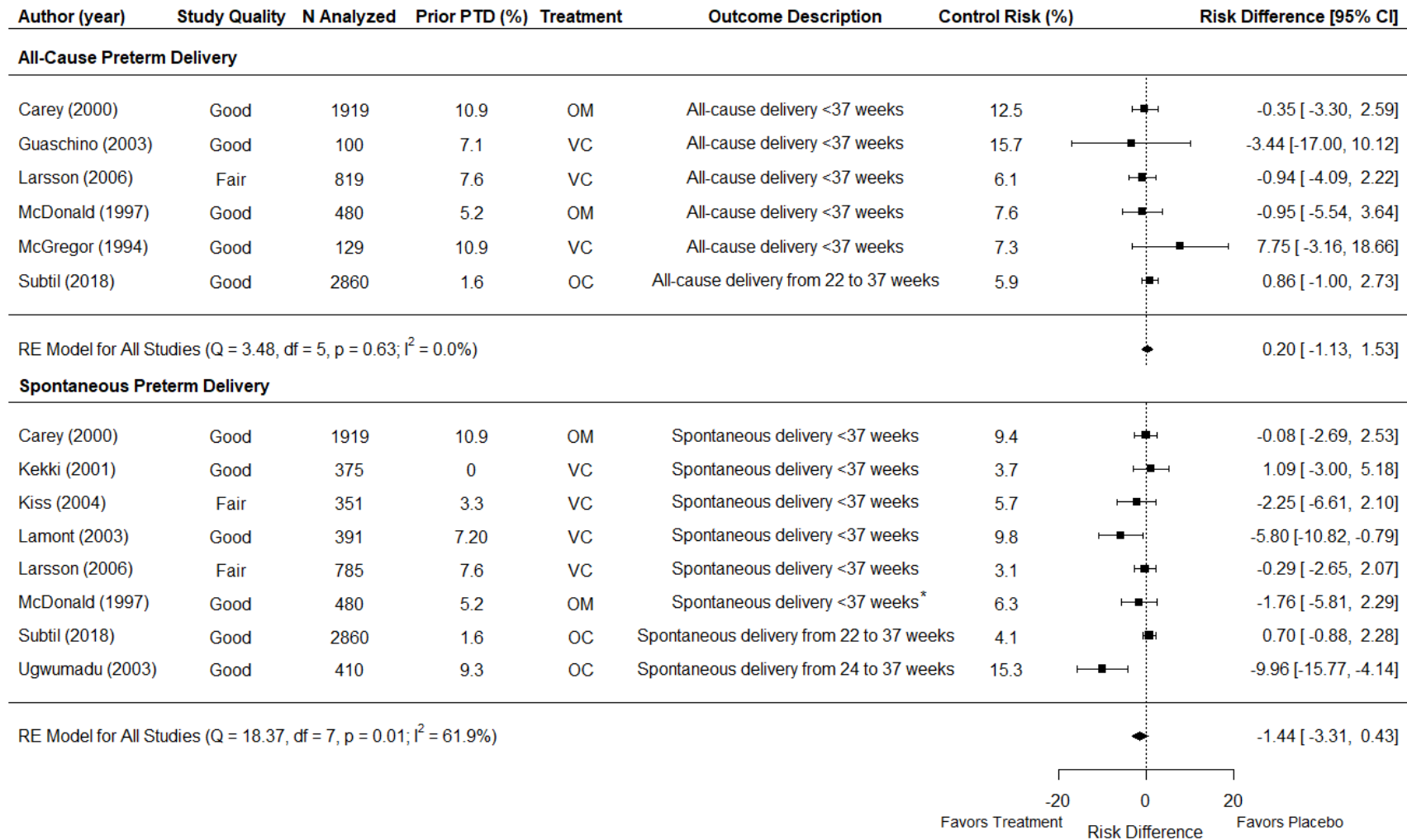
**Abbreviation:** KQ=key question.

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



**Abbreviation:** KQ=key question.

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



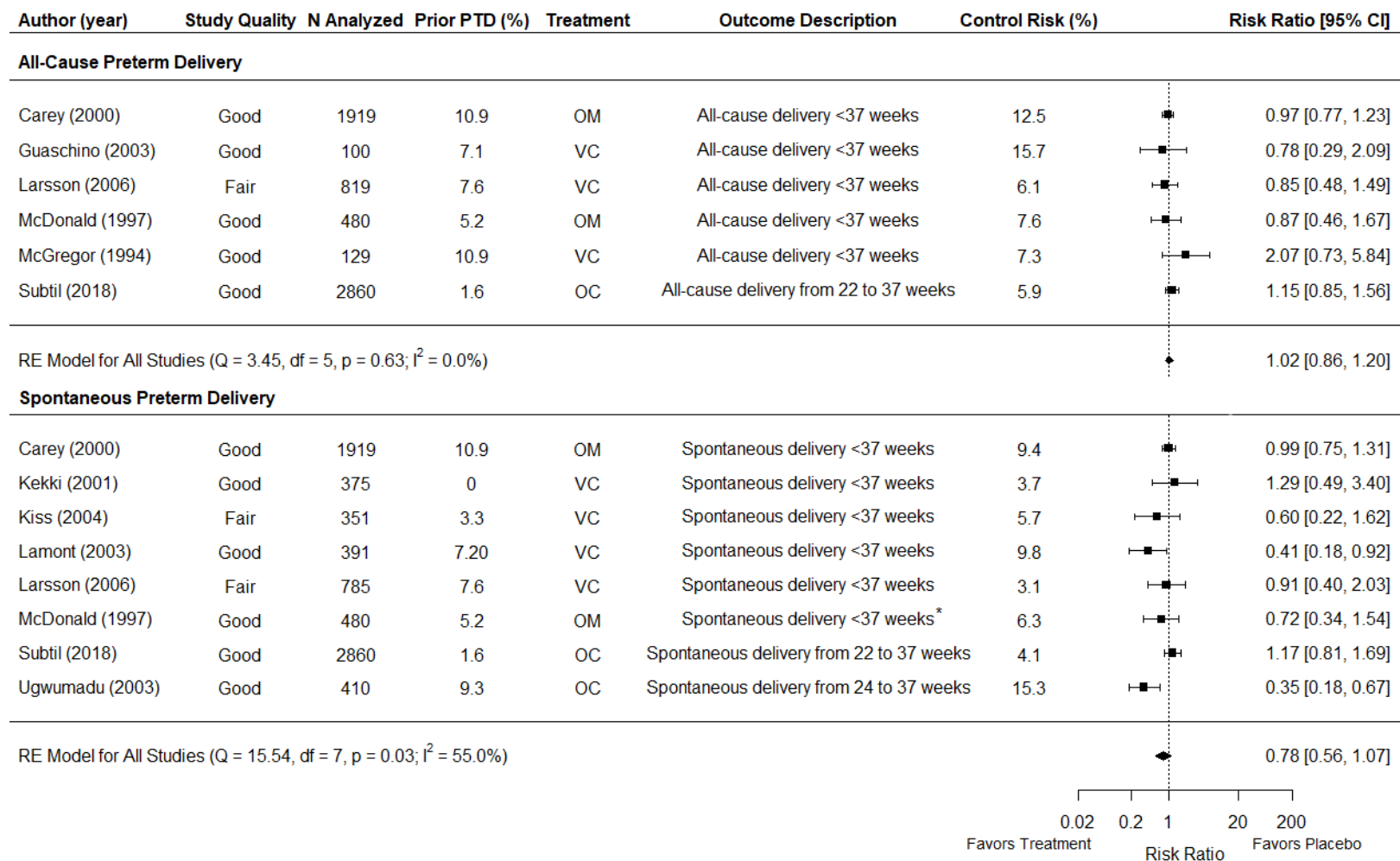
**Figure Note:** Mixed-methods test of moderators for all-cause vs. spontaneous preterm delivery: QM(df=1)=3.7044, p=0.0543.

\* 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**

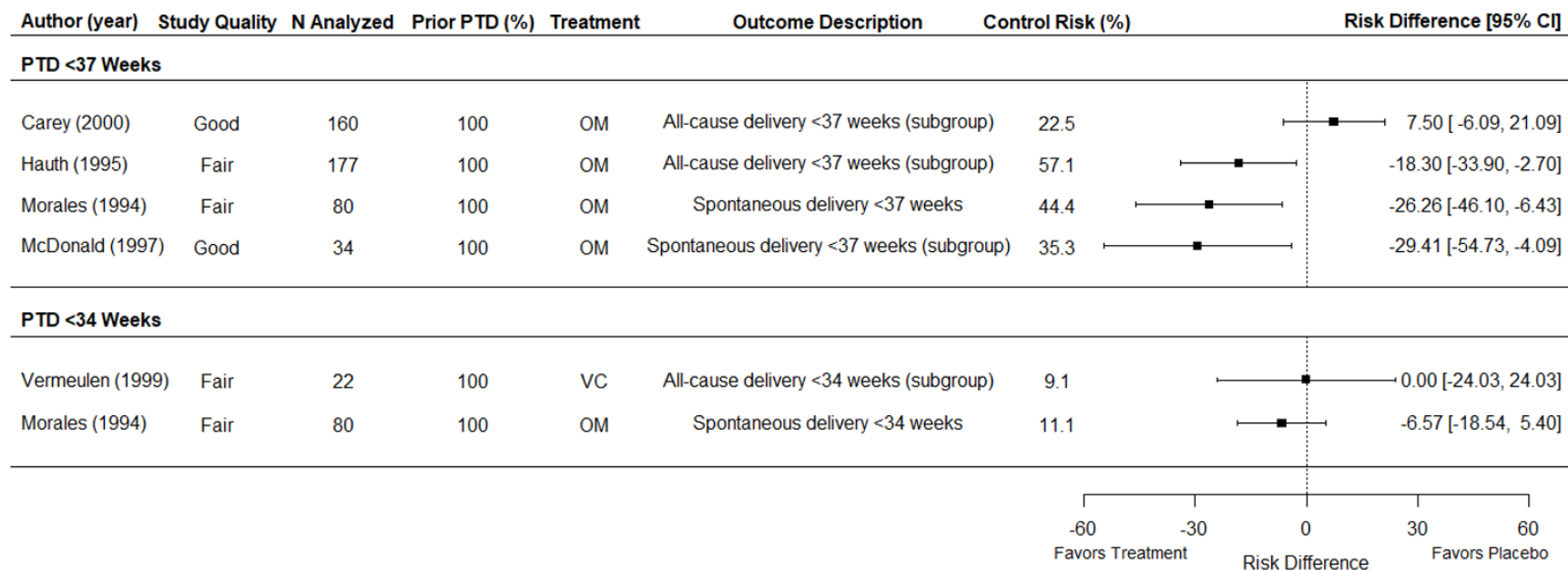


**Figure Notes:** Mixed-methods test of moderators for all-cause vs. spontaneous preterm delivery: p=0.0020.

\* 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.

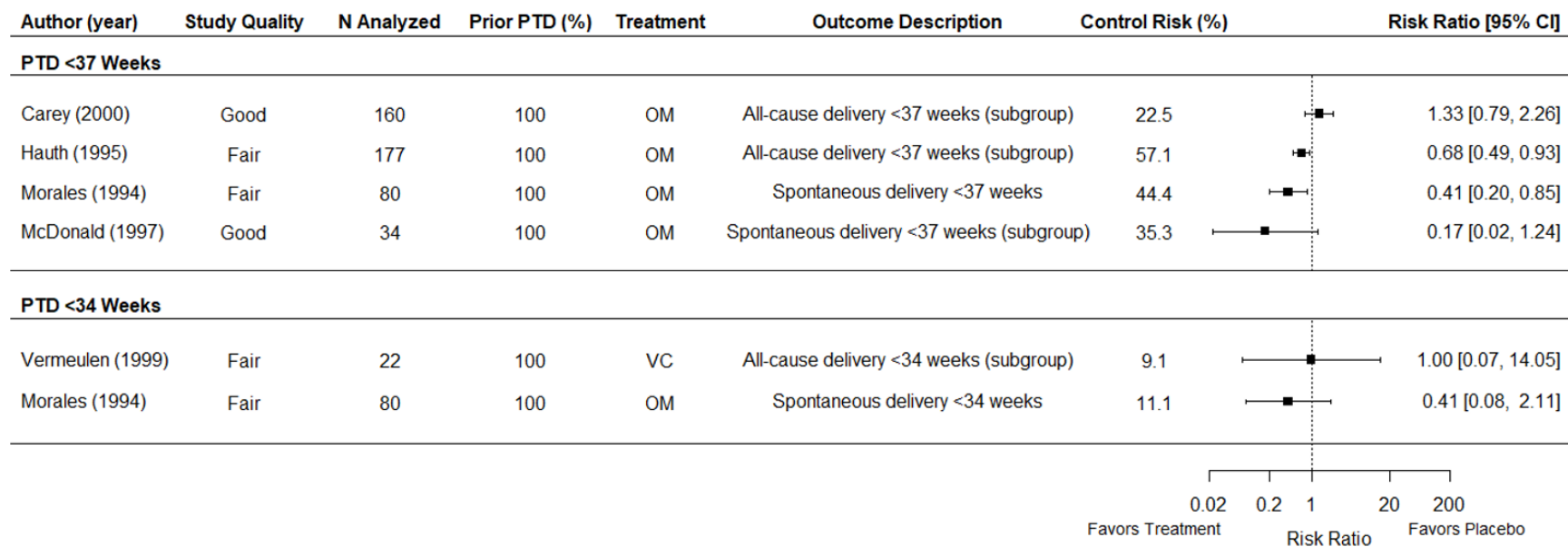
**Figure 5. Absolute Risk Difference for Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among Participants With a Prior Preterm Delivery**



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



**Figure Note:** Mixed-methods test of moderators for all-cause vs. 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 <sup>100</sup> ; 2005; Australia; BVBLUE, 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 BVBLUE 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)<br>Abnormal vaginal discharge or odor    | 0 (0) (presumably based on study entry criteria) | 0 (0) (presumably based on study entry criteria) |
| Briselden et al <sup>96</sup> ; 1994; United States; BD Affirm   | Cross-sectional; fair    | Women at a single center being seen for new genital complaints at a hospital-based STD clinic   | 176 enrolled and analyzed  | NR            | 300 (93%) African American<br>23 (7%) non-Hispanic white | 176 (100) (presumably based on study entry criteria)<br>New genital complaints                | NR   | NR   |
| Byun et al <sup>90</sup> ; 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)<br>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 <sup>95</sup> ; 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 <sup>110</sup> ; 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 <sup>103</sup> ; 2011; United States; Complete Amsel's clinical criteria | Cross-sectional; fair    | Women ages 16 to 55 years 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<br>308* (24%) white<br>218* (17%) Hispanic<br>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 <sup>88</sup> ; 2005; Spain; Complete Amsel's clinical criteria, modified Amsel's clinical 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 <sup>109</sup> ; 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<br>Positive for BV: 25.4 (7.7)<br>Negative for BV: 23.3 (6.5) | NR             | NR overall<br>Positive for BV: 47 (45)<br>Negative for BV: 41 (25)<br>Vaginal discharge, foul smelling odor, vaginal itching, or vaginal burning | 1 (0.4)          | 35 (13)  |
| Hay et al <sup>91</sup> ; 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)<br>Vaginal discharge   | NR               | NR   |
| Hellberg et al <sup>93</sup> ; 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<br>Positive for BV: 26.6 (NR)<br>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 <sup>101</sup> ; 2011; United States; BVBLUE, complete Amsel's clinical criteria | Cross-sectional; fair    | Nonmenstruating and nonpregnant women between ages 18 and 60 years, 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)<br>Abnormal vaginal odor, abnormal vaginal discharge, pruritis, vaginal burning or pain, vaginal irritation, or lower abdominal pain | NR               | 0 (0)<br>(presumably based on study entry criteria) |
| Hilmarsdottir et al <sup>104</sup> ; 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 <sup>105</sup> ; 2004; United States; Complete Amsel's clinical criteria         | Cross-sectional; fair    | Nonpregnant women between ages 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<br>190 (32%) white<br>4 (0.6%) Asian<br>3 (0.5%) Hispanic<br>6 (1%) other<br>32 (5%) multiethnic or biracial | 598 (100)<br>(presumably based on study entry criteria)<br>Untreated genital complaint  | NR               | 0 (0)<br>(presumably based on study entry criteria) |

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

| <b>Author; Year; Country; Tests Evaluated</b>   | <b>Study Design and Quality</b> | <b>Study Population and Setting</b>  | <b>Sample Size</b>         | <b>Mean Age (SD)</b> | <b>Race/Ethnicity</b>   | <b>No. (%) Symptomatic and Definition of Symptomatic (if Provided)</b>   | <b>No. (%) With HIV</b> | <b>No. (%) Pregnant</b>                             |
|---|---------------------------------|--|----------------------------|----------------------|---|--|-------------------------|---|
| Lowe et al <sup>97</sup> ; 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 U.S. 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<br>97 (18.1%) Hispanic<br>168 (31.4%) white<br>40 (7.5%) other | 547 (100) (presumably based on study entry criteria)<br>Vulvovaginal symptoms such as abnormal discharge, itching/irritation, malodor, vulvar burning, vulvar pain, vaginal discomfort, and others | NR                      | NR  |
| Mastrobattista et al <sup>89</sup> ; 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<br>23 (38%) white<br>15 (22%) Hispanic<br>3 (4%) Asian            | 0 (0) (presumably based on study entry criteria)   | NR                      | 69 (100) (presumably based on study entry criteria) |
| Myziuk et al <sup>102</sup> ; 2003; Canada; BVBLUE, complete Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test) | Cross-sectional; fair           | Nonmenstruating women age 16 years and older who presented for a pelvic examination, regardless of the reason, at a single-center STD 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 <sup>92</sup> ; 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 <sup>136</sup> ; 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 <sup>94</sup> ; 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 <sup>108</sup> ; 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 <sup>99</sup><br>Gaydos et al <sup>65</sup> ;<br>2018/2017;<br>United States;<br>BD Max, complete<br>Amsel's clinical criteria, modified<br>Amsel's clinical criteria, individual criteria (pH, vaginal discharge, clue cells, whiff test) | Cross-sectional;<br>fair | Women at least age 14 or 18 years (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<br>Parent study (N=1,667): 29.3 (9.4) | NR             | 1,760 (100) (presumably based on study entry criteria)<br>Abnormal discharge; painful or frequent urination; vaginal itching, burning, or irritation; painful or uncomfortable intercourse; vaginal odor | NR for BV test subgroup.<br>Parent study (N=1,667): 17 (1.0) positive, 257 (15.3) unknown | NR   |
| Sha et al <sup>106</sup> ;<br>2007;<br>United States;<br>Complete Amsel's clinical criteria   | Cross-sectional;<br>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 <sup>107</sup> ;<br>2013;<br>United States;<br>Complete Amsel's clinical criteria, modified<br>Amsel's clinical criteria  | Cross-sectional;<br>fair | Nonpregnant women ages 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)<br>Symptoms of vaginal discharge  | 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                                       |
|--|--------------------------|--|--|--|----------------|--|------------------|--|
| Sonnex et al <sup>137</sup> ; 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   |
| Witt et al <sup>98</sup> ; 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;<br>Year<br>Country                                 | Reference Test   | N (%) With<br>Confirmed BV<br>on Referent<br>Test | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive<br>Likelihood<br>Ratio | Negative<br>Likelihood<br>Ratio | Other Comments   |
|--|--|---|-------------------------|-------------------------|---------------------------------|---------------------------------|--|
| Briselden et al <sup>96</sup> ;<br>1994;<br>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 <sup>90</sup> ;<br>2016<br>South Korea          | Gram stain (Nugent score ≥7)   | 68 (34.9)   | 0.75 (NR)               | 0.89 (NR)               | 6.8* (4.1* to 11.4*)            | 0.28* (0.19* to 0.43*)          | None   |
| Cartwright et al <sup>95</sup> ;<br>2013;<br>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 <sup>97</sup> ;<br>2009;<br>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 <sup>98</sup> ;<br>2002;<br>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 sensitivity is 0.90 (95% CI, 0.85 to 0.94) and the specificity is 0.97 (95% CI, 0.96 to 0.98). When participant with Nugent score 4 to 6 are included and considered positive for BV, the sensitivity is 0.73 (95% CI, 0.69 to 0.78) and specificity 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.

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

| Author;<br>Year<br>Country  | Reference Test   | N (%) With<br>Confirmed BV<br>on Referent<br>Test | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive<br>Likelihood<br>Ratio | Negative<br>Likelihood<br>Ratio | Other Comments   |
|---|--|---|-------------------------|-------------------------|---------------------------------|---------------------------------|--|
| Schwebke et al <sup>99</sup><br>Gaydos et al <sup>65</sup> ;<br>2018/2017;<br>United States | Gram stain (Nugent score $\geq 7$ ); 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 <sup>65</sup> 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—BVBLUE (Key Question 2)**

| Author;<br>Year<br>Country                         | Reference<br>Test   | N (%) With<br>Confirmed BV<br>on Referent<br>Test | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive<br>Likelihood<br>Ratio | Negative<br>Likelihood<br>Ratio | Other Comments  |
|--|---|---|-------------------------|-------------------------|---------------------------------|---------------------------------|---|
| Bradshaw et al <sup>100</sup> ; 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 specificity of 0.97 (95% CI, 0.92 to 0.99). |
| Bradshaw et al <sup>100</sup> ; 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 <sup>101</sup> ; 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 <sup>102</sup> ; 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 <sup>100</sup> ; 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 <sup>110</sup> ; 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 <sup>103</sup> ; 2011; United States   | Gram stain (Nugent score ≥7)                           | HIV positive: 1,046 (34.8)<br>HIV negative: 2,347 (38.3) (from visits, not number of participants) | HIV positive: 0.58 (0.56 to 0.60)<br>HIV negative: 0.63 (0.60 to 0.66) | HIV positive: 0.90 (0.89 to 0.91)<br>HIV negative: 0.91 (0.90 to 0.92) | HIV positive: 5.6* (5.1* to 6.2*)<br>HIV negative: 6.8* (5.9* to 7.9*) | HIV positive: 0.47* (0.45* to 0.49*)<br>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 <sup>88</sup> ; 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 <sup>109</sup> ; 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 <sup>91</sup> ; 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 <sup>101</sup> ; 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 <sup>104</sup> ; 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)<br>Note: The number of false-positive results was incorrectly reported in the text.                                  |
| Landers et al <sup>105</sup> ; 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 <sup>102</sup> ; 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;<br>Year<br>Country  | Reference Test   | N (%) With<br>Confirmed BV on<br>Referent Test  | Sensitivity<br>(95% CI)  | Specificity<br>(95% CI)   | Positive<br>Likelihood<br>Ratio  | Negative<br>Likelihood<br>Ratio   | Other Comments  |
|---|--|---|--|---|--|---|---|
| Platz-Christensen<br>et al <sup>92</sup> ;<br>1995;<br>Sweden                               | Gram stain<br>(Spiegel’s criteria)   | 36 (33.3*)  | 0.94* (0.82* to<br>0.98*)  | 1.0* (0.95* to<br>1.0*)   | Infinite*  | 0.06* (0.01*<br>to 0.21*)   | Note: The study authors report<br>sensitivity and specificity for<br>Amsel’s clinical criteria as the<br>referent test and Gram stain as<br>the index test. |
| Sha et al <sup>106</sup> ;<br>2007;<br>United States  | Gram stain<br>(Nugent score ≥7)  | HIV positive: 6,050<br>(37.2*)<br>HIV negative: 1,880<br>(43.5*)<br>(from visits, not<br>number of<br>participants) | HIV positive:<br>0.36 (0.35 to<br>0.37)<br>HIV negative:<br>0.39 (0.36 to<br>0.41) | HIV positive:<br>0.971 (0.967<br>to 0.974)<br>HIV<br>negative:<br>0.978 (0.971<br>to 0.983) | HIV positive:<br>12.2* (10.8* to<br>13.7*)<br>HIV negative:<br>17.2* (13.2* to<br>22.5*) | HIV positive:<br>0.66* (0.65*<br>to 0.68*)<br>HIV<br>negative:<br>0.63* (0.61*<br>to 0.65*) | Only data from the HIV-<br>negative population were used<br>in our synthesis (i.e., SROC<br>and forest plot).   |
| Schwebke et<br>al <sup>108</sup> ;<br>1996;<br>United States                                | Gram stain<br>(Nugent score ≥7)  | 243 (39.4)  | 0.62 (0.55* to<br>0.68*)   | 0.97 (0.94*<br>to 0.98*)  | 17.8* (10.3* to<br>30.6*)  | 0.40* (0.34*<br>to 0.47*)   | If “any clue cells” criteria used<br>in place of 20% clue cells, the<br>sensitivity is 0.704 and<br>specificity is 0.944.                                   |
| Schwebke et al <sup>99</sup><br>Gaydos et al <sup>65</sup> ;<br>2018/2017;<br>United States | Gram stain<br>(Nugent score<br>≥7); participants<br>with Nugent score<br>4 to 6 were<br>excluded (N=213) | 783 (50.5*)   | 0.76 (0.72 to<br>0.79)   | 0.94 (0.92 to<br>0.96)  | 12.8* (9.2* to<br>18.0*)   | 0.26* (0.23*<br>to 0.30*)   | None  |
| Singh et al <sup>107</sup> ;<br>2013;<br>United States                                      | Gram stain<br>(Nugent score ≥7)  | 125 (63.5*)   | 0.72* (0.64* to<br>0.79*)  | 0.79*<br>(0.68*to<br>0.87*)   | 3.5* (2.2* to<br>5.5*)   | 0.35* (0.26*<br>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 <sup>88</sup> ; 2005; Spain   | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>89</sup> ; 2000; United States                             | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>108</sup> ; 1996; United States                                  | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>99</sup> ; Gaydos et al <sup>65</sup> ; 2018/2017; United States | Gram stain (Nugent score $\geq 7$ ); 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 <sup>107</sup> ; 2013; United States                                     | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>111</sup><br>Andrews et al <sup>127</sup><br>2000               | U.S.    | Good          | G1: Placebo (987)<br>G2: Oral metronidazole 1,000 mg dose four times on days 0, 2, 14, and 16 (966)                     | 0 (0)                  | G1: 407 (41.2)<br>G2: 436 (45.1)               | G1: 841 (85.2)<br>G2: 822 (85.1)                 | G1: 110 (11.1)<br>G2: 103 (10.7)                        | <ul style="list-style-type: none"> <li>All-cause and spontaneous PTD &lt;37, 35, and 32 weeks</li> <li>Birth weight &lt;2,500 and 1,500 g</li> <li>Subgroup findings for women with prior PTD; treatment for chlamydia, and BV clearance</li> <li>Any maternal tolerability-related side effects; GI symptoms; candidiasis</li> </ul> |
| Guaschino et al <sup>112</sup><br>2003   | Italy   | Fair          | G1: No treatment (57)<br>G2: Intravaginal clindamycin 2% cream once daily for 7 days (55)                               | 0 (0)                  | G1: 35 (61.4)<br>G2: 39 (70.9)                 | NR   | G1: 3 (5.3)<br>G2: 5 (9.1)                              | <ul style="list-style-type: none"> <li>All-cause PTD &lt;37 weeks;</li> <li>Birthweight &lt;2,500 g</li> <li>Preterm or term PROM</li> </ul>  |
| Hauth et al <sup>121</sup><br>1995   | U.S.    | Fair          | G1: Placebo (87)*<br>G2: Oral metronidazole (750 mg daily) for 7 days and erythromycin (999 mg daily) for 14 days (176) | NR                     | For parent study<br>G1: 30 (16)<br>G2: 84 (19) | For parent study<br>G1: 150 (79)<br>G2: 309 (71) | For subgroup with BV<br>G1: 56 (65.1)<br>G2: 121 (70.3) | <ul style="list-style-type: none"> <li>All-cause PTD &lt;37 weeks</li> <li>Subgroup findings among women with prior PTD</li> </ul>  |
| Kekki et al <sup>113</sup><br>2001<br>Kurkinen-Raty et al <sup>126</sup><br>2000 | Finland | Good          | G1: Placebo (188)<br>G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)                                  | 0 (0)                  | Mean parity<br>G1: 1.9<br>G2: 1.7              | NR   | 0 (0)   | <ul style="list-style-type: none"> <li>Spontaneous PTD &lt;37 weeks</li> <li>Maternal peripartum infection</li> <li>Subgroup findings among participants with clearance of BV and participants with IF</li> <li>Maternal candidiasis</li> </ul>   |

**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 <sup>114</sup><br>2004     | Austria   | Fair          | G1: No treatment (179) <sup>†</sup><br>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)<br>G2: NR (47.9)   | NR (2)                         | Between 33 and 36 weeks:<br>G1: 45 (2.1)<br>G2: 47 (2.2)<br>Between 23 and 32 weeks:<br>G1: 24 (1.1)<br>G2: 22 (1.1) | <ul style="list-style-type: none"> <li>• Spontaneous PTD &lt;37 weeks</li> <li>• Any maternal AEs</li> </ul>  |
| Lamont et al <sup>115</sup><br>2003   | U.K.      | Good          | G1: Placebo (201)<br>G2: Intravaginal clindamycin 2% cream, once daily for 3 days (208)   | 0 (0)                  | G1: 112 (56)<br>G2: 111 (53)     | G1: 63 (31)<br>G2: 58 (28)     | G1: 11 (8)<br>G2: 10 (7)   | <ul style="list-style-type: none"> <li>• Spontaneous PTD &lt;37 weeks</li> <li>• Birth weight &lt;2,500 and 1,500 g</li> <li>• Stillborn fetus</li> </ul>   |
| Larsson et al <sup>116</sup><br>2006  | Sweden    | Fair          | G1: No treatment (411)<br>G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)  | 0 (0)                  | G1: 187 (45.5)<br>G2: 186 (45.5) | NR                             | Among parous women<br>G1: 13/218 (6.0)<br>G2: 20/217 (9.2)   | <ul style="list-style-type: none"> <li>• All-cause PTD &lt;37 weeks</li> <li>• Spontaneous PTD &lt;37 and &lt;32 completed weeks</li> <li>• Any maternal severe AEs</li> <li>• Treatment withdrawal</li> </ul>  |
| McDonald et al <sup>117</sup><br>1997 | Australia | Good          | G1: Placebo (440)<br>G2: Oral metronidazole 800 mg daily for 2 days repeated at 28 weeks for women with persistence (439)   | 0 (0)                  | G1: 144 (32.7)<br>G2: 139 (31.7) | G1: 53 (12.3)<br>G2: 47 (10.8) | G1: 24 (5.5)<br>G2: 22 (5.0)   | <ul style="list-style-type: none"> <li>• All-cause and spontaneous PTD &lt;37 weeks</li> <li>• Preterm PROM</li> <li>• Subgroup findings for women with prior PTD</li> <li>• Any maternal AEs or tolerability-related side effects</li> <li>• Treatment withdrawal</li> </ul> |
| McGregor et al <sup>118</sup><br>1994 | U.S.      | Good          | G1: Placebo (69 analyzed)<br>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)  | <ul style="list-style-type: none"> <li>• All-cause PTD &lt;37 weeks</li> <li>• Preterm PROM</li> <li>• Preterm labor</li> <li>• Birthweight &lt;2,500 g</li> </ul>  |

**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   |
|--|-----------------|---------------|--|------------------------|---|----------------------------|------------------------------|---|
| Morales et al <sup>122</sup><br>1994   | U.S.            | Fair          | G1: Placebo (36 analyzed)<br>G2: Oral metronidazole 750 mg daily for 7 days (44 analyzed)  | NR                     | Mean parity<br>G1: 2.2 (1.1)<br>G2: 2.4 (1.2) | G1: 18 (50)<br>G2: 20 (45) | 80 (100)                     | <ul style="list-style-type: none"> <li>• Spontaneous PTD &lt;37 and 34 weeks</li> <li>• Preterm labor</li> <li>• PROM</li> <li>• Birthweight &lt;2,500 g</li> </ul>   |
| Subtil et al <sup>119</sup><br>2018    | France          | Good          | G1: Placebo (956)<br>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                           | <ul style="list-style-type: none"> <li>• All-cause and spontaneous PTD &lt;37 weeks</li> <li>• Spontaneous PTD &lt;32 weeks</li> <li>• Neonatal mortality</li> <li>• Any maternal severe AEs; any tolerability-related side effects; GI symptoms</li> <li>• Treatment withdrawal</li> </ul> |
| Ugwumadu et al <sup>120</sup><br>2003  | U.K.            | Good          | G1: Placebo (245) <sup>†</sup><br>G2: Oral clindamycin 600 mg daily for 5 days (249)   | NR                     | Mean parity<br>G1: 0.8 (1.0)<br>G2: 0.8 (1.1) | G1: 93 (39)<br>G2: 86 (36) | G1: 22 (9)<br>G2: 24 (10)    | <ul style="list-style-type: none"> <li>• Spontaneous PTD &lt;37 weeks</li> <li>• Subgroup findings among participants with intermediate flora</li> <li>• Any maternal AEs or tolerability-related side effects; GI symptoms</li> <li>• Treatment withdrawal</li> </ul>                      |
| Vermeulen et al <sup>123</sup><br>1999 | The Netherlands | Good          | G1: Placebo (11) <sup>§</sup><br>G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11)  | NR                     | Mean parity<br>G1: 1.4 (0.9)<br>G2: 1.6 (0.9) | NR                         | G1: 11 (100)<br>G2: 11 (100) | <ul style="list-style-type: none"> <li>• All-cause PTD &lt;34 weeks</li> <li>• Neonatal sepsis</li> <li>• Maternal candidiasis</li> <li>• Treatment withdrawal</li> </ul>   |

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

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

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

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

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| Author et al;<br>Publication Year;<br>Intervention (N<br>Analyzed)<br>Comparator (N<br>Analyzed)  | PTD <37 Weeks; N (%)<br>Effect Estimates (95% CI)   | Other PTD Outcomes; N<br>(%)<br>Effect Estimates (95% CI)   | Other Pregnancy Outcomes; N<br>(%)<br>Effect Estimates (95% CI) | Subgroup Analyses |
|---|---|---|---|-------------------|
| Larsson et al <sup>16</sup> ;<br>2006;<br><br>G1: no treatment (411)<br>G2: Intravaginal<br>clindamycin 2% cream,<br>once daily for 7 days<br>(408) | <p><b>All-cause PTD</b> (primary outcome)<br/>                     G1: 25 (6.1)<br/>                     G2: 21 (5.2)<br/>                     OR, 0.84 (0.48 to 1.47)<br/>                     Calculated ARD, -0.94%<br/>                     (-4.09% to 2.22%)<br/>                     Calculated RR, 0.85 (0.48 to 1.49)</p> <p><b>Spontaneous PTD (between 16 and 37 weeks)</b><br/>                     G1: 12/390 (3.1)<br/>                     G2: 11/395 (2.8)<br/>                     OR, 0.90 (0.40 to 2.02)<br/>                     Calculated ARD, -0.29%<br/>                     (-2.65% to 2.07%)<br/>                     Calculated RR, 0.91 (0.40 to 2.03)</p> | <p><b>Spontaneous PTD (between 16 and &lt;32 completed weeks)</b><br/>                     G1: 5/390 (1.3)<br/>                     G2: 1/395 (0.25)<br/>                     Calculated ARD, -1.03%<br/>                     (-2.25% to 0.19%)<br/>                     Calculated RR, 0.20 (0.02 to 1.68)</p> | 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;<br>Publication Year;<br>Intervention (N<br>Analyzed)<br>Comparator (N<br>Analyzed)  | PTD <37 Weeks; N (%)<br>Effect Estimates (95% CI)   | Other PTD Outcomes; N<br>(%)<br>Effect Estimates (95% CI) | Other Pregnancy Outcomes; N<br>(%)<br>Effect Estimates (95% CI)   | Subgroup Analyses  |
|---|---|---|---|--|
| <p>McDonald et al<sup>117</sup>;<br/>1997;</p> <p>G1: Placebo (428)<br/>G2: Oral metronidazole<br/>800 mg daily for 2 days<br/>and repeated at 28<br/>weeks gestation for<br/>positive test of cure<br/>(429)</p> | <p><b>All-cause PTD</b><br/>G1: 32 (7.5)<br/>G2: 31 (7.2)<br/>Calculated ARD, -0.95%<br/>(-5.54% to 3.64%)<br/>Calculated RR, 0.87 (0.46 to<br/>1.67)</p> <p><b>Spontaneous PTD (primary<br/>outcome)</b><br/>G1: 24 (5.6)<br/>G2: 20 (4.7)<br/>OR, 0.82 (0.43 to 1.57)<br/>Calculated ARD, -1.76%<br/>(-5.81% to 2.29%)<br/>Calculated RR, 0.72 (0.34 to<br/>1.54)</p> | <p>NR</p>   | <p><b>PPROM</b><br/>G1: 14 (3.3)<br/>G2: 12 (2.8)<br/>OR, 0.85 (0.36 to 1.98)<br/>Calculated ARD, -1.72% (-4.94%<br/>to 1.49%)<br/>Calculated RR, 0.59 (0.22 to 1.60)</p> | <p><b>All-cause PTD &lt;37 weeks among<br/>subgroup of women who were smear<br/>positive</b> (i.e., not including women with<br/>heavy growth of <i>G. vaginalis</i>)<br/>G1: 18/238 (7.6)<br/>G2: 16/242 (6.6)<br/>OR, 0.87 (0.41 to 1.83)<br/>Calculated ARD, -0.95% (-5.54% to 3.64%)<br/>Calculated RR, 0.87 (0.46 to 1.67)</p> <p><b>Spontaneous PTD &lt;37 weeks among<br/>subgroup of women who were smear<br/>positive</b> (i.e., not including women with<br/>heavy growth of <i>G. vaginalis</i>)<br/>G1: 15/238 (6.3)<br/>G2: 11/242 (4.5)<br/>OR, 0.71 (95% CI, 0.30 to 1.68)<br/>Calculated ARD, -1.76% (-5.81% to 2.30%)<br/>Calculated RR, 0.72 (0.34 to 1.54)</p> <p><b>Spontaneous PTD &lt;37 weeks among<br/>subgroup of women with prior PTD</b><br/>G1: 10/24 (41.7)<br/>G2: 2/22 (9.1)<br/>OR, 0.14 (0.01 to 0.84)<br/>Calculated ARD, -29.41% (-54.73% to<br/>-4.09%)<br/>Calculated RR, 0.17 (0.02 to 1.24)</p> |

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

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

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

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

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

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|--|--|---|---|--|
| Vermeulen et al <sup>123</sup> ;<br>1999;<br><br>G1: Placebo (11) <sup>§</sup><br>G2: Intravaginal<br>clindamycin 2% cream<br>once daily for 7 days at<br>26 weeks and again at<br>32 weeks (11) | NR for women with bacterial<br>vaginosis but was the<br>primary outcome for the<br>overall study | NR  | <b>Neonatal sepsis</b><br>G1: 0 (0)<br>G2: (0)                  | <b>All-cause PTD &lt;34 weeks among women<br/>with bacterial vaginosis</b><br>G1: 1 (9.1)<br>G2: 1 (9.1)<br>ARD 0% (95% CI, -24.03% to 24.03%) |

\* This study assessed the effect 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.

‡ Although the study included women with either intermediate flora or BV, the outcome reported here is for the subgroup with BV (Nugent score  $\geq 7$ ).

§ 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; PPRM=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;<br>Publication Year;<br>Intervention (N Analyzed)<br>Comparator (N Analyzed)  | Maternal Harms   |
|---|--|
| <p>Carey et al<sup>111</sup>;<br/>2000;</p> <p>G1: Placebo (859)<br/>G2: Oral metronidazole 1000 mg dose four times (845)</p>   | <p><b>Side effects</b><br/>G1: 88/966 (9.1%)<br/>G2: 206/953 (21.6%)<br/>Calculated ARD, 12.51% (95% CI, 9.33% to 15.69%)<br/>Calculated RR, 2.37 (95% CI, 1.88 to 3.00)</p> <p><b>GI symptoms</b><br/>G1: 72/966 (7.45%)<br/>G2: 188/953 (19.73%)<br/>Calculated ARD, 12.27% (95% CI, 9.25% to 15.29%)<br/>Calculated RR, 2.65 (95% CI, 2.05 to 3.42)</p> <p><b>Vomiting</b><br/>G1: 27/966 (2.80%)<br/>G2: 92/953 (9.65%)<br/>Calculated ARD, 6.86% (95% CI, 4.72% to 9.00%)<br/>Calculated RR, 3.45 (95% CI, 2.27 to 5.25)</p> <p><b>Treatment of candida infection</b><br/>G1: 47/966 (4.87%)<br/>G2: 114/953 (11.96%)<br/>Calculated ARD, 7.10% (95% CI, 4.63% to 9.56%)<br/>Calculated RR, 2.46 (1.78 to 3.41)</p> |
| <p>Kekki et al<sup>113</sup>;<br/>2001;<br/>Kurkinen-Raty et al<sup>126</sup>;<br/>2000;</p> <p>G1: Placebo (188)<br/>G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)</p>                   | <p><b>Vulvovaginal itching consistent with yeast infection</b><br/>G1: 6/188 (3.19%)<br/>G2: 6/187 (3.21%)<br/>Calculated ARD, 0.02% (95% CI, -3.55% to 3.58%)<br/>Calculated RR, 1.01 (95% CI, 0.33 to 3.06)</p>  |
| <p>Kiss et al<sup>114</sup>;<br/>2004</p> <p>G1: No treatment (176)<sup>†</sup><br/>G2: Intravaginal clindamycin 2% cream once daily for 6 days with test of cure and further treatment if positive (175)</p> | <p><b>AEs</b><br/>G1: 0<br/>G2: 0</p>  |

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

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



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

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

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

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

\* 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.

§ 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]).

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

**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)<br>Study Quality                  | Study Design, Years Covered   | Number of Participants,<br>Study Population(s)  | Exposure Description   | Summary of Outcomes   |
|---|---|---|--|---|
| Burtin et al (1995) <sup>133</sup><br>Fair      | Meta-analysis of 7 single or controlled-cohort studies published 1964 to 1987   | N not reported<br>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<br>Summary OR, 0.93 (95% CI, 0.73 to 1.18)<br><br>Incidence of any congenital anomalies<br>Summary OR, 0.96 (95% CI, 0.75 to 1.22)  |
| Caro-Paton et al (1997) <sup>134</sup><br>Fair  | Meta-analysis of 5 studies (4 cohort and 1 case control) published 1977 to 1994 | N=199,451<br>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<br>Summary OR, 1.08 (95% CI, 0.90 to 1.29)  |
| Czeizel et al (1998) <sup>131</sup><br>Fair     | Case control, 1980 to 1991  | N=47,963<br>Pregnant women in Hungary identified through registries   | Use of oral or intravenous metronidazole during pregnancy based on self-report, clinician prenatal care log books, or both               | Incidence of congenital abnormalities:<br>Exposure during 1st month: OR, 2.24 (95% CI, 1.30 to 3.85)<br>Exposure during 2 <sup>nd</sup> or 3 <sup>rd</sup> month: OR, 1.14 (95% CI, 0.89 to 1.46)<br>Exposure during 5 <sup>th</sup> through 9 <sup>th</sup> month: OR, 1.07 (95% CI, 0.95 to 1.20) |
| Diav-Citrin et al (2001) <sup>129</sup><br>Poor | Prospective cohort, 1989 to 1998  | N=857<br>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<br>RR, 1.13 [95% CI, 0.30 to 4.23)   |
| Sorensen et al (1999) <sup>130</sup><br>Fair    | Retrospective cohort, 1991 to 1996  | N=13,451<br>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<br>Adjusted OR, 0.44 (95% CI, 0.11 to 1.81)   |
| Thapa (1998) <sup>132</sup><br>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 years<br>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   |
|--|---|---|--|--|--|---|
| <b>KQ 1 Benefits of screening</b>              | No studies identified   |   |  |  |  |   |
| <b>KQ 2 Diagnostic test accuracy (by test)</b> |   |   |  |  |  |   |
| BD Affirm                                      | 5 cross-sectional studies <sup>90, 95-98</sup> ; N=2,936            | Pooled Sn, 0.87 (95% CI, 0.80 to 0.92)<br>Pooled Sp, 0.81 (95% CI, 0.73 to 0.88)<br>Pooled +LR, 4.6 (95% CI, 3.1 to 6.8)<br>Pooled -LR, 0.16 (95% CI, 0.11 to 0.26)                                     | Inconsistent*/precise <sup>†</sup>   | 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 <sup>65, 99</sup> ; N=1,338                 | Sn, 0.93 (95% CI, 0.91 to 0.94)<br>Sp, 0.92 (95% CI, 0.90 to 0.94)<br>+LR, 10.9 (95% CI 8.3 to 14.5)<br>-LR, 0.08 (95% CI 0.06 to 0.10)   | Unknown consistency/precise <sup>†</sup>   | Excluded participants with intermediate flora from analysis  | LOW <sup>§</sup> for adequate accuracy | Symptomatic women   |
| BV Blue  | 3 cross-sectional studies <sup>100-102</sup> ; N=864                | Sn, range 0.61 to 0.92 across studies<br>Sp, range 0.86 to 0.99 across studies  | Inconsistent <sup>†</sup> (more inconsistent for Sn than Sp)/precise <sup>¶</sup> (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 <sup>88, 91, 92, 99-110</sup> ; N=7,171  | Based on 14 of the 15 studies:<br>Pooled Sn, 0.76 (95% CI, 0.63 to 0.85)<br>Pooled Sp, 0.95 (95% CI, 0.89 to 0.98)<br>Pooled +LR, 14.1 (95% CI, 6.8 to 29.2)<br>Pooled -LR, 0.26 (95% CI, 0.17 to 0.39) | Inconsistent <sup>¶</sup> /precise <sup>**</sup> (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 <sup>88, 89, 99, 107, 108</sup> ; N=2,674 | Based on 4 of the 5 studies:<br>Pooled Sn, 0.67 (95% CI, 0.54 to 0.78)<br>Pooled Sp, 0.96 (95% CI, 0.93 to 0.98)<br>Pooled +LR, 17.3 (95% CI, 10.4 to 28.8)<br>Pooled -LR, 0.34 (95% CI, 0.24 to 0.48)  | Inconsistent <sup>††</sup> (more inconsistent for Sn than Sp)/precise <sup>¶</sup> (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                                   |
| <b>KQ 3 Harms of screening</b>                 | 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   |
|---------------------------------------|---|---|---|---|--|---|
| <b>KQ 4<br/>Benefits of treatment</b> | 6 RCTs <sup>111, 112, 116-119</sup> ;<br>N=6,307      | All-cause preterm delivery <37 weeks in general obstetric population:<br>Pooled ARD, 0.20% (95% CI, -1.13% to 1.53%)<br>Pooled RR, 1.02 (95% CI, 0.86 to 1.20)    | Consistent/<br>imprecise <sup>§§</sup>                  | 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 <sup>111, 113-117, 119, 120</sup> ;<br>N=7,571 | Spontaneous preterm delivery <37 weeks in general obstetric population:<br>Pooled ARD, -1.44% (95% CI, -3.31% to 0.43%)<br>Pooled RR, 0.78 (95% CI, 0.56 to 1.07) | Inconsistent <sup>  </sup> /<br>imprecise <sup>¶¶</sup> | All but 2 studies of good methodological quality; no reporting bias detected  | LOW for no benefit of treatment        | Same as previous row  |
|                                       | 3 RCTs <sup>111, 116, 119</sup><br>N=5,564            | Preterm delivery <32 weeks in general obstetric population<br>Pooled ARD, -0.30% (95% CI, -0.97% to 0.38%)<br>Pooled RR, 0.87 (95% CI, 0.54 to 1.42)              | Consistent/<br>precise <sup>###</sup>                   | 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 <sup>111, 112, 115, 118, 119</sup><br>N=5,377  | Birth weight <2,500 g in general obstetric population<br>Pooled ARD, 0.39% (95% CI, -1.74% to 2.53%)<br>Pooled RR, 1.03 (95% CI, 0.83 to 1.29)                    | Consistent/<br>imprecise <sup>***</sup>                 | All studies of good methodological quality; no reporting bias detected  | MODERATE for no benefit of treatment   | Same as previous row  |
|                                       | 3 RCTs <sup>111, 115, 119</sup><br>N=5,149            | Birth weight <1,500 g in general obstetric population<br>Pooled ARD, 0.06% (95% CI, -0.99% to 1.12%)<br>Pooled RR, 1.05 (95% CI, 0.50 to 2.18)                    | Consistent/<br>precise <sup>†††</sup>                   | All studies of good methodological quality; no reporting bias detected  | HIGH for no benefit of treatment       | Same as previous row  |
|                                       | 4 RCTs <sup>112, 117-119</sup><br>N=3,568             | PPROM or PROM in general obstetric population<br>Pooled ARD, 0.10% (95% CI, -1.32% to 1.52%)<br>Pooled RR, 1.11 (0.72 to 1.72)                                    | Consistent/<br>imprecise <sup>***</sup>                 | All studies of good methodological quality; no reporting bias detected; one study reported PROM while others reported PPRM                        | 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 <sup>111, 117, 121, 122</sup> ; N=451                                | Preterm delivery <37 weeks (all-cause or spontaneous) in women with prior preterm delivery<br>ARDs range from -29.4% to 7.5%<br>RRs range from 0.17 to 1.33<br>Results statistically significant in 3 of the 4 studies favoring treatment.  | Inconsistent <sup>§§§</sup> /imprecise <sup>    </sup> | 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 <sup>122, 123</sup> ; N=102  | Preterm delivery <34 weeks in women with prior preterm delivery<br>ARD 0% in one study and -6.57% (95% CI, -18.5% to 5.4%) in the other study.  | Consistent/imprecise <sup>    </sup>                   | 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 |
| <b>KQ 5 Harms of treatment (by harm)</b> |   |   |  |  |   |   |
| Maternal harms of treatment              | Intravaginal clindamycin<br>4 RCTs <sup>113, 114, 116, 123</sup><br>N=1,718 | Heterogenous outcomes reported. No serious AEs observed in 3 studies. <sup>114, 116, 117</sup><br>Infrequent side effects such as candidal vaginitis, troublesome discharge; withdrawals because of itching were infrequent and similar between groups when reported by groups <sup>113, 116, 123</sup>   | Consistent/imprecise <sup>###</sup>                    | Although RCTs were mostly of good methodological quality, AE outcome measurement and reporting were not well described and studies were not powered for AEs  | MODERATE for no difference in serious AEs or minor harms (intravaginal clindamycin)                 | Applies to treatment of asymptomatic pregnant women with BV   |
|  | Oral clindamycin<br>2 RCTs <sup>119, 120</sup> ; N=3,345                    | Serious AEs not observed in either group in 1 study; <sup>119</sup> not reported in the other study <sup>120</sup><br>Higher incidence of side effects with active treatment in 1 study (ARD, 1.79% [95% CI, 0.75% to 2.84%]) <sup>119</sup><br><br>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%]; <sup>119</sup> ARD, 3.65% [95% CI, -0.27% to 7.56%] <sup>120</sup> ) | Consistent/imprecise <sup>****</sup>                   |  | MODERATE for no difference in serious AEs but more minor harms (oral clindamycin and metronidazole) |   |

**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<br>2 RCTs <sup>111, 117</sup> ;<br>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%] <sup>111</sup> ; ARD, 2.56% [95% CI, -0.36% to 5.47%] <sup>117</sup> )  | Consistent/ imprecise <sup>††††</sup>          |   |  | Same as previous row  |
| Harms to children from in utero exposure to medication | 3 observational studies <sup>129-131</sup> ;<br>N=62,271<br><br>2 meta-analyses of observational studies <sup>133, 134</sup> ;<br>N>199,541 <sup>****</sup> | 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<br><br>Congenital malformations among children exposed to metronidazole in utero: Pooled OR, 0.96 (95% CI, 0.75 to 1.22) <sup>133</sup> Pooled OR, 1.08 (95% CI, 0.90 to 1.29) <sup>134</sup> | Consistent/ imprecise <sup>††††</sup>          | Studies of poor to fair methodological quality, did not address confounding, variation in outcome definition, potential for recall bias in case-control study<br><br>Older analyses that did not use current methods for conducting and reporting analyses, included studies were not assessed for risk of bias | INSUFFICIENT                           | Applies to metronidazole exposure across a range of indications (not specific to women with BV) |
|  | 1 observational study <sup>132</sup> ;<br>N=328,846 participants with 1,172,696 person-years  | Cancer incidence before age 5 years among children exposed to metronidazole: Adjusted RR, 0.81 (95% CI, 0.41 to 1.59).   | Consistency unknown/ imprecise <sup>§§§§</sup> | 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 CIs 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 posttest 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 sensitivity and specificity CIs for each study are reasonably similar and result in only small differences in posttest 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 sensitivity and specificity 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 specificity than for sensitivity (**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 specificity, but some imprecision in estimates of sensitivity (**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 CIs 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,  $I^2$  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,<sup>133</sup> and the other study included 199,451 participants;<sup>134</sup> 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 (CQs) 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 meta-analysis<sup>50</sup> of English-language studies published through 2005 pooled 24 cohort studies or control groups from randomized, controlled trials (RCTs), representing 24,190 patients. The vast majority of the studies were conducted in very highly developed countries (Europe, United States, 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 (OR) 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 at 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 U.S. 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 ( $p=0.36$ ),<sup>139</sup> asymptomatic

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pregnant women at average risk for preterm delivery diagnosed in the second trimester (OR, 1.1 to 1.8;  $P \geq 0.35$ ),<sup>140-143</sup> 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]).<sup>144</sup> 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.<sup>143, 145</sup> Low levels of *Lactobacillus crispatus* were also associated with preterm birth in one study.<sup>145</sup> 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.<sup>142, 146</sup>

### **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.<sup>7, 147-149</sup> The microbial profile of intermediate flora can vary substantially and may or may not include *Lactobacillus* strains or anaerobic bacteria.<sup>63, 150, 151</sup> 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.<sup>151</sup> Intermediate flora may not respond to treatment similarly as bacterial vaginosis. Two studies conducted in the United Kingdom 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%).<sup>149, 151</sup>

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).<sup>152</sup> 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).<sup>115, 120</sup> 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 a higher Nugent score (i.e., bacterial vaginosis). Both trials were multicenter trials conducted in the United Kingdom 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 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 of 4 to 6).<sup>120</sup> The study found an overall benefit of treatment. Though not powered to assess treatment by Nugent score, it noted a benefit across all scores but a maximal benefit in those with a Nugent 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 score of 4 or greater) to vaginal clindamycin or placebo with a second course of treatment for those with persistently abnormal Nugent score.<sup>115</sup> For all participants, preterm birth was decreased

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(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 a Nugent score of 7 or more compared to a Nugent score of 4 to 6.<sup>149</sup>

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's 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.<sup>126</sup> In a nonrandomized cohort study from Japan, asymptomatic women were screened in the early second trimester and women with a Nugent 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).<sup>153</sup>

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, with RRs ranging from 1.5 to 2.<sup>141, 154-157</sup> This association has remained strong even after controlling for differences in socioeconomic status, sexual practices, and other demographic variables.<sup>155</sup> 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).<sup>141, 157-161</sup> These characteristics are also all known risk factors for spontaneous preterm birth.<sup>162, 163</sup>

#### *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.<sup>162</sup> 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.<sup>164</sup> 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]).<sup>165</sup> In some populations, the risk of preterm birth appears to be higher if two or more vaginal infections, including bacterial

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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<sup>166, 167</sup> or vaginal douching.<sup>155, 157, 168</sup> Systematic reviews of reproductive age women have shown an association between bacterial vaginosis and herpes simplex, human immunodeficiency, and human papilloma viruses.<sup>169-171</sup> Altered levels of immune function such as TNF $\alpha$  polymorphisms,<sup>142</sup> level of defensins (human neutrophil peptides) in vaginal fluid,<sup>146</sup> and vaginal cytokine concentrations<sup>172</sup> 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 four (3%) visits, and whiff test at five (3%) visits. Bacterial vaginosis was diagnosed at 13 (17%) visits.<sup>173</sup> 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 *G. vaginalis* culture to diagnose bacterial vaginosis in pregnant patients. Out of around 570 respondents, 57 percent test only those who are symptomatic and 11 percent did not test for bacterial vaginosis at all in pregnant patients.<sup>174</sup>

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.<sup>175</sup> 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, among other indications. Adverse events attributed to metronidazole use include metallic taste, nausea, vomiting, diarrhea, candida infections, itching, and hypersensitivity.<sup>176-179</sup> A Cochrane Review conducted in 2009 reported on the effects of antimicrobial therapy on bacterial vaginosis in nonpregnant women. The review included RCTs 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.<sup>180</sup>

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 adverse events included headache (14.7%), bad taste (11.0%), diarrhea (3.7%), and anorexia (0.8%).<sup>181</sup> 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 adverse events was similar between treatment and placebo gel groups (19% vs. 16.1%, respectively).<sup>182</sup> The most frequently reported adverse events were vulvovaginal candida infection (5.6%) and headaches (2.2%).<sup>182</sup> Other reported adverse events 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 adverse events 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 adverse events. While the Cochrane review does not compare incidence of adverse events between vaginal and oral metronidazole, two randomized controlled studies reported that vaginal metronidazole was associated with fewer gastrointestinal complaints.<sup>176, 183</sup> 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 adverse events 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%).<sup>176</sup> Another RCT (N=112) compared metronidazole vaginal 5 g twice daily for 5 days and oral metronidazole 500 mg twice daily for 7 days and reported that gastrointestinal symptoms were the most common adverse event 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).<sup>183</sup>

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### *Clindamycin-Related Adverse Events*

Clindamycin, a lincosamide antibiotic, is another common treatment for bacterial vaginosis. Clindamycin can be administered in multiple forms, including orally or vaginally as ovules or creams.<sup>177, 178</sup> The 2009 Cochrane review includes studies comparing clindamycin cream and placebo groups; however, no analyses were conducted on adverse events 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 adverse events were nonbacterial vaginitis/cervicitis (18.5%), diarrhea (7.4%), headache (4.6%), abdominal pain (2.8%), and vaginal irritation following medication insertion (2.8%).<sup>184</sup> However, the authors reported that the adverse events 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).<sup>184</sup> Other RCTs included in the 2009 Cochrane Review corroborate that common AEs related to clindamycin<sup>185, 186</sup> include vaginal irritation, candidiasis, nausea, headache, metallic taste, and diarrhea.<sup>185-188</sup> 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 adverse events 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 adverse event rates (RR, 0.75 [95% CI, 0.54 to 1.05]).<sup>180</sup> 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<sup>185-187</sup> [N=611]). Rates of candidiasis (RR, 1.11 [95% CI, 0.78 to 1.58], based on four studies<sup>186, 187, 189, 190</sup> [N=986]), diarrhea (RR, 2.99 [95% CI, 0.12 to 72.85], based on one<sup>187</sup> study [N=407]), and vaginal irritation (RR, 1.59 [95% CI, 0.31 to 8.17], based on two<sup>186, 187</sup> 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   |
|--|---|
| <b>Gram stain</b> of vaginal fluid (“ <b>Nugent’s</b> ” criteria)  | <p>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:</p> <ul style="list-style-type: none"> <li>• Large Gram-positive rods               <ul style="list-style-type: none"> <li>○ 0 score: 4+ morphotypes present</li> <li>○ 1 score: 3+ morphotypes present</li> <li>○ 2 score: 2+ morphotypes present</li> <li>○ 3 score: 1+ morphotypes present</li> <li>○ 4 score: 0 morphotypes present</li> </ul> </li> <li>• Small Gram-negative to Gram-variable rods               <ul style="list-style-type: none"> <li>○ 0 score: 0 morphotypes present</li> <li>○ 1 score: 1+ morphotypes present</li> <li>○ 2 score: 2+ morphotypes present</li> <li>○ 3 score: 3+ morphotypes present</li> <li>○ 4 score: 4+ morphotypes present</li> </ul> </li> <li>• Curved Gram-variable rods               <ul style="list-style-type: none"> <li>○ 0 score: 0 morphotypes present</li> <li>○ 1 score: 1+ or 2+ morphotypes present</li> <li>○ 2 score: 3+ or 4+ morphotypes present</li> </ul> </li> </ul> <p>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 &gt;7.</p> |
| <b>Gram stain</b> of vaginal fluid (“ <b>Spiegel’s</b> ” criteria) | <p>Gram-stained vaginal fluid smears are evaluated under microscope (x1,000 with oil immersion):</p> <ul style="list-style-type: none"> <li>• Large Gram-positive bacilli morphology are assumed to be <i>Lactobacillus</i></li> <li>• Smaller Gram-variable bacilli morphology are assumed to be <i>Gardnerella</i></li> <li>• Other organisms are categorized by their respective morphology</li> <li>• Presence of these organisms’ morphologies are scored as 1+ for &lt;1 per field, 2+ for 1 to 5 per field, 3+ for 6 to 30 per field, and 4+ for &gt;30 per field</li> <li>• Bacterial vaginosis is diagnosed with 1 to 2+ score for <i>Lactobacillus</i> presence (i.e., few or none seen in the field) and &gt;1 or 2+ presence of other morphotypes</li> </ul>  |
| <b>Clinical diagnosis</b> (“ <b>Amsel</b> ” criteria)              | <p>3 out of 4 of the following:</p> <ul style="list-style-type: none"> <li>• Vaginal pH above 4.5</li> <li>• Presence of thin, homogenous vaginal discharge</li> <li>• Release of “fishy odor” from vaginal discharge on addition of 10% potassium hydroxide (the “amine” test)</li> <li>• Presence of clue cells (typically at least 20% of vaginal epithelial cells) in the discharge on wet mount</li> </ul>   |

**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<sup>191</sup>**

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

\*FDA is phasing out the use of the pregnancy categories, so new drugs will not be assigned a category.<sup>192</sup>

**Abbreviations:** 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) <sup>193</sup> | "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) <sup>194</sup>                                    | "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) <sup>191</sup>                                  | "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) <sup>195</sup>   | "Screening for BV is not recommended in asymptomatic women, even in pregnancy."  |
| British Association for Sexual Health and HIV (BASHH) (2012) <sup>196</sup>  | "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 for Health and Care Excellence (NICE)* (2011) <sup>197</sup>                                      | "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) <sup>198</sup>  | Same as current USPSTF recommendation.   |

\*This guideline is undergoing an update, expected to be published in July 2020.<sup>199</sup>

**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 = U.S. 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    |

### 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

## Appendix B1. Detailed Search Strategy

### 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

|              | <b>Include</b>  | <b>Exclude</b>   |
|--------------|---|--|
| Population   | <p><b>KQs 1, 3:</b> 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</p> <p><b>KQ 2:</b> Reproductive-age adolescents and women, including pregnant or nonpregnant study participants</p> <p><b>KQs 4, 5:</b> Pregnant adolescents and women diagnosed with bacterial vaginosis</p>   | <p><b>KQs 1, 3, 4, 5:</b> Nonpregnant adolescents and women</p> <p><b>KQs 1, 3:</b> Adolescents and women with symptomatic bacterial vaginosis</p>   |
| Intervention | <p><b>KQ 1, 3:</b> Routine screening for bacterial vaginosis using Gram stain (Nugent's criteria) or any tests listed under KQ 2.</p> <p><b>KQ 2:</b> Screening interventions:</p> <ul style="list-style-type: none"> <li>• Clinical assessment using complete or partial Amsel's clinical criteria</li> <li>• BD MAX™ Vaginal Panel</li> <li>• BD Affirm™ VP111 Microbial Identification Test</li> <li>• Colorimetric assessment of pH</li> <li>• VS-SENSE PRO™ (pH indicator vaginal swab)</li> <li>• OSOM® BVBLUE® (detects sialidase activity)</li> <li>• Other tests*</li> </ul> <p><b>KQs 4, 5:</b> Treatment interventions (oral or vaginal):</p> <ul style="list-style-type: none"> <li>• Metronidazole</li> <li>• Clindamycin</li> </ul> | <p><b>KQ 1:</b> Screening for multiple organisms or infections if the impact of screening specifically for bacterial vaginosis cannot be isolated.</p> <p><b>KQ 2:</b> Screening interventions: Tests for diagnosis of bacterial vaginosis that are obsolete or no longer being marketed</p> <p><b>KQs 4, 5:</b> Treatment interventions: Treatments not evaluated in pregnant women</p> <p>Interventions that are not FDA approved for treatment of BV:</p> <ul style="list-style-type: none"> <li>• Rifamixin</li> <li>• Dequalinium chloride</li> <li>• Oral or vaginal probiotics</li> <li>• Topical antiseptics</li> <li>• Treatment of partner (as sole strategy)</li> </ul> |
| Comparison   | <p><b>KQ 1:</b> No screening, usual care</p> <p><b>KQ 2:</b> Screening reference standards:</p> <ul style="list-style-type: none"> <li>• Gram stain (based on Nugent's criteria)</li> <li>• Clinical assessment using complete Amsel's clinical criteria</li> </ul> <p><b>KQs 4, 5:</b> Treatment interventions:</p> <ul style="list-style-type: none"> <li>• Placebo, delayed treatment, or no treatment</li> </ul>  | <p><b>KQ 1:</b> Studies with an active comparator group</p> <p><b>KQ 2:</b> Screening interventions that do not use an included reference standard</p> <p><b>KQs 4, 5:</b> Studies with an active comparator group (i.e., pharmacologic or nonpharmacologic treatment)</p>   |

## Appendix B2. Study Selection Criteria

|              | <b>Include</b>   | <b>Exclude</b>  |
|--------------|--|---|
| Outcomes     | <p><b>KQs 1, 4:</b><br/><i>Health Outcomes</i></p> <ul style="list-style-type: none"> <li>• All-cause preterm delivery (spontaneous and indicated deliveries prior to 37 weeks gestation)</li> <li>• Spontaneous preterm delivery</li> <li>• Indicated preterm delivery</li> <li>• Low birth weight</li> <li>• Preterm labor</li> <li>• Preterm premature rupture of membranes</li> <li>• 2nd trimester fetal loss</li> <li>• Spontaneous abortion</li> <li>• Intrauterine fetal demise</li> <li>• Neonatal sepsis</li> <li>• Neonatal death</li> </ul> <p><i>Intermediate Outcome</i></p> <ul style="list-style-type: none"> <li>• Clearing of bacterial vaginosis after treatment</li> </ul> <p><b>KQ 2:</b> Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, normalized frequencies (e.g., x of y tests are true positives or false positives)</p> <p><b>KQ 3:</b> Anxiety, distress</p> <p><b>KQ 5:</b> Harms related to fetal exposure to medication:</p> <ul style="list-style-type: none"> <li>• Teratogenesis (e.g., congenital anomalies)</li> <li>• Carcinogenesis</li> <li>• Maternal AEs, such as:</li> <li>• Tolerability</li> <li>• Vaginal candidiasis</li> <li>• Serious AEs (e.g., those resulting in the need for medical attention)</li> </ul> | <p><b>KQs 1, 2, 4:</b> Outcomes not specifically listed as included</p>   |
| Timing       | <p><i>Intervention timing:</i> Treatment provided after diagnosis</p> <p><i>Outcome timing:</i></p> <p><b>KQs 1, 3, 4, 5:</b> 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</p> <p><b>KQ 2:</b> Screening test and reference standard assessed at same encounter</p>   | <p><i>Outcome timing:</i></p> <p><b>KQs 1, 3, 4, 5:</b> Outcomes not measured during current pregnancy or within 30 days of delivery, except for harms related to fetal exposure</p> <p><b>KQ 2:</b> Screening test and reference standard not assessed at same encounter</p> |
| Setting      | <p>Any clinical care settings providing prenatal care, including general obstetrics practices, family medicine practices, and public health clinics</p> <p>Studies conducted in countries categorized as “very high” on the Human Development Index (as defined by the United Nations Development Programme)</p>   | <p>Studies conducted in countries not categorized as “very high” on the Human Development Index</p>   |
| Study design | <p><b>KQs 1, 4:</b> RCTs, controlled trials, or systematic reviews of RCTs or controlled trials that use study selection criteria similar to this review<sup>†</sup></p> <p><b>KQ 2:</b> Diagnostic test accuracy studies or systematic reviews of diagnostic test accuracy that use study selection criteria similar to this review<sup>†</sup></p> <p><b>KQs 3, 5:</b> RCTs, controlled trials, cohort studies, case-control studies, or systematic reviews that use study selection criteria similar to this review<sup>†</sup></p>   | <p>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</p>  |
| Language     | English language   | Languages other than English  |

## Appendix B2. Study Selection Criteria

|               | <b>Include</b>                 | <b>Exclude</b>   |
|---------------|--------------------------------|--|
| 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  $\geq 80\%$ ); 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<sup>200</sup>

## 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.

## Appendix C. Excluded Studies

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](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. Bothuynne-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, Pirota 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.

## Appendix C. Excluded Studies

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. GoldenCare™ 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.

## Appendix C. Excluded Studies

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.
44. Chawla R, Bhalla P, Chadha S, et al. Comparison of Hay's criteria with Nugent's scoring system for diagnosis of bacterial vaginosis. *Biomed Res Int.* 2013;2013:365194. doi: 10.1155/2013/365194. PMID: 23602465. Exclusion Code: X3.
45. Christiana Care Health Services. Clindamycin to reduce preterm birth in a low resource setting. February 29, 2013. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01800825>. NCT01800825. Exclusion Code: X3.
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.0b013e318210f0dc0. 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.
51. Czeizel AE, Puho EH, Kazy Z. The use of data set of the Hungarian case-control surveillance of congenital abnormalities for evaluation of birth outcomes beyond birth defects. *Cent Eur J Public Health.* 2007 Dec;15(4):147-53. PMID: 18786293. Exclusion Code: X8.
52. Danisco. PreFem: "what happens to the vaginal microbiota when a bv infection is treated with metronidazole?" June 14, 2017. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03187457>. NCT03187457. Exclusion Code: X4.
53. Darwish A, Elnshar E, Hamadeh S, et al. Treatment options for bacterial vaginosis in patients at high risk of preterm labor and premature rupture of membranes. *J Obstet Gynaecol Res.* 2007;33(6):781-7. doi: 10.1111/j.1447-0756.2007.00656.x. PMID: CN-00702328. Exclusion Code: X3.
54. Daswani B. Comparison of two topical formulations containing clindamycin and clotrimazole in patients with vaginal infections. September. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2011. Available from: <https://ClinicalTrials.gov/show/NCT01697826>. NCT01697826. Exclusion Code: X3.
55. Datcu R. Characterization of the vaginal microflora in health and disease. *Dan Med J.* 2014 Apr;61(4):B4830. PMID: 24814599. Exclusion Code: X1.
56. Datcu R, Gesink D, Mulvad G, et al. Vaginal microbiome in women from Greenland assessed by microscopy and quantitative PCR. *BMC Infect Dis.* 2013 Oct 16;13:480. doi: 10.1186/1471-2334-13-480. PMID: 21391758. Exclusion Code: X7.
57. Datcu R, Gesink D, Mulvad G, et al. Bacterial vaginosis diagnosed by analysis of first-void-urine specimens. *J Clin Microbiol.* 2014 Jan;52(1):218-25. doi: 10.1128/jcm.02347-13. PMID: 24096128. Exclusion Code: X5.
58. Davis JD, Connor EE, Clark P, et al. Correlation between cervical cytologic results and Gram stain as diagnostic tests for bacterial vaginosis. *Am J Obstet Gynecol.* 1997 Sep;177(3):532-5. PMID: 9322619. Exclusion Code: X5.

## Appendix C. Excluded Studies

59. Diaz-Cueto L, Dominguez-Lopez P, Tena-Alavez G, et al. Effect of clindamycin treatment on vaginal inflammatory markers in pregnant women with bacterial vaginosis and a positive fetal fibronectin test. *Int J Gynaecol Obstet*. 2009 Nov;107(2):143-6. doi: 10.1016/j.ijgo.2009.06.015. PMID: 21419384. Exclusion Code: X3.
60. Discacciati MG, Simoes JA, Amaral RG, et al. Presence of 20% or more clue cells: an accurate criterion for the diagnosis of bacterial vaginosis in Papanicolaou cervical smears. *Diagn Cytopathol*. 2006 Apr;34(4):272-6. doi: 10.1002/dc.20418. PMID: 16756982. Exclusion Code: X3.
61. Donders GG. Microscopy of the bacterial flora on fresh vaginal smears. *Infect Dis Obstet Gynecol*. 1999;7(4):177-9. doi: 10.1155/s1064744999000290. PMID: 10449264. Exclusion Code: X2.
62. Donders GG. Reducing infection-related preterm birth. *BJOG*. 2015 Jan;122(2):219. doi: 10.1111/1471-0528.13109. PMID: 25546046. Exclusion Code: X8.
63. Donders GG, Marconi C, Bellen G. Easiness of use and validity testing of VS-SENSE device for detection of abnormal vaginal flora and bacterial vaginosis. *Infect Dis Obstet Gynecol*. 2010;2010:504972. doi: 10.1155/2010/504972. PMID: 20953405. Exclusion Code: X6.
64. Dongfang Hospital Affiliated to Beijing University of Chinese M, Peking University First H, Beijing Compete Pharmaceutical Co L, et al. Honghe Fujie lotion for the treatment of bacterial vaginosis. February 26, 2018. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2019. Available from: <https://ClinicalTrials.gov/show/NCT03446443>. NCT03446443. Exclusion Code: X3.
65. Effik Italia S. p A. A study of the new medical device polybactum® (POLARIS). March. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02863536>. NCT02863536. Exclusion Code: X4.
66. Eriksson K, Forsum U, Bjornerem A, et al. Validation of the use of Pap-stained vaginal smears for diagnosis of bacterial vaginosis. *APMIS*. 2007 Jul;115(7):809-13. doi: 10.1111/j.1600-0463.2007.apm\_607.x. PMID: 17413534. Exclusion Code: X5.
67. Esim Buyukbayrak E, Kars B, Karsidag AY, et al. Diagnosis of vulvovaginitis: comparison of clinical and microbiological diagnosis. *Arch Gynecol Obstet*. 2010 Nov;282(5):515-9. doi: 10.1007/s00404-010-1498-x. PMID: 21160139. Exclusion Code: X3.
68. Eunice Kennedy Shriver, National Institute of Child Health and Human Development (NICHD),. Longitudinal study of vaginal flora. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00340275>. NCT00340275. Exclusion Code: X4.
69. Farr A, Kiss H, Hagmann M, et al. Routine use of an antenatal infection screen-and-treat program to prevent preterm birth: long-term experience at a tertiary referral center. *Birth*. 2015 Jun;42(2):173-80. doi: 10.1111/birt.12154. PMID: 25677078. Exclusion Code: X5.
70. Forsum U, Jakobsson T, Larsson PG, et al. An international study of the interobserver variation between interpretations of vaginal smear criteria of bacterial vaginosis. *APMIS*. 2002 Nov;110(11):811-8. PMID: 12596717. Exclusion Code: X7.
71. Fredricks DN, Fiedler TL, Thomas KK, et al. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. *J Clin Microbiol*. 2007 Oct;45(10):3270-6. doi: 10.1128/jcm.01272-07. PMID: 17274857. Exclusion Code: X5.
72. Gazi H, Degerli K, Kurt O, et al. Use of DNA hybridization test for diagnosing bacterial vaginosis in women with symptoms suggestive of infection. *APMIS*. 2006 Nov;114(11):784-7. doi: 10.1111/j.1600-0463.2006.apm\_485.x. PMID: 16544334. Exclusion Code: X3.
73. GenMont Biotech Incorporation. Analysis of ameliorative effects of oral probiotics on bacterial vaginosis. April 17, 2017. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03116789>. NCT03116789. Exclusion Code: X5.
74. Genovese C, Corsello S, Nicolosi D, et al. Alterations of the vaginal microbiota in the third trimester of pregnancy and pPROM. *Eur Rev Med Pharmacol Sci*. 2016 Aug;20(16):3336-43. PMID: 27608890. Exclusion Code: X5.

## Appendix C. Excluded Studies

75. Geva A, Bornstein J, Dan M, et al. The VI-SENSE-vaginal discharge self-test to facilitate management of vaginal symptoms. *Am J Obstet Gynecol.* 2006 Nov;195(5):1351-6. doi: 10.1016/j.ajog.2006.04.008. PMID: 17625772. Exclusion Code: X7.
76. Giacomini G, Calcinai A, Moretti D, et al. Accuracy of cervical/vaginal cytology in the diagnosis of bacterial vaginosis. *Sex Transm Dis.* 1998 Jan;25(1):24-7. PMID: 9437781. Exclusion Code: X6.
77. Giakoumelou S, Wheelhouse N, Cuschieri K, et al. The role of infection in miscarriage. *Hum Reprod Update.* 2016 Jan-Feb;22(1):116-33. doi: 10.1093/humupd/dmv041. PMID: 26386469. Exclusion Code: X2.
78. Gillet E, Meys J, Verstraelen H, et al. Association between bacterial vaginosis and cervical intraepithelial neoplasia: systematic review and meta-analysis (Provisional abstract). In *PLoS One* Exclusion Code: X4.
79. Gjerdingen D, Fontaine P, Bixby M, et al. The impact of regular vaginal pH screening on the diagnosis of bacterial vaginosis in pregnancy. *J Fam Pract.* 2000 Jan;49(1):39-43. PMID: 10678339. Exclusion Code: X6.
80. Goldenberg RL, Mwatha A, Read JS, et al. The HPTN 024 Study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth. *Am J Obstet Gynecol.* 2006 Mar;194(3):650-61. doi: 10.1016/j.ajog.2006.01.004. PMID: 16522393. Exclusion Code: X3.
81. Graceway Pharmaceutical, LLC. Dose ranging study of metronidazole vaginal gel in the treatment of bacterial vaginosis. January 24, 2010. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01055106>. NCT01055106. Exclusion Code: X4.
82. Grmek Kosnik I, Dermota U, Golle A. Frequency of detection of Gardnerella vaginalis in vaginal smears in the Upper Carniola region. *Acta Dermatovenerol Alp Pannonica Adriat.* 2016 Jun;25(2):31-3. PMID: 27348455. Exclusion Code: X6.
83. Guangzhou Yipinhong Pharmaceutical Co, LTD. The efficacy and safety study of clindamycin palmitate hydrochloride dispersible tablet treatment of bacterial vaginosis. March 15, 2017. In *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03080740>. NCT03080740. Exclusion Code: X4.
84. Haahr T, Jensen JS, Thomsen L, et al. Abnormal vaginal microbiota may be associated with poor reproductive outcomes: a prospective study in IVF patients. *Hum Reprod.* 2016 Apr;31(4):795-803. doi: 10.1093/humrep/dew026. PMID: 26911864. Exclusion Code: X5.
85. HaEmek Medical Center, Israel. Comparison between oral clindamycin vs metronidazole for the treatment of abnormal vaginal flora in high risk pregnancies. November 7, 2012. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01722708>. NCT01722708. Exclusion Code: X6.
86. Hakimi S, Farhan F, Farshbaf-Khalili A, et al. The effect of prebiotic vaginal gel with adjuvant oral metronidazole tablets on treatment and recurrence of bacterial vaginosis: a triple-blind randomized controlled study. *Arch Gynecol Obstet.* 2018 Jan;297(1):1-8. doi: 10.1007/s00404-017-4555-x. PMID: 28983665. Exclusion Code: X3.
87. Hanson L, VandeVusse L, Jerme M, et al. Probiotics for treatment and prevention of urogenital infections in women: a systematic review. *J Midwifery Womens Health.* 2016 May;61(3):339-55. doi: 10.1111/jmwh.12472. PMID: 27218592. Exclusion Code: X5.
88. Hardy L, Jespers V, Dahchour N, et al. Unravelling the bacterial vaginosis-associated biofilm: a multiplex gardnerella vaginalis and atopobium vaginae fluorescence in situ hybridization assay using peptide nucleic acid probes. *PLoS One.* 2015;10(8):e0136658. doi: 10.1371/journal.pone.0136658. PMID: 25291946. Exclusion Code: X5.
89. Haudongchun Co., Ltd. Clinical study to evaluate the efficacy of HUDC\_VT in patients with bacterial vaginosis. November 30, 2017. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03357666>. NCT03357666. Exclusion Code: X5.
90. Hauth JC, Macpherson C, Carey JC, et al. Early pregnancy threshold vaginal pH and Gram stain scores predictive of subsequent preterm birth in asymptomatic women. *Am J Obstet Gynecol.* 2003 Mar;188(3):831-5. PMID: 12634666. Exclusion Code: X6.

## Appendix C. Excluded Studies

91. Hay P, Tummon A, Ogunfile M, et al. Evaluation of a novel diagnostic test for bacterial vaginosis: 'the electronic nose'. *Int J STD AIDS*. 2003 Feb;14(2):114-8. doi: 10.1258/095646203321156881. PMID: 12662390. Exclusion Code: X5.
92. Hemalatha R, Mastromarino P, Ramalaxmi BA, et al. Effectiveness of vaginal tablets containing lactobacilli versus pH tablets on vaginal health and inflammatory cytokines: a randomized, double-blind study. *Eur J Clin Microbiol Infect Dis*. 2012 Nov;31(11):3097-105. doi: 10.1007/s10096-012-1671-1. PMID: 22777592. Exclusion Code: X5.
93. Hemalatha R, Ramalaxmi BA, Swetha E, et al. Evaluation of vaginal pH for detection of bacterial vaginosis. *Indian J Med Res*. 2013 Sep;138(3):354-9. PMID: 23221767. Exclusion Code: X3.
94. Hemmerling A, Harrison W, Schroeder A, et al. Phase 2a study assessing colonization efficiency, safety, and acceptability of *Lactobacillus crispatus* CTV-05 in women with bacterial vaginosis. *Sex Transm Dis*. 2010;37(12):745-50. doi: 10.1097/OLQ.0b013e3181e50026. PMID: CN-00781557. Exclusion Code: X5.
95. Hendler I, Andrews WW, Carey CJ, et al. The relationship between resolution of asymptomatic bacterial vaginosis and spontaneous preterm birth in fetal fibronectin-positive women. *Am J Obstet Gynecol*. 2007 Nov;197(5):488.e1-5. doi: 10.1016/j.ajog.2007.03.073. PMID: 17652029. Exclusion Code: X8.
96. Hilbert DW, Smith WL, Chadwick SG, et al. Development and validation of a highly accurate quantitative real-time PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol*. 2016 Apr;54(4):1017-24. doi: 10.1128/jcm.03104-15. PMID: 26818677. Exclusion Code: X5.
97. Hilbert DW, Smith WL, Chadwick SG, et al. Correction for Hilbert et al., Development and validation of a highly accurate quantitative real-time PCR assay for diagnosis of bacterial vaginosis. *J Clin Microbiol*. 2016 Jul;54(7):1930. doi: 10.1128/jcm.00831-16. PMID: 27343296. Exclusion Code: X2.
98. Hillier SL, Krohn MA, Nugent RP, et al. Characteristics of three vaginal flora patterns assessed by gram stain among pregnant women. Vaginal Infections and Prematurity Study Group. *Am J Obstet Gynecol*. 1992 Mar;166(3):938-44. PMID: 1372474. Exclusion Code: X7.
99. Hills RL. Cytolytic vaginosis and lactobacillosis. Consider these conditions with all vaginosis symptoms. *Adv Nurse Pract*. 2007 Feb;15(2):45-8. PMID: 16527508. Exclusion Code: X2.
100. Hitti J, Nugent R, Boutain D, et al. Racial disparity in risk of preterm birth associated with lower genital tract infection. *Paediatr Perinat Epidemiol*. 2007 Jul;21(4):330-7. doi: 10.1111/j.1365-3016.2007.00807.x. PMID: 16648432. Exclusion Code: X5.
101. Hoffman MK, Bellad MB, Charantimath US, et al. A comparison of colorimetric assessment of vaginal pH with Nugent score for the detection of bacterial vaginosis. *Infect Dis Obstet Gynecol*. 2017;2017:1040984. doi: 10.1155/2017/1040984. PMID: 28293099. Exclusion Code: X3.
102. Hogan VK, Culhane JF, Hitti J, et al. Relative performance of three methods for diagnosing bacterial vaginosis during pregnancy. *Matern Child Health J*. 2007 Nov;11(6):532-9. doi: 10.1007/s10995-007-0205-4. PMID: 17644631. Exclusion Code: X5.
103. Homayouni A, Bastani P, Ziyadi S, et al. Effects of probiotics on the recurrence of bacterial vaginosis: a review. *J Low Genit Tract Dis*. 2014 Jan;18(1):79-86. doi: 10.1097/LGT.0b013e31829156ec. PMID: 27784549. Exclusion Code: X5.
104. Honda H, Yokoyama T, Akimoto Y, et al. The frequent shift to intermediate flora in preterm delivery cases after abnormal vaginal flora screening. *Sci Rep*. 2014 Apr 25;4:4799. doi: 10.1038/srep04799. PMID: 24762852. Exclusion Code: X8.
105. Honest H, Bachmann LM, Knox EM, et al. The accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review (Provisional abstract). *BJOG*. 2004;111(5):409-22. PMID: DARE-12004001037. Exclusion Code: X7.
106. Honest H, Bachmann LM, Knox EM, et al. The accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review. *BJOG*. 2004 May;111(5):409-22. doi: 10.1111/j.1471-0528.2004.00124.x. PMID: 15104603. Exclusion Code: X7.
107. Hoyme UB. Rationale and rational therapy of bacterial vaginosis. *Geburtshilfe Frauenheilkd*. 2007;67(3):290-2. doi: 10.1055/s-2007-965195. Exclusion Code: X12.
108. Hoyme UB, Huebner J. Prevention of preterm birth is possible by vaginal pH screening, early diagnosis of bacterial vaginosis or abnormal vaginal flora and treatment. *Gynecol Obstet Invest*. 2010;70(4):286-90. doi: 10.1159/000314019. PMID: 21654113. Exclusion Code: X8.



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109. Hu CY, Li FL, Hua XG, et al. Longitudinal trajectory of vulvovaginal candidiasis, trichomoniasis, and bacterial vaginosis during pregnancy as well as the impact on pregnancy outcome: a preliminary study. *J Matern Fetal Neonatal Med.* 2018 Apr 23;1-121. doi: 10.1080/14767058.2018.1469125. PMID: 29685081. Exclusion Code: X3.
110. Huppert JS, Hesse EA, Bernard MC, et al. Accuracy and trust of self-testing for bacterial vaginosis. *J Adolesc Health.* 2012 Oct;51(4):400-5. doi: 10.1016/j.jadohealth.2012.01.017. PMID: 23543384. Exclusion Code: X6.
111. Ibss Biomed SA. Supplementation of standard antibiotic therapy with oral probiotics for bacterial vaginosis. November 25, 2013. In *ClinicalTrials.gov.* [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01993524>. NCT01993524. Exclusion Code: X4.
112. Indiana University School of Medicine. Recurrent bacterial vaginosis and vaginal acidifying gel trial. October 17, 2007. In *ClinicalTrials.gov.* [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00545181>. NCT00545181. Exclusion Code: X4.
113. Ishaque S, Yakoob MY, Imdad A, et al. Effectiveness of interventions to screen and manage infections during pregnancy on reducing stillbirths: a review. *BMC Public Health.* 2011 Apr 13;11 Suppl 3:S3. doi: 10.1186/1471-2458-11-s3-s3. PMID: 21501448. Exclusion Code: X1.
114. Isik G, Demirezen S, Donmez HG, et al. Bacterial vaginosis in association with spontaneous abortion and recurrent pregnancy losses. *J Cytol.* 2016 Jul-Sep;33(3):135-40. doi: 10.4103/0970-9371.188050. PMID: 27756985. Exclusion Code: X5.
115. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for use in genitourinary medicine clinics. *Sex Transm Infect.* 2002;78(6):413-5. doi: 10.1136/sti.78.6.413. Exclusion Code: X5.
116. Jafarnejhad F, Mask MK, Rakhshandeh H, et al. Comparison of the percentage of medical success for phytovagex vaginal suppository and metronidazole oral tablet in women with bacterial vaginosis. *Iranian Journal of Obstetrics, Gynecology and Infertility.* 2017;20(3):29-39. doi: 10.22038/ijogi.2017.8870. Exclusion Code: X12.
117. Jakovljevic A, Bogavac M, Nikolic A, et al. The influence of bacterial vaginosis on gestational week of the completion of delivery and biochemical markers of inflammation in the serum. *Vojnosanit Pregl.* 2014 Oct;71(10):931-5. PMID: 25526757. Exclusion Code: X3.
118. Janssen-Cila SA. A study to compare efficacy and safety of an ovule containing terconazole, clindamycin and fluocinolone versus an ovule containing metronidazole, nystatin and fluocinolone in the treatment of secondary vulvar/ or vaginal symptoms of infectious vaginitis/ and infectious vaginosis. June 3, 2013. In *ClinicalTrials.gov.* [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01867164>. NCT01867164. Exclusion Code: X4.
119. Jesse DE, Swanson MS, Newton ER, et al. Racial disparities in biopsychosocial factors and spontaneous preterm birth among rural low-income women. *J Midwifery Womens Health.* 2009 Jan-Feb;54(1):35-42. doi: 10.1016/j.jmwh.2008.08.009. PMID: 19114237. Exclusion Code: X5.
120. Joesoef MR, Schmid GP. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy (Structured abstract). *Clin Infect Dis.* 1995;20(Supplement 1):S72-s9. PMID: DARE-11995000850. Exclusion Code: X2.
121. Johnson HL, Ghanem KG, Zenilman JM, et al. Sexually transmitted infections and adverse pregnancy outcomes among women attending inner city public sexually transmitted diseases clinics. *Sex Transm Dis.* 2011 Mar;38(3):167-71. doi: 10.1097/OLQ.0b013e3181f2e85f. PMID: 21275914. Exclusion Code: X5.
122. Jones HE, Harris KA, Azizia M, et al. Differing prevalence and diversity of bacterial species in fetal membranes from very preterm and term labor. *PLoS One.* 2009 Dec 8;4(12):e8205. doi: 10.1371/journal.pone.0008205. PMID: 19997613. Exclusion Code: X5.
123. Jones NM, Holzman C, Friderici KH, et al. Interplay of cytokine polymorphisms and bacterial vaginosis in the etiology of preterm delivery. *J Reprod Immunol.* 2010 Dec;87(1-2):82-9. doi: 10.1016/j.jri.2010.06.158. PMID: 20573348. Exclusion Code: X5.

## Appendix C. Excluded Studies

124. Kaiser Permanente. A pilot study of oral tinidazole for women with recurrent bacterial vaginosis. May 10, 2006. In ClinicalTrials.gov. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00324142>. NCT00324142. Exclusion Code: X4.
125. Kampan NC, Suffian SS, Ithnin NS, et al. Evaluation of BV((R)) Blue Test Kit for the diagnosis of bacterial vaginosis. *Sex Reprod Healthc*. 2011 Jan;2(1):1-5. doi: 10.1016/j.srhc.2010.11.002. PMID: 22133886. Exclusion Code: X3.
126. Kiss H, Petricevic L, Martina S, et al. Reducing the rate of preterm birth through a simple antenatal screen-and-treat programme: a retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2010 Nov;153(1):38-42. doi: 10.1016/j.ejogrb.2010.06.020. PMID: 21668769. Exclusion Code: X8.
127. Koumans EH, Lane SD, Aubry R, et al. Evaluation of Syracuse Healthy Start's program for abnormal flora management to reduce preterm birth among pregnant women. *Matern Child Health J*. 2011 Oct;15(7):1020-8. doi: 10.1007/s10995-010-0661-0. PMID: 19795485. Exclusion Code: X8.
128. Kumar S, Suri V, Sharma M. Bacterial vaginosis in preterm labor. *Int J Gynaecol Obstet*. 2006 Oct;95(1):40-1. doi: 10.1016/j.ijgo.2006.05.022. PMID: 16828770. Exclusion Code: X3.
129. Kusters JG, Reuland EA, Bouter S, et al. A multiplex real-time PCR assay for routine diagnosis of bacterial vaginosis. *Eur J Clin Microbiol Infect Dis*. 2015 Sep;34(9):1779-85. doi: 10.1007/s10096-015-2412-z. PMID: 26117968. Exclusion Code: X5.
130. Lambert JA, Kalra A, Dodge CT, et al. Novel PCR-based methods enhance characterization of vaginal microbiota in a bacterial vaginosis patient before and after treatment. *Appl Environ Microbiol*. 2013 Jul;79(13):4181-5. doi: 10.1128/aem.01160-13. PMID: 23624483. Exclusion Code: X7.
131. Lamont RF, Hudson EA, Hay PE, et al. A comparison of the use of Papanicolaou-stained cervical cytological smears with Gram-stained vaginal smears for the diagnosis of bacterial vaginosis in early pregnancy. *Int J STD AIDS*. 1999 Feb;10(2):93-7. PMID: 10215113. Exclusion Code: X6.
132. Lamont RF, Nhan-Chang CL, Sobel JD, et al. Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2011 Sep;205(3):177-90. doi: 10.1016/j.ajog.2011.03.047. PMID: 22071048. Exclusion Code: X1.
133. Larsson P, Poutakidis G, Adolfsson A, et al. Treatment of bacterial vaginosis in early pregnancy and its effect on spontaneous preterm delivery and preterm premature rupture of membranes. *Clin Microbiol*. 2016;5(259):2. Exclusion Code: X8.
134. Larsson PG, Fahraeus L, Carlsson B, et al. Predisposing factors for bacterial vaginosis, treatment efficacy and pregnancy outcome among term deliveries; results from a preterm delivery study. *BMC Womens Health*. 2007 Oct 22;7:20. doi: 10.1186/1472-6874-7-20. PMID: 17510259. Exclusion Code: X8.
135. Larsson PG, Forsum U. Bacterial vaginosis--a disturbed bacterial flora and treatment enigma. *APMIS*. 2005 May;113(5):305-16. doi: 10.1111/j.1600-0463.2005.apm\_01.x. PMID: 16011656. Exclusion Code: X2.
136. Leitich H, Brunbauer M, Bodner-Adler B, et al. Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis (structured abstract). *Am J Obstet Gynecol*. 2003;188(3):752-8. PMID: DARE-12003009527. Exclusion Code: X1.
137. Levi AW, Harigopal M, Hui P, et al. Comparison of Affirm VPIII and Papanicolaou tests in the detection of infectious vaginitis. *Am J Clin Pathol*. 2011 Mar;135(3):442-7. doi: 10.1309/ajcp7tbn5vzuglzu. PMID: 20711427. Exclusion Code: X6.
138. Libman MD, Kramer M, Platt R. Comparison of Gram and Kopeloff stains in the diagnosis of bacterial vaginosis in pregnancy. *Diagn Microbiol Infect Dis*. 2006 Mar;54(3):197-201. doi: 10.1016/j.diagmicrobio.2005.09.017. PMID: 17522586. Exclusion Code: X6.
139. Lin DP, Pan BJ, Fuh JC, et al. Improving Gram-stained reproducible result by further adding clue cells in diagnosing bacterial vaginosis. *Kaohsiung J Med Sci*. 2002 Apr;18(4):164-70. PMID: 12164009. Exclusion Code: 13.

## Appendix C. Excluded Studies

140. London School of Hygiene. The effect of norethisterone enanthate on recurrent bacterial vaginosis. April 26, 2006. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02905890>. NCT02905890. Exclusion Code: X3.
141. Lowe NK, Ryan-Wenger NA. A clinical test of women's self-diagnosis of genitourinary infections. *Clin Nurs Res*. 2000 May;9(2):144-60. doi: 10.1177/105477380000900204. PMID: 12162239. Exclusion Code: X5.
142. Loyprasert-Thananimit S, Kuasuwan P, Nittayaboon K, et al. Validity evaluation of in-house preparation kit, vaginal pH paper test combined amine tube test, for the simple diagnosis of bacterial vaginosis. *J Med Assoc Thai*. 2012 Jun;95(6):747-51. PMID: 23472099. Exclusion Code: X3.
143. Luong ML, Libman M, Dahhou M, et al. Vaginal douching, bacterial vaginosis, and spontaneous preterm birth. *J Obstet Gynaecol Can*. 2010 Apr;32(4):313-20. doi: 10.1016/s1701-2163(16)34474-7. PMID: 21325838. Exclusion Code: X5.
144. Machado A, Castro J, Cereija T, et al. Diagnosis of bacterial vaginosis by a new multiplex peptide nucleic acid fluorescence in situ hybridization method. *PeerJ*. 2015;3:e780. doi: 10.7717/peerj.780. PMID: 25737820. Exclusion Code: X5.
145. Machado A, Cerca N. Multiplex peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) for diagnosis of bacterial vaginosis. *Methods Mol Biol*. 2017;1616:209-19. doi: 10.1007/978-1-4939-7037-7\_13. PMID: 28600771. Exclusion Code: X5.
146. Makarova LN, Kravtsov EG, Vasil'eva EA, et al. Modern methods for diagnosis of Gardnerella infection. *Bull Exp Biol Med*. 2000 Aug;130(8):780-2. PMID: 11177243. Exclusion Code: X3.
147. Malaguti N, Bahls LD, Uchimura NS, et al. Sensitive detection of thirteen bacterial vaginosis-associated agents using multiplex polymerase chain reaction. *Biomed Res Int*. 2015;2015:645853. doi: 10.1155/2015/645853. PMID: 24722380. Exclusion Code: X3.
148. Mancuso MS, Figueroa D, Szychowski JM, et al. Midtrimester bacterial vaginosis and cervical length in women at risk for preterm birth. *Am J Obstet Gynecol*. 2011;204(4):342.e1-5. doi: 10.1016/j.ajog.2010.11.003. PMID: 21183154. Exclusion Code: X5.
149. Marjan Industria e Comercio Ltda. Efficacy and safety study of metronidazole, nystatin and dexamethasone combination therapy in bacterial and fungal vaginal infections. July 10, 2014. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02186145>. NCT02186145. Exclusion Code: X3.
150. Mastrobattista JM, Klebanoff MA, Carey JC, et al. The effect of body mass index on therapeutic response to bacterial vaginosis in pregnancy. *Am J Perinatol*. 2008 Apr;25(4):233-7. doi: 10.1055/s-2008-1066875. PMID: 18548397. Exclusion Code: X7.
151. Mastromarino P, Vitali B, Mosca L. Bacterial vaginosis: a review on clinical trials with probiotics. *New Microbiol*. 2013;36(3):229-38. Exclusion Code: X5.
152. Matijevic R, Grgic O, Knezevic M. Vaginal pH versus cervical length in the mid-trimester as screening predictors of preterm labor in a low-risk population. *Int J Gynaecol Obstet*. 2010 Oct;111(1):41-4. doi: 10.1016/j.ijgo.2010.05.011. PMID: 23496149. Exclusion Code: X5.
153. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev*. 2007;1(1). Exclusion Code: X1.
154. McNamee KM, Dawood F, Farquharson RG. Mid-trimester pregnancy loss. *Obstet Gynecol Clin North Am*. 2014 Mar;41(1):87-102. doi: 10.1016/j.ogc.2013.10.007. PMID: 24491985. Exclusion Code: X2.
155. Medical University of South Carolina. Inflammation and treatment of bacterial vaginosis near term. July 22, 2008. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00720291>. NCT00720291. Exclusion Code: X7.
156. Medicis Global Service Corporation. Safety and efficacy study to treat bacterial vaginosis. June 18, 2012. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01621399>. NCT01621399. Exclusion Code: X4.

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157. Medinova AG. Comparative study of efficacy of 10 mg dequalinium chloride (fluomizin) in the local treatment of bacterial vaginosis. May 18, 2010. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2008. Available from: <https://ClinicalTrials.gov/show/NCT01125410>. NCT01125410. Exclusion Code: X4.
158. Meis PJ, Goldenberg RL, Mercer B, et al. The preterm prediction study: significance of vaginal infections. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*. 1995 Oct;173(4):1231-5. PMID: 7485327. Exclusion Code: X5.
159. Menard JP, Fenollar F, Henry M, et al. Molecular quantification of *Gardnerella vaginalis* and *Atopobium vaginae* loads to predict bacterial vaginosis. *Clin Infect Dis*. 2008 Jul 1;47(1):33-43. doi: 10.1086/588661. PMID: 19920869. Exclusion Code: X5.
160. Menard JP, Fenollar F, Raoult D, et al. Self-collected vaginal swabs for the quantitative real-time polymerase chain reaction assay of *Atopobium vaginae* and *Gardnerella vaginalis* and the diagnosis of bacterial vaginosis. *Eur J Clin Microbiol Infect Dis*. 2012 Apr;31(4):513-8. doi: 10.1007/s10096-011-1341-8. PMID: 22520996. Exclusion Code: X5.
161. Menard JP, Mazouni C, Fenollar F, et al. Diagnostic accuracy of quantitative real-time PCR assay versus clinical and Gram stain identification of bacterial vaginosis. *Eur J Clin Microbiol Infect Dis*. 2010 Dec;29(12):1547-52. doi: 10.1007/s10096-010-1039-3. PMID: 21051846. Exclusion Code: X5.
162. Menard JP, Mazouni C, Salem-Cherif I, et al. High vaginal concentrations of *Atopobium vaginae* and *Gardnerella vaginalis* in women undergoing preterm labor. *Obstet Gynecol*. 2010 Jan;115(1):134-40. doi: 10.1097/AOG.0b013e3181c391d7. PMID: 22082725. Exclusion Code: X5.
163. Mendonca K, Costa C, Ricci V, et al. Enzymatic assay to test diamines produced by vaginal bacteria. *New Microbiol*. 2015 Apr;38(2):267-70. PMID: 25107710. Exclusion Code: X6.
164. Minozzi M, Gerli S, Di Renzo GC, et al. The efficacy and safety of a single dose of polyhexamethylene biguanide gynaecologic solution versus a seven-dose regimen of vaginal clindamycin cream in patients with bacterial vaginosis. *Eur Rev Med Pharmacol Sci*. 2008 Jan-Feb;12(1):59-65. PMID: 18775597. Exclusion Code: X6.
165. Mission Pharmacal. Treatment of bacterial vaginosis with oral tinidazole. September 29, 2005. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00229216>. NCT00229216. Exclusion Code: X4.
166. Mitchell CM, Hitti JE, Agnew KJ, et al. Comparison of oral and vaginal metronidazole for treatment of bacterial vaginosis in pregnancy: impact on fastidious bacteria. *BMC Infect Dis*. 2009 Jun 10;9:89. doi: 10.1186/1471-2334-9-89. PMID: 19897689. Exclusion Code: X7.
167. Miyoshi J, Ohba T, Ohkuma M, et al. Efficacy of a prospective community-based intervention to prevent preterm birth. *J Perinat Med*. 2017 Jan 1;45(1):113-9. doi: 10.1515/jpm-2015-0408. PMID: 27089398. Exclusion Code: X8.
168. Mohammadzadeh F, Dolatian M, Jorjani M, et al. Diagnostic value of Amsel's clinical criteria for diagnosis of bacterial vaginosis. *Glob J Health Sci*. 2014 Oct 29;7(3):8-14. doi: 10.5539/gjhs.v7n3p8. PMID: 26204200. Exclusion Code: X3.
169. Moniri R, Behrashi M. Effects of metronidazole therapy on preterm labor in women with bacterial vaginosis. *Acta Med Iran*. 2009;47(3):181-4. Exclusion Code: X3.
170. Montse Palacio. Bacterial vaginosis in pregnancy: detection by weekly vaginal pH testing. December 1, 2008. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00799500>. NCT00799500. Exclusion Code: X14.
171. Morton AN, Bradshaw CS, Fairley CK. Changes in the diagnosis and management of bacterial vaginosis following clinical research. *Sex Health*. 2006 Sep;3(3):183-5. PMID: 17470593. Exclusion Code: X5.
172. Mulhem E, Boyanton BL, Jr., Robinson-Dunn B, et al. Performance of the Affirm VP-III using residual vaginal discharge collected from the speculum to characterize vaginitis in symptomatic women. *J Low Genit Tract Dis*. 2014 Oct;18(4):344-6. doi: 10.1097/igt.0000000000000025. PMID: 24832170. Exclusion Code: X6.
173. Nadeau HC, Subramaniam A, Andrews WW. Infection and preterm birth. *Semin Fetal Neonatal Med*. 2016 Apr;21(2):100-5. doi: 10.1016/j.siny.2015.12.008. PMID: 26778525. Exclusion Code: X2.

## Appendix C. Excluded Studies

174. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. *Expert Rev Anti Infect Ther*. 2007 Jun;5(3):343-8. doi: 10.1586/14787210.5.3.343. PMID: 17202272. Exclusion Code: X9.
175. Nailor MD, Sobel JD. Tinidazole for the treatment of vaginal infections. *Expert Opin Investig Drugs*. 2007 May;16(5):743-51. doi: 10.1517/13543784.16.5.743. PMID: 16307744. Exclusion Code: X5.
176. Nath K, Sarosy JW, Stylianou SP. Suitability of a unique 16S rRNA gene PCR product as an indicator of *Gardnerella vaginalis*. *Biotechniques*. 2000 Feb;28(2):222-4, 6. PMID: 10683728. Exclusion Code: X7.
177. National Institute of Allergy and Infectious Diseases. Safety and efficacy of 5% monolaurin vaginal gel administered intravaginally for the treatment of bacterial vaginosis. March 15, 2016. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2017. Available from: <https://ClinicalTrials.gov/show/NCT02709005>. NCT02709005. Exclusion Code: X4.
178. Nelson DB. Treatment and management of bacterial vaginosis in pregnancy: current and future perspectives. *Womens Health (Lond)*. 2006 Mar;2(2):267-77. doi: 10.2217/17455057.2.2.267. PMID: 16490998. Exclusion Code: X2.
179. Nelson DB, Bellamy S, Clothier BA, et al. Characteristics and pregnancy outcomes of pregnant women asymptomatic for bacterial vaginosis. *Matern Child Health J*. 2008 Mar;12(2):216-22. doi: 10.1007/s10995-007-0239-7. PMID: 19750853. Exclusion Code: X8.
180. Nelson DB, Bellamy S, Gray TS, et al. Self-collected versus provider-collected vaginal swabs for the diagnosis of bacterial vaginosis: an assessment of validity and reliability. *J Clin Epidemiol*. 2003 Sep;56(9):862-6. PMID: 14505771. Exclusion Code: X5.
181. Nelson DB, Bellamy S, Nachamkin I, et al. First trimester bacterial vaginosis, individual microorganism levels, and risk of second trimester pregnancy loss among urban women. *Fertil Steril*. 2007 Nov;88(5):1396-403. doi: 10.1016/j.fertnstert.2007.01.035. PMID: 18844645. Exclusion Code: X5.
182. Nelson DB, Bellamy S, Odibo A, et al. Vaginal symptoms and bacterial vaginosis (BV): how useful is self-report? Development of a screening tool for predicting BV status. *Epidemiol Infect*. 2007 Nov;135(8):1369-75. doi: 10.1017/s095026880700787x. PMID: 17532736. Exclusion Code: X5.
183. Nelson DB, Hanlon A, Hassan S, et al. Preterm labor and bacterial vaginosis-associated bacteria among urban women. *J Perinat Med*. 2009;37(2):130-4. doi: 10.1515/jpm.2009.026. PMID: 18591634. Exclusion Code: X5.
184. Nelson DB, Hanlon A, Nachamkin I, et al. Early pregnancy changes in bacterial vaginosis-associated bacteria and preterm delivery. *Paediatr Perinat Epidemiol*. 2014 Mar;28(2):88-96. doi: 10.1111/ppe.12106. PMID: 25518272. Exclusion Code: X5.
185. Nelson DB, Hanlon AL, Wu G, et al. First trimester levels of BV-associated bacteria and risk of miscarriage among women early in pregnancy. *Matern Child Health J*. 2015 Dec;19(12):2682-7. doi: 10.1007/s10995-015-1790-2. PMID: 26156825. Exclusion Code: X7.
186. Nelson DB, Komaroff E, Nachamkin I, et al. Relationship of selected bacterial vaginosis-associated bacteria to Nugent score bacterial vaginosis among urban women early in pregnancy. *Sex Transm Dis*. 2013 Sep;40(9):721-3. doi: 10.1097/olq.0000000000000001. PMID: 22535982. Exclusion Code: X5.
187. Nenadic DB, Pavlovic MD. Cervical fluid cytokines in pregnant women: relation to vaginal wet mount findings and polymorphonuclear leukocyte counts. *Eur J Obstet Gynecol Reprod Biol*. 2008 Oct;140(2):165-70. doi: 10.1016/j.ejogrb.2008.02.020. PMID: 18406509. Exclusion Code: X5.
188. Nenadic DB, Pavlovic MD, Motrenko T. A novel microscopic method for analyzing Gram-stained vaginal smears in the diagnosis of disorders of vaginal microflora. *Vojnosanit Pregl*. 2015 Aug;72(8):670-6. PMID: 24521723. Exclusion Code: X6.
189. Nigro G, Mazzocco M, Mattia E, et al. Role of the infections in recurrent spontaneous abortion. *J Matern Fetal Neonatal Med*. 2011 Aug;24(8):983-9. doi: 10.3109/14767058.2010.547963. PMID: 21397086. Exclusion Code: X7.
190. Novakov Mikic A, Stojic S. Study results on the use of different therapies for the treatment of vaginitis in hospitalised pregnant women. *Arch Gynecol Obstet*. 2015 Aug;292(2):371-6. doi: 10.1007/s00404-015-3638-9. PMID: 25651828. Exclusion Code: X5.
191. Nunns D, Mandal D, Farrand RJ, et al. A comparison of acridine orange, wet microscopy and Gram staining in the diagnosis of bacterial vaginosis. *J Infect*. 1997 May;34(3):211-3. PMID: 9200027. Exclusion Code: X6.

## Appendix C. Excluded Studies

192. Nwankwo TO, Aniebue UU, Umeh UA. Syndromic diagnosis in evaluation of women with symptoms of vaginitis. *Curr Infect Dis Rep*. 2017 Jan;19(1):3. doi: 10.1007/s11908-017-0558-9. PMID: 28210940. Exclusion Code: X5.
193. Nygren P, Fu R, Freeman M, et al. Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an update review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008 Feb 5;148(3):220-33. doi: 10.7326/0003-4819-148-3-200802050-00008. PMID: 18758800. Exclusion Code: X1.
194. Nyirjesy P, McIntosh M, Steinmetz J, et al. The effects of intravaginal clindamycin and metronidazole therapy on vaginal mobiluncus morphotypes in patients with bacterial vaginosis. *Sex Transm Dis*. 2007;34(4):197-202. doi: 10.1097/01.olq.0000235152.98601.d7. PMID: CN-00577377. Exclusion Code: X4.
195. Nyirjesy P, McIntosh MJ, Gattermeir DJ, et al. The effects of intravaginal clindamycin and metronidazole therapy on vaginal lactobacilli in patients with bacterial vaginosis. *Am J Obstet Gynecol*. 2006 May;194(5):1277-82. doi: 10.1016/j.ajog.2005.11.006. PMID: 17010117. Exclusion Code: X4.
196. Obata-Yasuoka M, Ba-Thein W, Hamada H, et al. A multiplex polymerase chain reaction-based diagnostic method for bacterial vaginosis. *Obstet Gynecol*. 2002 Oct;100(4):759-64. PMID: 12383546. Exclusion Code: X5.
197. Obiero J, Rulisa S, Ogongo P, et al. Nifuratel-Nystatin combination for the treatment of mixed infections of bacterial vaginosis, vulvovaginal candidiasis, and trichomonal vaginitis. *Cochrane Database Syst Rev*. 2018;2018(4). doi: 10.1002/14651858.CD013012. Exclusion Code: X5.
198. O'Brien RF. Bacterial vaginosis: many questions--any answers? *Curr Opin Pediatr*. 2005 Aug;17(4):473-9. PMID: 16012258. Exclusion Code: X2.
199. O'Dowd TC, West RR, Winterburn PJ, et al. Evaluation of a rapid diagnostic test for bacterial vaginosis. *Br J Obstet Gynaecol*. 1996 Apr;103(4):366-70. PMID: 8605135. Exclusion Code: X7.
200. Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. *Cochrane Database Syst Rev*. 2009 Jul 8(3):CD006055. doi: 10.1002/14651858.CD006055.pub2. PMID: 19588379. Exclusion Code: X4.
201. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or *Trichomonas vaginalis* in pregnancy: a systematic review (structured abstract). *Obstet Gynecol*. 2005;105(4):857-68. PMID: DARE-12005009900. Exclusion Code: X1.
202. Okwoli RN, Adinma JL, Nnaeze CN. Laboratory diagnosis of *Gardnerella vaginalis* vaginosis. *West Afr J Med*. 2002 Jul-Sep;21(3):244-7. PMID: 12744579. Exclusion Code: X3.
203. Oliver RS, Lamont RF. Infection and antibiotics in the aetiology, prediction and prevention of preterm birth. *J Obstet Gynaecol*. 2013 Nov;33(8):768-75. doi: 10.3109/01443615.2013.842963. PMID: 24219711. Exclusion Code: X2.
204. Oswaldo Cruz Foundation. Probiotics for the prevention of premature birth and neonatal related morbidity. March 15, 2006. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2009. Available from: <https://ClinicalTrials.gov/show/NCT00303082>. NCT00303082. Exclusion Code: X3.
205. Othman M, Alfirevic Z, Neilson JP. Probiotics for preventing preterm labour. In *Cochrane Database Syst Rev* Exclusion Code: X5.
206. Peking University Shenzhen Hospital. Oral metronidazole with lactobacillus vaginal suppositories to prevent recurrence of bacterial vaginosis. April 4, 2017. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03099408>. NCT03099408. Exclusion Code: X4.
207. Perlamutrov Y, Gomberg M, Chernova N, et al. A comparative efficacy of nifuratel and metronidazole in therapy of bacterial vaginosis associated with atropobium vaginae. In *Sex Transm Infect* Exclusion Code: X4.
208. Perote-Pedroso J, Castro V. Regular vaginal ph screening in the diagnosis of bacterial vaginosis in pregnancy and its impact on the incidence of preterm deliveries. *Int J Gynaecol Obstet*. 2015;131:E550-e1. PMID: CN-01106611. Exclusion Code: X3.
209. Petersen CS, Danielsen AG, Renneberg J. Direct or referral microscopy of vaginal wet smear for bacterial vaginosis: experience from an STD clinic. *Acta Derm Venereol*. 1999 Nov;79(6):473-4. PMID: 10598765. Exclusion Code: X6.

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210. Petrikos GL, Hadjisoteriou M, Daikos GL. PCR versus culture in the detection of vaginal *Ureaplasma urealyticum* and *Mycoplasma hominis*. *Int J Gynaecol Obstet*. 2007 Jun;97(3):202-3. doi: 10.1016/j.ijgo.2006.12.014. PMID: 17822329. Exclusion Code: X5.
211. Plummer EL, Garland SM, Bradshaw CS, et al. Molecular diagnosis of bacterial vaginosis: does adjustment for total bacterial load or human cellular content improve diagnostic performance? *J Microbiol Methods*. 2017 Feb;133:66-8. doi: 10.1016/j.mimet.2016.12.024. PMID: 28042056. Exclusion Code: X7.
212. Plummer EL, Vodstrcil LA, Danielewski JA, et al. Combined oral and topical antimicrobial therapy for male partners of women with bacterial vaginosis: acceptability, tolerability and impact on the genital microbiota of couples - a pilot study. *PLoS One*. 2018;13(1). doi: 10.1371/journal.pone.0190199. Exclusion Code: X4.
213. Potter B, Jhorden L, Porter M. Clinical inquiries. Should we screen for bacterial vaginosis in asymptomatic patients at risk for preterm labor? *J Fam Pract*. 2004 Oct;53(10):827-31. PMID: 15469780. Exclusion Code: X2.
214. Powell AM, Nyirjesy P. Recurrent vulvovaginitis. *Best Pract Res Clin Obstet Gynaecol*. 2014 Oct;28(7):967-76. doi: 10.1016/j.bpobgyn.2014.07.006. PMID: 25220102. Exclusion Code: X2.
215. Pratiksha G, Neha A, Anju H, et al. Significance of bacterial vaginosis and periodontal infection as predictors of preterm labor. *Bangladesh J Med Science*. 2016;15(3):441-9. doi: 10.3329/bjms.v15i3.14888. PMID: CN-01248237. Exclusion Code: X3.
216. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. *J Perinat Med*. 2007;35(2):93-9. doi: 10.1515/jpm.2007.039. PMID: 16643824. Exclusion Code: X2.
217. Prey M. Routine Pap smears for the diagnosis of bacterial vaginosis. *Diagn Cytopathol*. 1999 Jul;21(1):10-3. PMID: 10405800. Exclusion Code: X5.
218. Pruski P, MacIntyre DA, Lewis HV, et al. Medical swab analysis using desorption electrospray ionization mass spectrometry: a noninvasive approach for mucosal diagnostics. *Anal Chem*. 2017 Feb 7;89(3):1540-50. doi: 10.1021/acs.analchem.6b03405. PMID: 28208268. Exclusion Code: X5.
219. Quan M. Vaginitis: diagnosis and management. *Postgrad Med*. 2010 Nov;122(6):117-27. doi: 10.3810/pgm.2010.11.2229. PMID: 21350100. Exclusion Code: X2.
220. Raja I, Basavareddy A, Mukherjee D, et al. Randomized, double-blind, comparative study of oral metronidazole and tinidazole in treatment of bacterial vaginosis. *Indian J Pharmacol*. 2016;48(6):654-8. doi: 10.4103/0253-7613.194843. PMID: CN-01289976. Exclusion Code: X3.
221. Redelinghuys MJ, Ehlers MM, Dreyer AW, et al. Normal flora and bacterial vaginosis in pregnancy: an overview. *Crit Rev Microbiol*. 2016;42(3):352-63. Exclusion Code: X2.
222. Regionshospitalet Viborg, Skive. PNA FISH, PCR and gram staining for detection of bacterial vaginosis - a comparative clinical study in a Danish IVF setting. January 22, 2014. In *ClinicalTrials.gov*: . [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02042352>. NCT02042352. Exclusion Code: X4.
223. Reid F, Oakeshott P, Kerry SR, et al. Chlamydia related bacteria (Chlamydiales) in early pregnancy: community-based cohort study. *Clin Microbiol Infect*. 2017 Feb;23(2):119.e9-.e14. doi: 10.1016/j.cmi.2016.10.011. PMID: 27773758. Exclusion Code: X5.
224. Reid G, Burton J, Hammond JA, et al. Nucleic acid-based diagnosis of bacterial vaginosis and improved management using probiotic lactobacilli. *J Med Food*. 2004 Summer;7(2):223-8. doi: 10.1089/1096620041224166. PMID: 15298771. Exclusion Code: X5.
225. Rein MF, Shih LM, Miller JR, et al. Use of a lactoferrin assay in the differential diagnosis of female genital tract infections and implications for the pathophysiology of bacterial vaginosis. *Sex Transm Dis*. 1996 Nov-Dec;23(6):517-21. PMID: 8946639. Exclusion Code: X5.
226. Rittenschober-Bohm J, Waldhoer T, Schulz SM, et al. First trimester vaginal ureaplasma biovar colonization and preterm birth: results of a prospective multicenter study. *Neonatology*. 2018;113(1):1-6. doi: 10.1159/000480065. PMID: 28934751. Exclusion Code: X5.
227. Rodrigues FS, Peixoto S, Adami F, et al. Proposal of a new cutoff for Nugent criteria in the diagnosis of bacterial vaginosis. *J Microbiol Methods*. 2015 Aug;115:144-6. doi: 10.1016/j.mimet.2015.05.006. PMID: 26001874. Exclusion Code: X3.

## Appendix C. Excluded Studies

228. Roeters AM, Boon ME, van Haaften M, et al. Inflammatory events as detected in cervical smears and squamous intraepithelial lesions. *Diagn Cytopathol.* 2010 Feb;38(2):85-93. doi: 10.1002/dc.21169. PMID: 21384783. Exclusion Code: X4.
229. Rossi A, Rossi T, Bertini M, et al. The use of *Lactobacillus rhamnosus* in the therapy of bacterial vaginosis. Evaluation of clinical efficacy in a population of 40 women treated for 24 months. *Arch Gynecol Obstet.* 2010 Jun;281(6):1065-9. doi: 10.1007/s00404-009-1287-6. PMID: 20644497. Exclusion Code: X5.
230. Rumyantseva TA, Bellen G, Romanuk TN, et al. Utility of microscopic techniques and quantitative real-time polymerase chain reaction for the diagnosis of vaginal microflora alterations. *J Low Genit Tract Dis.* 2015 Apr;19(2):124-8. doi: 10.1097/igt.000000000000060. PMID: 25023332. Exclusion Code: X3.
231. Ryan-Wenger NA, Neal JL, Jones AS, et al. Accuracy of vaginal symptom self-diagnosis algorithms for deployed military women. *Nurs Res.* 2010 Jan-Feb;59(1):2-10. doi: 10.1097/NNR.0b013e3181c3b9dd. PMID: 20461391. Exclusion Code: X6.
232. Sagawa T, Negishi H, Kishida T, et al. Vaginal and cervical pH in bacterial vaginosis and cervicitis during pregnancy. *Hokkaido Igaku Zasshi.* 1995 Nov;70(6):839-46. PMID: 8582707. Exclusion Code: X7.
233. Saharan SP, Surve C, Raut V, et al. Diagnosis and prevalence of bacterial vaginosis. *J Postgrad Med.* 1993 Apr-Jun;39(2):72-3. PMID: 8169866. Exclusion Code: X3.
234. Sangkomkamhang US, Lumbiganon P, Prasertcharoensuk W, et al. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database Syst Rev.* 2015(2). doi: 10.1002/14651858.CD006178.pub3. PMID: CD006178. Exclusion Code: X1.
235. Sanu O, Lamont RF. Periodontal disease and bacterial vaginosis as genetic and environmental markers for the risk of spontaneous preterm labor and preterm birth. *J Matern Fetal Neonatal Med.* 2011 Dec;24(12):1476-85. doi: 10.3109/14767058.2010.545930. PMID: 21944221. Exclusion Code: X5.
236. Schellenberg J, Blake Ball T, Lane M, et al. Flow cytometric quantification of bacteria in vaginal swab samples self-collected by adolescents attending a gynecology clinic. *J Microbiol Methods.* 2008 Jun;73(3):216-26. doi: 10.1016/j.mimet.2008.03.004. PMID: 18423913. Exclusion Code: X5.
237. Schmidt H, Hansen JG. Diagnosis of bacterial vaginosis by wet mount identification of bacterial morphotypes in vaginal fluid. *Int J STD AIDS.* 2000 Mar;11(3):150-5. doi: 10.1258/0956462001915589. PMID: 10726936. Exclusion Code: X5.
238. Schmidt H, Hansen JG. Validity of wet-mount bacterial morphotype identification of vaginal fluid by phase-contrast microscopy for diagnosis of bacterial vaginosis in family practice. *APMIS.* 2001 Sep;109(9):589-94. PMID: 11878711. Exclusion Code: X5.
239. Schmitt M, Depuydt C, Stalpaert M, et al. Bead-based multiplex sexually transmitted infection profiling. *J Infect.* 2014 Aug;69(2):123-33. doi: 10.1016/j.jinf.2014.04.006. PMID: 24814157. Exclusion Code: X5.
240. Schwebke, Jr., Desmond R. Tinidazole vs metronidazole for the treatment of bacterial vaginosis. In *Am J Obstet Gynecol* Exclusion Code: X6.
241. Schwebke, Jr., Marrazzo J, Beelen A, et al. A Phase 3, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Evaluating the Safety and Efficacy of Metronidazole Vaginal Gel 1.3% in the Treatment of Bacterial Vaginosis. *Sex Transm Dis.* 2015;42(7):376-81. doi: 10.1097/OLQ.0000000000000300. PMID: CN-01162024. Exclusion Code: X4.
242. Schwebke J. The Women's Health II Medical Education Network \_Part 1: Understanding bacterial vaginosis: diagnosis, treatment, and improved outcomes. *J Fam Pract.* 2007 Sep;56(9 Suppl Women):S1-6; quiz S7-8. PMID: 16543864. Exclusion Code: X2.
243. Schwebke JR. Diagnostic methods for bacterial vaginosis. *Int J Gynaecol Obstet.* 1999 Nov;67 Suppl 1:S21-3. PMID: 10661732. Exclusion Code: X2.
244. Schwebke JR, Lee JY, Lensing S, et al. Home screening for bacterial vaginosis to prevent sexually transmitted diseases. *Clin Infect Dis.* 2016 Mar 01;62(5):531-6. doi: 10.1093/cid/civ975. PMID: 26611782. Exclusion Code: X4.



## Appendix C. Excluded Studies

245. Schwiertz A, Taras D, Rusch K, et al. Throwing the dice for the diagnosis of vaginal complaints? *Ann Clin Microbiol Antimicrob.* 2006 Feb 17;5:4. doi: 10.1186/1476-0711-5-4. PMID: 17687006. Exclusion Code: X6.
246. Secor M, Coughlin G. Bacterial vaginosis update. *Adv NPs PAs.* 2013 Aug;4(8):23-6. PMID: 24120172. Exclusion Code: X2.
247. Selim SA, El Alfy SM, Aziz MH, et al. Effective of metronidazole to bacterial flora in vagina and the impact of microbes on live birth rate during intracytoplasmic sperm injection (ICSI). *Arch Gynecol Obstet.* 2011 Dec;284(6):1449-53. doi: 10.1007/s00404-011-1857-2. PMID: 20221621. Exclusion Code: X3.
248. Shaaban O, Fetih G, Abdellah N, et al. Pilot randomized trial for treatment of bacterial vaginosis using in situ forming metronidazole vaginal gel. *J Obstet Gynaecol Res.* 2011;37(7):874-81. doi: 10.1111/j.1447-0756.2010.01457.x. PMID: CN-00812330. Exclusion Code: X3.
249. Sheehy O, Santos F, Ferreira E, et al. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf.* 2015;10(2):170-9. PMID: 26544959. Exclusion Code: X1.
250. Sheiness D, Dix K, Watanabe S, et al. High levels of *Gardnerella vaginalis* detected with an oligonucleotide probe combined with elevated pH as a diagnostic indicator of bacterial vaginosis. *J Clin Microbiol.* 1992 Mar;30(3):642-8. PMID: 1372621. Exclusion Code: X5.
251. Shennan A, Crawshaw S, Briley A, et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMETS Study. *BJOG.* 2006 Jan;113(1):65-74. doi: 10.1111/j.1471-0528.2005.00788.x. Exclusion Code: X7.
252. Shipitsyna E, Roos A, Dancu R, et al. Composition of the vaginal microbiota in women of reproductive age--sensitive and specific molecular diagnosis of bacterial vaginosis is possible? *PLoS One.* 2013;8(4):e60670. doi: 10.1371/journal.pone.0060670. PMID: 22774616. Exclusion Code: X5.
253. Shujatullah F, Khan HM, Khatoun R, et al. An evaluation of OSOM BV blue test in the diagnosis of bacterial vaginosis. *Asian Pac J Trop Med.* 2010;3(7):574-6. doi: 10.1016/S1995-7645(10)60139-3. Exclusion Code: X3.
254. Simcox R, Sin WT, Seed PT, et al. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. *Aust N Z J Obstet Gynaecol.* 2007 Oct;47(5):368-77. doi: 10.1111/j.1479-828X.2007.00759.x. PMID: 17877593. Exclusion Code: X1.
255. Simoes JA, Discacciati MG, Brolazo EM, et al. Clinical diagnosis of bacterial vaginosis. *Int J Gynaecol Obstet.* 2006 Jul;94(1):28-32. doi: 10.1016/j.ijgo.2006.04.013. PMID: 16817083. Exclusion Code: X3.
256. Skaraborg Hospital. Treatment of bacterial vaginosis in early pregnancy in skaraborg and the effect on spontaneous preterm delivery. January 28, 2015. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02348463>. NCT02348463. Exclusion Code: X9.
257. Skaraborg Hospital. Treatment of bacterial vaginosis combined with human lactobacilli. November 22, 2010. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01245322>. NCT01245322. Exclusion Code: X4.
258. Skaraborg Hospital. Will vaginal colonization of lactobacillus increase cure rate after treatment of bacterial vaginosis and chronic vulvovaginal candida. November 20, 2014. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02295579>. NCT02295579. Exclusion Code: X4.
259. Smayevsky J, Canigia LF, Lanza A, et al. Vaginal microflora associated with bacterial vaginosis in nonpregnant women: reliability of sialidase detection. *Infect Dis Obstet Gynecol.* 2001;9(1):17-22. doi: 10.1155/s1064744901000047. PMID: 11368254. Exclusion Code: X6.
260. Sobel JD. Antibiotic consideration in bacterial vaginosis. *Curr Infect Dis Rep.* 2009 Nov;11(6):471-5. PMID: 19743911. Exclusion Code: X2.
261. Sobel JD, Ferris D, Schwabke J, et al. Suppressant antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. *Am J Obstet Gynecol.* 2006 May;194(5):1283-9. doi: 10.1016/j.ajog.2005.11.041. PMID: 16517914. Exclusion Code: X4.

## Appendix C. Excluded Studies

262. Sobel JD, Hay P. Diagnostic techniques for bacterial vaginosis and vulvovaginal candidiasis - requirement for a simple differential test. *Expert Opin Med Diagn.* 2010 Jul;4(4):333-41. doi: 10.1517/17530059.2010.488688. PMID: 20027045. Exclusion Code: X2.
263. Sobel JD, Karpas Z, Lorber A. Diagnosing vaginal infections through measurement of biogenic amines by ion mobility spectrometry. *Eur J Obstet Gynecol Reprod Biol.* 2012 Jul;163(1):81-4. doi: 10.1016/j.ejogrb.2012.03.022. PMID: 23745304. Exclusion Code: X5.
264. Sobel JD, Nyirjesy P, Kessary H, et al. Use of the VS-sense swab in diagnosing vulvovaginitis. *J Womens Health (Larchmt).* 2009 Sep;18(9):1467-70. doi: 10.1089/jwh.2008.1305. PMID: 18226677. Exclusion Code: X7.
265. Sobel R, Sobel JD. Metronidazole for the treatment of vaginal infections. *Expert Opin Pharmacother.* 2015 May;16(7):1109-15. doi: 10.1517/14656566.2015.1035255. PMID: 25887246. Exclusion Code: X2.
266. Sodhani P, Garg S, Bhalla P, et al. Prevalence of bacterial vaginosis in a community setting and role of the pap smear in its detection. *Acta Cytol.* 2005 Nov-Dec;49(6):634-8. doi: 10.1159/000326251. PMID: 16450903. Exclusion Code: X3.
267. Song Y, He L, Zhou F, et al. Segmentation, splitting, and classification of overlapping bacteria in microscope images for automatic bacterial vaginosis diagnosis. *IEEE J Biomed Health Inform.* 2017 Jul;21(4):1095-104. doi: 10.1109/jbhi.2016.2594239. PMID: 27479982. Exclusion Code: X5.
268. Starpharma Pty Ltd. A phase 3 study of SPL7013 gel (VivaGel) for the treatment of bacterial vaginosis. April 16, 2012. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT01577537>. NCT01577537. Exclusion Code: X5.
269. Storti-Filho A, Estivalet Svidizinski TI, da Silva Souza RJ, et al. Oncotic colpocytology stained with Harris-Shorr in the observation of vaginal microorganisms. *Diagn Cytopathol.* 2008 Jun;36(6):358-62. doi: 10.1002/dc.20820. PMID: 19857387. Exclusion Code: X3.
270. Sturm PD, Moodley P, Nzimande G, et al. Diagnosis of bacterial vaginosis on self-collected vaginal tampon specimens. *Int J STD AIDS.* 2002 Aug;13(8):559-63. doi: 10.1258/095646202760159693. PMID: 12194740. Exclusion Code: X3.
271. Subtil D, Brabant G, Tilloy E, et al. Early clindamycin for bacterial vaginosis in low-risk pregnancy: the PREMEVA1 randomized, multicenter, double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 2014;210(1 suppl. 1):S3. doi: 10.1016/j.ajog.2013.10.036. PMID: CN-01062100. Exclusion Code: X9.
272. Sungkar A, Purwosunu Y, Aziz M, et al. Influence of early self-diagnosis and treatment of bacterial vaginosis on preterm birth rate. *Int J Gynaecol Obstet.* 2012;117(3):264-7. doi: 10.1016/j.ijgo.2012.01.007. PMID: CN-00880779. Exclusion Code: X3.
273. Swadpanich U, Lumbiganon P, Prasertcharoensook W, et al. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database Syst Rev.* 2008 Apr 16(2):Cd006178. doi: 10.1002/14651858.CD006178.pub2. PMID: 18425940. Exclusion Code: X1.
274. Symbiomix Therapeutics. Open-label study to evaluate the safety of a single dose of SYM-1219, a granule formulation containing 2 grams of secnidazole. May 25, 2015. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02452866>. NCT02452866. Exclusion Code: X4.
275. Symbiomix Therapeutics. A phase 3 study of SYM-1219 treatment of women and post-menarchal adolescent girls with bacterial vaginosis. April 16, 2015. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2015. Available from: <https://ClinicalTrials.gov/show/NCT02418845>. NCT02418845. Exclusion Code: X4.
276. Taha T, Kumwenda N, Kafulafula G, et al. Intermittent intravaginal antibiotic treatment of bacterial vaginosis in HIV-uninfected and -infected women: a randomized clinical trial. *PLoS Clin Trials.* 2007;2(2):e10TN: NCT00140764/*ClinicalTrials.gov*. doi: 10.1371/journal.pctr.0020010. PMID: CN-00641463. Exclusion Code: X3.
277. Taj U, Javeria M, Hanif A. Comparison of intravaginal versus oral metronidazole in the treatment of bacterial vaginosis in obstetrical patients. *Pakistan J Med Health Sciences.* 2017;11(2):519-22. PMID: CN-01403512. Exclusion Code: X3.

## Appendix C. Excluded Studies

278. Tam MT, Yungbluth M, Myles T. Gram stain method shows better sensitivity than clinical criteria for detection of bacterial vaginosis in surveillance of pregnant, low-income women in a clinical setting. *Infect Dis Obstet Gynecol.* 1998;6(5):204-8. doi: 10.1155/s1064744998000416. PMID: 9894174. Exclusion Code: X6.
279. Tan H, Fu Y, Yang C, et al. Effects of metronidazole combined probiotics over metronidazole alone for the treatment of bacterial vaginosis: a meta-analysis of randomized clinical trials. *Arch Gynecol Obstet.* 2017 Jun;295(6):1331-9. doi: 10.1007/s00404-017-4366-0. PMID: 28386675. Exclusion Code: X4.
280. Taylor-Robinson D, Morgan DJ, Sheehan M, et al. Relation between Gram-stain and clinical criteria for diagnosing bacterial vaginosis with special reference to Gram grade II evaluation. *Int J STD AIDS.* 2003;14(1):6. Exclusion Code: X6.
281. Teva Pharmaceuticals USA. Bioequivalence of metronidazole gel, 0.75% in the treatment of bacterial vaginosis. November 25, 2009. In *ClinicalTrials.gov*. [cited December 3, 2018]. Bethesda, MD: National Library of Medicine. 2003. Available from: <https://ClinicalTrials.gov/show/NCT01020396>. NCT01020396. Exclusion Code: X4.
282. Thinkhamrop J, Hofmeyr GJ, Adetoro O, et al. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. *Cochrane Database Syst Rev.* 2015 Jun 20(6):Cd002250. doi: 10.1002/14651858.CD002250.pub3. PMID: 26092137. Exclusion Code: X1.
283. Thomason JL, Anderson RJ, Gelbart SM, et al. Simplified gram stain interpretive method for diagnosis of bacterial vaginosis. *Am J Obstet Gynecol.* 1992 Jul;167(1):16-9. PMID: 1279973. Exclusion Code: X5.
284. Thompson C, McCabe K. An audit of the value of microscopy of gram-stained and wet film preparations for the diagnosis of bacterial vaginosis in a department of genitourinary medicine. *Int J STD AIDS.* 1994 Jan-Feb;5(1):69-70. PMID: 8142535. Exclusion Code: X6.
285. Thulkar J, Kriplani A, Agarwal N. Utility of pH test & Whiff test in syndromic approach of abnormal vaginal discharge. *Indian J Med Res.* 2010;131(3):445-8. Exclusion Code: X3.
286. Tokyol C, Aktepe OC, Cevrioglu AS, et al. Bacterial vaginosis: comparison of Pap smear and microbiological test results. *Mod Pathol.* 2004 Jul;17(7):857-60. doi: 10.1038/modpathol.3800132. PMID: 15073605. Exclusion Code: X3.
287. Tosun I, Aydin F, Kaklikkaya N, et al. Frequency of bacterial vaginosis among women attending for intrauterine device insertion at an inner-city family planning clinic. *Eur J Contracept Reprod Health Care.* 2003 Sep;8(3):135-8. PMID: 14667323. Exclusion Code: X3.
288. Udayalaxmi, Bhat G, Kotigadde S, et al. Comparison of the methods of diagnosis of bacterial vaginosis. *Journal of Clinical and Diagnostic Research.* 2011;5(3):498-501. Exclusion Code: X3.
289. Ugwumadu A. Role of antibiotic therapy for bacterial vaginosis and intermediate flora in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2007 Jun;21(3):391-402. doi: 10.1016/j.bpobgyn.2007.01.001. PMID: 16492583. Exclusion Code: X2.
290. Ugwumadu A, Reid F, Hay P, et al. Oral clindamycin and histologic chorioamnionitis in women with abnormal vaginal flora. *Obstet Gynecol.* 2006 Apr;107(4):863-8. doi: 10.1097/01.Aog.0000202399.13074.98. PMID: 16517046. Exclusion Code: X7.
291. University Hospital, Lille. Prevention of very preterm delivery by testing for and treatment of bacterial vaginosis. March 25, 2008. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00642980>. NCT00642980. Exclusion Code: X9.
292. University of Alabama at Birmingham. Treatment of bacterial vaginosis. May 11, 2006. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00324818>. NCT00324818. Exclusion Code: X4.
293. University of Alabama at Birmingham. Treatment of bacterial vaginosis (BV) with tinidazole. June 23, 2011. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00334633>. NCT00334633. Exclusion Code: X4.

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294. University of Alabama at Birmingham. Randomized controlled trial of treatment of male partners of women with BV. August 6, 2014. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02209519>. NCT02209519. Exclusion Code: X4.
295. University of British Columbia. BASIC (Boric Acid, Alternate Solution for Intravaginal Colonization) Study. November 27, 2008. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00799214>. NCT00799214. Exclusion Code: X4.
296. University of Pittsburgh. Comparing NAAT testing to standard methods for the diagnosis of vaginitis. July 30, 2014. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02203942>. NCT02203942. Exclusion Code: X14.
297. University of Washington. Bacterial vaginosis; a randomized trial to reduce recurrence. October 10, 2007. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00542074>. NCT00542074. Exclusion Code: X3.
298. van Belkum A, Koeken A, Vandamme P, et al. Development of a species-specific polymerase chain reaction assay for *Gardnerella vaginalis*. *Mol Cell Probes*. 1995 Jun;9(3):167-74. doi: 10.1006/mcpr.1995.0024. PMID: 7477009. Exclusion Code: X5.
299. van der Veer C, van Houdt R, van Dam A, et al. Accuracy of a commercial multiplex PCR for the diagnosis of bacterial vaginosis. *J Med Microbiol*. 2018 Sep;67(9):1265-70. doi: 10.1099/jmm.0.000792. PMID: 10.1099/jmm.0.000792. Epub 2018 Jul 9. PMID: 29648469. Exclusion Code: X5.
300. Vardar E, Maral I, Inal M, et al. Comparison of Gram stain and Pap smear procedures in the diagnosis of bacterial vaginosis. *Infect Dis Obstet Gynecol*. 2002;10(4):203-7. doi: 10.1155/s1064744902000236. PMID: 12648314. Exclusion Code: X3.
301. Varma R, Gupta JK. Antibiotic treatment of bacterial vaginosis in pregnancy: multiple meta-analyses and dilemmas in interpretation. *Eur J Obstet Gynecol Reprod Biol*. 2006 Jan 1;124(1):10-4. doi: 10.1016/j.ejogrb.2005.07.015. PMID: 19803898. Exclusion Code: X1.
302. Varma R, Gupta JK, James DK, et al. Do screening-preventative interventions in asymptomatic pregnancies reduce the risk of preterm delivery--a critical appraisal of the literature. *Eur J Obstet Gynecol Reprod Biol*. 2006 Aug;127(2):145-59. doi: 10.1016/j.ejogrb.2006.02.001. PMID: 16769019. Exclusion Code: X1.
303. Verstraelen H, Verhelst R. Bacterial vaginosis: an update on diagnosis and treatment. *Expert Rev Anti Infect Ther*. 2009;7(9):1109-24. Exclusion Code: X2.
304. Vidaeff AC, Ramin SM. From concept to practice: the recent history of preterm delivery prevention. Part II: Subclinical infection and hormonal effects. *Am J Perinatol*. 2006 Feb;23(2):75-84. doi: 10.1055/s-2006-931803. PMID: 16506112. Exclusion Code: X2.
305. Wang KD, Su JR. Quantification of *Atopobium vaginae* loads may be a new method for the diagnosis of bacterial vaginosis. *Clin Lab*. 2014;60(9):1501-8. PMID: 26482128. Exclusion Code: X3.
306. Wayne State University. Validation of a novel diagnostic, prognostic assay for bacterial vaginosis. July 9, 2014. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT02185456>. NCT02185456. Exclusion Code: X9.
307. Weissenbacher ER, Donders G, Unzeitig V, et al. A comparison of dequalinium chloride vaginal tablets (Fluomizin(R)) and clindamycin vaginal cream in the treatment of bacterial vaginosis: a single-blind, randomized clinical trial of efficacy and safety. *Gynecol Obstet Invest*. 2012;73(1):8-15. doi: 10.1159/000332398. PMID: 23934099. Exclusion Code: X4.
308. Western Galilee Hospital-Nahariya. Bacterial vaginosis screening and treatment to reduce infective complications, abortion and preterm delivery. June 26, 2007. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00491270>. NCT00491270. Exclusion Code: X14.

## Appendix C. Excluded Studies

309. Wiggins R, Crowley T, Horner PJ, et al. Use of 5-bromo-4-chloro-3-indolyl-alpha-D-N-acetylneuraminic acid in a novel spot test to identify sialidase activity in vaginal swabs from women with bacterial vaginosis. *J Clin Microbiol.* 2000 Aug;38(8):3096-7. PMID: 10921986. Exclusion Code: X5.
310. Wolrath H, Boren H, Hallen A, et al. Trimethylamine content in vaginal secretion and its relation to bacterial vaginosis. *APMIS.* 2002 Nov;110(11):819-24. PMID: 12588422. Exclusion Code: X5.
311. Youngkin EQ, Lester PB. Promoting self-care and secondary prevention in women's health: a study to test the accuracy of a home self-test system for bacterial vaginosis. *Appl Nurs Res.* 2010 Feb;23(1):2-10. doi: 10.1016/j.apnr.2008.02.002. PMID: 20207066. Exclusion Code: X6.
312. Yudin MH. Bacterial vaginosis in pregnancy: diagnosis, screening, and management. *Clin Perinatol.* 2005 Sep;32(3):617-27. doi: 10.1016/j.clp.2005.05.007. PMID: 16085023. Exclusion Code: X2.
313. Yudin MH, Landers DV, Meyn L, et al. Clinical and cervical cytokine response to treatment with oral or vaginal metronidazole for bacterial vaginosis during pregnancy: a randomized trial. *Obstet Gynecol.* 2003 Sep;102(3):527-34. PMID: 12962937. Exclusion Code: X6.
314. Yudin MH, Money DM. Screening and management of bacterial vaginosis in pregnancy. *J Obstet Gynaecol Can.* 2008 Aug;30(8):702-16. PMID: 18786293. Exclusion Code: X2.
315. Yudin MH, Money DM. No. 211-screening and management of bacterial vaginosis in pregnancy. *J Obstet Gynaecol Can.* 2017 Aug;39(8):e184-e91. doi: 10.1016/j.jogc.2017.04.018. PMID: 28729110. Exclusion Code: X2.
316. Zagazig University. Vaginal clindamycin cream plus vaginal probiotic for bacterial vaginosis. July 31, 2017. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT03234517>. NCT03234517. Exclusion Code: X3.
317. Zarshenas M, Jahed L, Abdali K. A comparison of therapeutic effects of the zataria multiflora vaginal cream and oral metronidazole tablet on the treatment of trichomonas vaginalis and bacterial vaginosis in reproductive aged women. *Int J Gynaecol Obstet.* 2015;131:E469. PMID: CN-01136195. Exclusion Code: X3.
318. Zhao TF, Zhong L, Luo D. Living preparation of lactobacillus versus metronidazole for bacterial vaginosis in pregnancy: a systematic review. *Chinese Journal of Evidence-Based Medicine.* 2010;10(11):1338-44. Exclusion Code: X12.
319. Zodiac Produtos Farmaceuticos S. A. Evaluate efficacy, tolerability & safety of combination of clindamycin and ketoconazole for the treatment of mixed-type vaginosis, bacterial vaginosis and candidiasis. April 28, 2009. In *ClinicalTrials.gov*. [cited December 4, 2018]. Bethesda, MD: National Library of Medicine. 2000-. Available from: <https://ClinicalTrials.gov/show/NCT00889356>. NCT00889356. Exclusion Code: X3.
320. Zozaya-Hinchliffe M, Lillis R, Martin DH, et al. Quantitative PCR assessments of bacterial species in women with and without bacterial vaginosis. *J Clin Microbiol.* 2010 May;48(5):1812-9. doi: 10.1128/jcm.00851-09. PMID: 20495228. Exclusion Code: X7.

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

| Author;<br>Year<br>Country                                     | Reference Test   | N (%) With<br>Confirmed<br>BV on<br>Referent Test | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive<br>Likelihood<br>Ratio | Negative<br>Likelihood<br>Ratio | Other Comments  |
|--|--|---|-------------------------|-------------------------|---------------------------------|---------------------------------|---|
| Bradshaw et al <sup>100</sup> ;<br>2005;<br>Australia          | Gram stain (Nugent score $\geq 7$ ); 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 <sup>88</sup> ;<br>2005;<br>Spain               | Gram stain (Nugent score $\geq 7$ )  | 22 (4.5)  | 0.75 (NR)               | 0.78 (NR)               | NR                              | NR                              | None  |
| Gutman et al <sup>109,†</sup> ;<br>2005;<br>United States      | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>91</sup> ;<br>1992;<br>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 <sup>93</sup> ;<br>2001;<br>Sweden              | Complete Amsel's clinical criteria   | 131 (13.7)  | 0.97 (NR)               | 0.86 (NR)               | NR                              | NR                              | None  |
| Mastrobattista et al <sup>89</sup> ;<br>2000;<br>United States | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>102</sup> ;<br>2003; Canada                  | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>136</sup> ;<br>2009;<br>United States         | Gram stain (Nugent's criteria) <sup>‡</sup>  | 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 $\geq 4.5$ 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 <sup>94</sup> ; 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 <sup>108</sup> ; 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 <sup>99</sup><br>Gaydos et al <sup>65</sup> ; 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;<br>Year<br>Country  | Reference Test   | N (%) With<br>Confirmed<br>BV on<br>Referent Test   | Sensitivity<br>(95% CI)   | Specificity<br>(95% CI)   | Positive<br>Likelihood<br>Ratio   | Negative<br>Likelihood<br>Ratio   | Other Comments |
|---|--|---|---|---|---|---|----------------|
| Bradshaw et al <sup>100</sup> ;<br>2005;<br>Australia   | Gram stain (Nugent score $\geq 7$ ); 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 <sup>88</sup> ;<br>2005;<br>Spain  | Gram stain (Nugent score $\geq 7$ )  | 22 (4.5)  | 0.14 (NR)   | 0.97 (NR)   | NR  | NR  | None           |
| Gutman et al <sup>109</sup> ;<br>2005;<br>United States                                       | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>91</sup> ;<br>1992;<br>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 <sup>93</sup> ;<br>2001;<br>Sweden   | Complete Amsel's clinical criteria   | 131 (13.7)  | 0.52 (NR)   | 0.95 (NR)   | NR  | NR  | None           |
| Myziuk et al <sup>102</sup> ;<br>2003;<br>Canada  | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>194</sup> ;<br>1994;<br>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 <sup>99</sup> ;<br>Gaydos et al <sup>65</sup> ;<br>2018/2017;<br>United States | Gram stain (Nugent score $\geq 7$ ); 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;<br>Year<br>Country                                     | Reference Test   | N (%) With<br>Confirmed<br>BV on<br>Referent Test   | Sensitivity<br>(95% CI)   | Specificity<br>(95% CI)   | Positive<br>Likelihood<br>Ratio  | Negative<br>Likelihood<br>Ratio   | Other Comments |
|--|--|---|---|---|--|---|----------------|
| Bradshaw et al <sup>100</sup> ;<br>2005;<br>Australia          | Gram stain (Nugent score $\geq 7$ ); 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 <sup>88</sup> ;<br>2005;<br>Spain               | Gram stain (Nugent score $\geq 7$ )  | 22 (4.5)  | 0.27 (NR)   | 0.99 (NR)   | NR   | NR  | None           |
| Gutman et al <sup>109</sup> ;<br>2005;<br>United States        | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>91</sup> ;<br>1992;<br>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 <sup>93</sup> ;<br>2001;<br>Sweden              | Complete Amsel's clinical criteria   | 131 (13.7)  | 0.99 (NR)   | 0.93 (NR)   | NR   | NR  | None           |
| Mastrobattista et al <sup>89</sup> ;<br>2000;<br>United States | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>102</sup> ; 2003;<br>Canada                  | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>94</sup> ;<br>1994;<br>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 <sup>99</sup><br>Gaydos et al <sup>65</sup> ;<br>2018/2017;<br>United States | Gram stain (Nugent score $\geq 7$ ); 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 <sup>137</sup> ;<br>1995;<br>U.K.  | Gram stain (Nugent score $\geq 7$ )  | 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;<br>Year<br>Country                                | Reference<br>Test  | N (%) With<br>Confirmed BV<br>on Referent<br>Test | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive<br>Likelihood<br>Ratio | Negative<br>Likelihood<br>Ratio | Other Comments |
|---|--|---|-------------------------|-------------------------|---------------------------------|---------------------------------|----------------|
| Bradshaw et al <sup>100</sup> ; 2005; Australia           | Gram stain (Nugent score $\geq 7$ ); 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 <sup>88</sup> ;† 2005; Spain               | Gram stain (Nugent score $\geq 7$ )  | 22 (4.5)  | 0.59 (NR)               | 0.94 (NR)               | NR                              | NR                              | None           |
| Gutman et al <sup>109</sup> ; 2005; United States         | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>91</sup> ; 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 <sup>93</sup> ; 2001; Sweden               | Complete Amsel's clinical criteria   | 131 (13.7)  | 1.0 (NR)                | 0.92 (NR)               | NR                              | NR                              | None           |
| Mastrobattista et al <sup>89</sup> ;‡ 2000; United States | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>102</sup> ; 2003; Canada                | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>92</sup> ;§ 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 <sup>136</sup> ; 2009; United States          | Gram stain (Nugent's criteria) <sup>  </sup>   | 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 <sup>94</sup> ; 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 <sup>108</sup> ; 1996; United States                                | Gram stain (Nugent score $\geq 7$ )  | 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 <sup>99</sup> Gaydos et al <sup>65</sup> ; 2018/2017; United States | Gram stain (Nugent score $\geq 7$ ); 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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality  | Interventions (N<br>Randomized)  | Key Inclusion and Exclusion Criteria  | Sample Characteristics   | Method of BV<br>Diagnosis and<br>Prevalence of BV   |
|--|--|---|--|---|
| <p>Carey et al<sup>111</sup>;<br/>2000;<br/>Andrews et al<sup>127</sup>;<br/>2003;</p> <p>United States;</p> <p>National Institute of Child Health and Human Development and National Institute of Allergy and Infectious Disease;</p> <p>Good</p> | <p>G1: Placebo (987)<br/>G2: Oral metronidazole 1,000 mg dose four times (966)<br/>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</p> | <p><i>Key inclusion criteria:</i><br/>Asymptomatic, pregnancy between 16 weeks 0 days and 23 weeks 6 days of gestation, tested positive for BV and negative for <i>T. vaginalis</i>.</p> <p><i>Key exclusion criteria:</i><br/>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.</p> | <p>Mean (SD) maternal age, years:<br/>G1: 23 (5)<br/>G2: 23 (6)<br/>N (%) nonwhite:<br/>G1: 841 (85.2)<br/>G2: 822 (85.1)<br/>Mean (SD) gestational age, weeks:<br/>G1: 19.8 (2.6)<br/>G2: 19.5 (2.5)<br/>N (%) nulliparous:<br/>G1: 407 (41.2)<br/>G2: 436 (45.1)<br/>Prior PTD:<br/>G1: 110 (11.1)<br/>G2: 103 (10.7)<br/>N (%) with symptoms of BV:<br/>G1: 0 (0)<br/>G2: 0 (0)</p> | <p>Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score <math>\geq 7</math>) combined with pH of vaginal sample <math>&gt;4.4</math></p> <p>BV prevalence among women tested for study entry: 33.6%</p> |
| <p>Guaschino et al<sup>112</sup>;<br/>2003;</p> <p>Italy;</p> <p>NR;</p> <p>Good</p>   | <p>G1: No treatment (57)<br/>G2: Intravaginal clindamycin 2% cream once daily for 7 days (55)</p>  | <p><i>Key inclusion criteria:</i><br/>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.</p> <p><i>Key exclusion criteria:</i><br/>Multiple gestation, symptomatic vaginal or urinary tract infection, antibiotic therapy in the previous 15 days, or contraindications to the use of clindamycin.</p>   | <p>Mean (SD) maternal age, years:<br/>G1: 29.1 (4.4)<br/>G2: 29.2 (4.6)<br/>N (%) nonwhite:<br/>NR<br/>Mean (SD) gestational age, weeks:<br/>G1: 19.2 (3.9)<br/>G2: 19.2 (3.9)<br/>N (%) nulliparous:<br/>G1: 35 (61.4)<br/>G2: 39 (70.9)<br/>Prior PTD:<br/>G1: 3 (5.3)<br/>G2: 5 (9.1)<br/>N (%) with symptoms of BV:<br/>G1: 0 (0)<br/>G2: 0 (0)</p>                                | <p><i>Gardnerella</i>, <i>Bacteroides</i>, and <i>Mobiluncus</i> morphotype screening on vaginal smear using Hillier et al methodology</p> <p>BV prevalence among women tested for study entry: 5.9%</p>                                |

**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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality   | Interventions (N Randomized)  | Key Inclusion and Exclusion Criteria  | Sample Characteristics  | Method of BV Diagnosis and Prevalence of BV   |
|---|---|---|---|---|
| <p>Hauth et al<sup>121</sup>;<br/>1995;</p> <p>United States;</p> <p>March of Dimes Birth Defects Foundation and an Agency for Health Care Policy Research;</p> <p>Fair</p>   | <p>G1: Placebo (87)*<br/>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)</p> | <p><i>Key inclusion criteria:</i><br/>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.</p> <p><i>Key exclusion criteria:</i><br/>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.</p> | <p>Mean (SD) maternal age, years (from parent study):<br/>G1: 23.6 (4.8)<br/>G2: 23.7 (4.9)<br/>N (%) nonwhite (from parent study):<br/>G1: 150 (79)<br/>G2: 309 (71)<br/>Mean (SD) gestational age, weeks (from parent study):<br/>G1: 22.9 (2.5)<br/>G2: 23.0 (2.3)<br/>N (%) nulliparous (from parent study):<br/>G1: 30 (16)<br/>G2: 84 (19)<br/>N (%) with prior PTD (from subgroup with BV):<br/>G1: 56 (65.1)<br/>G2: 121 (70.3)<br/>N (%) with symptoms of BV:<br/>NR</p> | <p>Three of four Amsel's clinical criteria plus few white blood cells and mixed flora on Gram stain of vaginal fluid based on criteria of Spiegel et al and Thomason et al</p> <p>BV prevalence among women tested for study entry: 42.1%</p> |
| <p>Kekki et al<sup>113</sup>;<br/>2001;<br/>Kurkinen-Raty et al<sup>126</sup>;<br/>2000;</p> <p>Finland;</p> <p>Helsinki University Central Hospital Research Funds, Pharmacia-Upjohn and Paulo Foundation;</p> <p>Good</p> | <p>G1: Placebo (188)<br/>G2: Intravaginal clindamycin 2% cream once daily for 7 days (187)</p>  | <p><i>Key inclusion criteria:</i><br/>Gravid women who were patients at antenatal clinics who screened positive for BV at their 10- to 17-week gestation antenatal clinical visit.</p> <p><i>Key exclusion criteria:</i><br/>Multiple pregnancies or history of preterm delivery.</p>   | <p>Mean (range) maternal age, years: 28.8 (17 to 43)<br/>N (%) nonwhite: NR<br/>Mean (SD) gestational age, weeks: NR; participants were randomized to treatment between 12 and 19 weeks<br/>N (%) nulliparous: NR but mean parity in G1 1.9 and mean parity in G2 1.7<br/>N (%) with prior PTD:<br/>0 (0)<br/>N (%) with symptoms of BV:<br/>0 (0)</p>  | <p>Gram stain of vaginal smear interpreted using criteria of Spiegel et al, interpreted as normal, intermediate flora, or BV</p> <p>BV prevalence among women tested for study entry: 10.4%</p>   |

**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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality  | Interventions (N Randomized)  | Key Inclusion and Exclusion Criteria  | Sample Characteristics  | Method of BV Diagnosis and Prevalence of BV  |
|--|---|---|---|--|
| <p>Kiss et al<sup>114</sup>; 2004;</p> <p>Austria;</p> <p>Health Austria and Federal Ministry of Education, Science and Culture;</p> <p>Fair</p> | <p>G1: No treatment (179)<sup>†</sup></p> <p>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)</p> | <p><i>Key inclusion criteria:</i></p> <p>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.</p> <p><i>Key exclusion criteria:</i></p> <p>Multiple gestations, women with subjective complaints (contractions, vaginal bleeding, or symptoms suggestive of vaginal infection).</p> | <p>Mean (SD) maternal age, years: 28.9 (5.6)</p> <p>N (%) nonwhite: NR (2)</p> <p>Mean (SD) gestational age, weeks: 17 (1.6)</p> <p>N (%) nulliparous:</p> <p>G1: NR (47.8)</p> <p>G2: NR (47.9)</p> <p>N (%) with prior PTD between 33 and 36 weeks:</p> <p>G1: 45 (2.1)</p> <p>G2: 47 (2.2)</p> <p>N (%) with prior PTD between 23 and 32 weeks:</p> <p>G1: 24 (1.1)</p> <p>G2: 22 (1.1)</p> <p>N (%) with symptoms of BV: 0 (0)</p>              | <p>Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score <math>\geq 7</math>)</p> <p>BV prevalence among women tested for study entry: 8.6%</p>   |
| <p>Lamont et al<sup>115</sup>; 2003;</p> <p>Lamont et al<sup>138</sup>; 2012;</p> <p>United Kingdom;</p> <p>Pharmacia/Upjohn;</p> <p>Good</p>    | <p>G1: Placebo (201)</p> <p>G2: Intravaginal clindamycin 2% cream, once daily for 3 days (208)</p>  | <p><i>Key inclusion criteria:</i></p> <p>Asymptomatic women ages 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.</p> <p><i>Key exclusion criteria:</i></p> <p>Known sensitivity to clindamycin, a history of antibiotic-related colitis, inflammatory bowel disease, or frequent periodic diarrhea.</p>         | <p>Mean (SD) maternal age, years:</p> <p>G1: 27 (5)</p> <p>G2: 27 (5)</p> <p>N (%) nonwhite:</p> <p>G1: 63 (31)</p> <p>G2: 58 (28)</p> <p>N (%) at 13 to 16 weeks gestation: 245 (60)</p> <p>N (%) at 20 weeks gestation or later:</p> <p>G1: 4 (2)</p> <p>G2: 6 (3)</p> <p>N (%) nulliparous:</p> <p>G1: 112 (56)</p> <p>G2: 111 (53)</p> <p>N (%) with prior PTD:</p> <p>G1: 11 (8)</p> <p>G2: 10 (7)</p> <p>N (%) with symptoms of BV: 0 (0)</p> | <p>Gram stain of vaginal smear scored according to Nugent et al criteria; women with intermediate flora (score 4 to 6) and women with bacterial vaginosis (score <math>\geq 7</math>) were randomized)</p> <p>BV prevalence among women tested for study entry: NR</p> |

**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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality   | Interventions (N<br>Randomized)  | Key Inclusion and Exclusion Criteria  | Sample Characteristics  | Method of BV<br>Diagnosis and<br>Prevalence of BV  |
|---|--|---|---|--|
| <p>Larsson et al<sup>116</sup>;<br/>2006;<br/><br/>Sweden;<br/><br/>Medical Research Council of Southeast Sweden and Linköping University;<br/><br/>Fair</p>  | <p>G1: No treatment (411)<br/>G2: Intravaginal clindamycin 2% cream, once daily for 7 days (408)</p>   | <p><i>Key inclusion criteria:</i><br/>Women, age 18 years or older, registered at an antenatal clinic who screened positive for BV at their initial antenatal visit.<br/><i>Key exclusion criteria:</i><br/>Antibiotic treatment in early pregnancy, symptomatic vaginal infection, therapeutic termination of pregnancy, early spontaneous miscarriage (&lt;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).</p> | <p>Mean (SD) maternal age, years:<br/>G1: 28.6 (4.97)<br/>G2: 28.5 (4.83)<br/>N (%) nonwhite: NR<br/>Mean (SD) gestational age:<br/>13 weeks, 6 days (18 days)<br/>N (%) nulliparous:<br/>G1: 187 (45.5)<br/>G2: 186 (45.5)<br/>N (%) prior PTD (among parous women):<br/>G1: 13/218 (6.0)<br/>G2: 20/217 (9.2)<br/>N (%) with symptoms of BV:<br/>0 (0)</p>  | <p>Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7)<br/><br/>BV prevalence among women tested for study entry: 9.3%</p>  |
| <p>McDonald et al<sup>117</sup>;<br/>1997;<br/><br/>Australia;<br/><br/>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;<br/><br/>Good</p> | <p>G1: Placebo (440)<br/>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)</p> | <p><i>Key inclusion criteria:</i><br/>Singleton, asymptomatic women attending their 18-week antenatal visit who subsequently screened positive for BV.<br/><i>Key exclusion criteria:</i><br/>Multiple pregnancy, age younger than 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.</p>  | <p>Mean (SD) maternal age, years:<br/>G1: 25.9 (5.6)<br/>G2: 26.6 (5.5)<br/>N (%) nonwhite:<br/>G1: 53 (12.3)<br/>G2: 47 (10.8)<br/>Mean (SD) gestational age, weeks (at randomization/treatment):<br/>G1: 24.1 (1.49)<br/>G2: 24.0 (1.59)<br/>N (%) nulliparous:<br/>G1: 144 (32.7)<br/>G2: 139 (31.7)<br/>N (%) with prior PTD:<br/>G1: 24 (5.5)<br/>G2: 22 (5.0)<br/>N (%) with symptoms of BV:<br/>0 (0%)</p> | <p>Vaginal swab for “heavy growth” of <i>G. vaginalis</i> or Gram stain interpreted as having numerous small gram variable bacilli resembling <i>G. vaginalis</i> and anaerobes; absence or reduction of lactobacilli, plus or minus the presence of clue cells<br/><br/>BV prevalence among women tested for study entry: 26.5%</p> |



**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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality   | Interventions (N Randomized)  | Key Inclusion and Exclusion Criteria   | Sample Characteristics  | Method of BV Diagnosis and Prevalence of BV  |
|---|---|--|---|--|
| <p>McGregor et al<sup>118</sup>; 1994;</p> <p>United States;</p> <p>University of Colorado Health Sciences Center and the Children's Hospital, Kempe Research Center;</p> <p>Good</p> | <p>G1: Placebo (N randomized NR; 69 analyzed)</p> <p>G2: Intravaginal clindamycin 2% cream, once daily for 7 days (N randomized NR; 60 analyzed)</p>          | <p><i>Key inclusion criteria:</i><br/>Women initiating prenatal care between 16 and 27 weeks gestation who tested positive for BV.</p> <p><i>Key exclusion criteria:</i><br/>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.</p>  | <p>Mean (range) maternal age, years: 23.8 (17 to 47)</p> <p>N (%) nonwhite: 87 (61.2)</p> <p>Mean (SD) gestational age, weeks: NR</p> <p>Mean parity (range): 1.0 (0 to 6)</p> <p>N (%) with prior PTD: 15 (10.9)</p> <p>N (%) with symptoms of BV: 0 (0)</p>   | <p>Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score <math>\geq 7</math>) and presence of <math>\geq 20\%</math> clue cells, plus two of the following three criteria: pH <math>&gt; 4.5</math>, positive whiff test, presence of discharge</p> <p>BV prevalence among women tested for study entry: NR</p> |
| <p>Morales et al<sup>122</sup>; 1994;</p> <p>United States;</p> <p>Department of Obstetrics and Gynecology, Orlando Regional Medical Center;</p> <p>Fair</p>                          | <p>G1: Placebo (N randomized NR, 36 analyzed)</p> <p>G2: Oral metronidazole 750 mg in three divided doses daily for 7 days (N randomized NR, 44 analyzed)</p> | <p><i>Key inclusion criteria:</i><br/>Women in the high-risk obstetric clinic with a singleton gestation between 13 and 20 weeks with a PTD in preceding pregnancy from either idiopathic preterm labor or premature rupture of membranes who screened positive for BV.</p> <p><i>Key exclusion criteria:</i><br/>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 intra-amniotic or urinary tract infection or incompetent cervix; antibiotics used 2 weeks before enrollment; fetal anomalies; second-trimester bleeding; and asymptomatic bacteriuria on initial screen.</p> | <p>Mean (SD) maternal age, years:<br/>G1: 25.1 (4.4)<br/>G2: 24.4 (3.7)</p> <p>N (%) black:<br/>G1: 18 (50)<br/>G2: 20 (45)</p> <p>Mean (SD) gestational age, weeks: NR</p> <p>Mean parity (SD):<br/>G1: 2.2 (1.1)<br/>G2: 2.4 (1.2)</p> <p>N (%) with prior PTD: 80 (100)</p> <p>N (%) with symptoms of BV: NR</p> | <p>Based on clinical criteria (homogeneous discharge, vaginal pH <math>&gt; 4.5</math>, presence of clue cells in wet-mount preparation, and fish-like amine odor when mixed with 10% potassium hydroxide solution) and no evidence of <i>Trichomonas</i></p> <p>BV prevalence among women tested for study entry: NR</p>                      |

**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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality  | Interventions (N Randomized)  | Key Inclusion and Exclusion Criteria  | Sample Characteristics  | Method of BV Diagnosis and Prevalence of BV   |
|--|---|---|---|---|
| Subtil et al <sup>119</sup> ;<br>2014;<br><br>France;<br><br>NR;<br><br>Good   | G1: Placebo (958)<br>G2: Oral clindamycin 600 mg daily for 4 days (943) <sup>†</sup><br>G3: Oral clindamycin 600 mg daily for 4 days, repeated twice at 1-month intervals (968) | <p><i>Key inclusion criteria:</i><br/>Pregnant women before 15 weeks gestation with BV, no previous late miscarriage (&gt;16 weeks gestation) or PTD.</p> <p><i>Key exclusion criteria:</i><br/>Gestation &gt;15 weeks, allergy to clindamycin, vaginal bleeding in the week prior to enrollment, planning to give birth in a different region of the country.</p>  | Mean (SD) maternal age, years:<br>G1: 27.7 (5.5)<br>G2/G3: 28.0 (5.4)<br>N (%) nonwhite: NR<br>Mean (SD) gestational age, weeks:<br>G1: 12.4 (2.1)<br>G2/G3: 12.3 (2.2)<br>N (%) nulliparous:<br>G1: 521 (54.3)<br>G2/G3: 969 (50.7)<br>N (%) with prior induced PTD:<br>G1: 14 (1.5)<br>G2/G3: 33 (1.7)<br>N (%) with symptoms of BV: NR           | Gram stain of vaginal smear interpreted according to criteria of Nugent et al (score ≥7)<br><br>BV prevalence among women tested for study entry: 6.7%  |
| Ugwumadu et al <sup>120</sup> ;<br>2003;<br><br>United Kingdom;<br><br>Research and Development Programme, NHS Executive London;<br><br>Good | G1: Placebo (245) <sup>§</sup><br>G2: Oral clindamycin 600 mg daily (in two divided doses) for 5 days (249)   | <p><i>Key inclusion criteria:</i><br/>Women age 16 years or older and 12 to 22 weeks pregnant seeking antenatal care who tested positive for abnormal vaginal flora or BV.</p> <p><i>Key exclusion criteria:</i><br/>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.</p> | Mean (SD) maternal age, years:<br>G1: 28.5 (5.4)<br>G2: 28.8 (5.6)<br>N (%) nonwhite:<br>G1: 93 (39)<br>G2: 86 (36)<br>Mean (SD) gestational age, weeks:<br>G1: 15.7 (2.6)<br>G2: 15.6 (2.6)<br>Mean parity (SD):<br>G1: 0.8 (1.0)<br>G2: 0.8 (1.1)<br>N (%) with prior spontaneous PTD:<br>G1: 22 (9)<br>G2: 24 (10)<br>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)<br><br>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;<br>Publication Year;<br>Country;<br>Sponsor;<br>Study Quality  | Interventions (N Randomized)  | Key Inclusion and Exclusion Criteria   | Sample Characteristics   | Method of BV Diagnosis and Prevalence of BV  |
|--|---|--|--|--|
| Vermeulen et al <sup>123</sup> ; 1999;<br><br>The Netherlands;<br><br>Praeventiefonds; the Hague, the Netherlands;<br><br>Good | G1: Placebo (11) <sup>†</sup><br>G2: Intravaginal clindamycin 2% cream once daily for 7 days at 26 weeks and again at 32 weeks (11) | <i>Key inclusion criteria:</i><br>Women with a viable singleton pregnancy without major fetal congenital anomalies, at <26 weeks of gestation and a history of spontaneous PTD.<br><i>Key exclusion criteria:</i><br>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, years:<br>G1: 30.9 (3.8)<br>G2: 31.4 (4.0)<br>N (%) nonwhite: NR<br>Mean (SD) gestational age, weeks:<br>G1: 20.4 (3.2)<br>G2: 19.6 (3.9)<br>Mean parity (SD):<br>G1: 1.4 (0.9)<br>G2: 1.6 (0.9)<br>N (%) with prior PTD:<br>G1: 11 (100)<br>G2: 11 (100)<br>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 effect 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.

<sup>†</sup>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.

<sup>‡</sup>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.

<sup>§</sup> 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.

<sup>†</sup> 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 of Randomized, Controlled Trials of Treatment of Bacterial Vaginosis to Prevent Preterm Delivery (KQ 4)**

| Author et al;<br>Publication Year;<br>Intervention (N Analyzed)<br>Comparator (N Analyzed)   | BV Clearance or Recurrence  |
|--|---|
| Carey et al <sup>111</sup> ;<br>2000;<br><br>G1: Placebo (859)<br>G2: Oral metronidazole 1,000 mg dose four times (845)  | Clearance of BV defined by Nugent score $\geq 7$ on Gram stain at followup visit after first course of treatment<br>G1: 321 (37.4)<br>G2: 657 (77.8)<br>Calculated ARD, 40.38% (95% CI, 36.1% to 44.66%)<br>Calculated RR, 2.08 (95% CI, 1.89 to 2.29)  |
| Guaschino et al <sup>112</sup> ;<br>2003;<br><br>G1: No treatment (37)<br>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<br>G1: 26 (70.3)<br>G2: 25 (75.8)<br>Calculated ARD, 5.49% (-15.26% to 26.34%)<br>Calculated RR, 1.08 (0.81 to 1.43)   |
| Kekki et al <sup>113</sup> ;<br>2001;<br>Kurkinen-Raty et al <sup>126</sup> ;<br>2000;<br><br>G1: Placebo (188)<br>G2: Intravaginal clindamycin 2% cream once daily for 7 days (187) | <p>Short-term clearance (within 1 week of treatment) based on Gram stain (Spiegel et al criteria)<br/>G1: 62/181 (34.3)<br/>G2: 119/181 (65.8)<br/>OR, 1.9 (1.3 to 2.8)<br/>Calculated ARD, 31.49% (21.72% to 41.27%)<br/>Calculated RR, 1.92 (1.53 to 2.41)</p> <p>Long-term clearance (mean, 34 weeks gestation; range from 30 to 36 weeks); patients with incomplete followup and intermediate flora were excluded<br/>G1: 68/125 (54.4)<br/>G2: 95/121 (78.5)<br/>Calculated ARD, 24.11% (12.72% to 35.50%)<br/>Calculated RR, 1.44 (1.20 to 1.74)</p> <p>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<br/>G1: 18/125 (14.4)<br/>G2: 8/125 (6.4)<br/>Calculated ARD, -8.0% (-15.50% to -0.50%)<br/>Calculated RR, 0.44 (0.20 to 0.98)</p> <p>Persistence (i.e., no clearance in short- or long-term followup); patients with incomplete followup and intermediate flora were excluded<br/>G1: 49/125 (39.2)<br/>G2: 8/121 (6.6)<br/>Calculated ARD, -32.59% (-42.22% to -22.95%)<br/>Calculated RR, 0.17 (0.08 to 0.34)</p> |

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

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

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

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

| <b>Author;<br/>Year;<br/>Study Design;<br/>Study Quality</b>               | <b>Country;<br/>Years Covered;<br/>Study Sponsor</b>  | <b>Study Population; Total N</b>   | <b>Exposed Group</b>   | <b>Comparison Group</b>  |
|--|---|--|--|--|
| Diav-Citrin et al <sup>129</sup> ;<br>2001;<br>Prospective cohort;<br>Poor | Israel;<br>1989 to 1998;<br>NR  | N=857<br>Women who contacted the Israeli Teratogen Information Service during pregnancy  | 228 women contacting the Information Service and who reported exposure to metronidazole<br>Mean maternal age: 20.7 (SD, 5.2)<br>Mean gestational age: 8 weeks (IQR, 6 to 10)<br>Mean daily dose: 973 mg (SD, 483.2)<br>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 nulliparous than the exposed group<br>Mean maternal age: 30.2 (SD, 5.0)<br>Mean gestational age: 10 weeks (IQR, 7 to 17) |
| Sorensen et al <sup>130</sup> ;<br>1999;<br>Retrospective cohort;<br>Fair  | Denmark;<br>1991 to 1996;<br>European Union BIO-MED programme, Danish Medical Research Council, North Jutland Research Council, Aarhus University Foundation, Helsefonden | N=13,451<br>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 <sup>132</sup> ;<br>1998;<br>Retrospective cohort;<br>Fair     | U.S.;<br>1975 to 1992;<br>National Cancer Institute   | N=328,846 participants;<br>1,172,696 person-years followup<br>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 NR  | 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   |
|--|---|
| <p>Diav-Citrin et al<sup>129</sup>; 2001</p> | <p>Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (including elective termination of pregnancy due to prenatally diagnosed anomalies):<br/>                     Exposed: 5/192 (2.60%)<br/>                     Unexposed: 12/579 (2.07%)<br/>                     RR, 1.13 (95% CI, 0.30 to 4.23; p=0.777)</p> <p>Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (excluding elective termination of pregnancy due to prenatally diagnosed anomalies)<br/>                     Exposed: 3/190 (1.58%)<br/>                     Unexposed: 8/575 (1.39%)<br/>                     RR, 1.26 (95% CI, 0.45 to 3.52; p=0.739)</p> <p>Major birth defects defined as having a structural abnormality that has serious medical, surgical, or cosmetic consequences (including elective termination of pregnancy due to prenatally diagnosed anomalies but excluding chromosomal abnormalities and genetic disorders)<br/>                     Exposed: 4/192 (2.08%)<br/>                     Unexposed: 10/577 (1.73%)<br/>                     RR, 1.20 (95% CI, 0.38 to 3.79)</p> <p>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)<br/>                     Exposed: 4/131 (3.05%)<br/>                     Unexposed: 12/579 (2.07%)<br/>                     RR, 1.47 (95% CI, 0.48 to 4.50)</p> <p>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)<br/>                     Exposed: 3/129 (2.33%)<br/>                     Unexposed: 8/575 (1.39%)<br/>                     RR, 1.67 (95% CI, 0.45 to 6.21)</p> |
| <p>Sorensen et al<sup>130</sup>; 1999</p>    | <p>Congenital anomalies (not further defined)<br/>                     Exposed: NR (2.4%)<br/>                     Unexposed: NR (5.2%)<br/>                     Crude OR, 0.44 (95% CI, 0.11 to 1.80)<br/>                     Adjusted OR, 0.44 (95% CI, 0.11 to 1.81); adjusted for maternal and gestational age, birth order, smoking status</p>  |



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

| Author; Year                      | Outcome  |
|-----------------------------------|--|
| Thapa et al <sup>132</sup> ; 1998 | Incidence of first primary cancer before age 5 years identified from the Tennessee Childhood Cancer Database, assembled from review of records from the four tertiary medical centers in Tennessee<br>Exposed: 9/79,716 person-years (rate 11.3 per 100,000)<br>Unexposed: 166/1,092,980 person-years (rate 14.2 per 100,000)<br>Adjusted RR, 0.81 (95% CI, 0.41 to 1.59); adjusted for maternal age younger 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)**

| <b>Author; Year; Study Quality</b>          | <b>Country; Years Covered; Study Sponsor</b>            | <b>Number of Participants; Study setting</b>                   | <b>Cases (N)</b>  | <b>Controls (N)</b>   | <b>Exposure and Measurement</b>   |
|---|---|--|---|---|---|
| Czeizel et al <sup>131</sup> ; 1998<br>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<br><br>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<br><br>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 <sup>131</sup> ; 1998 | <p>Total congenital abnormalities with exposure to metronidazole during 1st month of gestation, N (%)<br/> Cases: 29/17,300 (0.17%)<br/> Controls: 24/30,633 (0.08%)<br/> OR, 2.24 (95% CI, 1.30 to 3.85)</p> <p>Total congenital abnormalities with exposure to metronidazole during 2nd or 3rd month of gestation, N (%)<br/> Cases: 107/17,300 (0.62%)<br/> Controls: 162/30,633 (0.53%)<br/> OR, 1.14 (95% CI, 0.89 to 1.46)</p> <p>Total congenital abnormalities with exposure to metronidazole during 4th through 9th month of gestation, N (%)<br/> Cases: 457/17,300 (2.64%)<br/> Controls: 742/30,633 (2.42%)<br/> OR, 1.07 (95% CI, 0.95 to 1.20)</p> |

**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;<br>Year;<br>Study Quality                 | Years Covered by Search; Years Covered by Included Studies; Study Sponsor               | Number of Studies;<br>Number of Participants                   | Inclusion Criteria   |
|---|---|--|--|
| Burtin et al <sup>133</sup> ;<br>1995<br>Fair     | 1959 to 1999;<br>1964 to 1987;<br>Association Francaise pour la Recherche Therapeutique | 7 cohort studies;<br>NR  | Studies of any design that included at least 10 women exposed to metronidazole (oral or intravaginal) during pregnancy<br><br>Control group of unexposed women or women exposed exclusively during the third trimester |
| Caro-Paton et al <sup>134</sup> ;<br>1997<br>Fair | 1966 to 1996;<br>1977 to 1994;<br>NR  | 5 total; 4 cohort studies and 1 case-control study;<br>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;<br>Year;<br>Study Quality                  | Outcome   |
|--|---|
| Burtin et al <sup>133</sup> ;<br>1995;<br>Fair     | <p>Major congenital malformations observed in live-born infants, excluding spontaneous abortion and stillbirth:<br/>Summary OR, 0.93 (95% CI, 0.73 to 1.18); no significant heterogeneity (p=0.636)</p> <p>Any congenital malformations observed in live-born infants, excluding spontaneous abortion and stillbirth:<br/>Summary OR, 0.96 (95% CI, 0.75 to 1.22)</p> |
| Caro-Paton et al <sup>134</sup> ;<br>1997;<br>Fair | <p>Congenital malformations:<br/>Summary OR, 1.08 (95% CI, 0.90 to 1.29); no significant heterogeneity (p=0.32)</p>   |

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

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

| <b>Study Author (Year)</b>                   | <b>Overall Study Quality</b>  | <b>Comments</b>  |
|--|---|--|
| Bradshaw et al (2005) <sup>100</sup>         | 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) <sup>96</sup>         | Fair  | No information about whether a consecutive or random sample was enrolled   |
| Byun et al (2016) <sup>90</sup>              | Good  | None   |
| Cartwright et al (2013) <sup>95</sup>        | 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) <sup>110</sup>             | 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) <sup>103</sup>           | 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) <sup>88</sup>          | Good  | None   |
| Gutman et al (2005) <sup>109</sup>           | Fair  | Unclear whether patients were consecutively or randomly enrolled and whether referent test was interpreted without knowledge of index test   |
| Hay et al (1992) <sup>91</sup>               | Good  | None   |
| Hellberg et al (2001) <sup>93</sup>          | Good  | None   |
| Hillier et al (2011) <sup>101</sup>          | Fair  | Unclear method of sample enrollment; no information about masking of index and referent test results   |
| Hilmarsdottir et al (2006) <sup>104</sup>    | 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) <sup>105</sup>          | Fair  | Unclear whether consecutive or random sample enrollment used, masking of test results not reported   |
| Lin et al (2002) <sup>201</sup>              | 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) <sup>97</sup>              | Fair  | Unclear whether consecutive or random sample enrollment used, unclear criteria for positive referent test  |
| Mastrobattista et al (2000) <sup>89</sup>    | Fair  | Unclear whether consecutive or random sample enrollment used, no reporting of whether referent and index test results were masked  |
| Myziuk et al (2003) <sup>102</sup>           | Fair  | Unclear risk of bias in patient selection, index test, and reference test domains  |
| Platz-Christensen et al (1995) <sup>92</sup> | Good  | Uses Spiegel's criteria for referent test on Gram stain  |
| Rouse et al (2009) <sup>136</sup>            | Fair (pH and clue cells)<br>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" test and modified Amsel's clinical criteria resulting in high concern for bias for those two tests  |
| Schmidt et al (1994) <sup>94</sup>           | Good  | None   |
| Schwebke et al (1996) <sup>108</sup>         | Fair  | Unclear risk of bias in some domains, including patient selection and masking of index test results  |

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

| Study Author (Year)  | Overall Study Quality | Comments   |
|--|-----------------------|--|
| Schwebke (2018) <sup>99</sup><br>Gaydos (2017) <sup>65</sup> | Fair                  | Effect of excluding participants with intermediate Nugent scores from the analysis is unclear  |
| Sha et al (2007) <sup>106</sup>                              | 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) <sup>107</sup>                            | Fair                  | Unclear risk of bias due to patient selection and reference test (lack of information about masking)   |
| Sonnex et al (1995) <sup>137</sup>                           | Fair                  | No information about method of enrollment and no indication that index and referent tests were masked  |
| Witt et al (2002) <sup>98</sup>                              | 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**

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



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

| Study Author(s)<br>(Year(s))                    | Was a consecutive<br>or random sample<br>of patients<br>enrolled? | Was a case-<br>control<br>design<br>avoided? | Did the study<br>avoid<br>inappropriate<br>exclusions? | Could the<br>selection of<br>patients have<br>introduced bias? | Comments  |
|---|---|--|--|--|---|
| Bradshaw et al<br>(2005) <sup>100</sup>         | Unclear   | Yes  | Yes  | Unclear  | Unclear whether a consecutive or random sample was enrolled   |
| Briselden et al<br>(1994) <sup>96</sup>         | Unclear   | Yes  | Yes  | Unclear  | No information about whether a consecutive or random sample was enrolled  |
| Byun et al (2016) <sup>90</sup>                 | Unclear   | Yes  | Yes  | Low  | None  |
| Cartwright et al<br>(2013) <sup>95</sup>        | 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) <sup>110</sup>                | Unclear   | Yes  | Yes  | Unclear  | Unclear whether a consecutive or random sample of patients was enrolled   |
| Gallos et al (2011) <sup>103</sup>              | Unclear   | Yes  | Yes  | Unclear  | Unclear whether a consecutive or random sample of patients was enrolled   |
| Gratacos et al<br>(1999) <sup>88</sup>          | Yes   | Yes  | Yes  | Low  | None  |
| Gutman et al<br>(2005) <sup>109</sup>           | 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) <sup>91</sup>                  | Yes   | Yes  | Yes  | Low  | None  |
| Hellberg et al<br>(2001) <sup>93</sup>          | Yes   | Yes  | Unclear  | Low  | Cites another paper for detailed study enrollment criteria; the cited paper verifies that consecutive enrollment was used   |
| Hillier et al (2011) <sup>101</sup>             | Unclear   | Yes  | Yes  | Unclear  | Unclear how sample was enrolled   |
| Hilmarsdottir et al<br>(2006) <sup>104</sup>    | Unclear   | Yes  | Unclear  | Unclear  | No information about study inclusion/exclusion criteria or method of recruitment/enrollment   |
| Landers et al<br>(2004) <sup>105</sup>          | Unclear   | Yes  | Yes  | Unclear  | Unclear whether consecutive or random enrollment used   |
| Lin et al (2002) <sup>201</sup>                 | No  | No   | Unclear  | High   | Study used a case-control design with no information about inclusion/exclusion criteria   |
| Lowe et al (2009) <sup>97</sup>                 | Unclear   | Yes  | Yes  | Unclear  | Unclear whether a consecutive or random sample of women were enrolled   |
| Mastrobattista et al<br>(2000) <sup>89</sup>    | Unclear   | Yes  | Yes  | Unclear  | Unclear whether consecutive or random sample enrollment was used  |
| Myziuk et al (2003) <sup>102</sup>              | Unclear   | Yes  | Unclear  | Unclear  | Unclear whether a consecutive or random sample of patients were enrolled  |
| Platz-Christensen et al<br>(1995) <sup>92</sup> | Yes   | Yes  | Yes  | Low  | None  |

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

| <b>Study Author(s)<br/>(Year(s))</b>                         | <b>Was a consecutive<br/>or random sample<br/>of patients<br/>enrolled?</b> | <b>Was a case-<br/>control<br/>design<br/>avoided?</b> | <b>Did the study<br/>avoid<br/>inappropriate<br/>exclusions?</b> | <b>Could the<br/>selection of<br/>patients have<br/>introduced bias?</b> | <b>Comments</b>   |
|--|---|--|--|--|---|
| Rouse et al (2009) <sup>136</sup>                            | 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) <sup>94</sup>                           | Yes   | Yes  | Yes  | Low  | None  |
| Schwebke et al<br>(1996) <sup>108</sup>                      | Unclear   | Yes  | Unclear  | Unclear  | No information provided regarding how patients were identified for enrollment or study inclusion/exclusion criteria                   |
| Schwebke (2018) <sup>99</sup><br>Gaydos (2017) <sup>65</sup> | Yes   | Yes  | Yes  | Low  | None  |
| Sha et al (2007) <sup>106</sup>                              | Unclear   | Yes  | Unclear  | Unclear  | Review of cited study confirms enrollment methods   |
| Singh et al (2013) <sup>107</sup>                            | Unclear   | Yes  | Yes  | Unclear  | No information about whether participants were consecutively or randomly enrolled   |
| Sonnex et al<br>(1995) <sup>137</sup>                        | 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) <sup>98</sup>                              | 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**

| <b>Study Author(s)<br/>(Year(s))</b>      | <b>Were the index test results interpreted without knowledge of the results of the reference standard?</b> | <b>If a threshold was used, was it pre-specified?</b> | <b>Could the conduct or interpretation of the index test have introduced bias?</b> | <b>Comments</b>   |
|---|--|---|--|---|
| Bradshaw et al (2005) <sup>100</sup>      | Unclear  | Yes   | Unclear  | Masking of referent test results NR   |
| Briselden et al (1994) <sup>96</sup>      | Yes  | Yes   | Low  | Although not explicitly stated, it appears that separate personnel performed the index and referent tests   |
| Byun et al (2016) <sup>90</sup>           | Yes  | Yes   | Low  | None  |
| Cartwright et al (2013) <sup>95</sup>     | Unclear  | Yes   | Unclear  | No information as to whether index tests were interpreted without knowledge of referent test  |
| Chen et al (2018) <sup>110</sup>          | Unclear  | Yes   | Unclear  | No information provided   |
| Gallos et al (2011) <sup>103</sup>        | 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) <sup>88</sup>       | Yes  | Yes   | Low  | None  |
| Gutman et al (2005) <sup>109</sup>        | 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) <sup>91</sup>            | 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) <sup>93</sup>       | 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) <sup>101</sup>       | Unclear  | Yes   | Unclear  | No information about masking of test results  |
| Hilmarsdottir et al (2006) <sup>104</sup> | 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) <sup>105</sup>       | Unclear  | Yes   | Unclear  | Index text results not reported as masked   |
| Lin et al (2002) <sup>201</sup>           | Unclear  | Unclear   | High   | No information is provided regarding how the index test was performed or interpreted  |
| Lowe et al (2009) <sup>97</sup>           | Yes  | Yes   | Low  | None  |
| Mastrobattista et al (2000) <sup>89</sup> | Unclear  | Yes   | Unclear  | Unclear whether index tests were masked   |

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

| Study Author(s)<br>(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) <sup>102</sup>                           | Unclear   | Yes  | Unclear   | No information about whether persons performing Amsel's clinical criteria were masked to results of Gram stain, but since Gram stains often go to laboratory to be performed after clinic visit, it is unlikely the clinicians would have had those results. It is also not clear where BVBLUE was performed (in clinic vs. laboratory) or whether persons performing BVBLUE were masked to the other index and referent test results |
| Platz-Christensen et al (1995) <sup>92</sup>                 | 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) <sup>136</sup>                            | Yes   | Yes  | Low   | None  |
| Schmidt et al (1994) <sup>94</sup>                           | 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) <sup>108</sup>                         | 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) <sup>99</sup><br>Gaydos (2017) <sup>65</sup> | Yes   | Yes  | Low   | None  |
| Sha et al (2007) <sup>106</sup>                              | Unclear   | Yes  | Unclear   | No information about masking of results   |
| Singh et al (2013) <sup>107</sup>                            | Yes   | Yes  | Low   | Gram stain sent to off-site laboratory for testing so would not have been available to examining clinician performing the index test  |
| Sonnex et al (1995) <sup>137</sup>                           | Unclear   | Yes  | Unclear   | No information about masking of index test results and seems unlikely given only one study author   |
| Witt et al (2002) <sup>98</sup>                              | 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**

| <b>Study Author(s)<br/>(Year(s))</b>         | <b>Is the reference<br/>standard likely to<br/>correctly classify<br/>the target<br/>condition?</b> | <b>Were the reference<br/>standard results<br/>interpreted without<br/>knowledge of the<br/>results of the index<br/>test?</b> | <b>Could the<br/>reference<br/>standard, its<br/>conduct, or its<br/>interpretation<br/>have introduced<br/>bias?</b> | <b>Comments</b>   |
|--|---|--|---|---|
| Bradshaw et al<br>(2005) <sup>100</sup>      | Yes   | Unclear  | Unclear   | Masking of index test results NR  |
| Briselden et al<br>(1994) <sup>96</sup>      | Yes   | Yes  | Low   | None  |
| Byun et al<br>(2016) <sup>90</sup>           | Yes   | Yes  | Low   | None  |
| Cartwright et al<br>(2013) <sup>95</sup>     | 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 criteria as positive if also had positive Amsel's clinical criteria                     |
| Chen et al<br>(2018) <sup>110</sup>          | Yes   | Unclear  | Unclear   | No information provided   |
| Gallos et al<br>(2011) <sup>103</sup>        | Yes   | Yes  | Low   | None  |
| Gratacos et al<br>(1999) <sup>88</sup>       | Yes   | Yes  | Low   | None  |
| Gutman et al<br>(2005) <sup>109</sup>        | Yes   | Unclear  | Unclear   | Unclear whether referent test was interpreted without knowledge of index test diagnosis   |
| Hay et al (1992) <sup>91</sup>               | Yes   | Yes  | Low   | Reference standard is Spiegel's criteria  |
| Hellberg et al<br>(2001) <sup>93</sup>       | 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<br>(2011) <sup>101</sup>       | Yes   | Unclear  | Unclear   | No information about masking of test results  |
| Hilmarsdottir et al<br>(2006) <sup>104</sup> | Yes   | Yes  | Low   | None  |
| Landers et al<br>(2004) <sup>105</sup>       | Yes   | Unclear  | Unclear   | Referent test results not reported as masked  |
| Lin et al (2002) <sup>201</sup>              | Yes   | Unclear  | Unclear   | Unclear whether technicians who interpreted the Gram stain slides were masked to results of index test  |
| Lowe et al<br>(2009) <sup>97</sup>           | Unclear   | Yes  | Unclear   | The explicit criteria used to make clinical diagnosis are not stated  |
| Mastrobattista et al<br>(2000) <sup>89</sup> | Yes   | Unclear  | Unclear   | Unclear whether referent tests were masked  |
| Myziuk et al<br>(2003) <sup>102</sup>        | Yes   | Unclear  | Unclear   | No information as to whether laboratory staff were masked to results of either index tests  |

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

| <b>Study Author(s)<br/>(Year(s))</b>                         | <b>Is the reference<br/>standard likely to<br/>correctly classify<br/>the target<br/>condition?</b> | <b>Were the reference<br/>standard results<br/>interpreted without<br/>knowledge of the<br/>results of the index<br/>test?</b> | <b>Could the<br/>reference<br/>standard, its<br/>conduct, or its<br/>interpretation<br/>have introduced<br/>bias?</b> | <b>Comments</b>  |
|--|---|--|---|--|
| Platz-Christensen et al (1995) <sup>92</sup>                 | Unclear   | Yes  | Low   | Somewhat unclear whether Gram stain based on Spiegel's criteria is diagnostic for BV                 |
| Rouse et al (2009) <sup>136</sup>                            | Yes   | Unclear  | Unclear   | Unclear whether microbiology laboratory had results of index test                                    |
| Schmidt et al (1994) <sup>94</sup>                           | Yes   | No   | Low   | Referent test is composed of index test components, so not possible to mask                          |
| Schwebke et al (1996) <sup>108</sup>                         | Yes   | Unclear  | Unclear   | No explicit mention that the central laboratory was masked to results of index test                  |
| Schwebke (2018) <sup>99</sup><br>Gaydos (2017) <sup>65</sup> | Yes   | Yes  | Low   | None   |
| Sha et al (2007) <sup>106</sup>                              | Yes   | Unclear  | Unclear   | No information about masking of results  |
| Singh et al (2013) <sup>107</sup>                            | Yes   | Unclear  | Unclear   | No information about whether off-site laboratory personnel were masked to results of the index tests |
| Sonnex et al (1995) <sup>137</sup>                           | Yes   | Unclear  | Unclear   | No information about masking of referent test results and seems unlikely given only one study author |
| Witt et al (2002) <sup>98</sup>                              | 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 Randomized, Controlled Trials: Part 1**

| 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) <sup>100</sup>  | 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                                      | Effect of excluding participants with intermediate flora from some analysis unknown |
| Briselden et al (1994) <sup>96</sup>  | 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) <sup>90</sup>       | 5 patients were excluded because of inadequate sample quality.   | Concurrent collection   | Yes   | Yes  | Yes   | Yes   | Low  | None  |
| Cartwright et al (2013) <sup>95</sup> | 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) <sup>110</sup>      | None mentioned.  | Concurrent collection   | Yes   | Yes  | Yes   | Unclear   | Low  | No information about eligible sample and sample analyzed                            |
| Gallos et al (2011) <sup>103</sup>    | 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) <sup>88</sup>   | NR   | Concurrent collection   | Yes   | Yes  | Yes   | Unclear   | Low  | The number of potentially eligible but not enrolled participants is NR              |
| Gutman et al (2005) <sup>109</sup>    | NR   | Concurrent collection   | Yes   | Yes  | Yes   | Yes   | Low  | The number of potential eligible but not enrolled participants is NR                |
| Hay et al (1992) <sup>91</sup>        | 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 Randomized, Controlled Trials: Part 1**

| <b>Study Author(s) (Year(s))</b>             | <b>Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded</b>  | <b>Describe the time interval and any interventions between index test(s) and reference standard</b> | <b>Was there an appropriate interval between index test(s) and reference standard?</b> | <b>Did all patients receive a reference standard?</b> | <b>Did patients receive the same reference standard?</b>                                  | <b>Were nearly all patients (&gt;80%) included in the analysis?</b> | <b>Could the patient flow have introduced bias?</b>                 | <b>Comments</b>  |
|--|--|--|--|---|---|---|---|--|
| Hellberg et al (2001) <sup>93</sup>          | 55 (5.4%) of patients were excluded for missing records.   | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Hillier et al (2011) <sup>101</sup>          | None   | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Hilmarsdottir et al (2006) <sup>104</sup>    | NR   | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Landers et al (2004) <sup>105</sup>          | 50 participants were excluded from analysis for reasons not reported.  | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Lin et al (2002) <sup>201</sup>              | NR   | Unclear timing, presumably concurrent collection.  | Yes  | Yes   | Yes   | Unclear   | Low   | None   |
| Lowe et al (2009) <sup>97</sup>              | 12 women were excluded for incomplete data.  | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Mastrobattista et al (2000) <sup>89</sup>    | 2 patients were excluded for poor-quality specimens.   | Concurrent collection  | Yes  | Yes   | Yes   | Yes   | Low   | None   |
| Myziuk et al (2003) <sup>102</sup>           | 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) <sup>92</sup> | 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) <sup>136</sup>            | 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 test and modified Amsel's clinical criteria | Yes   | Low for pH and clue cells, high for whiff test and modified Amsel's | High level of missing data for whiff test and modified Amsel's clinical criteria   |



**Appendix E Table 6. Study Quality Ratings for Randomized, Controlled Trials: Part 1**

| <b>Study Author(s) (Year(s))</b>                             | <b>Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded</b>  | <b>Describe the time interval and any interventions between index test(s) and reference standard</b> | <b>Was there an appropriate interval between index test(s) and reference standard?</b> | <b>Did all patients receive a reference standard?</b> | <b>Did patients receive the same reference standard?</b> | <b>Were nearly all patients (&gt;80%) included in the analysis?</b> | <b>Could the patient flow have introduced bias?</b> | <b>Comments</b>   |
|--|--|--|--|---|--|---|---|---|
| Schmidt et al (1994) <sup>94</sup>                           | 8 excluded for missing data.   | Concurrent collection  | Yes  | Yes   | Yes  | Yes   | Low   | None  |
| Schwebke et al (1996) <sup>108</sup>                         | 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) <sup>99</sup><br>Gaydos (2017) <sup>65</sup> | 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) <sup>106</sup>                              | 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) <sup>107</sup>                            | Three participants excluded for missing data.  | Concurrent collection  | Yes  | Yes   | Yes  | Yes   | Low   | None  |
| Sonnex et al (1995) <sup>137</sup>                           | No information   | Concurrent collection  | Yes  | Yes   | Yes  | Unclear   | Low   | Unclear whether study had any women enrolled who were not analyzed  |

**Appendix E Table 6. Study Quality Ratings for Randomized, Controlled Trials: Part 1**

| 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) <sup>98</sup> | The study authors excluded the participants with intermediate flora from their analysis. Data were provided and we are able to calculate the sensitivity and specificity 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 2**

| <b>Study Author (Year)</b>            | <b>Overall Study Quality Rating</b> | <b>Overall Rationale for Study Quality Rating</b>  |
|---------------------------------------|-------------------------------------|--|
| Cary et al (2000) <sup>111</sup>      | Good                                | None   |
| Guaschino et al (2003) <sup>112</sup> | Good                                | None   |
| Hauth et al (1995) <sup>121</sup>     | Fair                                | Using data from a subgroup analysis that was not prespecified  |
| Kekki et al (2001) <sup>113</sup>     | Good                                | None   |
| Kiss et al (2004) <sup>114</sup>      | 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) <sup>115</sup>    | Good                                | None   |
| Larsson et al (2006) <sup>116</sup>   | 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) <sup>117</sup>  | Good                                | None   |
| McGregor et al (1994) <sup>118</sup>  | 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) <sup>122</sup>   | 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) <sup>119</sup>    | Good                                | None   |
| Ugwumadu et al (2003) <sup>120</sup>  | 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) <sup>123</sup> | Good                                | None   |

**Abbreviations:** BV=bacterial vaginosis.

**Appendix E Table 8. Study Quality Ratings for Randomized, Controlled Trials: Part 3**

| 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) <sup>111</sup>      | Yes                                 | No information   | No  | Some concerns                                 | No information on method of randomization and no information about allocation concealment   |
| Guaschino et al (2003) <sup>112</sup> | Probably yes                        | Yes  | Probably no   | Low   | None  |
| Hauth et al (1995) <sup>121</sup>     | Yes                                 | Yes  | No  | Low   | None  |
| Kekki et al (2001) <sup>113</sup>     | Probably yes                        | Yes  | No information  | Low   | None  |
| Kiss et al (2004) <sup>114</sup>      | 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) <sup>115</sup>    | Yes                                 | Yes  | No  | Low   | None  |
| Larsson et al (2006) <sup>116</sup>   | Yes                                 | No information   | No  | Some concerns                                 | No information about allocation concealment   |
| McDonald et al (1997) <sup>117</sup>  | Yes                                 | Yes  | Probably no   | Low   | The placebo group contained 14% of study population younger than age 20 years compared with only 6% in intervention group   |
| McGregor et al (1994) <sup>118</sup>  | 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) <sup>122</sup>   | 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) <sup>119</sup>    | Yes                                 | Yes  | No  | Low   | None  |
| Ugwumadu et al (2003) <sup>120</sup>  | Yes                                 | Yes  | No  | Low   | None  |
| Vermeulen et al (1999) <sup>123</sup> | Probably yes                        | Probably yes   | No  | Low   | The article does say that randomization (which was for women with prior PTD) 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 4

| 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) <sup>111</sup>      | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Guaschino et al (2003) <sup>112</sup> | 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 birth weight outcomes. |
| Hauth et al (1995) <sup>121</sup>     | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Kekki et al (2001) <sup>113</sup>     | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Kiss et al (2004) <sup>114</sup>      | 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) <sup>115</sup>    | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Larsson et al (2006) <sup>116</sup>   | 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) <sup>117</sup>  | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| McGregor et al (1994) <sup>118</sup>  | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Morales et al (1994) <sup>122</sup>   | No  | No  | NA  | NA   | No   | NA   | Low   | None  |
| Subtil et al (2018) <sup>119</sup>    | No  | No  | NA  | NA   | No   | NA   | Lo  | None  |

**Appendix E Table 9. Study Quality Ratings for Randomized, Controlled Trials: Part 4**

| 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) <sup>120</sup>  | No  | No  | NA  | NA   | No   | NA   | Low   | None     |
| Vermeulen et al (1999) <sup>123</sup> | No  | No  | NA  | NA   | No   | NA   | Low   | None     |

**Abbreviations:** NA=not applicable.

**Appendix E Table 10. Study Quality Ratings for Randomized, Controlled Trials: Part 5**

| <b>Study Author(s)<br/>(Year)</b>     | <b>Were outcome data available for all, or nearly all, participants randomized?</b> | <b>Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?</b> | <b>Is there evidence that results were robust to the presence of missing outcome data?</b> | <b>Bias arising from missing outcome data?</b> | <b>Comments</b>  |
|---------------------------------------|---|---|--|--|--|
| Cary et al (2000) <sup>111</sup>      | Yes   | NA  | NA   | Low  | 1,757/1,953 (90.0%) returned for followup visit and 1,919/1,953 (98.2%) had outcome data available   |
| Guaschino et al (2003) <sup>112</sup> | Yes   | NA  | NA   | Low  | No treatment group: Data for followup 51/57 (89.5%)<br>Clindamycin group: Data for followup 49/55 (89.1%)  |
| Hauth et al (1995) <sup>121</sup>     | Yes   | NA  | NA   | Low  | 616/624 (98.7%) had followup data  |
| Kekki et al (2001) <sup>113</sup>     | Yes   | NA  | NA   | Low  | BV clearance outcome<br>G1: 90.4% followup<br>G2: 90.9% followup<br>Preterm delivery<br>G1: 100%<br>G2: 100%   |
| Kiss et al (2004) <sup>114</sup>      | Yes   | NA  | NA   | Low  | 4,155/4,492 (93.8%) completed the study  |
| Lamont et al (2003) <sup>115</sup>    | Yes   | NA  | NA   | Low  | Pregnancy outcomes:<br>Placebo: 201/201 (100%)<br>Clindamycin: 208/208 (100%)<br>Visit 2 followup for repeat Gram stain<br>Placebo: 190/201 (95%)<br>Clindamycin: 178/208 (86%)  |
| Larsson et al (2006) <sup>116</sup>   | Yes   | NA  | NA   | Low  | 8,791/9,025 (97.4%)  |
| McDonald et al (1997) <sup>117</sup>  | Yes   | NA  | NA   | Low  | 429/439 (97.7%) in treatment group; 428/440 (97.2%) in placebo group   |
| McGregor et al (1994) <sup>118</sup>  | 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) <sup>122</sup>   | No  | Unclear   | No   | Some concerns                                  | Data available for 80/94 (85%) of participants who 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) <sup>119</sup>    | Yes   | NA  | NA   | Low  | 941/943 (99.8%) in treatment group; 963/968 (99.5%) in placebo group   |
| Ugwumadu et al (2003) <sup>120</sup>  | 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 5**

| Study Author(s)<br>(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) <sup>123</sup> | 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 6**

| Study Author(s)<br>(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) <sup>111</sup>      | No information   | Probably no  | Yes  | Low   | None   |
| Guaschino et al (2003) <sup>112</sup> | No information   | No   | Yes  | Low   | None   |
| Hauth et al (1995) <sup>121</sup>     | No   | NA   | Yes  | Low   | None   |
| Kekki et al (2001) <sup>113</sup>     | 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) <sup>114</sup>      | No information   | Probably no  | Yes  | Low   | None   |
| Lamont et al (2003) <sup>115</sup>    | No information   | No   | Yes  | Low   | None   |
| Larsson et al (2006) <sup>116</sup>   | No information   | Probably no  | Yes  | Low   | None   |
| McDonald et al (1997) <sup>117</sup>  | No   | NA   | Yes  | Low   | None   |
| McGregor et al (1994) <sup>118</sup>  | No information   | No   | Yes  | Low   | None   |
| Morales et al (1994) <sup>122</sup>   | NI   | Probably no  | Yes  | Low   | None   |
| Subtil et al (2018) <sup>119</sup>    | No   | NA   | Yes  | Low   | None.  |
| Ugwumadu et al (2003) <sup>120</sup>  | NI   | No   | Yes  | Low   | None   |
| Vermeulen et al (1999) <sup>123</sup> | 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 7**

| Study Author(s)<br>(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) <sup>111</sup>      | No   | No   | Low  | None   |
| Guaschino (2003) <sup>112</sup> | No   | No   | Low  | None   |
| Hauth (1995) <sup>121</sup>     | No   | Yes  | Some concerns                                    | We are using data 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) <sup>113</sup>     | No   | No   | Low  | None   |
| Kiss (2004) <sup>114</sup>      | 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) <sup>115</sup>    | No   | No   | Low  | None   |
| Larsson (2006) <sup>116</sup>   | No   | No   | Low  | None   |
| McDonald (1997) <sup>117</sup>  | No   | No   | Low  | None   |
| McGregor (1994) <sup>118</sup>  | No   | No   | Low  | None   |
| Morales (1994) <sup>122</sup>   | Probably no  | No   | Low  | None   |
| Subtil (2018) <sup>119</sup>    | 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) <sup>120</sup>  | 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) <sup>123</sup> | 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**

| <b>Study Author(s)<br/>(Year(s))</b>       | <b>Overall Quality Rating</b> | <b>Overall Rationale for Quality Rating</b>   |
|--|-------------------------------|---|
| Diav-Citrin et al<br>(2001) <sup>129</sup> | Poor                          | Authors did not address potential confounding, high degree of missing data in both the exposed and control groups |
| Sorensen et al<br>(1999) <sup>130</sup>    | Fair                          | Authors did not fully address confounding; some bias from lack of information about how outcome was defined       |
| Thapa et al<br>(1998) <sup>132</sup>       | 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 confounding of the effect of intervention? | Was the analysis based on splitting participants' follow up time according to intervention? | Were intervention discontinuations or switches likely related to factors prognostic for the outcome? | Did the authors use appropriate analyses method that controlled for all the important confounding domains? | Were confounding 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 confounding domains adjusted for measured validly and reliably by the variables available? | Overall bias due to confounding | Comments   |
|---|---|---|--|--|--|--|--|---|---------------------------------|--|
| Diav-Citrin et al (2001) <sup>129</sup> | 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) <sup>130</sup>    | 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) <sup>132</sup>       | 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 health care 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)<br>(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) <sup>129</sup> | 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) <sup>130</sup>    | No  | NA  | NA   | Yes  | NA  | Low  | Used population-based data sources for selection into the study  |
| Thapa et al (1998) <sup>132</sup>       | 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)<br>(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) <sup>129</sup> | Yes                                       | Yes   | No   | Low  | None     |
| Sorensen et al (1999) <sup>130</sup>    | Yes                                       | Yes   | No   | Low  | None     |
| Thapa et al (1998) <sup>132</sup>       | Yes                                       | Yes   | No   | Low  | None     |

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

| Study Author(s)<br>(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<br>(2001) <sup>129</sup> | No  | NA  | Low  | None     |
| Sorensen et al<br>(1999) <sup>130</sup>    | No information  | No information  | Low  | None     |
| Thapa et al<br>(1998) <sup>132</sup>       | No  | NA  | Low  | None     |

**Abbreviation:** NA=not applicable.

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

| <b>Study Author(s)<br/>(Year(s))</b>    | <b>Were outcome data available for all, or nearly all, participants?</b> | <b>Were participants excluded due to missing data on intervention status?</b> | <b>Were participants excluded due to missing data on other variables needed for the analysis?</b> | <b>Are the proportion of participants and reasons for missing data similar across interventions?</b> | <b>Is there evidence that results were robust to the presence of missing data?</b> | <b>Overall bias due to missing data</b> | <b>Comments</b>   |
|---|--|---|---|--|--|---|---|
| Diav-Citrin et al (2001) <sup>129</sup> | 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) <sup>130</sup>    | 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) <sup>132</sup>       | 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)<br>(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) <sup>129</sup> | 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) <sup>130</sup>    | 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) <sup>132</sup>       | 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**

| <b>Study Author(s)<br/>(Year(s))</b>    | <b>Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?</b> | <b>Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention outcome relationship?</b> | <b>Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?</b> | <b>Overall bias in selection of the reported result</b> | <b>Comments</b> |
|---|--|---|--|---|-----------------|
| Diav-Citrin et al (2001) <sup>129</sup> | No   | No  | No   | Low   | None            |
| Sorensen et al (1999) <sup>130</sup>    | No   | No  | No   | Low   | None            |
| Thapa et al (1998) <sup>132</sup>       | 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) <sup>131</sup> | 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) <sup>131</sup> | Yes   | Yes  | Can't say  | Cases: 82%<br>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) <sup>131</sup> | Yes   | Yes  | Yes  | No  | Cannot say  | Yes                               |

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

| <b>Study Author(s)<br/>(Year(s))</b>      | <b>Overall Study Quality</b> | <b>Rationale for Study Quality</b>   |
|---|------------------------------|--|
| Burtin et al<br>(1995) <sup>133</sup>     | 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<br>(1997) <sup>134</sup> | 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**

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

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



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

| <b>Study Author(s)<br/>(Year(s))</b>   | <b>Were efforts made to minimize error in data collection?</b> | <b>Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?</b> | <b>Were all relevant study results collected for use in the synthesis?</b> | <b>Was risk of bias (or methodological quality) formally assessed using an appropriate tool?</b> | <b>Were efforts made to minimize error in risk of bias assessment?</b> | <b>Concerns regarding methods used to collect data and appraise studies</b> |
|--|--|---|--|--|--|---|
| Burtin et al (1995) <sup>133</sup>     | No information   | Probably yes  | No information   | No   | No information   | Unclear or some concerns  |
| Caro-Paton et al (1997) <sup>134</sup> | No information   | Probably yes  | No information   | No   | No information   | Unclear or some concerns  |

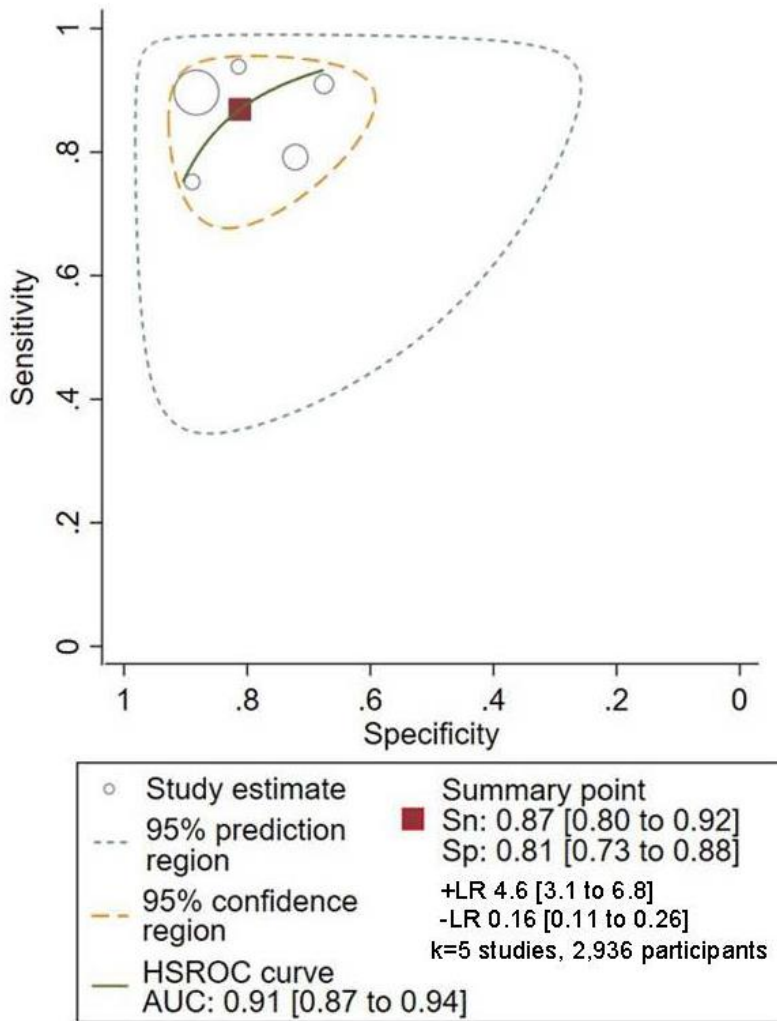
**Appendix E Table 28. Study Quality Ratings for Meta-Analyses: Part 5**

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

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

| 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) <sup>133</sup>     | No information  | Yes   | Yes   |
| Caro-Paton et al (1997) <sup>134</sup> | No information  | Yes   | Yes   |

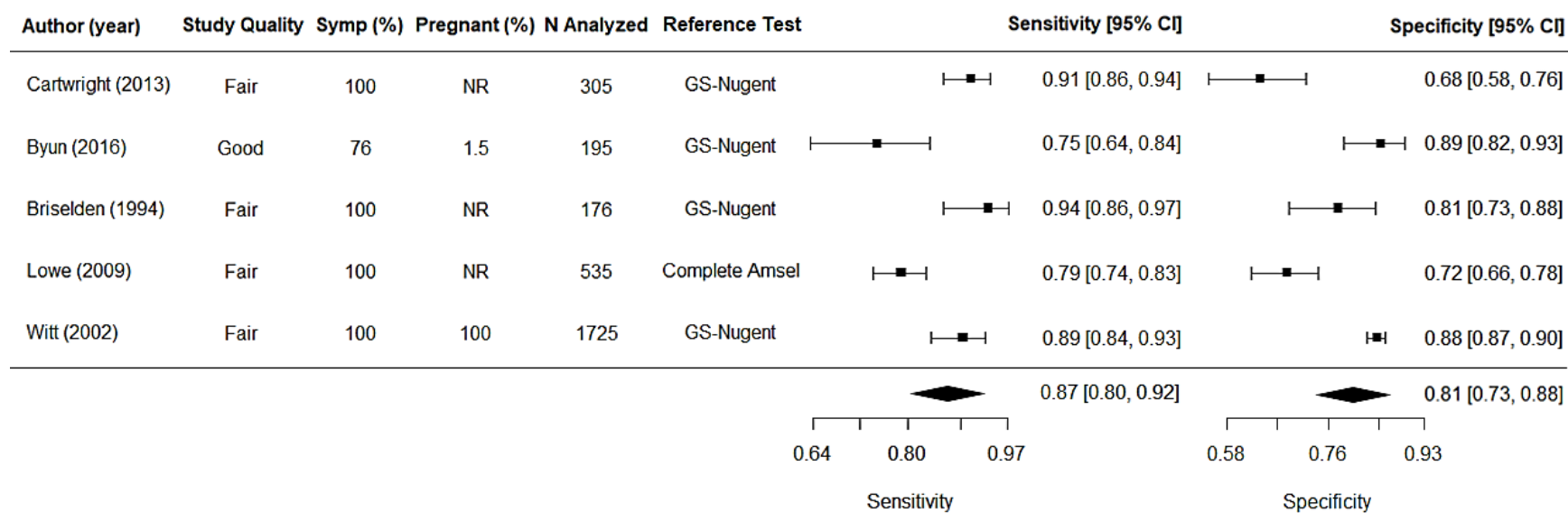
**Appendix F Figure 1. Summary Receiver Operating Characteristics Curve for Diagnostic Test Accuracy of the BD Affirm VPIII Test**



**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.

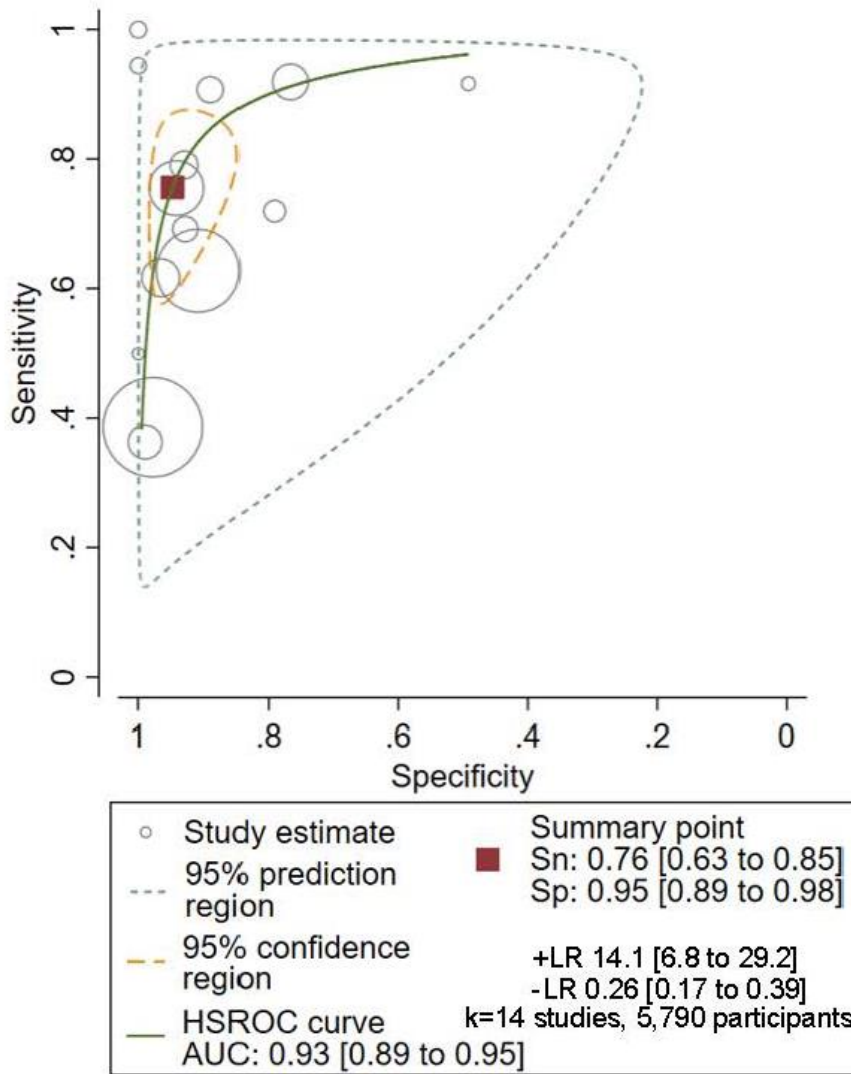
**Abbreviations:** AUC=area under the curve; HSROC=hierarchical summary receiver operating characteristic; Sn=sensitivity; Sp=specificity.

**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.

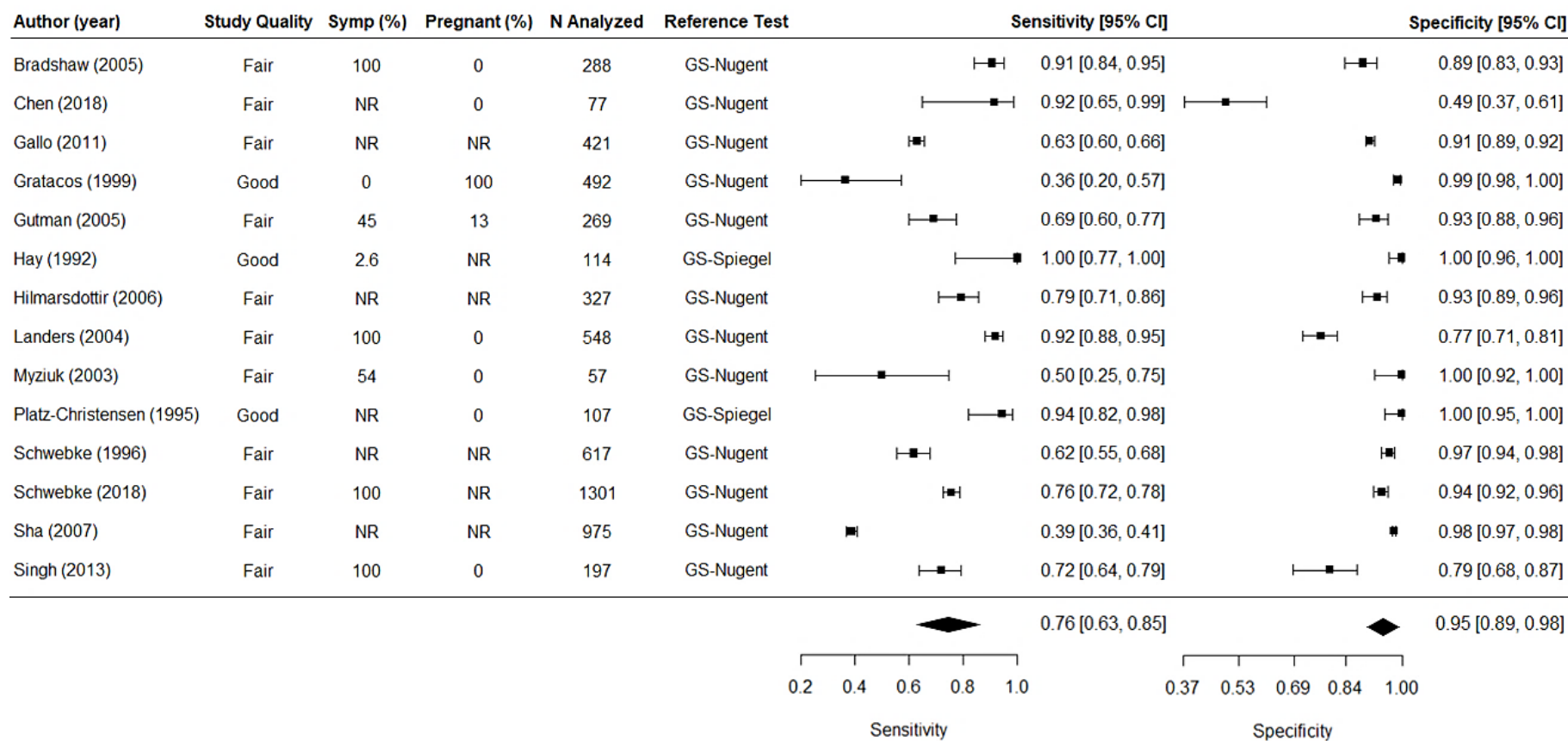
**Appendix F Figure 3. Summary Receiver Operating Characteristics Curve for Complete Amsel's Clinical Criteria Compared With Gram Stain**



**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.

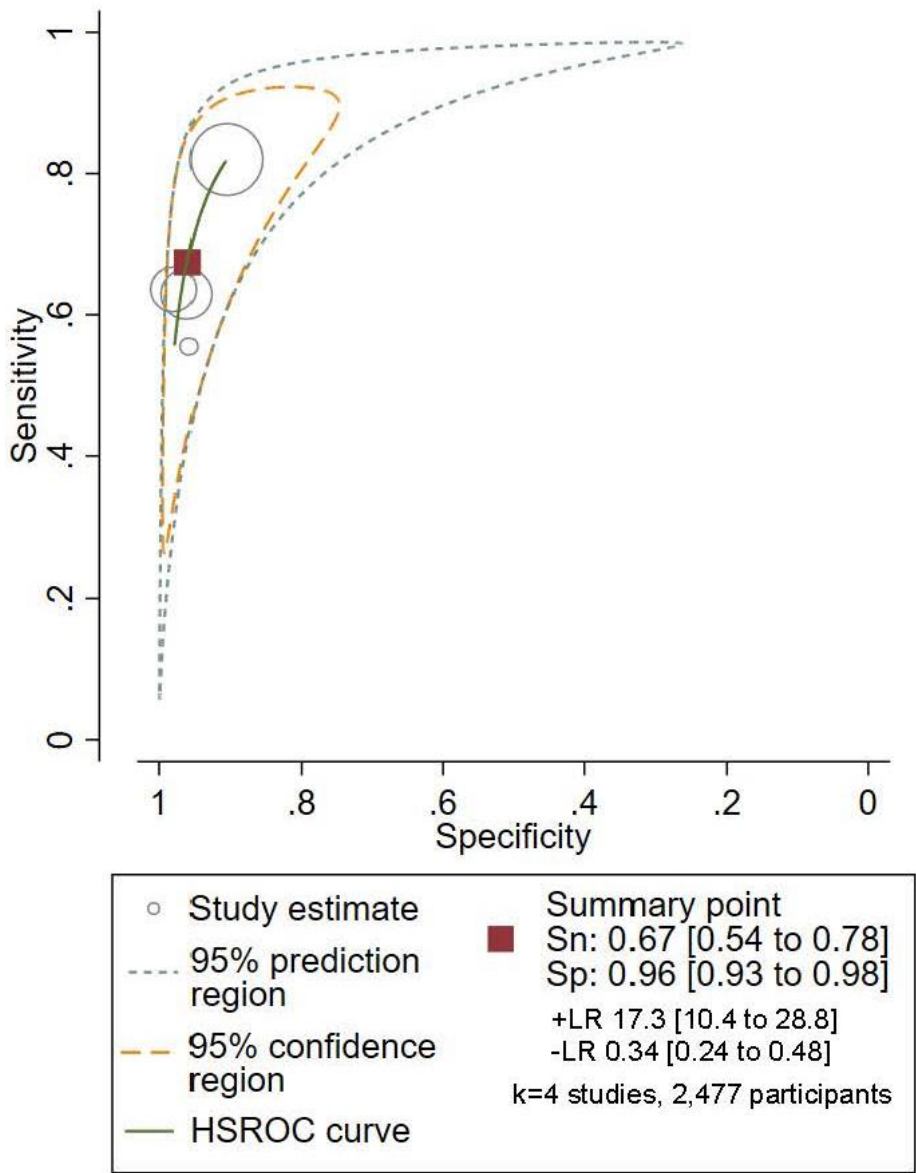
**Abbreviations:** AUC=area under the curve; HSROC=hierarchical summary receiver operating characteristic; Sn=sensitivity; Sp=specificity.

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



**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**

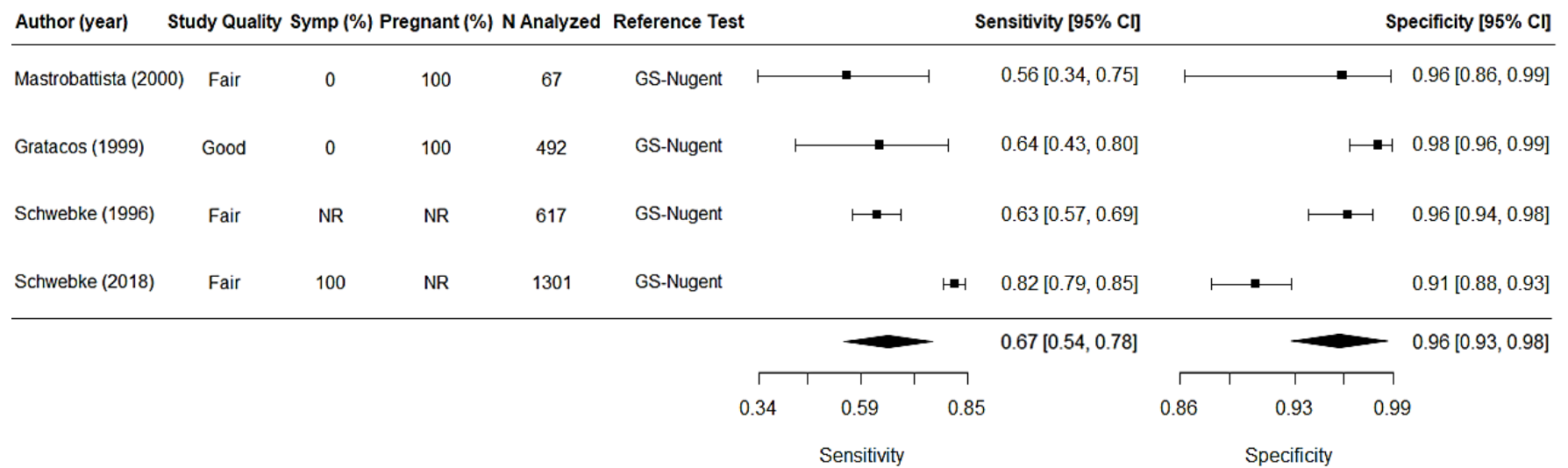


**Figure Notes:** The 95 percent confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling variation (i.e., chance). It is the region within which we expect the true pooled summary point to lie. It can be used to assess precision of the 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.

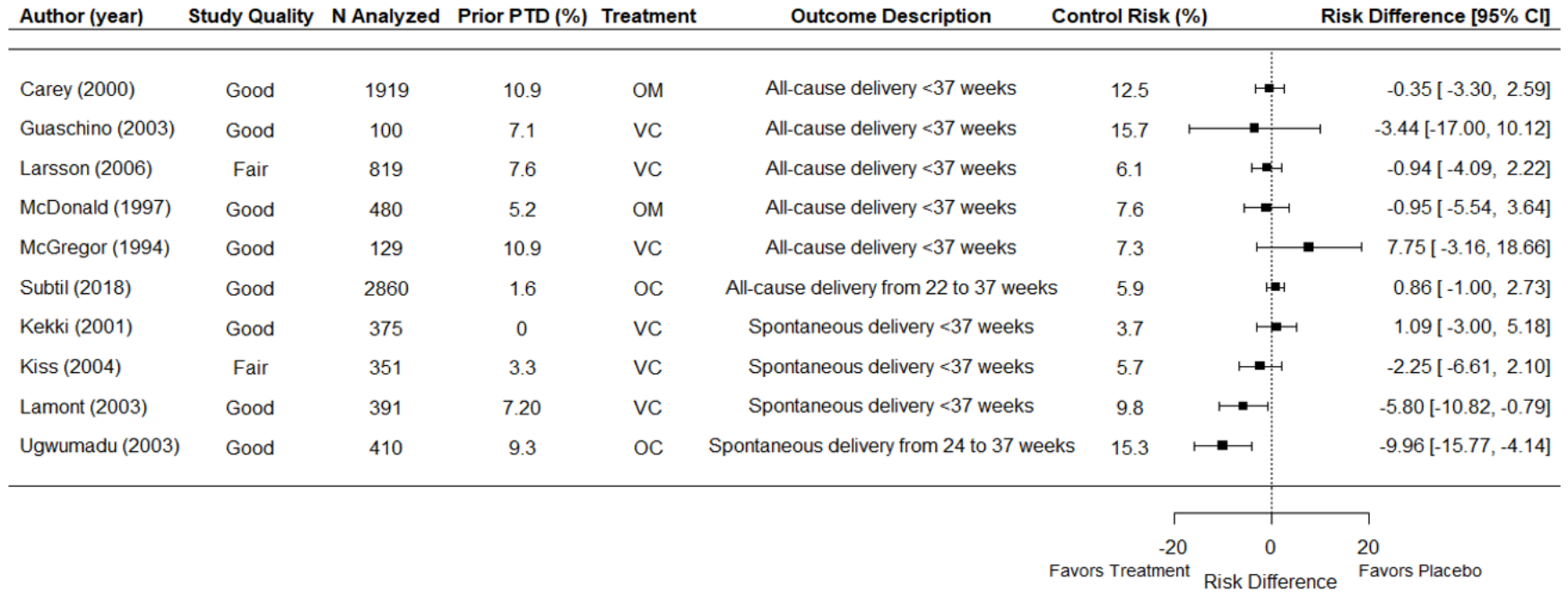


**Appendix F Figure 6. Forest Plot of Diagnostic Test Accuracy Studies Evaluating Modified Amsel’s Clinical Criteria**



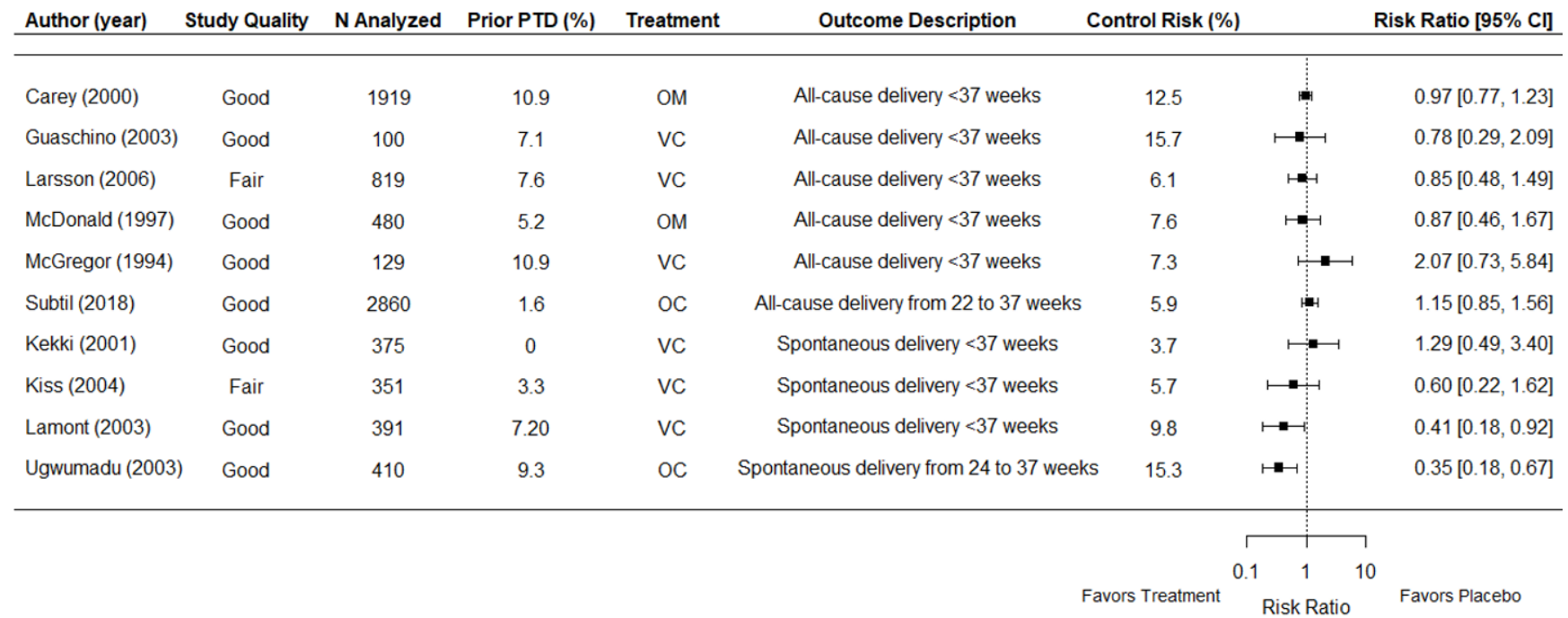
**Abbreviations:** CI=confidence interval; GS=Gram stain; N=Number of participants; NR=not reported; Symp=symptomatic.

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



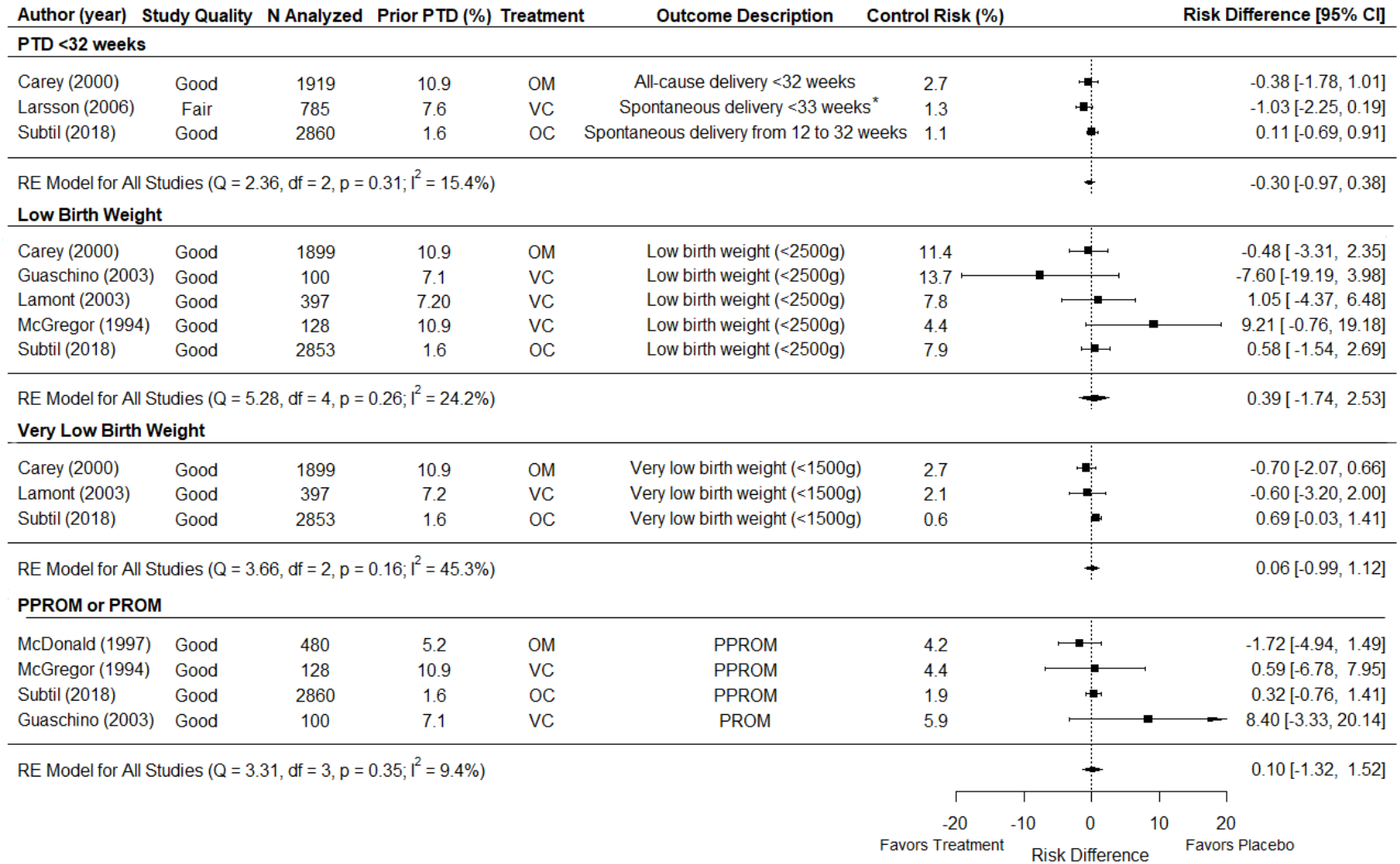
**Abbreviations:** CI=confidence interval; OC=oral clindamycin; N=number of participants; OM=oral metronidazole; PTD=preterm delivery; VC=intravaginal clindamycin.

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



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

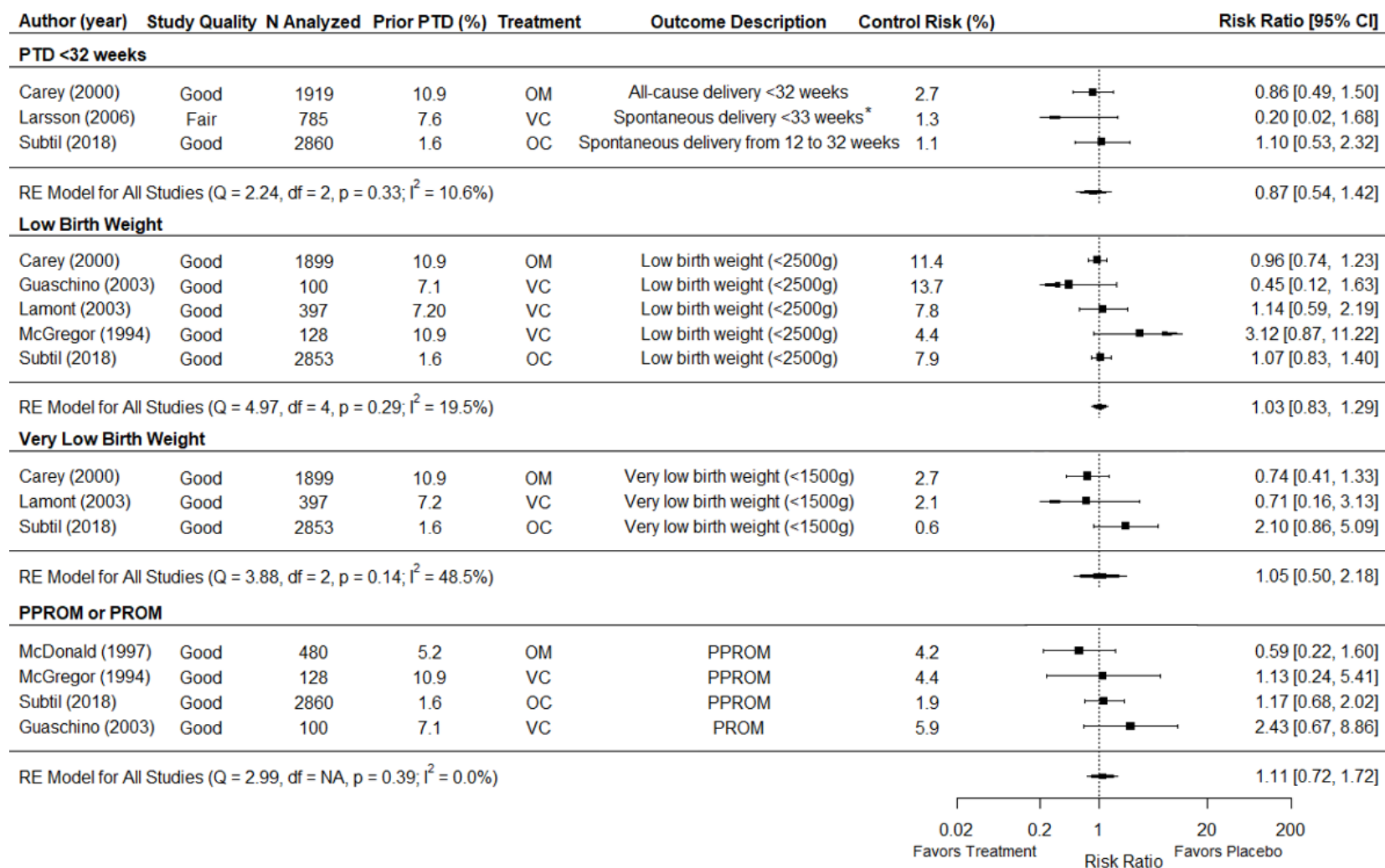
**Appendix G Figure 3. Absolute Risk Difference of Various Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among a General Obstetric Population**



\* 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.

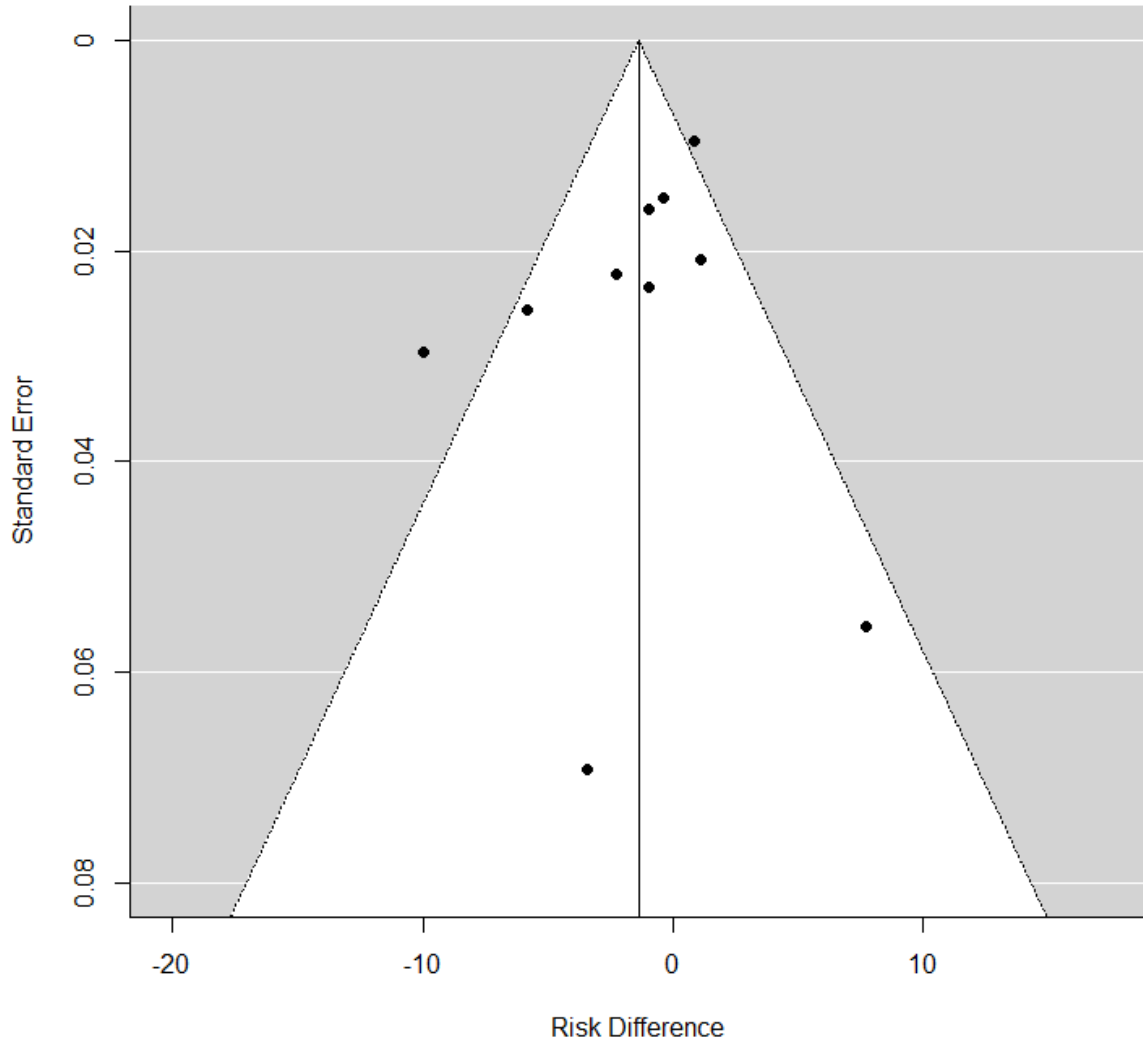
### Appendix G Figure 4. Risk Ratio for Various Preterm Delivery Outcomes From Treatment of Bacterial Vaginosis Among a General Obstetric Population



\* 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 Unstratified by Outcome in General Obstetric Population



## Appendix H. Evaluation of Test Accuracy Using Likelihood Ratios and Posttest Probabilities

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 posttest 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).

**Appendix H Table 1. Likelihood Ratios and Posttest Probabilities After Positive and Negative Tests**

| Test  | +LR  | Posttest Probability After Positive Test | -LR  | Posttest 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%                                     |
| BDBLUE (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%                                     |
| BDBLUE (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%                                     |
| BDBLUE (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.<sup>82, 202</sup>

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