



Tratamiento antibiótico para la pareja sexual de mujeres con vaginosis bacteriana: Una revisión sistemática

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*A nuestras familias por apoyarnos en todo momento,
A nuestros tutores por tantas enseñanzas, risas y
experiencias.
A nuestra Universidad por brindárnoslo todo.*

Resumen

La vaginosis bacteriana es una infección muy frecuente, con una prevalencia que varía entre el 10% y el 50%. Los microorganismos asociados con la VB han sido aislados de la flora normal del tracto masculino y su presencia podría estar relacionada con la recurrencia de la infección luego del tratamiento. De esta manera, el tratamiento a la pareja sexual podría ofrecer las ventajas de disminuir la recurrencia de la infección, romper la cadena de infección y posiblemente disminuir la carga de la enfermedad. El objetivo de la revisión fue Determinar la efectividad y seguridad del tratamiento antibiótico concurrente a la pareja sexual de mujeres tratadas para VB.

Siete Ensayos clínicos controlados (1026 participantes) cumplieron los criterios de inclusión, cuatro de ellos fueron patrocinados por la industria. Encontramos con evidencia de alta calidad que el tratamiento antibiótico no incrementa la tasa de mejora clínica o sintomática durante la primera semana (RR 0.9, IC 95% 0.96 a 1.03; RR 1.06, IC 95% 1.00 a 1.12 respectivamente), entre la primer y cuarta semana (RR 1.02, IC 95% 0.94 a 1.11; RR 0.93, IC 95% 0.84 a 1.03 respectivamente) o después de la cuarta semana (RR 0.98, IC 95% 0.90 a 1.07; RR 1.03 con IC 95% 0.90 a 1.17 respectivamente). Con calidad de evidencia baja el tratamiento antibiótico no llevó a una menor tasa de recurrencia durante la primer y cuarta semana (RR 1.28, IC 95% 0.68 a 2.43) o después de la cuarta semana de tratamiento (RR 1.00, IC 95% 0.67 a 1.52) pero incrementó la frecuencia de eventos adversos reportados por los compañeros sexuales (RR 2.55, IC 1.55 a 4.18).

Palabras clave: Compañeros sexuales, Vaginosis bacteriana, Tratamiento

Abstract

Bacterial vaginosis (BV) is an infection that has a prevalence between 10% to 50% worldwide. BV results in an imbalance of the normal vaginal flora. Microorganisms associated with BV have been isolated from the normal flora of the male genital tract, and their presence could be related to the recurrence of BV after antibiotic treatment. Therefore, the treatment of sexual partners could decrease the recurrence of infection and possibly the burden of the disease. The objective of the revision was to assess the effectiveness in women and the safety in men of concurrent antibiotic treatment for the sexual partners of women treated for BV.

Seven RCTs (1026 participants) met our inclusion criteria, and pharmaceutical industry funded four of these trials. Based on high quality evidence, antibiotic treatment does not increase the rate of clinical or symptomatic improvement in women during the first week (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.96 to 1.03; RR 1.06, 95% CI 1.00 to 1.12, respectively), between the first and fourth week (RR 1.02, 95% CI 0.94 to 1.11; RR 0.93, 95% CI 0.84 to 1.03, respectively) or after the fourth week (RR 0.98, 95% CI 0.90 to 1.07; RR 1.03, 95% CI 0.90 to 1.17, respectively). With low quality evidence antibiotic treatment does not led to a lower recurrence during the first and fourth week (RR 1.28, 95% CI 0.68 to 2.43) or after the fourth week of treatment (RR 1.00, 95% CI 0.67 to 1.52) in women, but increases the frequency of adverse events reported by sexual partners (RR 2.55, 95% CI 1.55 to 4.18).

Key words: sexual partners, bacterial vaginosis, treatment.

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Summary

Background

Bacterial vaginosis (BV) is an infection that has a prevalence between 10% to 50% worldwide. BV results in an imbalance of the normal vaginal flora. Microorganisms associated with BV have been isolated from the normal flora of the male genital tract, and their presence could be related to the recurrence of BV after antibiotic treatment. Therefore, the treatment of sexual partners could decrease the recurrence of infection and possibly the burden of the disease.

Objectives

To assess the effectiveness in women and the safety in men of concurrent antibiotic treatment for the sexual partners of women treated for BV.

Search methods

We searched the Cochrane Sexually Transmitted Infections Group Specialized Register (23 July 2016), CENTRAL (1991 to 23 July 2016), MEDLINE (1946 to 23 July 2016), Embase (1974 to 23 July 2016), LILACS (1982 to 23 July 2016), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (23 July 2016), ClinicalTrials.gov (23 July 2016) and the Web of Science™ (2001 to 23 July 2016). We also handsearched conference proceedings, contacted trial authors and reviewed the reference lists of retrieved studies.

Selection criteria

Randomized controlled trials (RCTs) that compared the concurrent use of any antibiotic treatment with placebo, no intervention or any other intervention by the sexual partners of women treated for BV.

Data collection and analysis

Three review authors independently assessed trials for inclusion, extracted data and assessed the risk of bias in the included studies. We resolved any disagreements through consensus. We assessed the quality of the evidence using the GRADE approach.

Main results

Seven RCTs (1026 participants) met our inclusion criteria, and pharmaceutical industry funded four of these trials. Five trials (854 patients) compared any antibiotic treatment of sexual partners with placebo. Based on high quality evidence, antibiotic treatment does not increase the rate of clinical or symptomatic improvement in women during the first week (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.96 to 1.03; 712 participants, four

studies; RR 1.06, 95% CI 1.00 to 1.12; 577 patients, three studies, respectively), between the first and fourth week (RR 1.02, 95% CI 0.94 to 1.11; 590 participants, three studies; RR 0.93, 95% CI 0.84 to 1.03; 444 participants, two studies; respectively) or after the fourth week (RR 0.98, 95% CI 0.90 to 1.07; 572 participants, four studies; RR 1.03, 95% CI 0.90 to 1.17; 296 participants, two studies; respectively). Antibiotic treatment does not lead to a lower recurrence during the first and fourth week (RR 1.28, 95% CI 0.68 to 2.43; 218 participants, one study; low quality evidence) or after the fourth week of treatment (RR 1.00, 95% CI 0.67 to 1.52; 372 participants, three studies; low quality evidence) in women, but increases the frequency of adverse events (most frequently gastrointestinal symptoms) reported by sexual partners (RR 2.55, 95% CI 1.55 to 4.18; 477 participants, three studies; low quality evidence).

Two trials (172 participants) compared any antibiotic treatment for sexual partners with no intervention. When we compared it with no intervention, the effects of antibiotic treatment on recurrence rate after the fourth week (RR 1.71, 95% CI 0.65 to 4.55; 51 participants, one study), clinical improvement between the first and fourth week (RR 0.93, 95% CI 0.70 to 1.25; 152 participants, two studies) and symptomatic improvement after the fourth week (RR 0.66, 95% CI 0.39 to 1.11; 70 participants, one study) were imprecise and there were no differences between groups. We downgraded the quality of the evidence to low or very low.

Authors' conclusions

High quality evidence shows that antibiotic treatment for sexual partners of women with BV, compared with placebo, does not increase the rate of clinical or symptomatic improvement during the first, between the first and fourth or after the fourth week into the women. Low quality evidence suggests that antibiotic treatment does not lead to a lower recurrence rate during the first and fourth or after the fourth week of treatment into the women, but increases the frequency of adverse events reported by sexual partners. Finally, compared with no intervention, antibiotic treatment does not decrease the recurrence rate after the fourth week and does not increase the frequency of clinical or symptomatic improvement between the first and fourth or after the fourth week into the women, respectively.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for the sexual partners of women with bacterial vaginosis

Review question

We assessed the effectiveness in women and the safety in men of concurrent antibiotic treatment for the sexual partners of women treated for bacterial vaginosis (BV).

Background

Bacterial vaginosis (BV) is an infection that has a prevalence between 10% to 50% worldwide. BV results in an imbalance of the normal vaginal flora. Microorganisms associated with BV have been isolated from the normal flora of the male genital tract, and their presence could be related to the recurrence of infection after antibiotic treatment. Therefore, the treatment of sexual partners could offer the advantages of decreasing the recurrence of infection and possibly reducing the burden of the disease.

Trial characteristics

Cochrane researchers searched the available literature up to the 23 July 2016 and included seven trials with 1026 participants. The trials included sexually-active non-pregnant women between 17 and 56 years of age, either single or married, with symptomatic BV. Four studies only included women involved into a monogamous heterosexual relationship and there was no information about this for the remaining trials. Six trials used 5-nitroimidazoles to treat the sexual partner, four trials used metronidazole and two trials used tinidazole; only one study used a lincosamide for treatment. Five trials compared antibiotic versus placebo (854 participants) and two trials compared antibiotic treatment with no intervention (172 participants). Pharmaceutical companies funded four of the included trials.

Key results

Compared with placebo, antibiotic treatment for the sexual partners of women treated for BV had no effects on clinical or symptomatic improvement in women, regardless of the time period over which the trials assessed these outcomes (during the first, between the first and fourth, or after the fourth week). Furthermore, antibiotic treatment of the sexual partner may have no effect on the recurrence of BV up to 12 weeks after treatment, but may increase the frequency of minor adverse events reported by sexual partners. Compared with no intervention, treatment of sexual partners of women with BV may have no effect on decreasing the recurrence rate or over the frequency of clinical or symptomatic improvement between the first and fourth or after the fourth week, respectively.

Quality of evidence

The quality of evidence was high for the outcomes of clinical and symptomatic improvement. The quality of evidence was very low for recurrence due to some limitations regarding risk of bias and imprecision.

BACKGROUND

Description of the condition

Secretions from the vagina (known as vaginal discharge) are a normal occurrence and result from cervical secretion and other components derived from micro-organisms that colonize the vaginal flora, mostly lactobacilli (Mylonas 2011). Lactobacilli play a predominant role in vaginal homeostasis through the production of lactic acid, hydrogen peroxide and bacteriocins, which are compounds that control the overgrowth of pathogenic micro-organisms (Taylor 2013). An increase in the amount of vaginal discharge is usually associated with the presence of a genital tract infection (Mylonas 2011). Women with an abnormal vaginal discharge most commonly have bacterial vaginosis (BV) (39.6%) or, less frequently, vulvovaginal candidiasis (11%) or trichomoniasis (0.8%); however, the exact etiology of the vaginal discharge can change according to the population (Ángel-Müller 2012). BV is thought to arise as a result of an imbalance in the normal vaginal flora when lactobacilli decrease in concentration and are replaced by anaerobic and facultative aerobic bacteria (Taylor 2013), such as *Gardnerella vaginalis* (40%) or, less frequently, by *Mycoplasma hominis*, *Clostridia* (Mirmonsef 2012), *Peptostreptococcus* or *Mobiluncus* (Mylonas 2011). Although the precise cause of this dysbacteriosis is not completely understood, some factors, such as high sexual activity, a new sexual partner and risky sexual behavior (Bradshaw 2005; Mirmonsef 2012; Mylonas 2011), could contribute to this condition (Mylonas 2011).

BV is found worldwide with a prevalence between 10% and 50%, and is usually higher among sex workers, the HIV-positive population, black and Hispanic women (Kenyon 2013), and among women with a new or a high number of sexual partners (Marrazzo 2011). Having three or more male sexual partners in the past 12 months has been identified as a risk factor for BV (Marrazzo 2011). Also, having a female sexual partner has been reported to increase the risk of BV by 60% (Smart 2004). The burden of BV is related not only to the prevalence of the condition, but also to a reduction in quality of life, as well as to anxiety and self-conscious feelings relating to the fear of exclusion due to the foul smell associated with the infection (Bilardi 2013). The bacteria associated with BV may be carried by male genitalia, but men are usually asymptomatic (Nelson 2012). The direct cost of BV care has been evaluated in pregnant women, and is particularly related to the complications of pregnancy that derive from it: in a study evaluating a population from the USA, the Netherlands and the UK it was estimated that the overall cost of BV was around one thousand million USD a year (Oleen-Burkey 1995). BV has also been associated with a risk of acquiring a sexually transmitted infection (STI), such as pelvic

inflammatory disease (Mirmonsef 2012; Taylor 2013), and infections caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and HIV (Mirmonsef 2012), and with a higher risk of developing cervical cancer (Gillet 2012), and even subfertility (Taylor 2013). In addition, BV may increase the risk of adverse perinatal outcomes, such as low birth weight, preterm delivery and very low birth weight (Sangkomkamhang 2008), and may result in approximately 80,000 excess preterm births every year in the USA (Goldenberg 2005).

The Amsel criteria and Gram staining can be used to diagnose BV, and Gram staining is considered the gold standard for this purpose (Workowski 2015). The Nugent scoring system is applied to Gram stains of vaginal smears to visually estimate the numbers of lactobacilli and BV-associated organisms; a Nugent score of zero to three is considered healthy, four to six is intermediate and a score of seven to ten implies the presence of BV (Brotman 2011). This method has a number of disadvantages: a trained professional is required for the interpretation of results and the Gram stain is unable to detect some microorganisms, such as *Ureaplasma* and *Mycoplasma* (Taylor 2013). When Gram staining is not possible, the Amsel criteria provide a good clinical tool for the diagnosis of BV, which requires the presence of at least three of the following four criteria (Taylor 2013).

- Homogeneous, thin, white vaginal discharge.
- Presence of clue cells on microscopic examination.
- A pH greater than 4.5.
- A positive 'whiff test' (a fishy odour after 10% potassium hydroxide is added).

In vitro cultures for *G. vaginalis* are of limited utility because although cultures in almost all women with a symptomatic infection are positive, 50% of the cultures from healthy asymptomatic women are also positive (Mylonas 2011). Finally, in some circumstances a diagnosis can be reached through combining the medical history with the clinical characterization of the discharge during a gynaecological examination (Ministerio de Salud y Protección Social 2013). This approach, the syndromic approach, is based on the assumption that genital tract infections share some common symptoms and signs thus making it possible to assign them a specific etiology without the need for a laboratory test (Ministerio de Salud y Protección Social 2013).

BV is not currently considered a STI but it is well-recognized that both have many aspects in common (Morris 2001). Several studies have reported an association between BV and the coexistence of STIs, risky sexual behaviours, young age at first sexual intercourse, sharing sexual toys, and a new or multiple male or female partners (Chavez 2009; Fethers 2008; Fethers 2009; Marrazzo 2005; Morris 2001). Furthermore, BV is unusual in women without a history of sexual contact (Fethers 2009), and its prevalence is less frequent in women who report that they regularly use condoms or have a stable sexual partner (Chavez 2009; Fethers 2008); these findings are consistent with a strong association between BV and sexual activity (Fethers 2009).

Additionally, some studies have proposed that the bacteria associated with BV may be carried by the male genitalia (Nelson 2012), based on the microbiological isolation of the

micro-organisms associated with this infection in the flora of the penis and urethra in male partners of infected females (Mandar 2013; Nelson 2012). This is particularly notable in uncircumcized males in whom the presence of a major surface of contact could have a major role as a reservoir, and favour the occurrence of an infection after sexual intercourse (Bukusi 2011; Mehta 2012). Bacteria associated with BV have been isolated from the normal flora of the male coronal sulcus and urethra, and could be related to infection in female partners and to the recurrence of infection after treatment (seen in about 20% of individuals and defined as three or more proven episodes of BV in 12 months) (Colli 1997; Cook 1992). Another mechanism for infection could be the mechanical transfer of perineal enteric bacteria from the flora of the male genitalia through unprotected and protected intercourse (Mandar 2013).

Description of the intervention

As BV is considered to arise from an imbalance in the normal vaginal flora (Taylor 2013), treatment includes the administration of antibiotics, such as nitroimidazoles, lincosamides, macrolides (e.g. erythromycin) and, in some circumstances, penicillins (Oduyebo 2009; Workowski 2015), the objective being to eradicate the abnormal vaginal bacterial flora (Mylonas 2011). 5-Nitroimidazole derivatives are available for oral and intravaginal administration (Workowski 2015). These medications are absorbed completely after oral intake and the volume of distribution of these agents approximates to that of total body water because they are associated with a low level of protein binding (Lamp 1999). 5-Nitroimidazole derivatives penetrate well into body tissues and fluids, with the exception of the placenta, and are eliminated in the urine after being metabolized in the liver (Brunton 2011; Trevor 2012). The side effects of 5-nitroimidazoles are usually mild and the most common are headache, nausea, dry mouth and a metallic taste (Brunton 2011; Trevor 2012). The regimens recommended for the treatment of BV include metronidazole 500 mg orally twice a day for seven days or metronidazole gel 0.75% one full applicator (5 g) intravaginally once a day for five days; tinidazole 2 g orally once daily for one or two days or 1 g orally once daily for five days; or secnidazole 1 g or 2 g orally in single doses (Oduyebo 2009; Workowski 2015).

Clindamycin, the most representative of the lincosamides, is almost completely absorbed following oral administration (Bouazza 2012), with a half-life of about three hours, and is widely distributed into fluids and tissues (Bouazza 2012; Gatti 1993). More than 80% of this agent is bound to plasma proteins, primarily α_1 -acid glycoprotein (Flaherty 1996); it is metabolized in the liver by cytochrome P450 3A4 and is excreted in the urine and bile (Trevor 2012; Wynalda 2003, Yasuda 2008). The most common side effects related to the administration of clindamycin include diarrhoea and, in a small number of individuals, pseudomembranous colitis (Gurwith 1977). Rash can occur in about 10% of individuals; other reactions, such as Stevens-Johnson syndrome, the reversible elevation of transaminases, granulocytopenia, thrombocytopenia and anaphylactic reactions, are less frequent (Brunton 2011). Regimens suggested for the treatment of BV include clindamycin cream 2% one full applicator (5 mg) intravaginally at bedtime for seven days; clindamycin 300 mg orally twice daily for seven days; or clindamycin ovules 100 mg intravaginally once at bedtime for three days (Workowski 2015).

The serum half-life of erythromycin is approximately two hours (Josefsson 1982; Zuckerman 2011). The drug is metabolized in the liver by cytochrome P450 3A4 and 2% to 5% is eliminated in an active form in the urine (Trevor 2012; Zuckerman 2011). Cholestatic hepatitis is the most notable side effect of macrolides and hepatotoxicity has also been observed (Derby 1993). Large doses have been associated with abdominal cramps, nausea,

vomiting and diarrhoea (Zuckerman 2011). Among the recognized allergic reactions are fever, eosinophilia and skin eruptions, which may occur alone or in combination; all disappear shortly after therapy is suspended (Brunton 2011). Erythromycin for the treatment of BV is used at a dose of 333 mg oral three times daily for 14 days in combination with metronidazole (Brocklehurst 2013). Some studies have used the aminopenicillin amoxicillin for the treatment of BV (Amit 2013; Brocklehurst 2013). This agent is a semi-synthetic penicillin with a half-life of almost 80 minutes, which binds to proteins in the plasma and is excreted renally (Brocklehurst 2013). The most important side effects associated with amoxicillin are nausea, vomiting, rash and antibiotic-associated colitis. The use of ampicillin is now generally avoided due to the emergence of ampicillin-resistant bacteria in individuals with BV (Amit 2013).

How the intervention might work

To date, the evidence regarding whether to treat or not the sexual partner of a woman with BV is inconclusive (Mehta 2013; Potter 1999). As frequently-used antibiotics for treating BV are widely distributed into the fluids and tissues of the human body (Bouazza 2012; Brunton 2011; Gatti 1993; Trevor 2012), the treatment of sexual partners could eliminate the abnormal flora present in the male genital area that may promote relapse in, or reinfection of, women with BV (Bradshaw 2006).

The 5-nitroimidazole derivatives are agents with antiprotozoal and antibacterial properties (Amit 2013). When a 5-nitroimidazole enters the cellular environment, it is reduced by the pyruvate ferredoxin oxidoreductase system present in bacterial mitochondria, which modifies its chemical structure (Amit 2013). Pyruvate ferredoxin oxidoreductase generates adenosine triphosphate (ATP) via the oxidative decarboxylation of pyruvate; in the presence of a structurally modified 5-nitroimidazole, the electrons that would be transferred to hydrogen ions during the generation of ATP are captured by the nitro group (Amit 2013). This disruption of ATP production promotes the formation of intermediate compounds and free radicals that are highly toxic to the bacteria (Brunton 2011). The lincosamides bind to the 50S subunit of bacterial ribosomes and consequentially suppress bacterial protein synthesis (Brunton 2011; Trevor 2012). The macrolides (e.g. erythromycin) are bacteriostatic agents that inhibit protein synthesis by binding reversibly to the 50S ribosomal subunits of sensitive microorganisms (Brunton 2011; Trevor 2012).

The administration of any effective and safe intervention to the sexual partner of a woman with BV could offer the advantages of decreasing the recurrence of infection, thus breaking the chain of infection and possibly decreasing the prevalence of STIs, reducing the burden associated with the condition and impacting positively on the sexual and reproductive health of the woman (Mehta 2013).

Why it is important to do this review

This systematic review is of paramount importance as some studies suggest that BV exhibits a behaviour similar to that of an STI (Potter 1999). However, there is still some uncertainty regarding whether recurrence of BV in women could be due to a failure to eradicate the causative organism(s) or a consequence of reinfection by the sexual partner (Bradshaw 2006). Currently, the treatment of sexual partners of women with BV is not recommended (Workowski 2015), but this is based on the critical appraisal of individual clinical trials (none of which provide conclusive evidence regarding the efficacy and safety of male sex partner treatment for women with BV (Mehta 2013)) rather than a synthesis of the available clinical evidence (Mehta 2012; Potter 1999). If the treatment of sexual partners were found to reduce the rate of recurrence of BV then this could reduce costs. However, it would need to be weighed against the possible risk of antibiotic resistance that could arise from the additional multiple treatments such a policy would involve. There is therefore a need for high-quality systematic reviews to improve the clinical management of BV (Madhivanan 2013). This systematic review will facilitate the synthesis of the current evidence, and recognize its strengths and weakness, address the uncertainty of the current knowledge and make it possible to assess the effectiveness and safety of this intervention.

OBJECTIVES

To assess the effectiveness in women and the safety in men of concurrent antibiotic treatment for the sexual partners of women treated for BV.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials, published and unpublished, that compared the concurrent use of any antibiotic treatment (any concentration, frequency, duration and route) with placebo, no intervention or any other intervention (any concentration, frequency, duration and route) by the sexual partners of women treated for bacterial vaginosis (BV). We excluded quasi-randomized trials because this approach produces effect estimates that indicate more extreme benefits compared with those generated by randomized controlled clinical trials (Higgins 2011). We also excluded cross-over trials and cluster-randomized trials because of the nature of the condition (Higgins 2011).

Types of participants

The sexual partners (either male or female) of women treated for non-recurrent BV.

Types of interventions

Any antibiotic treatment (at any concentration, frequency, duration and route) versus one of the following.

- Placebo.
- No intervention.
- Any other intervention different to antibiotic treatment (any concentration, frequency, duration and route).

Types of outcome measures Primary outcomes

- Recurrence of BV in women treated for BV (proportion of participants who were previously healthy following treatment for BV that developed a new episode of BV, according to Amsel's criteria or any other clinical criteria).
- Clinical improvement (according to Amsel's criteria or any other clinical criteria) in women treated for BV.
- Symptomatic improvement defined as the (self-reported) improvement or disappearance of symptoms in women treated for BV.
- Serious adverse events of the intervention (hypersensitivity, pseudomembranous colitis or

Stevens-Johnson syndrome) in sexual partners of women treated for BV.

Secondary outcomes

- Minor adverse events of the intervention during therapy (metallic taste, nausea, vomiting, diarrhoea or headache) in sexual partners of women treated for BV.
- Cost-effectiveness of the intervention. The primary outcomes (recurrence, clinical and symptomatic improvement) were assessed during the first week, between the first and fourth week and after the fourth week. We assessed adverse events of the intervention during therapy.

Search methods for identification of studies

We identified as many relevant randomized controlled trials (RCTs) of “antibiotic treatment” for the “sexual partner of the woman being treated for bacterial vaginosis” as possible, irrespective of language of publication, publication date and publication status (published, unpublished, in press or in progress). We used both the electronic searching of bibliographic databases and hand-searching, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Electronic searches

We contacted the Information specialist of the Cochrane Sexually Transmitted Infections Group in order to implement a comprehensive search strategy to identify as many relevant RCTs as possible in the electronic databases. We used a combination of controlled vocabulary (MeSH, Emtree terms, Health Sciences Descriptors -DeCS for its acronym in Spanish-, including exploded terms) and free-text terms (considering spelling variants, synonyms, acronyms and truncation) for “sexual partner of the woman being treated for bacterial vaginosis” and “antibiotic treatment”, with field labels, proximity operators and boolean operators. We have listed our search strategies in the ‘Appendices’ section (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7).

We searched the following electronic databases. • Cochrane Sexually Transmitted Infections Group

Specialized Register (searched 23 July 2016). • Cochrane Central Register of Controlled Trials

(CENTRAL), Ovid platform (searched from Cochrane Library Issue 1, 1991 to 23 July 2016).

- MEDLINE, Ovid platform (searched from 1946 to 23 July 2016).
- MEDLINE In-Process & Other Non-Indexed Citations, Ovid platform (searched from 1966 to 23 July 2016).

- MEDLINE Daily Update, Ovid platform (searched from 1966 to 23 July 2016).
- Embase (searched from 1974 to 23 July 2016).
- LILACS (Latin American and Caribbean Health Sciences Literature, IAHx interface; searched from 1982 to 23 July 2016).

For MEDLINE, we used the Cochrane highly sensitive search strategy for identifying RCTs: sensitivity and precision maximizing version (2008 revision), Ovid format ([Higgins 2011](#)). We combined the LILACS search strategy with the RCT filter of the IAHx interface.

Searching other resources

We searched the following resources for additional trials. • Trial registers:

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (apps.who.int/trialsearch/): searched 23 Jul 2016;
- ClinicalTrials.gov (clinicaltrials.gov/): searched 23 July 2016.
- Web of Science™: searched from 2001 to 23 July 2016.

We contacted the trial authors of all RCTs we identified by other methods and handsearched the conference proceeding abstracts of the following events.

- International Society for Sexually Transmitted Diseases Research (ISSTD) (www.isstdr.org/) scientific meetings: 2007, 2009 and 2011.
- British Association for Sexual Health and HIV (BASHH) (www.bashh.org/) scientific meetings: 2004, 2006, 2007 and 2009.
- The International Congress on Infectious Diseases (ICID) (www.isid.org/): 2010 and 2012.
- International Union against Sexually Transmitted Infections (IUSTI) (www.iusti.org/) conferences and meetings: 2011 and 2012.
- International Society for Infectious Diseases (ISID) (www.isid.org/): 2011.
- International Meeting on Emerging Diseases and Surveillance (IMED) (www.isid.org/): 2007, 2009 and 2011.
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (www.icaac.org/): 2011 and 2012.

- International Federation of Gynecology and Obstetrics (FIGO) (www.who.int/figo) World Congress: 2012.

We also handsearched previous systematic reviews and other relevant publications on the same topic and the reference lists of all RCTs identified by other methods.

Data collection and analysis Selection of studies

Three review authors (JA-G, DAV-C and EMS-B) independently assessed the titles and abstracts of the records we retrieved from the search strategy for inclusion. Three review authors independently performed the final selection of trials for inclusion and we resolved any disagreements through discussion. We listed all excluded studies and the reasons for exclusion in a “[Characteristics of excluded studies](#)” table and we constructed a PRISMA diagram to illustrate the study selection process ([Figure 1](#)).

Data extraction and management

We designed a data extraction form, which we pilot tested with one of the included studies. Three review authors (CFG-A, DAV-C and EMS-B) independently extracted the data from the included studies using the finalized data extraction form. We resolved any disagreements regarding the extracted data through discussion until we reached a consensus.

We extracted data on the following items.

- Location of the trial and setting.
- Trial design.
- Power calculation performed.
- Inclusion and exclusion criteria.
- Baseline information of the participants in order to have comparable intervention groups at entry (age, marital status, contraceptive habits, sexual intercourse during treatment, history of sexually transmitted infections (STIs), sexual behavioral history).
- Total number of intervention groups.
- Types of interventions: antibiotic type (any concentration, frequency, duration and route).
- Types of comparison: placebo, no intervention or any other intervention (any concentration, frequency, duration and route).
- Number of participants enrolled, randomized and excluded after randomization and analysed.
- Number of participants lost to follow-up in the groups.
- Outcomes stated in the methods versus outcomes reported in the results.
- How the trial authors defined the secondary outcomes.
- Differences

between groups for outcome assessment. • Time of follow-up in participants for specific outcomes. • How the trial authors validated adverse event reports. • Funding sources reported. • Ethical issues: use of signed informed consent and ethics approval.

For eligible studies, two review authors (CFG-A and MYM-V) entered the data into Review Manager (RevMan) (RevMan 2014), and checked them for accuracy. When information regarding any of the above was unclear, we contacted authors of the original reports to ask for further details. For a single RCT report, we extracted data directly into a data collection form; in cases of multiple reports, we extracted data from each report separately and then combined information across data collection forms.

Assessment of risk of bias in included studies

Two review authors (CFG-A and JA-G) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by consensus or we consulted a third review author (MYM-V). The review authors that assessed the risk of bias in the included studies were theme and methodology experts. In order to collect missing information, we planned to contact the study investigators using open-ended questions.

1. Random sequence generation (checking for possible selection bias)

We described, for each included study, the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the method as follows.

- Low risk of bias (any truly random process, e.g. random number table; computer random number generator).
- High risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number).
- Unclear risk of bias.

2. Allocation concealment (checking for possible selection bias)

For each included study we reported the method used to conceal allocation to interventions prior to assignment and we assessed whether intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment. We assessed the methods as follows.

- Low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes).

- High risk of bias (open random allocation; unsealed or non opaque envelopes, alternation; date of birth).
- Unclear risk of bias.

3a. Blinding of participants and personnel (checking for possible performance bias)

We described, for each included study, the methods used, if any, to blind study participants and personnel from the knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would have been unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as follows.

- Low, high or unclear risk of bias for participants.
- Low, high or unclear risk of bias for personnel.

3b. Blinding of outcome assessment (checking for possible detection bias)

We described the methods used, if any, to blind outcome assessors from the knowledge of which intervention a participant received for each included study. We assessed blinding separately for different outcomes or classes of outcomes. We also assessed methods used to blind outcome assessment as at either low, high or unclear risk of bias.

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described, for each included study, and for each outcome or class of outcomes, the completeness of the data including attrition and exclusions from the analysis. We stated whether the trial authors reported attrition and exclusions and the number of participants included in the analysis at each stage (compared with the total number of randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where an included study reported sufficient information, we re-included missing data in the analyses we undertook. We assessed methods as follows.

- Low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups).
- High risk of bias (e.g. numbers or reasons for missing data imbalance across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomization).
- Unclear risk of bias. We used a cut-off point of 20% to determine whether a study was at low or high risk of bias according to the level of missing data.

5. Selective reporting (checking for reporting bias)

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as follows.

- Low risk of bias (where it was clear that the study authors reported all of the study's prespecified outcomes and all expected outcomes of interest).
- High risk of bias (where the study authors did not report all of the study's prespecified outcomes; the study authors did not prespecify one or more reported primary outcomes; the study authors incompletely reported the outcomes of interest and so we could not use them; the study failed to include the results of a key outcome that we would expect them to have reported).
- Unclear risk of bias.

6. Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described, for each included study, any important concerns we had about other possible sources of bias. We assessed whether each included study was free of other problems that could put it at risk of bias. We assessed methods as follows.

- Low risk of other bias.
- High risk of other bias.
- Unclear risk of other bias.

Overall risk of bias

We made explicit judgments about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias by undertaking sensitivity analyses (see the 'Sensitivity analysis' section).

Measures of treatment effect Dichotomous data

For dichotomous data, we reported the results as risk ratios (RRs) with 95% confidence intervals (CIs). The RR is used as a relative effect measure, which works well with a low or high rate of events, and is easy to interpret and use in clinical practice.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardized mean difference to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

The units of analysis were individuals instead of couples. We assessed the effect of the intervention independently in the partner and the woman that constitute the couple. The sexual partner of the woman was randomized to the intervention or comparison group, but all the women included in the study received treatment for BV.

Where we identified a clinical trial that randomized participants to several intervention groups, we determined which intervention groups were relevant. To avoid confusion for the reader, we included all the intervention groups of the study in the 'Characteristics of included studies' table (in the notes cell), and provided a detailed description only of the intervention groups that were relevant to this review, and we only used these groups in our analyses. Finally, in order to overcome a unit-of-analysis error for a study that could contribute multiple correlated comparisons, we combined all relevant experimental intervention groups of the studies into a single group and also combined all relevant control intervention groups into a single control group, in order to create a single pairwise comparison (Higgins 2011).

Dealing with missing data

We identified the levels of attrition in the included trials and we performed analyses for all outcomes, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing. We explored the impact of including trials with high levels of missing data in the overall assessment of treatment effects by using sensitivity analysis (see the 'Sensitivity analysis' section).

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau², I² statistic and Chi² test values (Higgins 2011). We regarded heterogeneity as substantial if the I² statistic value was greater than 40% and if either the Tau² value was greater than zero or there was a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

We planned to explore publication bias through assessment of funnel plot asymmetry and formal tests. For continuous outcomes, we planned to use the test proposed by Egger 1997, and for dichotomous outcomes we planned to use the test proposed by Harbord 2006. However, we included fewer than 10 trials in the meta-analysis so we did not perform these analyses.

Data synthesis

We performed statistical analyses using RevMan (RevMan 2014). We used a fixed-effect model to combine data when it was reasonable to assume that studies estimated the same underlying treatment effect i.e. where trials examined the same intervention, and we judged the trials' populations and methods to be sufficiently similar. We used a random-effects model if there were clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials or, if we detected substantial statistical heterogeneity, to produce an overall summary if an average treatment effect across trials

was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

'Summary of findings' table

We used the GRADE approach in order to produce a 'Summary of findings' table for the outcomes recurrence after treatment, clinical and symptomatic improvement and minor or serious adverse events ([Higgins 2011](#)). We downgraded the quality of evidence depending on the presence of the following factors.

- Study limitations.
- Inconsistency of results.
- Indirectness of evidence.
- Imprecision.
- Publication bias.

Subgroup analysis and investigation of heterogeneity

We planned to explore the following potential sources of heterogeneity using subgroup analyses.

- Comparison of different antibiotic types (5-nitroimidazole, lincosamides or any other antibiotic type).
- Comparison of different durations of antibiotic therapy (single versus multiple doses).
- Comparison of women with monogamous relationships and women with multiple sexual partners.

We restricted subgroup analyses to the primary outcomes: • Recurrence after treatment in the women. • Clinical improvement. • Symptomatic improvement.

Given that the safety and effectiveness of health interventions can differ within and between populations, we proposed a subgroup analysis according to low- versus high-income countries. For fixed-effect inverse variance meta-analyses we assessed differences between subgroups by interaction tests. For fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by inspection of the CIs of the subgroups: non-overlapping CIs indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We performed sensitivity analyses based on aspects of the review that may have affected the results; for example, the impact of including trials at high or unclear risk of bias for

incomplete outcome data domain. We also carried out a sensitivity analysis to explore the inclusion of the effects of fixed-effect or random-effects analysis for outcomes with statistical heterogeneity.

RESULTS

Description of studies

Results of the search

We searched the available literature up to 23 July 2016 and retrieved a total of 110 references, of which we screened 80 after we removed duplicates. Of these, we initially screened the full-text articles of 20 references. Seven published trials met our inclusion criteria (Colli 1997; Heikkinen 1989; Mengel 1989; Moi 1989; Swedberg 1985; Vejtorp 1988; Vutyavanich 1993). We excluded 12 studies (see the 'Characteristics of excluded studies' table) and one trial is currently recruiting participants (see the 'Characteristics of ongoing studies' table). We have presented a PRISMA diagram in Figure 1 to illustrate the study selection process.

Included studies

The seven included trials had a total of 1026 participants and sample sizes ranged from 82 to 250 participants. These trials were from Denmark (Vejtorp 1988), Finland (Heikkinen 1989), Italy (Colli 1997), Thailand (Vutyavanich 1993), the USA (Mengel 1989; Swedberg 1985), and one trial involved the participation of institutions located in four Nordic countries namely Denmark, Finland, Norway and Sweden (Moi 1989). Three trials were multicentric (Colli 1997; Mengel 1989; Moi 1989), only one trial implemented a valid method for sample size calculation (Colli 1997), and all trials included outpatients and were published in English.

Population

The included studies recruited sexually-active non-pregnant women between 17 and 56 years of age, either single or married, with symptomatic BV. Four studies only included women who were involved into a monogamous heterosexual relationship (Colli 1997; Mengel 1989; Moi 1989; Vutyavanich 1993), and there was no information about this for the remaining trials (Heikkinen 1989; Swedberg 1985; Vejtorp 1988). All included trials used the Amsel's criteria to diagnose the presence of the condition and required the discovery of at least three of these four criteria, in the absence of clinical evidence of mucopurulent cervicitis, trichomoniasis, genital herpes, papilloma virus or candidiasis. The included studies excluded participants with a recent history of systemic or topical antibiotic treatment for other condition different to bacterial vaginosis (BV). There were no restrictions regarding the concurrent use of contraceptive methods during the treatment period, except for Colli 1997, which excluded barrier method users. Four studies specified the contraceptive method at entry (Heikkinen 1989; Moi 1989; Vejtorp 1988; Vutyavanich

1993), and the most frequently used was the birth control pill, followed by intrauterine device, tubal resection and the condom. Two trials allowed sexual activity during the study (Moi 1989; Vutyavanich 1993), while Colli 1997 invited the participants to abstain. The remaining included trials did not mention whether sexual intercourse allowed or advised against. Finally, most women were treated with 5-nitroimidazoles, namely the most commonly prescribed metronidazole (Mengel 1989; Moi 1989; Swedberg 1985; Vejtorp 1988), followed by tinidazole (Heikkinen 1989; Vutyavanich 1993). One study used clindamycin cream at bed time (Colli 1997).

Interventions

All included trials used the oral route to provide the sexual partner's treatment. The most frequently reported intervention was the use of 5-nitroimidazoles in six studies (Heikkinen 1989; Mengel 1989; Moi 1989; Swedberg 1985; Vejtorp 1988; Vutyavanich 1993). Four of these trials used metronidazole as treatment (Mengel 1989; Moi 1989; Swedberg 1985; Vejtorp 1988), while two trials used tinidazole (Heikkinen 1989; Vutyavanich 1993). Only one study used a lincosamide for treatment (Colli 1997).

The schemes used for metronidazole included 2 g as a single dose (Mengel 1989; Swedberg 1985), 2 g on day one and day three (Moi 1989; Vejtorp 1988), and 500 mg twice daily for seven days (Swedberg 1985). The included studies that used tinidazole gave a 2 g single dose (Vutyavanich 1993), or 1 g for four days (Heikkinen 1989). One study provided clindamycin 150 mg four times daily for seven consecutive days (Colli 1997). None of the included trials assessed the effectiveness of other antibiotic treatments occasionally prescribed in clinical practice, such as aminopenicillins and macrolides.

Comparisons

Five trials used placebo (Colli 1997; Mengel 1989; Moi 1989; Vejtorp 1988; Vutyavanich 1993). Two trials compared the effectiveness of concurrent antibiotic treatment for the sexual partners with no intervention (Heikkinen 1989; Swedberg 1985).

Outcomes

None of the primary or secondary outcomes were reported by the totality of the retrieved clinical trials and there were some differences in reporting and definition of the outcomes between trials. Four included studies reported recurrence (Colli 1997; Heikkinen 1989; Moi 1989; Vejtorp 1988), and their presence was established based on the application of Amsel criteria on healthy participants following treatment for BV, with the exception of Moi 1989, which also required the reappearance of symptoms. Only one study assessed this outcome between the first and fourth week (Moi 1989), and the other three studies assessed for this outcome posterior to the fourth week.

Seven studies reported clinical improvement after treatment (Colli 1997; Heikkinen 1989; Mengel 1989; Moi 1989; Swedberg 1985; Vejtorp 1988; Vutyavanich 1993), and used the definition of the absence of Amsel's criteria through physical exam plus wet mount. Four

trials assessed clinical improvement at the first week (Colli 1997; Moi 1989; Vejtorp 1988; Vutyavanich 1993), five trials assessed this outcome between the first and fourth week (Colli 1997; Heikkinen 1989; Moi 1989; Swedberg 1985; Vutyavanich 1993), and four trials assessed it after the fourth week (Colli 1997; Mengel 1989; Moi 1989; Vejtorp 1988). On the other hand, four studies monitored symptomatic improvement (Heikkinen 1989; Moi 1989; Vejtorp 1988; Vutyavanich 1993). Three trials evaluated symptomatic improvement at the first week (Moi 1989; Vejtorp 1988; Vutyavanich 1993), two trials assessed it between the first and fourth week (Moi 1989; Vutyavanich 1993), and three trials reported it after the fourth week (Heikkinen 1989; Moi 1989; Vejtorp 1988).

Finally, three trials reported the frequency of minor adverse events during treatment. Two of them captured the information through symptoms reported by participants (Colli 1997; Vutyavanich 1993), and the other trial used a questionnaire (Mengel 1989). The minor side effects reported in sexual partners of women treated for BV were the presence of nausea, stomachache, metallic taste and dizziness. We did not obtain any data on the secondary outcomes serious adverse events and cost-effectiveness of the intervention.

Length of follow-up

There were some differences in length of follow-up between the included studies, which followed participants for either three (Swedberg 1985), four (Vutyavanich 1993), five (Vejtorp 1988), eight (Mengel 1989) or 12 weeks (Moi 1989; Colli 1997; Heikkinen 1989).

Excluded studies

We excluded 13 studies for the following reasons: 10 studies were not RCTs or did not provide a comparison group (all sexual partners were treated) and two studies did not provide a valid intervention (the sexual partners did not received antibiotic treatment or not all women were treated) (see the 'Characteristics of excluded studies' table). One trial is currently recruiting participants (see the 'Characteristics of ongoing studies' table).

Risk of bias in included studies

We have summarized the 'Risk of bias' assessment in Figure 2 and Figure 3. Also, we provided additional details of the included trials in the 'Characteristics of included studies' tables.

Allocation

Random sequence generation (checking for possible selection bias)

Four trials adequately reported the random sequence generation method by using a computer-generated randomisation list, so that selection bias at entry was low (Mengel 1989; Swedberg 1985; Vejtorp 1988; Vutyavanich 1993). The remaining included trials did not report the random sequence generation methods, and the risk of selection bias at entry was unclear (Colli 1997; Heikkinen 1989; Moi 1989).

Allocation concealment (checking for possible selection bias)

Two trials adequately implemented a valid allocation concealment method using sequentially numbered drugs containers (Mengel 1989), or by pharmacy-controlled allocation (Swedberg 1985); thus the risk of selection bias at entry in these trials was low. The five remaining included trials did not report the method used to conceal allocation to interventions prior to assignment, and the risk of selection bias at entry was unclear (Colli 1997; Heikkinen 1989; Moi 1989; Vejtorp 1988; Vutyavanich 1993).

Blinding

Five trials used placebo for the control group to blind trial participants and personnel, and we judged the risk of performance bias as low (Colli 1997; Mengel 1989; Moi 1989; Vejtorp 1988; Vutyavanich 1993). The trial authors assessed two outcomes, recurrence and clinical improvement objectively, in contrast with other outcomes, such as symptomatic improvement and side effects pain, which were subjectively evaluated. However, we judged that the blinding of the outcome assessors from knowledge of which intervention each participant received prevented the risk of detection bias.

The remaining two trials compared the concurrent use of antibiotic treatment with no intervention (Heikkinen 1989; Swedberg 1985). Swedberg 1985 was unblinded to personnel and trial participants and was at high risk of performance bias. However, we appraised the outcome clinical improvement as at low risk of detection bias. This is because it was objectively assessed with Amsel's criteria, and lack of blinding of the outcome assessor was unlikely to affect the results. We considered Heikkinen 1989 as at high risk of performance and detection bias because was unblinded to personnel and trial participants. Also, the outcomes recurrence and symptomatic improvement were subjectively assessed and lack of blinding of the outcome assessor was likely to affect the results. The trial authors objectively assessed the outcome of clinical cure through Amsel's criteria, which made detection bias unlikely for this outcome.

Incomplete outcome data

Three trials appropriately stated the attrition and exclusions at each stage and the reasons were balanced across groups (Mengel 1989; Vejtorp 1988; Vutyavanich 1993). In addition, the level of missing data was not over 20% and the attrition or exclusion probably was unrelated to the outcomes, which made attrition bias unlikely.

We assessed two trials as at unclear risk of bias (Colli 1997; Moi 1989). In Colli 1997, we judged the outcomes of clinical cure at 1, 4 and 12 weeks and gastrointestinal symptoms as at low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups). However, we assessed the outcome of recurrence as at high risk of bias because the level of missing data was over 20%. Something similar occurred with Moi 1989, where we judged the outcomes of symptomatic improvement and clinical cure at the first and fourth week as at low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups). However, for the same outcomes at 12 weeks, the risk of bias was high according to the level of missing data (greater than 20%).

Two trials had missing data greater than 20% and did not state the reasons why ([Heikkinen 1989](#); [Swedberg 1985](#)); the trial authors conducted the analyses only for those participants who were completely treated (per protocol analysis). We assessed these trials as at high risk of bias.

Selective reporting

The trial protocol was unavailable for each of the included trials ([Colli 1997](#); [Heikkinen 1989](#); [Mengel 1989](#); [Moi 1989](#); [Swedberg 1985](#); [Vejtorp 1988](#); [Vutyavanich 1993](#)). It is unclear whether or not the published reports included all the expected outcomes, including those that were prespecified. The report had insufficient information to permit judgment of “yes” or “no”, and we rated this factor as at unclear risk of bias in each of the included trials.

Other potential sources of bias

Pharmaceutical companies funded four trials ([Heikkinen 1989](#); [Moi 1989](#); [Swedberg 1985](#); [Vejtorp 1988](#)), and academic institutions sponsored two trials ([Mengel 1989](#); [Vutyavanich 1993](#)). One trial did not mention the funding sources ([Colli 1997](#)). We judged one trial, [Mengel 1989](#), as at high risk of bias because of the nature and direction of their results. The remaining studies appeared to be free from other sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Any antibiotic treatment versus placebo; [Summary of findings 2](#) Any antibiotic treatment versus no intervention; [Summary of findings 3](#) Any antibiotic treatment versus placebo

1. Any antibiotic treatment versus placebo

Five trials ([Colli 1997](#); [Mengel 1989](#); [Moi 1989](#); [Vejtorp 1988](#); [Vutyavanich 1993](#)) including 854 participants compared any antibiotic treatment versus placebo. They did not all contribute data to each outcome.

1.1. Recurrence of BV between the first and fourth week

Only one trial reported on this outcome ([Moi 1989](#)). There was no evidence of significant difference between antibiotic treatment and placebo in the recurrence between first and fourth week of treatment (RR 1.28, 95% CI 0.68 to 2.43; 218 participants, one study; [Analysis 1.1](#)). The quality of evidence was low due to the limitations of imprecision.

1.2. Recurrence of BV after the fourth week

The results correspond to the meta-analysis of three trials ([Colli 1997](#); [Moi 1989](#); [Vejtorp 1988](#)). There was no evidence of significant difference between antibiotic treatment and placebo in recurrence of BV after the fourth week of treatment (RR 1.00, 95% CI 0.67 to 1.52; 372 participants, three studies; I² statistic = 17%; [Analysis 1.2](#); [Figure 4](#)). The quality of the evidence was very low due to the limitations of imprecision.

1.3. Clinical improvement during the first week

The results correspond to the meta-analysis of four trials (Colli 1997; Moi 1989; Vejtorp 1988; Vutyavanich 1993). There was no evidence of significant difference in clinical improvement during the first week (RR 0.99, 95% CI 0.96 to 1.03; 712 participants, four studies; I² statistic = 14%; Analysis 1.3; Figure 5). The quality of the evidence was high.

1.4. Clinical improvement between the first and fourth week

The results correspond to the meta-analysis of three trials (Colli 1997; Moi 1989; Vutyavanich 1993). There was no evidence of significant difference in clinical improvement between the first and fourth week (RR 1.02, 95% CI 0.94 to 1.11; 590 participants, three studies; I² statistic = 31%; Analysis 1.4; Figure 6). The quality of the evidence was high.

1.5. Clinical improvement after the fourth week

The results correspond to the meta-analysis of four trials (Colli 1997; Moi 1989; Vejtorp 1988; Mengel 1989). There was no evidence of significant difference in clinical improvement after the fourth week (RR 0.98, 95% CI 0.90 to 1.07; 572 participants, four studies; I² statistic = 0%; Analysis 1.5; Figure 7). The quality of the evidence was high.

1.6. Symptomatic improvement during the first week

The results correspond to the meta-analysis of three trials (Moi 1989; Vejtorp 1988; Vutyavanich 1993). Antibiotic treatment was not associated with a significant symptomatic improvement during the first week (RR 1.06, 95% CI 1.00 to 1.12; 577 participants, three studies; I² statistic = 0%; Analysis 1.6; Figure 8). The quality of the evidence was high.

1.7. Symptomatic improvement between the first and fourth week

Two trials informed this outcome (Moi 1989; Vutyavanich 1993). There was no evidence of significant difference in this outcome (RR 0.93, 95% CI 0.84 to 1.03; 444 participants, two studies; I² statistic = 0%; Analysis 1.7). The quality of the evidence was high.

1.8. Symptomatic improvement after the fourth week

Two trials informed this outcome (Moi 1989; Vejtorp 1988). There was no evidence of significant difference in this outcome (RR 1.03, 95% CI 0.90 to 1.17; 296 participants, two studies; I² statistic = 0%; Analysis 1.8). The quality of the evidence was high.

1.9. Minor adverse events during therapy in the sexual partner

The results correspond to the meta-analysis of three trials (Colli 1997; Mengel 1989; Vutyavanich 1993). Antibiotic treatment was associated with a significant minor adverse events report during therapy in sexual partner (RR 2.55, 95% CI 1.55 to 4.18; 477

participants, three studies; I² statistic = 0%; [Analysis 1.9](#); [Figure 9](#)). The quality of the evidence was low due to the limitations of imprecision.

2. Any antibiotic treatment versus no intervention

Two trials including 172 participants compared the effectiveness of concurrent antibiotic treatment for the sexual partners with no intervention.

2.1. Recurrence of BV after the fourth week

One trial informed this outcome ([Heikkinen 1989](#)). There was no evidence of statistically significance difference in recurrence of BV after the fourth week (RR 1.71, 95% CI 0.65 to 4.55; 51 participants, one study; [Analysis 2.1](#)). The quality of the evidence was very low due to the limitations of imprecision, blinding and incomplete outcome data domains.

2.2. Clinical improvement between the first and fourth week

Two trials informed this outcome ([Heikkinen 1989](#); [Swedberg 1985](#)) There was no evidence of statistically significance difference in this outcome (RR 0.93, 95% CI 0.70 to 1.25; 152 participants, two studies; I² statistic = 62%; [Analysis 2.2](#)). The quality of the evidence was very low due to the limitations of imprecision, substantial heterogeneity, blinding and incomplete outcome data domains.

2.3. Symptomatic improvement after the fourth week

One trial informed this outcome ([Heikkinen 1989](#)). There was no evidence of statistically significance difference in symptomatic improvement after the fourth week (RR 0.66, 95% CI 0.39 to 1.11; 70 participants, one study; [Analysis 2.3](#)). The quality of the evidence was very low due to the limitations of imprecision, blinding and incomplete outcome data domains.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses to explore the heterogeneity sources that we found in the analyses of “recurrence” for the comparison antibiotic versus placebo. For this analysis we explored whether differences by antibiotic type (5-Nitroimidazoles versus Lincosamides) reduced the heterogeneity in the overall effect size. The tests for subgroup effect were not significantly different when we explored heterogeneity source by antibiotic type (assessed after the fourth week, $P = 0.16$, [Analysis 3.1](#)). We did not perform subgroup analysis by antibiotic doses (single versus multiple), because the included trials did not provide enough information for this outcome.

In the analyses of “clinical improvement” for the comparison antibiotic versus placebo, neither of the tests for subgroup effect showed evidence of statistically significant differences, analysing by antibiotic type (assessed during first week, $P = 0.53$, [Analysis](#)

[3.2](#); between the first and fourth week, $P = 0.53$, [Analysis 3.3](#); and after the fourth week, $P = 0.92$, [Analysis 3.4](#)) or by antibiotic doses (assessed during first week, $P = 0.18$, [Analysis](#)

4.1; between the first and fourth week, $P = 0.12$, [Analysis 4.2](#); and after the fourth week, $P = 0.76$, [Analysis 4.3](#)). The effects of the intervention for these outcomes did not change according to the intervention characteristics.

In the analyses of “symptomatic improvement” for the comparison antibiotic versus placebo, neither of the tests for subgroup effect showed evidence of statistically significant differences, analysing by antibiotic doses (assessed during first week, $P = 0.29$, [Analysis 4.4](#); and between the first and fourth week, $P = 0.71$, [Analysis 4.5](#)). We did not perform subgroup analysis by antibiotic type because the included trials did not provide the required information for these analyses. However, for the analyses “minor adverse events during therapy” for the same comparison, neither of the tests for subgroup effect showed evidence of statistically significant differences, analysing by antibiotic type ($P = 0.49$, [Analysis 3.5](#)) or by dose ($P = 0.49$, [Analysis 4.6](#)).

We did not perform the subgroup analysis according to kind of relationship, because not all of the included trials, provided enough information on these basal conditions. Finally we neither analysed by income classifications (low- versus high-income) because all retrieved studies were performed in a high-income country.

Sensitivity analysis

We explored the impact of including trials at high or unclear risk of bias for incomplete outcome data domain in the overall assessment of treatment effects. For the comparison antibiotic treatment versus placebo, neither of the test effects showed evidence of statistically significant differences regardless of the outcome assessed (recurrence, clinical or symptomatic improvement and minor adverse events) or the period of time during which it was measured (during the first, between the first and fourth or after the fourth week).

In this sense, we observed the following results for low risk studies. • Recurrence after the fourth week (RR 0.96, 95% CI 0.48 to 1.92; 98 participants, one study; [Vejtorp 1988](#)) • Clinical improvement during first week (RR 0.99, 95% CI 0.93 to 1.05; 242 participants, two studies; I² statistic = 66%; [Vejtorp 1988](#); [Vutyavanich 1993](#)); between the first and fourth week (RR 1.13, 95% CI 0.95 to 1.35; 233 participants, one study; [Vutyavanich 1993](#)); and after the fourth week (RR 1.03, 95% CI 0.90 to 1.17; 243 participants, two studies; I² statistic = 0%; [Mengel 1989](#); [Vejtorp 1988](#)).

• Symptomatic improvement during first week (RR 1.06, 95% CI 0.98 to 1.14; 348 participants, two studies; I² statistic = 40%; [Vejtorp 1988](#); [Vutyavanich 1993](#)); between the first and fourth week (RR 0.95, 95% CI 0.83 to 1.08; 232 participants, one study; [Vutyavanich 1993](#)); and after the fourth week (RR 1.03, 95% CI 0.83 to 1.29; 107 participants, one study; [Vejtorp 1988](#)).

• Minor adverse events of the intervention during therapy (RR 2.76, 95% CI 1.60 to 4.77; 339 participants, two studies; I² statistic = 0%, [Mengel 1989](#); [Vutyavanich 1993](#)).

We did not perform a sensitivity analysis for the comparison of antibiotic versus no intervention, because we assessed all of the included trials as at high risk of bias for incomplete outcome data domain.

DISCUSSION

Summary of main results

Seven RCTs (1026 participants) met our inclusion criteria of this review, and industry funded four of these trials. Five trials (854 patients) compared any antibiotic treatment for the treatment of sexual partners with placebo. Based on high quality evidence antibiotic treatment does not increase the rate of clinical or symptomatic improvement in women during the first week (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.96 to 1.03; 712 participants, four studies; RR 1.06, 95% CI 1.00 to 1.12; 577 patients, three studies, respectively), between the first and fourth week (RR 1.02, 95% CI 0.94 to 1.11; 590 participants, three studies; RR 0.93, 95% CI 0.84 to 1.03; 444 participants, two studies; respectively) or after the fourth week (RR 0.98, 95% CI 0.90 to 1.07; 572 participants, four studies; RR 1.03, 95% CI 0.90 to 1.17; 296 participants, two studies; respectively). Antibiotic treatment does not lead to a lower recurrence rate during the first and fourth week (RR 1.28, 95% CI 0.68 to 2.43; 218 participants, one study; low quality evidence) or after the fourth week of treatment (RR 1.00, 95% CI 0.67 to 1.52; 372 participants, three studies; low quality evidence) in women, but increases the frequency of adverse events (most frequently gastrointestinal symptoms) reported by sexual partners (RR 2.55, 95% CI 1.55 to 4.18; 477 participants, three studies; low-certainty evidence) see the 'Summary of findings' tables [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#).

Two trials (172 participants) compared any antibiotic treatment for the sexual partners with no intervention. When we compared it with no intervention, the effects of antibiotic treatment on recurrence rate after the fourth week (RR 1.71, 95% CI 0.65 to 4.55; 51 participants, one study), clinical improvement between the first and fourth week (RR 0.93, 95% CI 0.70 to 1.25; 152 participants, two studies) and symptomatic improvement after the fourth week (RR 0.66, 95% CI 0.39 to 1.11; 70 participants, one study) were imprecise and there were no differences between groups. We downgraded the quality of the evidence to low or very low.

Overall completeness and applicability of evidence

We conducted a comprehensive search to retrieve all published and unpublished RCTs. We were able to evaluate all primary outcomes except for serious adverse events and the secondary outcome of cost effectiveness of the intervention that were not reported in any

trial. The applicability of the evidence into the target population (the sexual partners of women treated for non-recurrent bacterial vaginosis (BV)) is broad because the retrieved trials were conducted in different clinical settings. In this sense, the result of this systematic review can be applied into clinical practice regardless of the marital status, the form of relationship (monogamous or not), the concurrent use of contraceptive methods or the frequency of sexual intercourse during the treatment. On the other hand, the interventions analysed in the review encompass multiple clinical scenarios that are common in current practice: various antibiotic regimens including 5-nitroimidazoles and lincosamides with different schemes single dose, and treatments from two to seven days. Finally, because the included studies only assessed the safety and effectiveness of the intervention for heterosexual relationships, the results should not be extrapolated to a different population.

Quality of the evidence

We considered five of the seven included trials to be at low risk of bias. These studies corresponded to the comparison of any antibiotic treatment versus placebo, and consequently with high confidence on the effect estimate for most outcomes. However, for the comparison any antibiotic treatment versus non-intervention, the confidence on the effect estimate was very low due to trial limitations (lack of blinding and incomplete outcome data), inconsistency (unexplained variability in some results) and some imprecise results (few participants and outcome events with wide CIs). We could not evaluate publication bias, because there were too few included trials into each comparison (see the 'Summary of findings' tables: [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#)).

Potential biases in the review process

This systematic review has many strengths regarding the review process: we adhered to the predefined objectives and study eligibility criteria; our literature search included an appropriate range of databases and sources, including relevant additional methods to identify relevant reports and retrieve as many eligible studies as possible; and we assessed all studies adequately for risk of bias. Two authors performed data extraction independently. However, we have some concerns about publication bias. Publication bias is a possibility because the included trials were mostly funded by industry and due to the limited number of trials for each comparison.

Agreements and disagreements with other studies or reviews

There are two previous systematic reviews published on this topic ([Mehta 2012](#); [Potter 1999](#)). Our review includes one study that the previous two reviews did not include ([Heikkinen 1989](#)). The authors of those reviews considered that a meta-analysis could not

be conducted due to significant risk of bias in the retrieved studies and by some limitations about heterogeneity; however, these were not a limiting issue for a meta-analysis. Also, as we have shown, the included studies (particularly for the antibiotic treatment versus placebo comparison) are of high quality, there is no significant heterogeneity and we have presented the meta-analyses.

Our conclusions, about the lack of benefit following sexual partner treatment, agree with the recommendation of some important guidelines where this is not recommended (Workowski 2015; van Schalkwyk 2015). However, these recommendations were not based on a systematic and explicit approach.

AUTHORS' CONCLUSIONS

Implications for practice

Given the high quality evidence for most outcomes we assessed in this Cochrane Review, there is no benefit of antibiotic treatment compared with placebo for sexual partners of women with BV. Also, there is no increase in the rate of clinical or symptomatic improvement during the first, between the first and fourth or after the fourth week of treatment into the women. There is still some uncertainty due to the low quality of evidence, which suggests that antibiotic treatment does not lead to a lower recurrence rate during the first and fourth or after the fourth week of treatment into the women, but increases the frequency of adverse events reported by sexual partners.

Implications for research

Due to the high quality of evidence for most included outcomes in this Cochrane Review, future studies that evaluate the same outcomes will probably not change our conclusions. However, there is a need for high-quality RCTs that assess recurrence rate adequately, treatment of female partners, treatment for pregnant patients, use of other antibiotic treatments occasionally prescribed in clinical practice such as aminopenicillins and macrolides, and cost effectiveness of interventions. Therefore, study authors should focus their investigations on these problems in the future.

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Characteristics of studies

Characteristics of included studies

Colli 1997

Methods	Setting: Italy, outpatient clinic. Trial design: multicentre randomized clinical trial, parallel, 2 arms. Funding sources: not mentioned. Ethical issues: ethical board and signed consent.
Participants	Age of participants: from 18 to 45 years. Inclusion criteria: sexually-active women with 1 current sexual partner. Clinical diagnosis of bacterial vaginosis (BV) and whose partner agreed to be treated. The study authors defined BV as the presence of clue cells on a wet mount slide plus at least 2 of the following. <ul style="list-style-type: none">• Vaginal discharge with pH greater than 4.5.• Increased thin homogeneous vaginal discharge that adheres to vaginal walls.• Release of amine odour from a sample of the discharge after addition of 10% KOH. Exclusion criteria: patients treated with systemic or topical antibacterial agents in the 2 weeks before diagnosis of BV; use of intrauterine device or condom; clinical evidence of mucopurulent cervicitis, candidiasis, trichomoniasis, herpes genitalis, papilloma virus, <i>Chlamydia trachomatis</i> , or <i>Neisseria gonorrhoeae</i> infection.
	Population

	Number of participants: 139 women, 139 men.
	Baseline characteristics: sexually-active women with 1 current sexual partner. Women were treated with clindamycin 2% cream, administered intravaginally at bed time for 7 days. Participants were invited to abstain from intercourse during the treatment period and for 1 week after the end of treatment. Most participant couples were married (intervention 66% versus placebo 75%), did not use contraception method (intervention 66% versus placebo 63%) and lacked a previous history of pelvic infection (intervention 79% versus placebo 68%) or male urethritis (intervention 98% versus placebo 95%).
Interventions	Total number of intervention groups: Two groups. Intervention: clindamycin hydrochloride capsules, 150 mg by mouth 4 times daily for 7 consecutive days. Comparison: placebo.
Outcomes	The trial included evaluation at 1, 4 and 12 weeks after the start of treatment. The participants and their partners had a clinical examination, including the collection of samples of vaginal discharge to check for clue cells, the determination of vaginal pH, and a KOH test. At both visits, the participant and her partner were asked about medication side effects. The study authors defined cure as the absence of clue cells plus at least 2 of the following: vaginal pH less than 4.5; negative 10% KOH sniff test or grossly normal vaginal discharge (defined as translucent white, flocculent, low volume). The study authors defined recurrence as participants previously healthy after treatment that developed a new episode of BV (Amsel criteria). Participants reported adverse events as symptoms.
Notes	None

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“...This was a double blind, randomised, controlled trial...” Comment: there was insufficient information to enable us to make a judgement.

Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information to enable us to make a judgement.
Blinding of participants and personnel (performance bias)	Low risk	The trial authors did not adequately report the method implemented to blind study participants and personnel from knowledge of which intervention a participant received. "The clinicians were blind to the study treatment..." Comment: this was probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	The trial authors did not adequately report the method implemented to blind outcome assessment from knowledge of which intervention a participant received. Comment: there was insufficient information to enable us to make a judgement.
Incomplete outcome data (attrition bias)	Unclear risk	For the outcomes clinical cure at 1, 4 and 12 weeks and gastrointestinal symptoms the risk of bias was low (e.g. no missing outcome data; missing outcome data was balanced across groups). However, for the outcome recurrence, the risk of bias was high according to the level of missing data (greater than 20%).
Selective reporting (reporting bias)	Unclear risk	The report did not have sufficient information to permit a judgment of "yes" or "no".
Other bias	Low risk	This study appeared to be free of other sources of bias.

Heikkinen 1989

Methods

Setting: Finland, outpatient of primary care.

Trial design: single randomized clinical trial, parallel, 2 arms.

Funding sources: Orion pharmaceutical.

Ethical issues: not mentioned.

Participants	<p>Age of participants: from 19 to 53 years.</p> <p>Inclusion criteria: women with malodorous vaginal discharge and anaerobic vaginosis, which was based on the identification of clue cells in the PAP smear, pH of the vaginal discharge (greater than 4.5) and a positive amine test.</p> <p>Screening negative for <i>Neisseria gonorrhoea</i>, <i>Chlamydia trachomatis</i>, <i>Candida albicans</i> and <i>Trichomonas vaginalis</i>.</p> <p>Exclusion criteria: presence of <i>N. gonorrhoea</i>, <i>C. trachomatis</i>, <i>C. albicans</i> or <i>T. vaginalis</i>.</p> <p>Population</p> <p>Number of participants: 90 women, 90 men.</p> <p>Baseline characteristics: the women were treated with oral tinidazole 500 mg twice a day for 4 days or oral tinidazole 150 mg twice a day for 7 days or intravaginal tinidazole 500 mg at bedtime for 14 days. The trial authors did not provide any more information.</p>
Interventions	<p>Total number of intervention groups: Two groups.</p> <p>Intervention: oral tinidazol 1 g for 4 days.</p> <p>Control: no treatment.</p>
Outcomes	<p>The trial included evaluation at 1 and 3 months after the start of treatment. Women had a clinical examination, including the collection of PAP smear to check for clue cells, the determination of vaginal pH, and a KOH test.</p> <p>Cure was defined as the absence of symptoms of BV or absence of clinically verified BV (Amsell criteria)</p> <p>Relapse was defined as patients who were asymptomatic after treatment and again developed symptoms of BV. Adverse events were not reported.</p>
Notes	None

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospective randomised trial" Comment: there was insufficient information to enable us to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information to enable us to make a judgement.
Blinding of participants and personnel (performance bias)	High risk	There was no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias)	High risk	There was no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by a lack of blinding. The outcomes symptomatic of improvement and relapse were subjectively assessed and the lack of blinding could have affected the results. The outcome of clinical cure was assessed objectively and the lack of blinding could not have affected the results.
Incomplete outcome data (attrition bias)	High risk	We judged the risk of bias as high for all outcomes according to the level of missing data (greater than 20%). For Group A, 7 participants were lost to follow-up. In Group B 6 participants dropped out and in Group C 4 participants discontinued the trial.
Selective reporting (reporting bias)	Unclear risk	The report had insufficient information to permit judgment of "yes" or "no".

Other bias	Low risk	Industry sponsored this trial. However, because the result were not positive, the study would be free of other sources of bias.
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Mengel 1989

Methods

Setting: USA, outpatient of primary care.

Trial design: multicentric randomized clinical trial, parallel, 2 arms.

Funding sources: grants from the research committee, American Academy of Family Physicians; Family Health Foundation of America; Washington Academy of Family Physicians, and the Washington Family Health Foundation.

Ethical issues: ethical board and signed consent.

Participants

Age of participants: from 18 to 40 years.

Inclusion criteria: women with vaginal discharge fulfilled 3 of the 4 Amsel criteria. Participants were required to have a telephone and only 1 current sexual partner.

Exclusion criteria: pregnant or menopausal; had used antibiotics or vaginal medication in the previous month; clinical evidence of a mucopurulent cervical discharge or genital herpes, or had *T. vaginalis* or *C. albicans* on wet mounts or KOH preparation of their vaginal discharge; contraindications to metronidazole; history of seizure disorder, peripheral neuropathy, cancer or liver disease; prescription with warfarin, phenytoin or phenobarbital.

Population

Number of participants: 161 women, 98 men

Baseline characteristics: sexually-active women with 1 current sexual partner. Women were treated with metronidazole 500 mg twice a day for 7 days or 2 g single doses. Participants were not invited to abstain from intercourse during the treatment period. The participants included single and married couples, nulliparous and multiparous women. Most

Interventions	<p>participant couples used a contraception method, and lacked a previous history of pelvic infection and male urethritis.</p> <p>Total number of intervention groups: Two groups.</p> <p>Intervention: 2 g metronidazole oral single dose.</p> <p>Comparison: placebo.</p>
Outcomes	<p>The trial included evaluations at 2 and 8 weeks after the onset of the treatment. Women had a clinical examination, including the collection of samples of vaginal discharge to check for clue cells, gram staining and KOH test; sexual partners were contacted by phone for instructions. At the follow-up visits participants completed a questionnaire on symptoms and medication side effects, and underwent a pelvic examination.</p> <p>The trial authors defined cure as the absence of at least 3 of the 4 Amsell criteria. They did not define recurrence. Participants reported adverse events as symptoms of BV.</p>
Notes	None

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>"Randomization was accomplished by blocks of varying sizes (4, 8 or 12) so that an equal number of women in each block entered each of the four treatment groups".</p> <p>Comment: this was probably done.</p>
Allocation concealment (selection bias)	Low risk	<p>"Randomization was accomplished by blocks of varying sizes (4, 8 or 12) so that an equal number of women in each block entered each of the four treatment groups"</p> <p>Comment: this was probably done. We considered that the authors implemented a valid</p>

Blinding of participants and personnel (performance bias)	Low risk	<p>randomized method which implies that the allocation concealment was probably through the use of consecutively numbered sealed opaque envelopes.</p> <p>“placebo was used to ensure that both subjects and physicians did not know the subject's treatment”</p> <p>"metronidazole was identically coloured and shaped to placebo".</p> <p>Comment: this was probably done.</p>
Blinding of outcome assessment (detection bias)	Low risk	<p>“placebo was used to ensure that both subjects and physicians did not know the subject's treatment”</p> <p>"metronidazole was identically coloured and shaped to placebo". The outcomes of cure rate and side effect were objectively assessed. Comment: this was probably done.</p>
Incomplete outcome data (attrition bias)	Low risk	<p>20% or fewer participants were excluded and also intention to treat analyses was reported.</p>
Selective reporting (reporting bias)	Unclear risk	<p>The report had insufficient information to permit a judgment of “yes” or “no”.</p>
Other bias	High risk	<p>This trial was supported by grants from the research committee, American Academy of Family Physicians; Family Health Foundation of America; Washington Academy of Family Physicians, and the Washington Family Health Foundation.</p>

Moi 1989

Methods

Setting: Sweden, Denmark, Finland and Norway. Outpatient clinic.

Trial design: multicentric randomized clinical trial, parallel, 2 arms.

Funding sources: grants from Rhone-Paulenc Pharma Norden AS and Örebro County Council Research Committee.

Ethical issues: ethical board and signed consent.

Participants

Age of participants: from 17 to 56 years.

Inclusion criteria: non-pregnant sexually-active women with 3 of the 4 Amsel criteria. Women had 1 male consort with whom they had sexual intercourse without using a condom, at least once a week during the study period.

Exclusion criteria: pregnancy or lactation; haematological or neurological disease; history of allergy to metronidazole; antibiotic treatment in the preceding week.

Population

Number of participants: 241 women: 241 men

Baseline characteristics: women were treated with 2 g metronidazole on days 1 and 3. A few of the men were circumcized. Participants were not invited to abstain from intercourse during the treatment period. Women had 1 male consort with whom they had sexual intercourse without using a condom. The most frequently used contraception method was oral contraceptives or IUCD.

Interventions

Total number of intervention groups: Two groups.

Intervention: oral metronidazole 2 g, that was repeated 2 days later.

Comparison: placebo.

Outcomes

The trial included evaluation at 1, 4, and 12 weeks after starting treatment. The trial asked participants about symptoms of BV and had a clinical examination including collection of samples of vaginal discharge to check for odour of the discharge, vaginal pH, KOH test and wetness of the vaginal discharge. The trial authors defined cure as the disappearance of at least 2 previous signs or symptoms reported. The trial authors defined recurrence as participants who were previously healthy after treatment but developed a new episode of BV (Amsell criteria). Adverse events were not reported.

Notes None

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly allocated to one of two groups for a double blind trial". Comment: there was insufficient information to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information to make a judgement
Blinding of participants and personnel (performance bias)	Low risk	"They were randomly allocated to one of two groups for a double blind trial", "Whose male consorts were given inert but identical placebo tablets". Comment: this was probably done.
Blinding of outcome assessment (detection bias)	Low risk	"They were randomly allocated to one of two groups for a double blind trial", "Whose male consorts were given inert but identical placebo tablets". Comment: this was probably done.
Incomplete outcome data (attrition bias)	Unclear risk	For the outcomes of symptomatic improvement and clinical cure at first and fourth week the risk of bias was low

		(e.g. no missing outcome data; missing outcome data balanced across groups). For the same outcomes but assessed at 12 weeks, the risk of bias was high according to the level of missing data (greater than 20%).
Selective reporting (reporting bias)	Unclear risk	The report had insufficient information to permit judgment of “yes” or “no”.
Other bias	Low risk	The trial was sponsored by industry. However, because the results were not positives, the study would be free of other sources of bias.

Swedberg 1985

Methods

Setting: USA, outpatient of family practice clinic.

Trial design: single randomized clinical trial, parallel, 2 arms.

Funding sources: Searle Pharmaceuticals and School of Human Medicine, University of Wyoming.

Ethical issues: ethical board and signed consent.

Participants

Age of participants: from 18 to 45 years.

Inclusion criteria: non-pregnant women symptomatic for BV; 3 of the 4 Amsel criteria; absence of uterine infection, mucopurulent cervicitis, trichomoniasis or yeast on microscopic examination.

Exclusion criteria: antibiotics or vaginal cream in the previous 30 days; history of allergy to metronidazole.

Population

Number of participants: 82 women, 82 men.

Number of participants who received the intervention: 14 (single 2-g dose) and 13 (7-day regimen).

	<p>Number of participants who received other(s) intervention(s) or placebo: No treatment was administered to 55 participants, 32 in the 2-g single dose group and 23 in the seven day regimen group.</p>
	<p>Baseline characteristics: women were treated with metronidazole 500 mg twice a day for 7 days or 2 g single doses. The trial authors did not provide more information.</p>
Interventions	<p>Total number of intervention groups: Two groups. Intervention: single oral 2 g or 500 mg of metronidazole twice daily for 7 days. Comparison: no intervention.</p>
Outcomes	<p>The trial included evaluation at 7 to 10 and 21 days after starting treatment. All participants had a clinical examination, including the collection of samples of vaginal discharge to check for clue cells, KOH test, vaginal pH and cultures for gonorrhoea. At both visits, the participants were evaluated by a Likert-type questionnaire for symptoms of vaginitis (vulvar itching, vulvar burning, odour and quantity of discharge).</p> <p>Cure was defined if <i>G vaginalis</i> was not isolated on culture and if symptoms had markedly improved or been absent (Likert-type questionnaire). The participants reported adverse events as symptoms.</p>
Notes	None

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated random number list". Comments: this was probably done.
Allocation concealment (selection bias)	Low risk	"Regimen dispensed by the clinic pharmacist" Comment: this was probably done. Telephone or central randomization.

Blinding of participants and personnel (performance bias)	High risk	There was no blinding or incomplete blinding, and the outcome or outcome measurement is likely to have been influenced by a lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	"The clinical practitioner and the laboratory personnel were "blinded" in that they did not know to which treatment group the patient would be assigned". Comment: this was probably done.
Incomplete outcome data (attrition bias)	High risk	More than 20% were excluded: "18 did no return at 21 days after treatment, 14 were excluded because they failed to return at 7 – 10 day".
Selective reporting (reporting bias)	Unclear risk	The report had insufficient information to permit judgment of "yes" or "no".
Other bias	Low risk	Searle Pharmaceuticals provided the medication, Other funds for this project were provided by the School of Human Medicine, University of Wyoming. Comment: sponsored by industry. However, because the result were not positives, the study would be free of other sources of bias.

Vejtorp 1988

Methods

Setting: Denmark, outpatient clinic.

Trial design: single randomized clinical trial, parallel, 2 arms.

Funding sources: Rhone-Poulenc Pharma Norden A/S.

Ethical issues: ethical board and sign consent.

Participants	<p>Age of participants: from 17 to 50 years.</p> <p>Inclusion criteria: non-pregnant women with 3 of the 4 Amsel criteria.</p> <p>Exclusion criteria: women diagnosed with Candida or trichomonal infection; mucopurulent cervical discharge; tenderness of the uterus or adnexa; adnexal masses.</p> <p>Population</p> <p>Number of participants: 126 women, 126 men.</p> <p>Baseline characteristics: women were treated with 2 g metronidazole on days 1 and 3. Most participant couples used a contraception method (birth control pill and IUCD). The trial authors did not provide any more information.</p>
Interventions	<p>Total number of intervention groups: Two groups.</p> <p>Intervention: metronidazole tablets, 2 g on days 1 and 3.</p> <p>Comparison: placebo.</p>
Outcomes	<p>The trial included evaluation at 1 and 5 weeks after the start of treatment. The women had a clinical examination, including the collection of samples of vaginal discharge to check for clue cells, the determination of vaginal pH, and a KOH test. At both visits, the participant and her partner were asked about medication side effects.</p> <p>The trial authors defined cure as the absence or symptoms of BV (increased discharge, malodour, burning sensation or itching) and without at least 3 of the 4 Amsell criteria.</p> <p>The trial authors defined recurrence as participants that were clinically cured after treatment and then developed a new episode of BV (Amsel criteria).</p> <p>Adverse events were not reported.</p>
Notes	<p>None.</p>

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“The partners were allocated to receive metronidazole or placebo by random allocation in blocks of four” Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information to make a judgement.
Blinding of participants and personnel (performance bias)	Low risk	The trial authors did not adequately report the method implemented to blind study participants and personnel from knowledge of which intervention a participant received. "The women were treated with metronidazole tablets, 2 g on days 1 and 3. The partner was given the same treatment or a placebo". Comment: this was probably done.
Blinding of outcome assessment (detection bias)	Low risk	The trial authors did not adequately report the method implemented to blind study participants and personnel from knowledge of which intervention a participant received. "The women were treated with metronidazole tablets, 2 g on days 1 and 3. The partner was given the same treatment or a placebo". Comment: this was probably done.
Incomplete outcome data (attrition bias)	Low risk	20% or fewer participants were excluded and also intention to treat analyses was reported.
Selective reporting	Unclear risk	The report did not have sufficient information to permit a judgment

(reporting bias)		of “yes” or no”.
Other bias	Low risk	Rhone-Poulenc Pharma Norden A/S supported the trial. Comment: this trial was sponsored by industry. However, because the results were not positive, the study would be free of other sources of bias.

Vutyavanich 1993

Methods

Setting: Thailand, outpatient clinic.

Trial design: single randomized clinical trial, parallel, 2 arms.

Funding sources: Faculty of Medicine, Chiang Mai University.

Ethical issues: ethical board and signed consent.

Participants

Age of participants: from 17 to 40 years.

Inclusion criteria: symptomatic patients with 3 of the 4 Amsel criteria; 1 current sexual partner with whom had regular sexual intercourse.

Exclusion criteria: pregnant, lactating, or menopausal women; candidal or trichomonal infection; adnexal masses or mucopurulent cervical discharge, or tenderness of the uterus or adnexa; contraindications to nitroimidazole; inability to attend follow-up visits; antibiotic or other treatment for vaginitis in the previous month.

Population

Number of participants: 250 women, 250 men.

Baseline characteristics: sexually-active women with 1 current sexual partner whom had regular sexual intercourse. Women were treated with single dose of tinidazole 2 g. Most participant couples used a contraception method of tubal resection (intervention 32% versus placebo 28%), oral pill (intervention 17% versus placebo 26%) or DMPA (intervention 12% versus placebo 9%) and lacked a previous

Interventions	<p>history of STI diseases (intervention 88% versus placebo 81%).</p> <p>Total number of intervention groups: Two groups.</p> <p>Intervention: a single oral dose of 2 g tinidazole.</p> <p>Comparison: placebo.</p>
Outcomes	<p>The trial included evaluation at 1 and 4 weeks after the start of treatment. The women had a clinical examination, including the collection of samples of vaginal discharge to check for clue cells, the determination of vaginal pH and a KOH test. At both visits, the participant and her partner were asked about of any symptoms after taking the medication.</p> <p>The trial authors defined clinical cure as the proportion of women who remained without at least 2 of the 4 criteria for BV (Amsell criteria). The trial authors defined symptomatic improvement as participants with an absence of symptoms of BV (abnormal vaginal discharge or pruritus vulvae, or both). The participants reported adverse events as symptoms.</p>
Notes	<p>None.</p>

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were randomized into two groups using a table of random numbers". Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: there was insufficient information to make a judgement.
Blinding of participants and personnel (performance bias)	Low risk	"Either 2 g tinidazole or identical-looking placebo packed similarly in packets of four tablets". Comment: this was probably done.
Blinding of outcome assessment (detection bias)	Low risk	"Either 2 g tinidazole or identical-looking placebo packed similarly in packets of four tablet". Comment: this was probably done.

Incomplete outcome data (attrition bias)	Low risk	20% or fewer participants were excluded and also intention to treat analyses was reported.
Selective reporting (reporting bias)	Unclear risk	The report had insufficient information to permit a judgment of “yes” or “no”.
Other bias	Low risk	The study was supported by grant from the Faculty of Medicine Endowment Fund for Medical Research, Chiang Mai University. Comment: the industry probably did not influence the results.

Footnotes

Abbreviations: BV: bacterial vaginosis. PAP: Papanicolaou ; IUCD:intrauterine device, USA: United States of America, DMPA: Depot medroxyprogesterone acetate.

Characteristics of excluded studies

Brenner 1986

Reason for exclusion

Randomized controlled trial (RCT), but all sexual partners were treated.

Bukusi 2011

Reason for exclusion

RCT, but sexual partners did not received antibiotic treatment.

Eschenbach 1983

Reason for exclusion

RCT, but all sexual partners were treated.

Giraldo 2013

Reason for exclusion	Not a RCT.
Hagström 1983	
Reason for exclusion	Not a RCT.
Høvik 1983	
Reason for exclusion	RCT, but all sexual partners were treated.
Jerve 1984	
Reason for exclusion	Not a RCT.
Koumans 2002	
Reason for exclusion	Not a RCT.
Larsson 2011	
Reason for exclusion	Not a RCT.
Mehta 2012	
Reason for exclusion	Not a RCT.
Potter 1999	
Reason for exclusion	Not a RCT.
Sharma 2005	
Reason for exclusion	RCT, but all sexual partners were treated.

Footnotes

Abbreviations: RCT: randomized controlled trial.

Characteristics of ongoing studies

NCT02209519

Study name	Randomized controlled trial of treatment of male partners of women With BV
Methods	Double-blinded RCT
Participants	Male partners of women with recurrent BV
Interventions	Metronidazole 500 mg PO twice a day for 7 days versus placebo capsules PO twice a day for 7 days.
Outcomes	Recurrence of BV in the female, recurrence/persistence of BV, number of couples with concordance of biotypes/strains of <i>Gardnerella vaginalis</i> and time to recurrence.
Starting date	February 2015
Contact information	Jane R Schwebke, MD; e-mail: schwebke@uab.edu
Notes	Study sponsor: University of Alabama at Birmingham

Abbreviations: BV: bacterial vaginosis. RCT: randomized controlled trial. PO: per os.

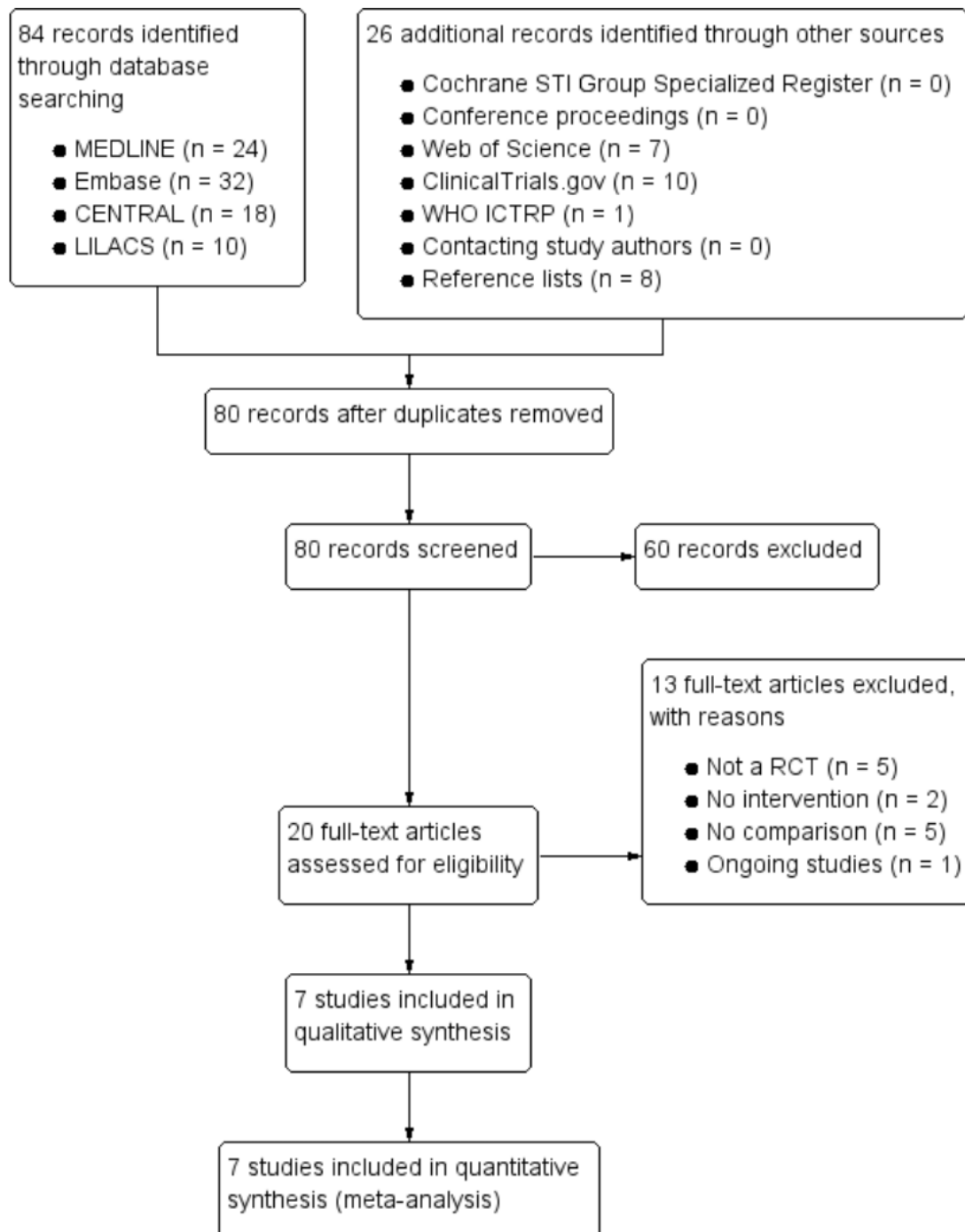
Figure 1. Study flow diagram.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

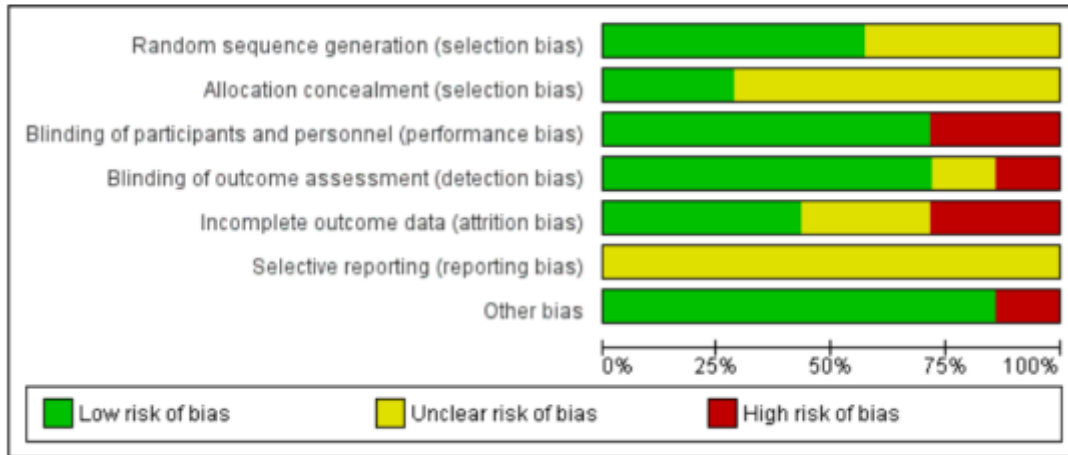
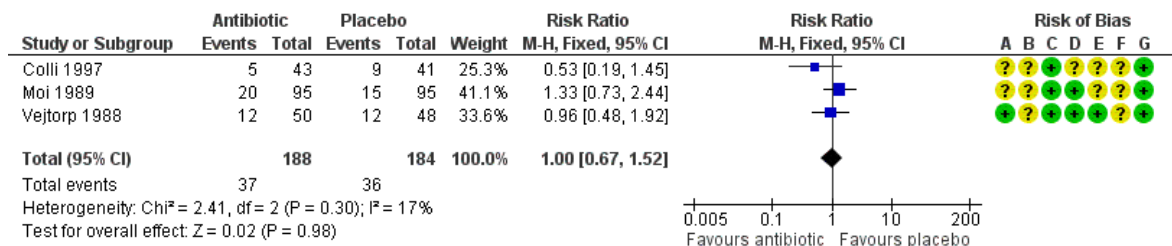


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Colli 1997	?	?	+	?	?	?	+
Heikkinen 1989	?	?	-	-	-	?	+
Mengel 1989	+	+	+	+	+	?	-
Moi 1989	?	?	+	+	?	?	+
Swedberg 1985	+	+	-	+	-	?	+
Vejtorp 1988	+	?	+	+	+	?	+
Vutyavanich 1993	+	?	+	+	+	?	+

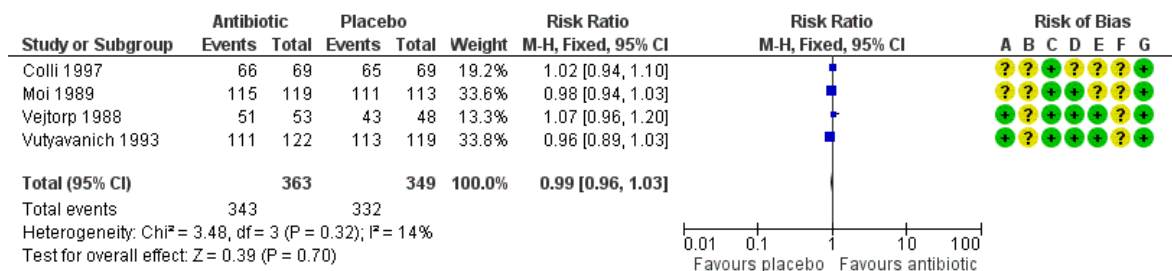
Figure 4. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.2 Recurrence of BV after the fourth week.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

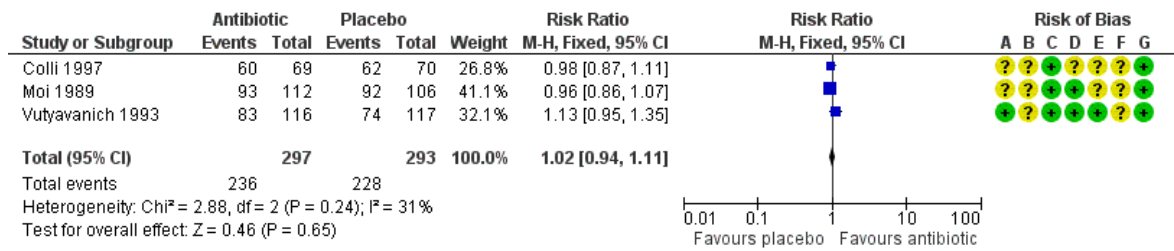
Figure 5. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.3 Clinical improvement during the first week.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

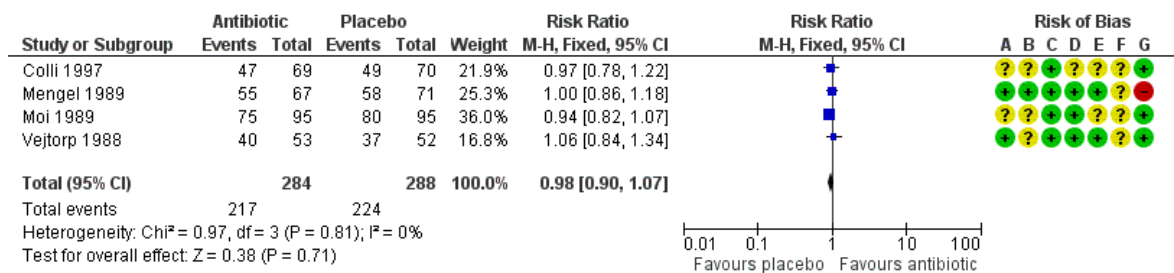
Figure 6. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.4 Clinical improvement between the first and fourth week.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

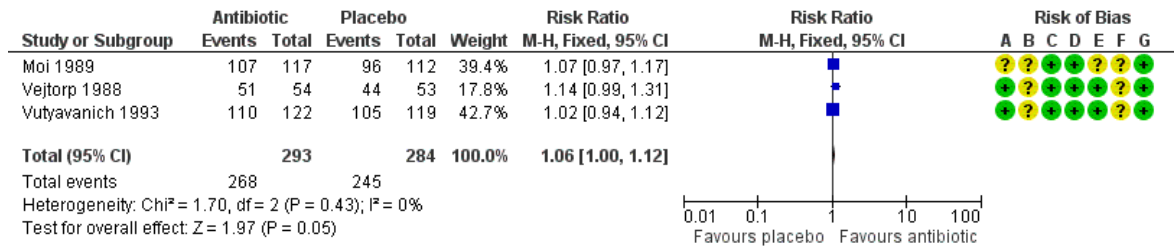
Figure 7. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.5 Clinical improvement after the fourth week.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

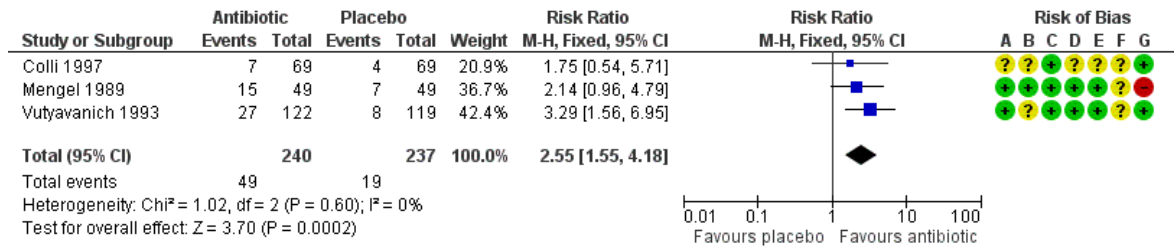
Figure 8. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.6 Symptomatic improvement during the first week.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 9. Forest plot of comparison: 1 Any antibiotic treatment versus placebo, outcome: 1.9 Minor adverse events during therapy in sexual partner



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Any antibiotic treatment versus placebo for the sexual partners of woman with bacterial vaginosis					
Patient or population: sexual partners of women with bacterial vaginosis Setting: outpatient clinic Intervention: any antibiotic treatment Comparison: placebo					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with any antibiotic treatment			
Recurrence follow-up 4 to 12 weeks	Study population		RR 1.00 (0.67 to 1.52)	372 (3 RCTs)	⊕○○○ very low ^{1,2}
	196 per 1000	196 per 1000 (131 to 297)			
Clinical improvement follow-up 1 to 4 weeks	Study population		RR 1.02 (0.94 to 1.11)	590 (3 RCTs)	⊕⊕⊕⊕ high
	778 per 1000	794 per 1000 (731 to 864)			
Clinical improvement follow-up 4 to 12 weeks	Study population		RR 0.98 (0.90 to 1.07)	572 (4 RCTs)	⊕⊕⊕⊕ high
	778 per 1000	762 per 1000 (700 to 832)			
Symptomatic improvement during the first week	Study population		RR 1.06 (1.00 to 1.12)	577 (3 RCTs)	⊕⊕⊕⊕ high
	863 per 1000	914 per 1000 (863 to 966)			
Symptomatic improvement follow-up 1 to 4 weeks	Study population		RR 0.93 (0.84 to 1.03)	444 (2 RCTs)	⊕⊕⊕⊕ high
	801 per 1000	745 per 1000 (673 to 825)			
Symptomatic improvement follow-up 4 to 12 weeks	Study population		RR 1.03 (0.90 to 1.17)	296 (2 RCTs)	⊕⊕⊕⊕ high
	743 per 1000	766 per 1000 (689 to 870)			
Minor adverse events in sexual partner follow-up: 1 to 12 weeks	Study population		RR 2.55 (1.55 to 4.18)	477 (3 RCTs)	⊕⊕○○ low ³
	80 per 1000	204 per 1000 (124 to 335)			

*The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).
 Abbreviations: CI: confidence interval; RR: risk ratio; OR: odds ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 1 level for significant imprecision as the 95%CI was below 0.75 and over 1.25.

²Downgraded by 2 levels for imprecision as the 95%CI crosses through 0.75 and 1.25 and OIS is not achieved.

³Downgraded by 2 levels for imprecision because the Optimal information size (OIS) was not achieved.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Any antibiotic treatment versus no intervention					
Patient or population: sexual partners of women with bacterial vaginosis					
Setting: outpatient clinic					
Intervention: any antibiotic treatment					
Comparison: no intervention					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with no intervention	Risk with any antibiotic treatment			
Recurrence follow-up 4 to 12 weeks	Study population		RR 1.71 (0.65 to 4.55)	51 (1 RCT)	⊕○○○ very low ^{1,2}
	194 per 1000	333 per 1000 (126 to 885)			
Clinical improvement follow-up 1 to 4 weeks	Study population		RR 0.93 (0.70 to 1.25)	152 (2 RCTs)	⊕○○○ very low ^{1,2,3}
	851 per 1000	792 per 1000 (596 to 1000)			
Symptomatic improvement follow-up 4 to 12 weeks	Study population		RR 0.66 (0.39 to 1.11)	70 (1 RCT)	⊕○○○ very low ^{1,2}
	630 per 1000	416 per 1000 (246 to 700)			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio; OR: odds ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 2 levels due to imprecision as OIS was not achieved and the 95% CI crosses through 0.75 and 1.25.²Downgraded by 2 levels as there were some limitations on blinding and incomplete outcome data domains.³Downgraded by 1 level for substantial heterogeneity (I² statistic is greater than 40%).

Any antibiotic treatment versus placebo					
Patient or population: sexual partners of women with bacterial vaginosis Setting: outpatient clinics Intervention: any antibiotic treatment Comparison: placebo					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with any antibiotic treatment			
Recurrence follow-up 1 to 4 weeks	Study population		RR 1.28 (0.68 to 2.43)	218 (1 RCT)	⊕⊕○○ low ¹
	132 per 1000	169 per 1000 (90 to 321)			
Clinical improvement during the first week	Study population		RR 0.99 (0.96 to 1.03)	712 (4 RCTs)	⊕⊕⊕⊕ high
	951 per 1000	942 per 1000 (913 to 980)			

*The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
 Abbreviations: CI: confidence interval; RR: risk ratio; OR: odds ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 2 levels for imprecision as the 95% CI crosses through 0.75 and 1.25 and OIS is not achieved.