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# Antiseptics and disinfectants for the treatment of vaginal discharge in non-pregnant women (Protocol)

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[Intervention Protocol]

# Antiseptics and disinfectants for the treatment of vaginal discharge in non-pregnant women

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the safety and effectiveness of antiseptics and disinfectants for the treatment of vaginal discharge in non-pregnant women.

# BACKGROUND

## Description of the condition

A normal and healthy vaginal ecosystem is defined by an acidic environment (pH less than 4.5), which is inhospitable for most bacteria and viruses. This acidic environment is associated with the presence of lactobacilli and hydrogen peroxide ($H_2O_2$); a decrease of these buffer agents is linked with vaginal infections (Verstraelen 2009). Vaginal discharge syndrome represents a group of vaginal infections that are characterized by abnormal vaginal secretion, irritation, vulvar itching and sometimes vaginal odour (CDC 2017). In most cases, it is diagnosed by clinical signs (Gaitán-Duarte 2013). The most common vaginal infections with vaginal discharge as the main clinical symptom are: bacterial vaginosis (BV), vulvovaginal candidiasis (VC), and trichomoniasis (TV), which is a sexually transmitted infection (Gaitán-Duarte 2013; Sherrard 2011). Prevalence varies from 40% for BV, to 12% for VC and less than 1% for trichomoniasis (Angel 2012).

Bacterial vaginosis is an infection characterized by a change in the vaginal flora due to the decrease of lactobacilli, an increase in vaginal pH and anaerobic bacteria such as *Gardnerella vaginalis, genital mycoplasma*, anaerobic Gram-negative rods, Gram-positive cocci (Beigi 2004; Petersen 2002; Verstraelen 2012). Symptomatic patients are evidenced by foul-smelling, profuse vaginal discharge (which is thin, white and homogenous, and coats the walls of the vagina and vestibule) and no signs of vulvar or vaginal inflammation (Verstraelen 2009). BV is not a sexual infection, though it is associated with sexual intercourse (Amaya-Guio 2016). It can remit spontaneously or it can be persistent or recurrent, especially when the woman engages in vaginal douching or frequent sexual activity (which can cause changes in vaginal pH and lead to the decrease or lack of lactobacilli), or when lactobacilli are attacked by specific viruses and are subsequently unable to recolonize the vagina due to the overgrowth of anaerobic bacteria (Sherrard 2011).

Bacterial vaginosis is a significant genital tract infection; published studies have found it to be associated with pelvic inflammatory disease, intrauterine infections, post-procedural gynaecological infections, and predisposition to an increased risk of sexually transmitted diseases, such as trichomoniasis, gonorrhea, chlamydia and the human immunodeficiency virus (HIV) (Verstraelen 2009). Vulvovaginal candidiasis is caused by an overgrowth of *Candida albicans* (90%), *C. glabrata*,*C. tropicalis*, and other species (Sherrard 2011). This infection has inflammatory symptoms such as edema, erythema, vulvar excoriation, fissure formation, pruritus, superficial dyspareunia, dysuria, irritation, curdy vaginal discharge and soreness (Molteni 2004). Trichomoniasis is the most common non-viral sexually transmitted infection, caused by an anaerobic protozoan called *Trichomonas vaginalis* (humans are the only known hosts). The symptoms include dysuria, itching, vulvar irritation, "strawberry" cervix visible to naked eye (2%), and occasionally, abdominal pain and greenish-yellow, foamy, foul-smelling vaginal discharge (Klissinger 2015; Jeffery 2017).

The diagnosis of VB as the other two infections (VC and TV) in the vaginal discharge syndrome is by manly clinical symptoms. Treatment for vaginal discharge syndrome mainly includes antimicrobials, such as imidazoles (metronidazole or tinidazole) for VB and TV, or used as antifungal agents (clotrimazole or fluconazole) and lincosamines (clindamycin) for VB.

## Description of the intervention

Alternative treatments for vaginal infections include antiseptic and disinfectant agents, which are safe if they are administered in adequate concentrations, regardless of whether they are in the form of vaginal suppositories, bioadhesive gels, aerosols or pessaries (Petersen 2002; Verstraelen 2009; Verstraelen 2012). Antiseptics and disinfectants have been used for almost half a century. They act by eradicating anaerobic bacteria related to vaginal infection, and facilitating the proliferation of lactobacilli; no cases of bacterial resistance have been observed (Novakov 2010; Verstraelen 2009; Verstraelen 2012). In Italy, antiseptics and disinfectants have been used since 1977 for intravaginal application, the most common being benzydamine, a non-steroidal anti-inflammatory drug with local antimicrobial anesthetic activity (Hay 1997).

These agents could be used as alternatives to traditional antibiotic treatment because: 1) the main pathogens of the most common vaginal infections (such as *G. vaginalis*, *Trichomonas vaginalis* and yeast) have low resistance to them; 2) they could be used as post-treatment prophylaxis operative, and 3) their broad antimicrobial activity could be appropriate for the treatment of non-specific vaginitis (Petersen 2002). However, the use of antiseptics and disinfectants is not popular because, when administered in vaginal douches, they have been linked to an increased risk of vaginal infections, especially bacterial vaginosis (Verstraelen 2012).

There are different types of vaginal antiseptics, most of them available in the form of vaginal douche. A systematic review comparing the use of local antiseptics (hydrogen peroxide, polyhexamethylene biguanide gel, or chlorhexidine in a vaginal gel or pessary) with metronidazole (oral and vaginal) or intravenous clindamycin, did not find any differences in cure rates between treatments (Verstraelen 2012). Only 20% of participants had a mild transient burn after vaginal application with chlorhexidine gel. In the group given hydrogen peroxide, the cure rates were 62.5%; in the group given metronidazole, the cure rate was 78.6% but with more gastrointestinal side effects (48.6% versus 13.9%, P value less than 0.001) (Verstraelen 2012). Intravaginal ozonized olive oil has been proposed for the treatment of recurrent vulvovaginal candidiasis, with purported symptomatic and microbiological improvement rates similar to intravaginal clotrimazole (P value greater than 0.05) (Lavazzo 2011). Likewise for candidiasis, boric acid has been used in intravaginal creams, with microbiological cure rates (40% to 100%) and recurrences (0% to 45.5%) similar to ketoconazole, itraconazole, nystatin, clotrimazole (Sosto 2011). Thymol and eugenol are antiseptics used in vaginal douches for bacterial vaginosis, which have shown similar symptomatic improvement rates to intravaginal metronidazole (Sosto 2011).

The vagina acts as a reservoir for a wide variety of micro-organisms in immunocompromised patients — as in HIV infection — but infections of the vagina do not present as isolated infections in these people, which is why they end up being treated by broad-spectrum antibiotics. The recurrence of vaginal candidiasis is common in patients with advanced HIV infections, and indications for prophylactic antimycotic treatment are uncertain. Studies of clotrimazole and fluconazole showed that invasive infections could be prevented, and that continued long-term exposure to antifungal agents, such as fluconazole, can lead to refractory infections (Powderly 1995). Although there is some evidence showing benefits of using broad-spectrum antiseptics in oral and dental hygiene, der-

matology, oncology, pulmonology, and in patients with HIV infection, there was no clear evidence for vaginal use (Powderly 1995).

### How the intervention might work

There are very broad types of antiseptics and disinfectants — such as chlorhexidine 0.25% to 0.5%, dequalinium chloride, hydrogen peroxide, octenidine, polyhexamethylene biguanide and povidone iodine — each with different mechanisms of action (Petersen 2002; Verstraelen 2009; Verstraelen 2012; Molteni 2004). In view of the desire to achieve better outcomes in the long term, antiseptics and disinfectants have two important mechanisms of action: 1) to decrease the number of all causal agents of vaginal discharge syndrome and the recolonization of the native flora of the vagina, and 2) to increase the number of micro-organisms of the native vaginal flora, by applying lyophilized lactobacilli (Novakov 2010; Wewalka 2002). The most common antiseptics and disinfectants, and their mechanisms of action, are as follows.

- Benzydamine: antagonist on vasoactive amines, stabilizes the cell and lysosomal membranes and inhibits the prostaglandins involved in inflammatory processes (Hay 1997).
- Chlorhexidine: a local antiseptic with bacteriostatic, bactericidal and fungistatic activity (Molteni 2004).
- Povidone iodine: a bactericide, fungicide and virucide, which has a broad-spectrum antiseptic effect (Dattani 1982; Wewalka 2002; Winceslaus 1996).
- Hydrogen peroxide: has a wide range of action against micro-organisms; has bactericidal, virucidal, and even sporicidal effects; is used in cleaning the vagina and eradicates the foul odor of secretions (Winceslaus 1996).
- Dequalinium chloride: has rapid bactericidal activity and a broad spectrum of action, including anaerobic bacteria, aerobic Gram-positive and Gram-negative bacteria, fungi and protozoa (Petersen 2002)
- Polycarbophil: is a weak acid capable of adhering to the cells of the vaginal epithelium, and acts as a bacteriostatic buffer in the vaginal secretions (Verstraelen 2009).

Although povidone-iodine and chlorhexidine have been widely used in vaginal discharge syndrome, caution should be exercised in patients with HIV, since HIV infection may increase when epithelial integrity is threatened by local products. (Hay 2012)

Side effects, such as pelvic inflammatory disease, are explained mainly during ovulation, and high levels of estrogen used in the more flexible cervix and more abundant mucus, the registry as well as the pressure of the vaginal shower develop a ascending infection (Zhang 1997). We also know that vaginal acidity is important to control the excessive growth of bacteria during the menstrual period, as a vagina with a raised pH can act as a reservoir for the start of BV. The interaction between the menstrual cycle and the showers translates into a time of instability of the vaginal flora can increase the risk of BV and with it the rise of these genes towards the tube. (Rebecca 2008)

### Why it is important to do this review

One of the main complaints from women in daily consultations concerns the symptoms of vaginal discharge. The usual treatment, as recommended by the Centers for Disease Control and Prevention (CDC), is with antibiotics with high cure rates (CDC 2017); however these have the disadvantage of frequent recurrences, which lead to the need for re-treatment and increase the risk of induced resistance. That is why the use of antiseptics and disinfectants is proposed for prevention and treatment, however these interventions have received little investigation and most systematic reviews have methodological flaws when assessed with AMSTAR. At present there are not enough results to suggest that antiseptics and disinfectants are effective for vaginal discharge syndrome, since the reports have been contradictory (Dattani 1982; Novakov 2010). This is why more studies are needed to draw conclusions about the long-term effectiveness and safety of these interventions. In addition, efforts and strategies are needed to prevent opportunistic diseases in patients with advanced-stage HIV infection.

## OBJECTIVES

To assess the safety and effectiveness of antiseptics and disinfectants for the treatment of vaginal discharge in non-pregnant women.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomized controlled trials (RCTs) with a parallel-group design. We will exclude quasi-randomized trials because this design produces effect estimates that indicate exaggerated benefits compared with those generated by RCTs (Higgins 2011). We will also exclude cross-over trials because the acute nature of the condition and cluster-randomized trials because the unit of analysis will be individual participants (Higgins 2011).

#### Types of participants

We will include non-pregnant women who present with non-recurrent vaginal discharge that is clinically or microbiologically compatible with bacterial vaginosis or fungal infection.

We will divide participants into two groups: those with a syndromic diagnosis (based on the presence of common and reasonably consistent signs and symptoms) and those with an etiological diagnosis (based on laboratory-confirmed tests).

#### Types of interventions

##### *Experimental intervention*

- Any antiseptic or disinfectant (at any concentration, frequency and duration of therapy)

##### *Comparators*

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

#### Types of outcome measures

##### *Primary outcomes*

- Clinical improvement, defined as the proportion of participants without vaginal discharge at clinical assessment . If the frequency of clinical improvement is high the clinical improvement failure proportion will be considered as negative result to estimate the RR

- Symptomatic improvement, defined as the (self-reported) improvement or disappearance of symptoms associated with the discharge.
- Recurrence of vaginal discharge (self reported), defined as the proportion of participants who were previously healthy following treatment and who developed a new episode of vaginal discharge, according to any clinical or microbiological criteria.
- Serious adverse event, defined as the proportion of participants who experienced any adverse effect, life-threatening or which required hospitalisation or discontinuation of therapy or intervention to prevent permanent impairment or damage.

#### *Secondary outcomes*

- Minor adverse events of therapy (e.g. dryness, burning, erythema, irritation, ulceration, erosion, edema, flaking, or induration).
- Patient's satisfaction with treatment.
- Cost-effectiveness of the intervention.

## Search methods for identification of studies

We will attempt to identify all eligible RCTs of "antiseptics and disinfectants" for "vaginal discharge", irrespective of language of publication, publication date and publication status (published, unpublished, in press or in progress). We will use both the electronic searching of bibliographic databases and handsearching, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Electronic searches

We will contact 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 electronic databases. We will use a combination of controlled vocabulary (Medical Subject Headings, Emtree terms, DeCS, including exploded terms) and free-text terms (considering spelling variants, synonyms, acronyms and truncation) for "vaginal discharge" and "antiseptics and disinfectants", with field labels, proximity operators and boolean operators. We have listed our search strategies in Appendices.

We will search the following electronic databases:

- Cochrane Sexually Transmitted Infections Group Specialized Register;
- Cochrane Central Register of Controlled Trials (CENTRAL), Ovid platform: 1991 to present;
- MEDLINE, Epub Ahead of print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, and MEDLINE: 1946 to present;
- Embase: 1947 to present;
- LILACS, IAHx interface: 1982 to present;
- Web of Science®: inception to present.

### Searching other resources

We will search the following resources for additional trials.

1. Trial registers, from inception to present:

- WHO International Clinical Trials Registry Platform (ICTRP) portal (http://apps.who.int/trialsearch/);
- ClinicalTrials.gov (http://clinicaltrials.gov/).

2. Grey literature database, "OpenGrey" (http://www.opengrey.eu/): inception to present.

3. Proceedings of the following conferences, from inception to present:

- The International Society for Sexually Transmitted Diseases Research (ISSTDR) (http://www.isstdr.org/);
- The British Association for Sexual Health and HIV (BASHH) (http://www.bashh.org/);
- International Congress on Infectious Diseases (ICID) (http://www.isid.org/);
- International Union against Sexually Transmitted Infections (IUSTI) (http://www.iusti.org/);
- International Society for Infectious Diseases (ISID) (http://www.isid.org/);
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (http://www.icaac.org/);
- The International Federation of Gynecology and Obstetrics (FIGO) (http://www.figo.org/).

4. We will also handsearch 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

Two review authors (AMP-L and AMT-C) will independently assess the titles and abstracts of studies retrieved. They will also perform the final selection of trials and any disagreement will be resolved through discussion with arbitration by the other two authors (JA-G and CFG-A).

### Data extraction and management

We will design a form to extract data. For eligible studies, all four review authors (AMP-L, AMT-C, JA-G and CFG-A) will extract the data independently using the agreed form. Any disagreement about extracted data will be resolved through discussion until a consensus is reached.

We will extract data on the following characteristics.

- Methods:
  - trial setting and design;
  - power calculation performed (whether performed or not).
- Participants:
  - inclusion and exclusion criteria;
  - number of participants enrolled, randomized, and excluded after randomization and analyzed;
  - number of participants lost to follow-up in the groups;
  - baseline information of the participants in order to have comparable intervention groups at entry (age, sexual activity, contraceptive habits, history of sexually transmitted infections, sexual behavioral history);
  - total number of intervention groups.

- Interventions:
  * types of interventions: antiseptics or disinfectants (any concentration, frequency and duration of therapy);
  * types of comparison: placebo, no intervention, or any antibiotic treatment;
  * primary and secondary outcomes, and how they were defined and measured;
  * differences between groups for outcome assessment.
- Outcomes:
  * length of participants' follow-up for specific outcomes;
  * how adverse event reports were validated;
  * funding sources reported;
  * ethical issues: informed consent and ethics approval.

One review author (CFG-A) will enter extracted data into Review Manager 5 (RevMan 2014) and a second review author (JA-G) will check them for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to ask for further details. For a single RCT report, we will extract data directly into a data collection form; in cases of multiple reports, we will extract data from each report separately and then reconcile the information across data collection forms.

### Assessment of risk of bias in included studies

Two review authors (AMP-L and AMT-C) will independently assess the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011), which addresses the following domains:

- selection bias (random sequence generation and allocation concealment);
- performance bias (blinding of participants and personnel);
- detection bias (blinding of outcome assessors);
- attrition bias (incomplete outcome data);
- reporting bias (selective reporting);
- other bias.

Judgments will be assigned as recommended in section 8.5 of the *Cochrane Handbook* (Higgins 2011). Disagreements will be resolved by discussion. We will describe all judgments fully and present the conclusions in the 'Risk of bias' table, which will be incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

#### *Overall risk of bias*

We will apply the criteria defined by Higgins 2016 for assessing the overall risk of bias. To summarize the quality of the evidence we will consider the domains of sequence generation, blinding of outcome assessor, and incomplete outcome data, in order to classify each study as having either: low risk of bias (where we judge all of the three domains as being at low risk of bias); high risk of bias (where we judge at least one of the three domains as being at high risk of bias); unclear risk of bias (where we judge all of the three domains as being at unclear risk of bias); and moderate risk of bias in the remaining cases.

### Measures of treatment effect

For dichotomous data, we will present 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 it is easy to interpret and use in clinical practice.

We will perform meta-analysis separately for participants with syndromic and etiological diagnosis. Syndromic management implies an approach in which clinical diagnosis was based on the presence of common and reasonably consistent signs and symptoms, without resorting to techniques for laboratory confirmation (Gaitán-Duarte 2013).

### Unit of analysis issues

The unit of analysis will be individual participants. In addition, we expect that eligible studies would have collected and analyzed a single measurement for each outcome from each participant.

Where a clinical trial is identified that randomized participants to several intervention groups, we will determine which intervention groups are relevant. To avoid confusion for the reader, we will include all the intervention groups of the study in the 'Characteristics of included studies' table (in the notes cell), and provide a detailed description only of the intervention groups relevant to this review, and only these groups will be used in analyses. Finally, in order to overcome a unit-of-analysis error for a study that could contribute multiple, correlated comparisons, we will combine all relevant experimental intervention groups of the studies into a single group and also combine all relevant control intervention groups into a single control group, in order to create a single pair-wise comparison (Higgins 2011). We will explore this through sensitivity analyses (see: Sensitivity analysis).

### Dealing with missing data

We will report the percentage of observations with missing data and use sensitivity analyses to assess the effect of missing data on our findings. We plan to analyze study participants in the groups to which they were randomly allocated regardless of which or how much treatment they received. In our analyses, the numerator for each outcome in each study group will be the number of participants randomly allocated to that group for whom outcome data are available. The denominator for each outcome in each trial group will be the number of participants randomly allocated to that group at the start of the trial, irrespective of how randomized participants have missing data for that outcome. We will contact the study investigators in order to obtain the missing data.

### Assessment of heterogeneity

We will first examine statistical heterogeneity of intervention effect across studies by looking at the graphical display of results in each forest plot. If confidence intervals for the results of individual studies have poor overlap, we will consider this to be an indication of substantial heterogeneity.We will formally assess statistical heterogeneity in each meta-analysis using the $Chi^2$ test of homogeneity, with significance defined at the alpha-level of 10% and we will assess quantify statistical heterogeneity with the $I^2$ statistic, using the following values for interpretation:

- 0% to 40%: statistical heterogeneity may be negligible;
- 40% to 70%: statistical heterogeneity may be moderate;
- more than 70%: statistical heterogeneity may be substantial.

If study results are reasonably consistent ($I^2$ statistic < 40%), we will use the fixed-effect method to conduct meta analysis. In the

presence of moderate statistical heterogeneity (i.e. $I^2$ statistic 40 - 70%), we will use the random-effects method to pool study data (Higgins 2011) and investigate the source of the inconsistency using subgroup analyses (see below) . If heterogeneity is substancial ($I^2$ statistic > 70%), we will assess the source of heterogeneity by considering the variability in study participants, interventions, and outcomes studied. We will only pool data from studies that have participants, interventions, and outcomes that are reasonably homogeneous. If there would not be explanation of heterogeneity after subgroup analysis we will not pool the data and we will use descritiptive data

### Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate publication bias using a funnel plot. We will first assess funnel plot asymmetry visually, and then use formal tests. For dichotomous outcomes we will use the test proposed in Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform sensitivity analyses to investigate the source.

### Data synthesis

We will carry out statistical analyses using Review Manager 5 (RevMan 2014). We will conduct separate analyses for syndromic and etiological diagnose. Because the WHO (WHO 2005) and other clinical practice guidelines (Gaitán-Duarte 2013) recommend syndromic management for low-income countries, we will present as the primary analysis the effects of the intervention based on those studies that implemented this approach, and as secondary analysis we will present the results from trials that used etiological diagnosis.

We will use a fixed-effect meta-analysis for combining data, where it is reasonable to assume that studies estimated the same underlying treatment effect (i.e. where trials examined the same intervention, and the trial populations and methods are judged to be sufficiently similar). If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use a random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials.

### Subgroup analysis and investigation of heterogeneity

If substantial statistical heterogeneity is present and is not caused by data errors, we will explore the following potential sources using subgroup analyses. We have pre-defined subgroups as follows:

- immunocompetent versus immunocompromised (e.g. due to HIV or diabetes mellitus);
- intervention type: antiseptics or disinfectants;
- infection type: bacterial vaginosis or fungal (for included studies with etiological diagnosis).

We will restrict subgroup analyses to the primary outcomes:

- clinical improvement;
- symptomatic improvement;
- serious adverse event.

### Sensitivity analysis

We will perform a sensitivity analysis for aspects of the review that might affect the results, for example, where there is risk of bias associated with the flaws of the included trials based on overall 'Risk of bias' assessment (trials with a low overall risk of bias, versus those with unclear and high risk of bias).

#### *Overall quality of the body of evidence: 'Summary of findings' table*

We will prepare a 'Summary of findings' table using GRADEpro GDT 2015 and Cochrane methods. This table will evaluate the overall quality of the body of evidence for the main review outcomes for the review comparison antiseptics and disinfectants versus placebo, and for the comparison antiseptics and disinfectants versus antibiotics, These outcomes are:

1. clinical improvement

2. Symptomatic improvement,

3. Recurrence of vaginal discharge

4. Serious adverse events

. We will assess the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). Judgments about evidence quality (high, moderate, low or very low) will be made by two review authors working independently, with disagreements resolved by discussion. Judgments will be justified, documented, and incorporated into reporting of results for each outcome. We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review.

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## APPENDICES

### Appendix 1. Search strategies

**MEDLINE/CENTRAL* (Ovid)**

1. exp Vaginosis, Bacterial/
2. (vagin$ adj5 bacteri$).tw.
3. 1 or 2
4. exp Bacterial Infections/
5. (bacteri$ adj5 infection$).tw.
6. 4 or 5
7. exp Vaginitis/
8. vaginiti*.tw.
9. vaginosis.tw.
10. colpitis.tw.
11. kolpitis.tw.
12. (vaginal adj5 discharge).tw.
13. or/7-12
14. 6 and 13
15. 3 or 14
16. exp Anti-Infective Agents, Local/
17. antiinfective$.tw.
18. anti-infective$.tw.
19. (anti adj1 infective$).tw.

**Verstraelen 2009**

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**WHO 2005**

World Health Organization. Sexually transmitted and other reproductive tract infections: a guide to essential practice. Geneva (Switzerland): Department of Reproductive Health and Research, Family Health International (FHI) and The Population Council's FRONTIERS in Reproductive Health Programs, 2005.

**Winceslaus 1996**

Winceslaus SJ, Calver G. Recurrent bacterial vaginosis-an old approach to a new problem. *International journal of STD & AIDS* 1996;**7**(4):284-7.

**Zhang 1997**

Zhang J, Thomas AG, Leybovich E. Vaginal douching and adverse health effects: a meta-analysis. *American Journal of Public Health* 1997;**87**(7):1207-11.

20.antiseptic$.tw.
21.microbicid$.tw.
22.antibacterial$.tw.
23.(anti adj1 bacterial$).tw.
24.anti-bacterial$.tw.
25.antimicrobial.tw.
26.exp Disinfectants/
27.d?sinfect$.tw.
28.exp Benzydamine/
29.benzidamin$.tw.
30.exp Chlorhexidine/
31.chlor?hexidin$.tw.
32.clohexidin$.tw.
33.(cida adj1 stat).tw.
34.cida-stat.tw.
35.cidastat.tw.
36.exp Povidone-Iodine/
37.(povidone adj5 iodine$).tw.
38.povidone-iodine$.tw.
39.pvp-i.tw.
40.pvp-iodine$.tw.
41.(polyvinylpyrrol?done adj5 iodine$).tw.
42.iodopovidone.tw.
43.(polyvidone adj5 iodine).tw.
44.exp Hydrogen Peroxide/
45.(peroxide adj5 hydrogen).tw.
46.h2o2.tw.
47.hydroperoxide.tw.
48.(dihydrogen adj5 dioxide).tw.
49.(hydrogen adj5 dioxide).tw.
50.(hydrogen adj5 superoxide).tw.
51.exp Dequalinium/
52.dequalinium.tw.
53.polycidine.tw.
54.decamine.tw.
55.polycarbophil.tw.
56.polycarbofil.tw.
57.or/16-56
58.randomized controlled trial.pt.
59.controlled clinical trial.pt.
60.randomized.ab.
61.placebo.ab.
62.clinical trials as topic.sh.
63.randomly.ab.
64.trial.ti.
65.58 or 59 or 60 or 61 or 62 or 63 or 64
66.exp animals/ not humans.sh.
67.65 not 66
68.15 and 57 and 67

*In CENTRAL 58-67 don´t apply

**EMBASE (embase.com)**

1. 'vaginosis, bacterial'/exp
2. (vagin* NEAR/5 bacteri*):ab,ti
3. #1 OR #2
4. 'bacterial infections'/exp
5. (bacteri* NEAR/5 infection*):ab,ti
6. #4 OR #5
7. 'vaginitis'/exp
8. vaginiti*:ab,ti
9. vaginosis*:ab,ti
10. colpitis*:ab,ti
11. kolpitis*:ab,ti
12. (vaginal NEAR/5 discharge):ab,ti
13. #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. #6 AND #13
15. #3 OR #14
16. 'topical antiinfective agent'/exp
17. 'antiinfective agent'/exp
18. antiinfective*:ab,ti
19. anti-infective*:ab,ti
20. (anti NEAR/1 infective*):ab,ti
21. antiseptic*:ab,ti
22. microbicid*:ab,ti
23. antibacterial*:ab,ti
24. (anti NEAR/1 bacterial*):ab,ti
25. anti-bacterial*:ab,ti
26. antimicrobial:ab,ti
27. 'disinfectant agent'/exp
28. d?sinfect*:ab,ti
29. 'benzydamine'/exp
30. benzidamin*:ab,ti
31. 'chlorhexidine'/exp
32. 'chlorhexidine acetate'/exp
33. 'chlorhexidine gluconate'/exp
34. chlor?hexidin*:ab,ti
35. clohexidin*:ab,ti
36. (cida NEAR/1 stat):ab,ti
37. cida-stat:ab,ti
38. cidastat:ab,ti
39. 'povidone iodine'/exp
40. (povidone NEAR/5 iodine*):ab,ti
41. povidone-iodine*:ab,ti
42. pvp-i:ab,ti
43. pvp-iodine*:ab,ti
44. (polyvinylpyrrol?done NEAR/5 iodine*):ab,ti
45. iodopovidone:ab,ti
46. (polyvidone NEAR/5 iodine):ab,ti
47. 'hydrogen peroxide'/exp
48. (peroxide NEAR/5 hydrogen):ab,ti
49. h2o2:ab,ti
50. hydroperoxide:ab,ti
51. (dihydrogen NEAR/5 dioxide):ab,ti

52.(hydrogen NEAR/5 dioxide):ab,ti
53.(hydrogen NEAR/5 superoxide):ab,ti
54.'dequalinium'/exp
55.dequalinium:ab,ti
56.polycidine:ab,ti
57.decamine:ab,ti
58.'polycarbophil'/exp
59.polycarbophil:ab,ti
60.polycarbofil:ab,ti
61.#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
62."randomized controlled trial"/de
63."controlled clinical study"/de
64.random*:ti,ab
65.randomization/de
66."intermethod comparison"/de
67.placebo:ti,ab
68.(compare OR compared OR comparison):ti
69.((evaluated OR evaluate OR evaluating OR assessed OR assess) AND (compare OR compared OR comparing OR comparison)):ab
70.(open NEAR/1 label):ti,ab
71.((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab
72."double blind procedure"/de
73.(parallel NEXT/1 group*):ti,ab
74.(crossover OR "cross over"):ti,ab
75.((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab
76.(assigned or allocated):ti,ab
77.(controlled NEAR/7 (study OR design OR trial)):ti,ab
78.(volunteer OR volunteers):ti,ab
79.trial:ti
80."human experiment"/de
81.#62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80
82.#15 AND #61 AND #81 AND [embase]/lim

## CONTRIBUTIONS OF AUTHORS

All authors of this investigation contributed to writing the first draft of the protocol and subsequent amendments.

## DECLARATIONS OF INTEREST

AMPA: none known.

JA-G: none known.

CFG-A: none known.

AMTC:none known.

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- No sources of support supplied

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