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Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush) (Review)

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[Intervention Review]

Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush)

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ABSTRACT

Background

Anti-fungals are available for oral and intra-vaginal treatment of uncomplicated vulvovaginal candidiasis.

Objectives

The primary objective of this review is to assess the relative effectiveness (clinical cure) of oral versus intra-vaginal anti-fungals for the treatment of uncomplicated vulvovaginal candidiasis. Secondary objectives include the assessment of the relative effectiveness in terms of mycological cure, in addition to safety, side effects, treatment preference, time to first relief of symptoms, and costs.

Search methods

We searched CENTRAL, MEDLINE, Embase, and two trials registers on 29 August 2019 together with reference checking and citation searching.

Selection criteria

We included randomised controlled trials published in any language comparing at least one oral anti-fungal with one intra-vaginal anti-fungal in women (aged 16 years or over) with a mycological diagnosis (positive culture, microscopy for yeast, or both) of uncomplicated vulvovaginal candidiasis. We excluded trials if they solely involved participants who were HIV positive, immunocompromised, pregnant, breast feeding or diabetic.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane.

Main results

This review includes 26 trials (5007 participants). Eight anti-fungals are represented. All but three trials included participants with acute vulvovaginal candidiasis. Trials were conducted in Europe: UK (3), Croatia (2). Finland (2), the Netherlands (2), Germany (1), Italy (1), Sweden

(1) and one trial across multiple European countries, USA (7) Thailand (2), Iran (2), Japan (1) and Africa (Nigeria) (1). The duration of follow-up varied between trials. The overall risk of bias of the included trials was high.

There was probably little or no difference shown between oral and intra-vaginal anti-fungal treatment for clinical cure at short-term follow-up (OR 1.14, 95% CI 0.91 to 1.43; 13 trials; 1859 participants; moderate-certainty evidence) and long-term follow-up (OR 1.07, 95% CI 0.77 to 1.50; 9 trials; 1042 participants; moderate-certainty evidence). The evidence suggests that if the rate of clinical cure at short-term follow-up with intra-vaginal treatment is 77%, the rate with oral treatment would be between 75% and 83%; if the rate of clinical cure at long term follow-up with intra-vaginal treatment is 84%, the rate with oral treatment would be between 80% and 89%. Oral treatment probably improves mycological cure over intra-vaginal treatment at short term (OR 1.24, 95% CI 1.03 to 1.50: 19 trials; 3057 participants; moderate-certainty evidence) and long-term follow-up (OR 1.29, 95% CI 1.05 to 1.60; 13 trials; 1661 participants; moderate-certainty evidence). The evidence suggests that if the rate of mycological cure at short-term follow-up with intra-vaginal treatment is 80%, the rate with oral treatment would be between 80% and 85%; if the rate of mycological cure at long-term follow-up with intra-vaginal treatment is 66%, the rate with oral treatment would be between 67% and 76%.

In terms of patient safety, there is a low risk of participants withdrawing from the studies due to adverse drug effects for either treatment (23 trials; 4637 participants; high-certainty evidence). Due to the low certainty of evidence, it is undetermined whether oral treatments reduced the number of side effects compared with intra-vaginal treatments (OR 1.04, 95% CI 0.84 to 1.29; 16 trials; 3155 participants; low-certainty evidence). The evidence suggests that if the rate of side effects with intra-vaginal treatment is 12%, the rate with oral treatment would be between 10% and 15%. We noted that the type of side effects differed, with intra-vaginal treatments being more often associated with local reactions, and oral treatments being more often associated with systemic effects including gastro-intestinal symptoms and headaches. Oral treatment appeared to be the favoured treatment preference over intra-vaginal treatment or no preference (12 trials; 2206 participants), however the data were poorly reported and the certainty of the evidence was low. There was little or no difference in time to first relief of symptoms between oral and intra-vaginal treatments: four trials favoured the oral treatment, four favoured intra-vaginal, one study reported no difference and one was unclear. The measurements varied between the 10 trials (1910 participants) and the certainty of the evidence was low. Costs were not reported in any of the trials.

Authors' conclusions

Oral anti-fungal treatment probably improves short- and long-term mycological cure over intra-vaginal treatment for uncomplicated vaginal candidiasis. Oral treatment was the favoured treatment preference by participants, though the certainty of this evidence is low.

The decision to prescribe or recommend an anti-fungal for oral or intra-vaginal administration should take into consideration safety in terms of withdrawals and side effects, as well as cost and treatment preference. Unless there is a previous history of adverse reaction to one route of administration or contraindications, women who are purchasing their own treatment should be given full information about the characteristics and costs of treatment to make their own decision. If health services are paying the treatment cost, decision-makers should consider whether the higher cost of some oral anti-fungals is worth the gain in convenience, if this is the patient's preference.

PLAIN LANGUAGE SUMMARY

Do antifungal medicines for vaginal yeast infections (thrush) work better if taken by mouth (orally) or placed in the vagina (intravaginally)?

What is thrush?

Thrush (also called candidiasis) is a common vaginal infection caused by a type of fungus called a yeast. Symptoms include itching and irritation around the vagina and a white discharge. Thrush is usually harmless but it can be uncomfortable.

Thrush is usually treated with antifungal medicines. These can be taken by mouth (orally) or placed in the vagina (intravaginally).

Why we did this Cochrane Review

We wanted to find out if oral antifungal medicines work better than intravaginal antifungal medicines to treat thrush infections.

What did we do?

We searched for studies of antifungal medicines to treat thrush that compared an oral antifungal with an intravaginal antifungal.

We looked for randomised controlled studies, in which the treatments received were decided at random, because these studies usually give the most reliable evidence about the effects of treatments.

We were interested in how well - and how fast - antifungal medicines could get rid of yeast infections and improve symptoms; whether they had any unwanted effects; and whether women preferred oral or intravaginal treatment.

Search date: we included evidence published up to 29 August 2019.

What we found

We found 26 studies in 5007 women with thrush who were treated with antifungal medicines called azoles. The studies were conducted in Europe, the USA, Thailand, Iran, Japan and Nigeria. Eight azoles were studied: 2 oral (fluconazole and itraconazole) and 6 intravaginal (butoconazole, clotrimazole, econazole, miconazole, sertaconazole and terconazole).

The studies measured whether oral and intravaginal antifungal medicines led to:

- no symptoms (clinical cure);
- no yeasts found in the vagina (mycological cure); or
- unwanted effects that caused women to stop treatment.

No studies reported the costs of the oral or intravaginal antifungal medicines.

What are the results of our review?

Clinical cure (no symptoms) was similar for oral and intravaginal antifungal medicines in both the short term (5 to 15 days; 13 studies), and long term (2 to 12 weeks; 9 studies). Whether an antifungal medicine is oral or intravaginal probably makes little to no difference to getting rid of thrush symptoms.

However, oral antifungal medicines probably cleared yeast from the vagina (mycological cure) better than intravaginal ones in both the short term (19 studies) and long term (13 studies).

Only three women stopped using their antifungal medicine because of unwanted effects (23 studies); the risk of women stopping treatment with oral or intravaginal antifungal medicines is low.

The numbers of unwanted effects reported were similar: whether an antifungal medicine is oral or intravaginal might make little to no difference to unwanted effects (13 studies). Headache and digestive symptoms were more common with oral antifungal medicines; unwanted effects of intravaginal antifungals commonly affected only the vaginal area.

Our results suggested that women might prefer taking an oral antifungal medicine to an intravaginal one (12 studies).

Whether an antifungal medicine is oral or intravaginal may make little to no difference to how quickly thrush gets better.

How reliable are these results?

We are moderately confident in our findings for clinical and mycological cure of thrush. These results might change if further evidence becomes available. We are confident about the low risk of women stopping treatment because of unwanted effects of antifungal medicines, and further evidence is unlikely change this.

We are less confident about the numbers of unwanted effects, preferred treatment, and how quickly symptoms get better. These results are likely to change if further evidence becomes available.

Ten studies received support from pharmaceutical companies; this could have affected how the studies were designed, conducted and reported. The results from some studies varied widely and were not reported consistently; and the women knew which treatment they had, which could have affected the results reported.

Conclusions

Oral antifungal medicines probably clear yeast from the vagina better than intravaginal antifungal medicines, although there is probably little to no difference between them for getting rid of thrush symptoms.

The risk of women stopping treatment because of unwanted effects is low for both oral and intravaginal antifungal medicines.

Summary of findings 1. Oral versus intra-vaginal antifungal treatment of uncomplicated vulvovaginal candidiasis

Oral versus intra-vaginal antifungal treatment of uncomplicated vulvovaginal candidiasis.

Patient or population: women aged 16 and over with uncomplicated vulvovaginal candidiasis

Settings: various settings (single and multi-centre obs/gyn or other outpatient clinics) in Europe, USA, Japan, Thailand, Iran, Africa/Nigeria

Intervention: oral antifungal treatment of uncomplicated vulvovaginal candidiasis (fluconazole and itraconazole)

Comparison: Intra-vaginal antifungal treatment of uncomplicated vulvovaginal candidiasis (butoconazole, clotrimazole, econazole, miconazole, sertaconazole and terconazole)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed control risk (intra-vaginal treatment)	Corresponding intervention risk (oral treatment)				
Clinical cure (short term: 5 to 15 days)	767 per 1000	790 per 1000 (750 to 825)	OR 1.14 (0.91 to 1.43)	1859 (13 RCTs)	Moderate[1] ⊕⊕⊕	
Clinical cure (long term; 2 to 12 weeks)	838 per 1000	847 per 1000 (799 to 886)	OR 1.07 (0.77 to 1.50)	1042 (9 RCTs)	Moderate[1] ⊕⊕⊕	
Mycological cure (short term; 5 to 15 days)	796 per 1000	829 per 1000 (801 to 854)	OR 1.24 (1.03 to 1.50)	3057 (19 RCTs)	Moderate[1] ⊕⊕⊕	
Mycological cure (long term; 2 to 12 weeks)	662 per 1000	716 per 1000 (673 to 758)	OR 1.29 (1.05 to 1.60)	1661 (13 RCTs)	Moderate[1] ⊕⊕⊕	
Safety (withdrawals due to adverse effects)	-	-	-	4637 (23 RCTs)	High ⊕⊕⊕⊕	Measured by number of withdrawals due to adverse reactions. Three trials reported withdrawals due to adverse drug reactions (one participant in each trial). Two withdrawals were from the intra-vaginal treatment group (both miconazole ACCELERATE 2002; Timonen

						1992a), and one was from the oral treatment group (fluconazole, Stein 1991)
Side effects (patient-reported side effects)	119 per 1000	123 per 1000 (102 TO 148)	OR 1.04 (CI 0.84 to 1.29)	3155 (16 RCTs)	Low[1, 2] ⊕⊕	Three trials were not included in the meta-analysis because they did not provide any indication of the direction or magnitude of the relative treatment effect, as they reported there were no side effect events for either treatment group (Mikamo 1995; Škerk V 2006; Slavin 1992) Two further trials were also not included in the meta-analyses because they did not provide numerical data about side effect events (Goode 1992; Roongpisuthipong 2010). Lastly, Van Heusden 1994 was not included in the estimates because a denominator was unclear.
Treatment preference	-	-	-	2206 (12 RCTs)	Low[1, 3] ⊕⊕	Poorly reported. Unable to determine preference in one trial (Tobin 1992). One study reported no preference (Van Heusden 1990). 10/12 studies preferred oral treatment (compared with intra-vaginal or no preference)
Time to first relief of symptoms	-	-	-	1910 (10 RCTs)	Low[1, 4] ⊕⊕	Time to first relief measurements varied between studies. Four trials favoured intra-vaginal (ACCELERATE 2002; Murina 2012;Seidman 2005; Slavin 1992. Two trials reported little or no difference (Adetoro 1990; Mendling 2004), and one study showed mixed effects (Timonen 1992a)
Costs	Not reported in any study					-

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;**RCT:** Randomised controlled trial.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded 1 level for serious concern for risk of bias.
[2] Downgraded 1 level for substantial heterogeneity across and within subgroups.
[3] Downgraded 1 level for inconsistencies associated with reporting.
[4] Downgraded 1 level - unable to determine precise effects.

BACKGROUND

Description of the condition

Previous estimates suggest that 75% of women experience at least one episode of vulvovaginal candidiasis (thrush) before the menopause (Sobel 2007). Candidiasis is the term that is used generically for vaginal infections produced by Candida species. *Candida albicans* (*C. albicans*) is the species most often associated with candidiasis, however, other yeasts (e.g. *C. glabrata, C. krusei*) can also cause this infection (Gonçalves 2016).

Description of the intervention

Vulvovaginal candidiasis is treated with a variety of anti-fungal drugs (Martindale 2017) that are administered by the oral or local (intra-vaginal) route. The decision to use a specific anti-fungal depends upon its safety, effectiveness, cost and patient preference.

How the intervention might work

There are several classes of anti-fungals with various molecular targets and modes of action (Odds 2003). Therapy for vaginal infection is dominated by the azole class, which includes both oral and intra-vaginal drugs (Pappas 2004). Azoles work by inhibiting the synthesis of fungal lipids, especially ergosterol, which results in damage to the cell membrane leading to cell death (Ghannoum 1999).

Why it is important to do this review

This review was last updated in 2007. Since then, the pattern of resistance to antifungals could have changed, and as such it is important to identify and include new studies that have been conducted in contemporary populations.

OBJECTIVES

The primary objective of this review is to assess the relative effectiveness (clinical cure) of oral versus intra-vaginal anti-fungals for the treatment of uncomplicated vulvovaginal candidiasis. Secondary objectives include the assessment of the relative effectiveness in terms of mycological cure, in addition to safety, side effects, treatment preference, time to first relief of symptoms and costs.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials irrespective of publication type or language.

Types of participants

Women (aged 16 years or over) with uncomplicated vulvovaginal candidiasis. For the purpose of this review, uncomplicated vaginal candidiasis refers to acute episodes of this infection (i.e. less than four episodes in 12 months). The diagnosis of vulvovaginal candidiasis was confirmed mycologically (i.e. a positive culture or microscopy, or both for yeast). Studies were excluded if they solely involved participants who were HIV positive, immunocompromised, pregnant, breast feeding or diabetic. Trials that randomised participants with acute and chronic infections were included if the results for the participants with acute infection were presented separately, or, if less than 20% of participants had chronic vaginal candidiasis.

Types of interventions

- Trials that compared any of the imidazole or triazole anti-fungal drugs administered by the intra-vaginal route (butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, omoconazole, oxiconazole, sertaconazole, terconazole, and tioconazole) with orally administered imidazole or triazole anti-fungals (fluconazole, itraconazole).
- Trials that compared more than two anti-fungals were included if they compared oral and intra-vaginal routes of administration, with each two-way comparison (i.e. oral versus intra-vaginal) being treated separately.

We excluded trials that involved ketoconazole (oral and intra-vaginal) due to its limited licence in many countries.

Types of outcome measures

Primary outcomes

- Clinical cure of the infection, both short (5 to 15 days) and long term (2 to 12 weeks), as measured by the disappearance of symptoms either on examination or by self-report

Secondary outcomes

- Mycological cure; both short (5 to 15 days) and long term (2 to 12 weeks) as determined by laboratory test(s) indicating no presence of vulvovaginal candidiasis either by mycological culture or microscopy
- Safety: as measured by the number of patient withdrawals due to adverse reactions
- Side effects: incidence of self-reported adverse reactions (sometimes reported as side effects)
- Treatment preference (of route of administration): measured by self-report
- Time to first relief (of symptoms): measured by self-report
- Costs

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 29 August 2019:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 8) in the Cochrane Library;
- MEDLINE Ovid (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Versions) (1946 onwards);
- Embase Ovid (1974 to 29 August 2019);

Search strategies are comprised of keywords and controlled vocabulary terms. The development of the final search strategy was done with the assistance of Maria Teresa Vallejo, the Information Specialist for the Sexually Transmitted Infections Cochrane Review Group. We included studies regardless of publication type or language of publication. Detailed search strategies are included in Appendix 1.

Searching other resources

In addition, we searched WHO ICTRP and ClinicalTrials.gov for ongoing trials. We also handsearched the reference lists of any relevant systematic reviews retrieved via the electronic searches.

Data collection and analysis

Selection of studies

For this update, pairs of review authors from HD, JO, JW, MCW and MES independently read all the titles and abstracts retrieved from the electronic searches to identify potentially eligible publications. We retrieved full-text papers for all selected publications. Two review authors from HD, JO, JW, MCW and MES independently assessed their eligibility against the inclusion criteria. We selected studies for the review according to the prespecified inclusion criteria and resolved disagreements by discussion. We collated multiple reports for the same study, so that each study rather than each report is the unit of interest

Data extraction and management

Two review authors from HD, JO, JW, MCW and MES independently completed data extraction capturing data on the following characteristics and outcomes of each trial:

- the anti-fungal used, dose, frequency and duration of administration;
- type of setting;
- participants;
- outcome measures;
- methodological quality.

Assessment of risk of bias in included studies

Two review authors from AM, HD, JO, JW and MES independently assessed the risk of bias for each included study using the Cochrane 'Risk of bias' tool as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We scored each criterion, for each study, as low risk, unclear risk, or high risk of bias and used the following determinations/consideration when making our judgments for these domains. We resolved any disagreements by discussion.

- Random allocation of treatment: "low risk" if a random process was used (e.g. random numbers), or if the authors stated explicitly that the trial groups were generated by random allocation.
- Allocation concealment: "low risk" if the unit of randomisation was by patient or episode of care, and some form of centralised randomisation scheme was used (e.g. sealed opaque envelopes).
- Blinding of participants and personnel: "low risk" if participants would be blinded to whether they were getting oral or vaginal interventions (e.g. received both treatments with one a placebo).
- Blinding of outcome assessors to participants' assignment status: "low risk" if the authors stated explicitly that the outcome measures were assessed blindly. For clinical outcomes and time to first relief, blinding was reported as "high risk" if the patients could influence the findings by biased reporting. For mycological outcomes, blinding was reported as "low risk" if these were derived from objective tests and not influenced by the patient or assessor.
- Incomplete outcome data: "high risk" if greater than 10% of participants who were culture positive for yeast were lost to follow-up. The follow-up of the longest duration was used for this assessment.
- Selective reporting: "low risk" if reported the results of all outcomes measured.
- Other potential sources of bias: "low risk" if there were no other sources of bias identified.

Measures of treatment effect

The primary analysis was a comparison of the relative effectiveness of oral versus intra-vaginal anti-fungals for each outcome described in the Types of outcome measures. We undertook meta-analyses using a fixed-effect model to pool the odds ratios of trials that were homogenous in terms of the outcome measures that were used or that could be calculated. Where it was not possible to undertake a meta-analysis, we report the effects in narrative.

If there were multiple intervention groups in a study, which meant that including all comparisons separately would result in some participants being included in the analysis more than once, we combined the groups to create a single pair-wise comparison as outlined in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We calculated odds ratios for the dichotomous outcomes of clinical and mycological cure. In all trials, women were randomised to treatment group (by the investigators) on the basis of their clinical symptoms. At the point of randomisation, a swab was taken for mycological culture. Following randomisation some participants were excluded because they tested negative for candida. To have used the number of participants randomised as the denominator would have underestimated the efficacy of the individual anti-fungals. Therefore, the denominator used was the number of randomised participants who were culture-positive for yeast prior to receiving an anti-fungal.

We calculated odds ratios for side effects using the number of participants reporting side effects reported in the studies.

The relative safety of both routes of administration was assessed using the number of withdrawals due to adverse drug reactions. We calculated this outcome by assessing whether there were any withdrawals reported in the trials (yes, no, or not reported).

Treatment preference was assessed by recording the number of people that preferred oral treatment versus the number of people that preferred intra-vaginal treatment (and the number of people that had no preference, where relevant) for each study. We then summed the number of trials that found that overall oral treatment was preferred, intra-vaginal was preferred, and no preference.

There was variation in how time to first relief of symptoms was reported in the trials (e.g. mean time, median time, proportion of patients who experienced relief at specific time points), therefore the data could not be combined. We recorded in an additional table the findings from each study that assessed this outcome.

Unit of analysis issues

All the included studies were randomised controlled trials with a parallel design. The participants were individually allocated to the treatment or control groups. There were no cross-over or cluster-randomised trials and no unit of analysis issues. We included the per protocol results in the meta-analysis.

Dealing with missing data

There were little missing data. Where trials had limited or unclear data for an outcome, they were included in the narrative synthesis of results but excluded from meta-analysis.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic, quantifying the percentage of the total variation across studies that is due to heterogeneity rather than chance; smaller percentages suggest less observed heterogeneity (Deeks 2011).

Assessment of reporting biases

We used funnel plots to assess the likelihood of publication bias.

Data synthesis

We used the fixed-effect Mantel-Haenszel analysis method to combine outcome data from the trials. Studies that did not have clear numerators or denominators for an outcome were not included in the meta-analysis for that outcome. We provide a descriptive synthesis where data were reported in a form that could not be entered into meta-analysis.

We analysed individual drug comparisons when there were sufficient trials to do so. Comparisons included fluconazole versus clotrimazole, itraconazole versus clotrimazole, fluconazole versus miconazole, fluconazole versus econazole, itraconazole versus econazole, fluconazole versus butoconazole, fluconazole versus fenticonazole, fluconazole versus terconazole, and fluconazole versus sertaconazole. Single-dose anti-fungal regimens were compared as well as single- versus multiple-dose treatment.

Subgroup analysis and investigation of heterogeneity

We performed several subgroup analyses.

Sensitivity analysis

Sensitivity analyses were also performed using the methodological quality criteria (see above) and are described in the text. For the sensitivity analyses, methodological quality was assessed using the following criteria and incorporated into the analyses for selection bias, blinding of the outcome assessor and incomplete outcome data.

Selection bias included the assessment for both random allocation and allocation concealment. Random allocation of treatment was considered as "done" if a random process was used (e.g. random numbers), or if the authors stated explicitly that the trial groups were generated by random allocation. Allocation concealment was "done" if the unit of randomisation was by patient or episode of care, and some form of centralised randomisation scheme was used (e.g. sealed opaque envelopes). In order for selection bias to be considered low risk, both random allocation and allocation concealment had to be considered as done. If these criteria were not met, then the study was removed and the analysis repeated only including those studies that met the criteria for selection bias.

Blinding of the outcome assessor was considered "done" if outcome assessors were blinded to participants' assignment status; this was regarded as "done" if the authors stated explicitly that the outcome measures were assessed blindly. If the criteria were not met, then the study was removed and the analysis repeated only including those studies that met the criteria for blinded outcome assessor.

Incomplete outcome data was considered "done" if follow-up in the study at the longest time point was 90% or greater. If the criteria were not met, then the study was removed and the analysis repeated only including those studies that met the criteria for incomplete outcome data.

Summary of findings

We graded our confidence in the evidence and summarised the findings in a 'Summary of findings' table using the approach recommended by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group (Guyatt 2008). We compared the effectiveness of oral versus intra-vaginal anti-fungals for the treatment of uncomplicated vulvovaginal candidiasis for each of the following important outcomes: clinical cure, mycological cure, safety, side effects, treatment preference, time to first relief of symptoms and costs. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and risk of bias) to assess the certainty of the evidence as it relates the outcomes (Guyatt 2008). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

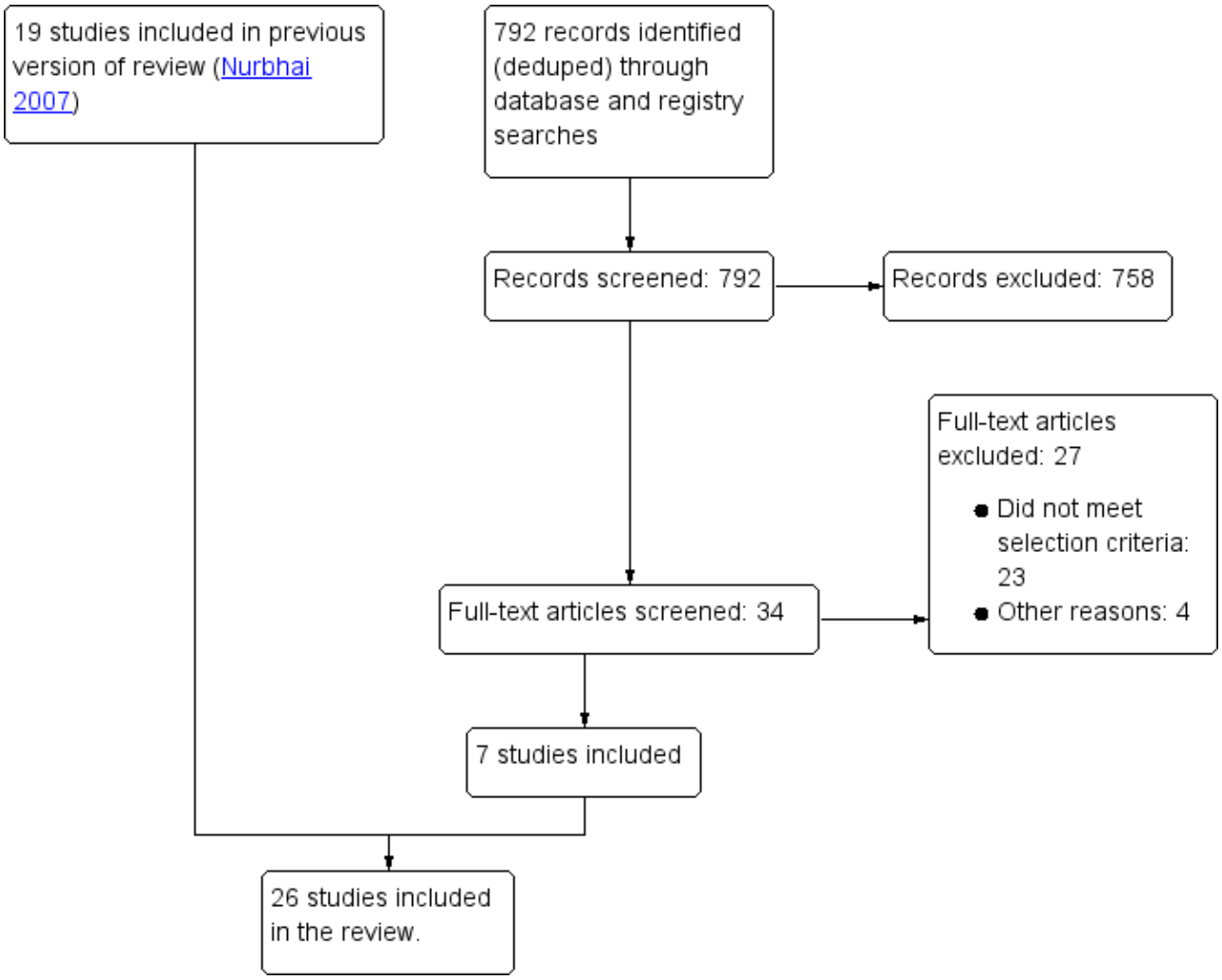
Description of studies

See: Characteristics of included studies

Results of the search

For this update, we retrieved 792 records from database and registry searches, of which 758 were ineligible. We obtained full-text articles for the remaining 34 records, seven of which fulfilled the inclusion criteria for this review (ACCELERATE 2002; Coric 2006; Murina 2012; Roongpisuthipong 2010; Sanam 2009; Sekhavat 2011; Škerk V 2006). The total number of trials included in this review is 26 (Figure 1). We identified two systematic reviews to handsearch (Matheson 2017, van Schalkwyk 2016).

Figure 1. Study flow diagram.



Included studies

Study design and population

We included 26 randomised controlled trials involving 5007 women between the ages of 16 and 65 (where reported). Four trials did not report age of the participants (Boag 1991, Coric 2006, Goode 1992, Mendling 2004). One trial stated an age range of 15 to 50 years, however only eight of 188 participants were under 16 years (Roongpisuthipong 2010). One trial presented median age for participants by trial group (26 years in one treatment group and 25 years in the other) (Murina 2012).

All of the included studies confirmed the clinical diagnosis of vaginal candidiasis using mycological culture or microscopy, or both. Two trials used microscopy only to provide mycological confirmation of the diagnosis (Slavin 1992; Woolley 1995. There was variation amongst the remaining trials regarding the definition used to confirm the mycological diagnosis. Some trials reported positive "yeast culture" (Boag 1991, Mendling 2004, Osser 1991, Timonen 1992b, Timonen 1992a), whilst others reported positive quote: "culture of Candida species" (Adetoro 1990, Andersen 1989, Mikamo 1995, Mikamo 1995, O-Prasertsawat 1995, Sobel 1995, Stein 1991, Stein 1993, Tobin 1992, Van Heusden 1990, Van Heusden 1994, Woolley 1995). Two trials reported mycological confirmation of "Candidiasis" but did not mention a specific species (Goode 1992, Seidman 2005), and one trial reported quote: "positive 10% KOH preparation for budding yeast and/or pseudohypha" (KOH = potassium hydroxide) (ACCELERATE 2002). The Seidman 2005 trial did not perform yeast cultures. In only one study (Adetoro 1990), was mycological cure defined as the absence of *Candida albicans*. The terminology most often used in reporting mycological cure was the absence of growth of *Candida* species.

Twenty-three trials included women with acute vulvovaginal candidiasis; three trials included participants with chronic vulvovaginal candidiasis (Osser 1991, Sobel 1995, Timonen 1992b). In one of these three trials, the results for clinical cure and mycological cure for acute vulvovaginal candidiasis were presented separately from participants with chronic infection, therefore, the results for this trial were generated from the acute participants only for these outcomes (Sobel 1995). Of the 258 participants randomised in the trial by Osser and colleagues, 33 (13%) had chronic vulvovaginal candidiasis (Osser 1991, and in the trial by Timonen and colleagues,13 (16%) of the participants had chronic yeast infections. The duration of follow-up varied between trials (see additional Table 1). For the purpose of this review, the

outcome measures that were presented at between five and 15 days were included in the short-term follow-up comparisons, and the outcome measures that were presented at between two and 12 weeks were included in the long-term follow-up comparisons. Outcome measures that were presented at time points outside these follow-up periods were excluded. There is slight overlap between the duration of short- and long-term follow-up as a result of the trial by Timonen (Timonen 1992b). Ethnicity of the trial populations was not reported in any trial. The trials were published between 1989 (Andersen 1989) and 2012 (Murina 2012).

Setting

Thirteen trials were conducted in Europe: three in the UK (Boag 1991; Tobin 1992; Woolley 1995); two in Croatia (Coric 2006, Škerk V 2006), Finland (Timonen 1992a; Timonen 1992b) and the Netherlands (Van Heusden 1990 Van Heusden 1994); one each in Germany (Mendling 2004), Italy (Murina 2012), Sweden (Osser 1991); and one trial was conducted across multiple European countries (Andersen 1989). Additionally, seven studies were conducted in the USA, (ACCELERATE 2002,Goode 1992, Seidman 2005, Slavin 1992, Sobel 1995, Stein 1991, Stein 1993); one in Japan (Mikamo 1995); two each in Thailand (O-Prasertsawat 1995, Roongpisuthipong 2010), Iran (Sanam 2009, Sekhavat 2011); and one in Africa/Nigeria (Adetoro 1990). Trials were conducted at both single (n = 10) and multi-centred sites (n = 11) and five trials did not specify the setting, or were unclear.

Intervention

In total, eight anti-fungals were represented: two oral treatments; fluconazole and itraconazole,and six intra-vaginal treatments; butoconazole, clotrimazole, econazole, miconazole, sertaconazole and terconazole. Fluconazole was compared with clotrimazole in 15 trials (17 comparisons) (Adetoro 1990; Andersen 1989; Boag 1991;Coric 2006; Goode 1992; Mendling 2004 (two comparisons); Mikamo 1995 (two comparisons); O-Prasertsawat 1995; Roongpisuthipong 2010; Sekhavat 2011; Škerk V 2006; Sobel 1995; Stein 1991;Van Heusden 1994; Woolley 1995); miconazole in three trials (ACCELERATE 2002; Timonen 1992a; Van Heusden 1990), and terconazole (Slavin 1992), econazole (Osser 1991), butoconazole (Seidman 2005), sertaconazole Roongpisuthipong 2010 and fenticonazole (Murina 2012) in one trial each. Itraconazole was compared with clotrimazole in four trials (Sanam 2009; Stein 1993; Tobin 1992; Woolley 1995; and econazole in one trial (Timonen 1992b).

Outcomes

Thirteen studies reported clinical cure (short term): Coric 2006; Goode 1992; Murina 2012; Osser 1991; Sanam 2009; Seidman 2005; Sekhavat 2011; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992b; Van Heusden 1990; Woolley 1995.

Nine studies reported clinical cure (long term): Goode 1992; Murina 2012; Osser 1991; Škerk V 2006; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992b; Van Heusden 1990.

Twenty studies reported mycological cure (short term): Adetoro 1990; Andersen 1989; Boag 1991; Coric 2006; Goode 1992; Mendling 2004; Mikamo 1995; O-Prasertsawat 1995; Osser 1991; Roongpisuthipong 2010; Sanam 2009; Sekhavat 2011; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992a; Timonen 1992b; Tobin 1992; Van Heusden 1990; Woolley 1995.

Fifteen studies reported mycological cure (long term): Adetoro 1990; Andersen 1989; Goode 1992; Mendling 2004; Mikamo 1995; O-Prasertsawat 1995; Osser 1991; Roongpisuthipong 2010; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992a; Timonen 1992b; Tobin 1992; Van Heusden 1990.

Twenty-three studies reported safety: ACCELERATE 2002; Adetoro 1990; Andersen 1989; Goode 1992; Mendling 2004; Mikamo 1995; Murina 2012; O-Prasertsawat 1995; Osser 1991; Roongpisuthipong 2010; Sanam 2009; Seidman 2005; Sekhavat 2011; Škerk V 2006; Slavin 1992; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992a; Timonen 1992b; Tobin 1992; Van Heusden 1990; Van Heusden 1994

Twenty-two studies reported side effects: ACCELERATE 2002; Adetoro 1990; Andersen 1989; Goode 1992; Mendling 2004; Mikamo 1995; Murina 2012; O-Prasertsawat 1995; Osser 1991; Roongpisuthipong 2010; Sanam 2009; Seidman 2005; Sekhavat 2011; Škerk V 2006; Slavin 1992; Sobel 1995; Stein 1993; Stein 1991; Timonen 1992a;Timonen 1992b; Van Heusden 1990; Van Heusden 1994.

Twelve studies reported treatment preference: Adetoro 1990; Andersen 1989; Coric 2006; Osser 1991; Sekhavat 2011; Slavin 1992; Stein 1993; Timonen 1992b; Timonen 1992a; Tobin 1992; Van Heusden 1990; Van Heusden 1994.

Ten studies reported time to first relief: ACCELERATE 2002; Adetoro 1990; Andersen 1989; Coric 2006; Mendling 2004; Murina 2012; Seidman 2005; Slavin 1992; Timonen 1992a; Tobin 1992.

No studies reported on cost.

Compliance and sources of support

Compliance checks were undertaken in seven trials (ACCELERATE 2002; Boag 1991; O-Prasertsawat 1995; Osser 1991; Seidman 2005; Slavin 1992; Sobel 1995). One trial reported 99.3% compliance (ACCELERATE 2002), and one did not report the rate or the numbers of compliance (O-Prasertsawat 1995). The remainder of these trials reported 100% of participants complied with treatment. Pharmaceutical industry support was reported in 10 trials (ACCELERATE 2002; Adetoro 1990; Andersen 1989; Osser 1991; Roongpisuthipong 2010; Sobel 1995; Stein 1991; Stein 1993; Timonen 1992b; Tobin 1992). We were unable to determine industry support for one trial (Škerk V 2006).

Excluded studies

We excluded 27 articles at full-text review. Twenty-three of these clearly did not meet the eligibility criteria and were excluded. Four of these studies appeared to meet the eligibility criteria, but while conducting data extraction, we determined that they were not eligible and were subsequently excluded (EUCTR2005-001360-31-IT; Fan 2015; Li 2015; Zhou 2016). We have provided an explanation for their exclusion in the Characteristics of excluded studies table along with the five studies excluded in the last published version of the review (Nurbhai 2007).

Risk of bias in included studies

See: Characteristics of included studies

The risk of bias tables are presented in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' summary: reviewers judgements about each risk of bias domain for each included study. Blank or empty spaces represent outcomes that were not reported/assessed.

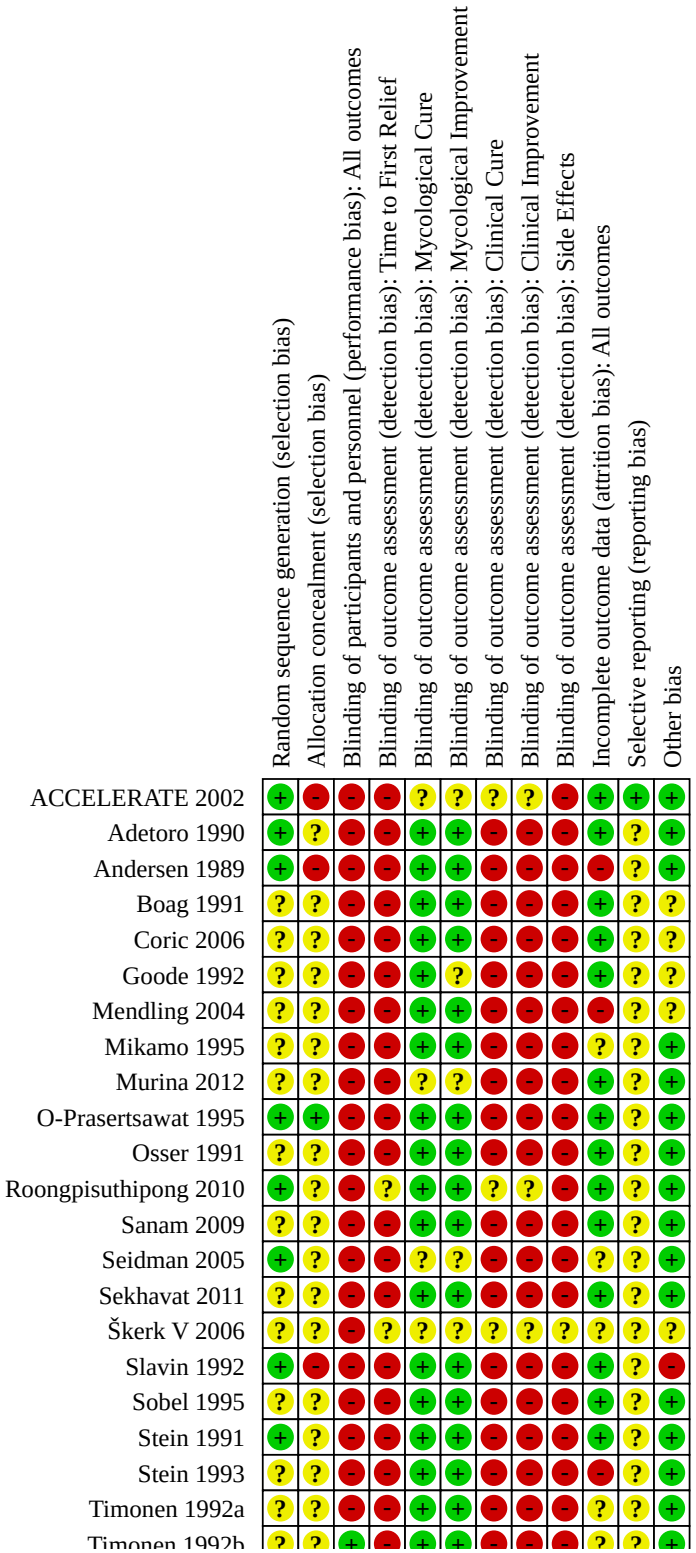


Figure 2. (Continued)

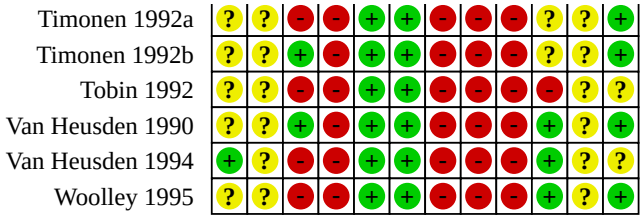
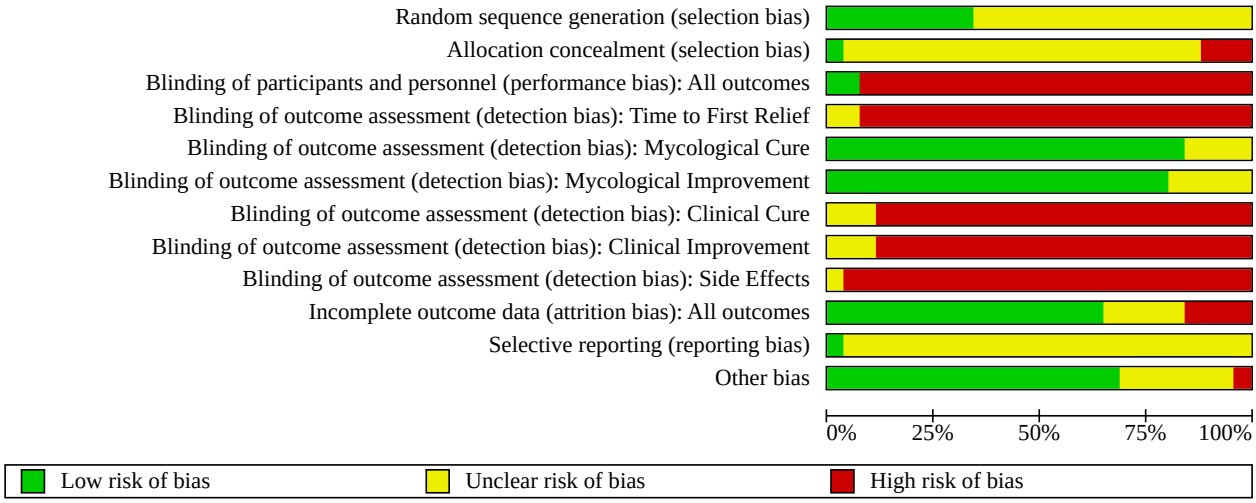


Figure 3. 'Risk of bias' graph: reviewers judgements about each risk of bias domain presented as percentages across all included studies. White spaces in the figure represent outcomes that were not reported/assessed.



Allocation

Random sequence generation was adequately described in nine trials (ACCELERATE 2002; Adetoro 1990; Andersen 1989; O-Prasertsawat 1995; Roongpisuthipong 2010; Seidman 2005; Slavin 1992; Stein 1991; Van Heusden 1994), and allocation concealment was conducted appropriately in one (O-Prasertsawat 1995). Three trials were at high risk for allocation concealment (ACCELERATE 2002; Andersen 1989; Slavin 1992).

Blinding

Blinding of participants was graded as high risk for all trials except Timonen 1992b and Van Heusden 1990, as participants would be aware whether they were getting oral or vaginal interventions. For clinical outcomes, blinding was reported as high risk as the patients could influence the findings by biased reporting. Mycological outcomes were reported as low risk because these were derived from objective tests and not influenced by the patient or assessor. Blinding participants would be difficult unless women receiving active intra-vaginal treatment also received an oral placebo and vice versa, with the latter being more problematic.

Incomplete outcome data

Four trials were at high risk for incomplete outcome data (Andersen 1989; Mendling 2004; Stein 1993; Tobin 1992). In one trial, attrition was greater than 10% at the second follow-up (27 to 62 days) (Andersen 1989). In the second trial, over 25% was lost to follow-up in all groups with no explanation provided, though the intention-to-treat data were reported (Mendling 2004). The third trial lost 36.8% of the total number of participants at the second follow-up at four weeks (Stein 1993). Twenty per cent were lost to follow-up in the fourth trial (Tobin 1992).

Selective reporting

No trials were classified as high risk for selective outcome reporting.

Other potential sources of bias

Eighteen trials had a low risk of other potential sources of bias and seven had an unclear risk. One trial was categorised as high risk due to baseline imbalances and participants' history of infections (Slavin 1992).

Effects of interventions

See: **Summary of findings 1** Oral versus intra-vaginal antifungal treatment of uncomplicated vulvovaginal candidiasis

See: Summary of findings 1 for the main comparison.

1 Oral versus intra-vaginal antifungal treatment of uncomplicated vulvovaginal candidiasis

Clinical cure

Fourteen trials reported this outcome. Short-term clinical cure (five to 15 days) was evaluated in 13 trials (Analysis 1.1); and long-term clinical cure (two to 12 weeks) was evaluated in nine trials (Analysis 1.2). There was little or no difference between oral and intra-vaginal anti-fungals for clinical cure at either time point; short term (0dds ratio (OR) 1.14, 95% confidence interval (CI) 0.91 to 1.43; 13 trials; 1859 participants) and long term (OR 1.07, 95% CI 0.77 to 1.50; 9 trials; 1042 participants). We downgraded the certainty of the evidence for these outcomes to moderate due to serious concern for risk of bias due to lack of blinding of participants and outcome assessors.

The evidence suggests that if the rate of clinical cure at short-term follow-up with intra-vaginal treatment is 77%, the rate with oral treatment would be between 75% and 83%; if the rate of clinical cure at long-term follow-up with intra-vaginal treatment is 84%, the rate with oral treatment would be between 80% and 89%.

There was also little or no difference between interventions for any of the subgroup analyses (see subgroups in the data and analysis tables (Analysis 1.1; Analysis 1.2)

One trial, (ACCELERATE 2002) was not included in the single dose versus single dose analyses because, although the participants in the intra-vaginal group were given a single dose of miconazole, they were also provided with miconazole nitrate (2%) external vulvar cream to be applied up to twice daily to the vulvar area.

Three studies compared a single dose of oral therapy versus six to seven days intra-vaginal therapy on clinical cure. All three studies had data for short-term follow-up, and the meta-analysis indicated single dose oral therapy probably achieves slightly better clinical cure than six to seven days intra-vaginal therapy (OR 1.57, 95% CI 1.03 to 2.42; 427 participants) (Analysis 5.1). Two of these studies had data for long-term follow-up and this effect was not seen in the meta-analysis (OR 0.99, 95% CI 0.54 to 1.83; 266 participants) (Analysis 5.2). No studies compared single-dose oral therapy versus three-day intra-vaginal therapy on clinical cure.

Mycological cure

Twenty trials reported short-term mycological cure (Analysis 1.3) and 15 reported long-term mycological cure (Analysis 1.4). Mycological cure was probably improved with oral anti-fungals compared with intra-vaginal anti-fungals; short-term follow-up (OR 1.24, 95% CI 1.03 to 1.50; 19 trials; 3057 participants) and at long-term follow-up (OR 1.29, 95% CI 1.05 to 1.60, 13 trials; 1661 participants). We downgraded the certainty of the evidence to moderate due to imprecision of the confidence intervals.

The evidence suggests that if the rate of mycological cure at short -term follow-up with intra-vaginal treatment is 80%, the rate with oral treatment would be between 80% and 85%; if the rate of mycological cure at long-term follow-up with intra-vaginal treatment is 66%, the rate with oral treatment would be between 67% and 76%.

We excluded two trials from the meta-analysis. One trial reported long-term mycological response using percentages and we were unable to convert the data to raw numbers (Mendling 2004). We also excluded a second trial due to lack of clarity regarding numbers and definition of cure (Roongpisuthipong 2010).

The clinical significance of this finding is uncertain given that *Candida albicans* is found routinely in asymptomatic women.

One subgroup analysis (Analysis 1.3.5) (derived from one trial) showed a difference with short-term mycological cure favouring itraconazole compared with econazole (OR 3.55, 95% CI 1.29 to 9.77; 75 participants). Two subgroup analyses showed a difference with long-term mycological cure, both of which favoured fluconazole. The first of these analyses (Analysis 1.4.1) comprised seven trials of fluconazole compared with clotrimazole (OR 1.31, 95% CI 1.00 to 1.71; 1015 participants), and the second analysis (Analysis 1.4.4) compared fluconazole with econazole (OR 2.17, 95% CI 1.06 to 4.42; 177 participants).

There was little or no difference between oral and intra-vaginal anti-fungals administered as single-dose treatments on mycological cure (single-dose oral anti-fungal therapy versus single -dose intra-vaginal anti-fungal therapy (Analysis 4.3); single-dose oral therapy versus three-day intra-vaginal therapy (Analysis 3.1, Analysis 3.2); single-dose oral therapy versus six- to seven-day intra-vaginal therapy (Analysis 5.3, Analysis 5.4).

Safety

Withdrawal due to adverse drug effects was used as a measure of anti-fungal safety. Data from 23 trials (4637 participants) were included in the assessment of this outcome, either because they specifically reported on withdrawals due to adverse events, or they reported data which indicated there were either no side effects or minor side effects only (no adverse events). Of these 23 trials, three reported withdrawals (Analysis 1.5). One trial reported that one participant discontinued the miconazole treatment because of a severe burning sensation in the vagina (Timonen 1992a); a second trial reported one withdrawal from fluconazole due to diarrhoea (Stein 1991), and a third trial reported a withdrawal from the miconazole group due to severe vulvovaginal burning (ACCELERATE 2002). No withdrawals due to adverse drug reactions were reported in any other trial. We did not downgrade the certainty of the evidence as we did not have any major concerns for each quality domain. Given that the overall number of withdrawals were low, there was low risk of withdrawal due to adverse drug effects for either treatment.

Side effects

Twenty-two trials (4423 participants) evaluated side effects (ACCELERATE 2002; Adetoro 1990; Andersen 1989; Goode 1992; Mendling 2004; Mikamo 1995; Murina 2012; O-Prasertsawat 1995; , Roongpisuthipong 2010; Sanam 2009; Seidman 2005; Sekhavat 2011; Škerk V 2006; Slavin 1992; Sobel 1995; Stein 1993; Stein 1991; Timonen 1992a;Timonen 1992b; Van Heusden 1990; Van Heusden 1994). We were unable to include six trials in the meta-analysis. Two trials did not provide numerical data about side-effect events, indicating that side effects were minimal (Goode

1992; Roongpisuthipong 2010). A further three trials reported no side effects events for either treatment group, so these trials were not included in the meta-analysis as they did not provide any indication of the direction or magnitude of the relative treatment effect (Mikamo 1995; Škerk V 2006;Slavin 1992). Lastly, Van Heusden 1994 was not included in the estimates because a denominator was unclear.

It is undetermined whether oral treatments reduced the number of side effects compared with intra-vaginal treatments (OR 1.04, 95% CI 0.84 to 1.29; 16 trials; 3155 participants; low-certainty evidence). The evidence suggests that if the rate of side effects with intra-vaginal treatment is 12%, the rate with oral treatment would be between 10% and 15%.

Anti-fungals administered intra-vaginally were more often associated with local reactions (e.g. irritation, "burning", pruritus) than with those administered by the oral route, but systemic effects were also reported (i.e. headache). The oral route of administration was associated with a wide range of systemic effects including gastro-intestinal side effects and headache.

We downgraded the certainty of the evidence to low due to high risk of bias and substantial heterogeneity across and within subgroups. The outcome was self-reported, and trials used different thresholds for side effects, i.e. some reported all adverse events occurring during the evaluation period and some reported only adverse events that were specifically related to the treatment.

Due to the certainty of evidence being low, we are uncertain whether oral treatments reduced the number of side effects compared with intra-vaginal treatments (Analysis 1.6, Analysis 2.5, Analysis 5.5).

Treatment preference

Twelve trials (2206 participants) reported a preference for the route of anti-fungal administration (Adetoro 1990; Andersen 1989; Coric 2006; Osser 1991; Sekhavat 2011; Slavin 1992; Stein 1993; Timonen 1992b; Timonen 1992a; Tobin 1992; Van Heusden 1990; Van Heusden 1994) (Analysis 1.7). These data were poorly reported. Two trials made statements about treatment preference but no quantitative data were presented (Adetoro 1990; Stein 1993). The inconsistencies associated with reporting the preferred route of administration limit the use of these data. Almost all trials that reported patient preference favoured oral treatment (compared with intra-vaginal or no preference), with proportions ranging from 52% of women favouring oral treatment in the trial by Van Heusden (Van Heusden 1994), to 93% in the Timonen trial (Timonen 1992a). The trial by Tobin 1992 provided data on whether participants preferred the study treatment to previous treatments received, with a higher proportion of the oral treatment group responding affirmatively compared to the intra-vaginal treatment group, however it was not reported whether previous treatments were oral or vaginal. We downgraded the certainty of the evidence to low due to the high risk of bias shown in the trials and inconsistencies with reporting the preferred route of administration.

Time to first relief of symptoms

Ten trials (1910 participants) evaluated time to first relief (ACCELERATE 2002; Adetoro 1990; Andersen 1989; Coric 2006, Mendling 2004; Murina 2012; Seidman 2005; Slavin 1992; Timonen 1992a; Tobin 1992). There was little or no difference in time to first relief of symptoms between oral and intra-vaginal treatments. Four trials favoured the oral treatment, four favoured intra-vaginal, one study reported no difference and one was unclear. There was considerable variation in the methods used to derive this outcome and as such, no direct comparisons can be made (Analysis 1.8). There was also variation in the way the data were reported. For example, five trials reported the median time to first relief (ACCELERATE 2002; Andersen 1989; Mendling 2004; Seidman 2005; Slavin 1992), three trials reported the mean time to first relief (Murina 2012; Slavin 1992; Tobin 1992), and four trials reported the proportion of patients reporting initial relief at certain time points (e.g. 12 hours, 24 hours) (ACCELERATE 2002; Coric 2006; Seidman 2005; Timonen 1992a). No specific data were reported for this outcome by Adetoro 1990. We downgraded the certainty of the evidence to low due to high risk of bias for blinding and imprecision due to self-report.

Cost

None of the included trials reported cost or economic data. No trial reported the relative cost-effectiveness of the two modes of treatment (oral and intra-vaginal).

Sensitivity Analyses

Sensitivity analyses are reported in Table 2. Four main outcomes were considered; short- and long-term clinical cure and short- and long-term mycological cure. In all of the analyses for selection bias or blinded outcome assessor, there were either no comparisons or one comparison which made any comparison to the full sample of studies difficult.

In the analyses for incomplete outcome data, there was a sufficient number of studies classified as low risk of bias to compare to the whole sample for the four outcomes. All four of the sensitivity analyses had odds ratios that fell within the confidence intervals of the odds ratios for the same outcome including all the studies, suggesting that the difference between the odds ratio for the sensitivity analyses was similar to the odds ratio for the entire sample.

Other analyses

Publication bias

Based on our searches of trial registers, we did not identify any relevant and completed trials that remained unpublished. Through the database searches, we found one trial that was published as a conference abstract only. This trial looked at secondary outcomes of safety, side effects, and time to first relief (ACCELERATE 2002). We were able to obtain the full details of the trial from the author and the manufacturer. The funnel plots were fairly symmetrical (Figure 4; Figure 5; Figure 6; Figure 7; Figure 8).

Figure 4. Funnel plot of comparison: 1 Oral vs Intra-vaginal, outcome: 1.1 Clinical cure (short term).

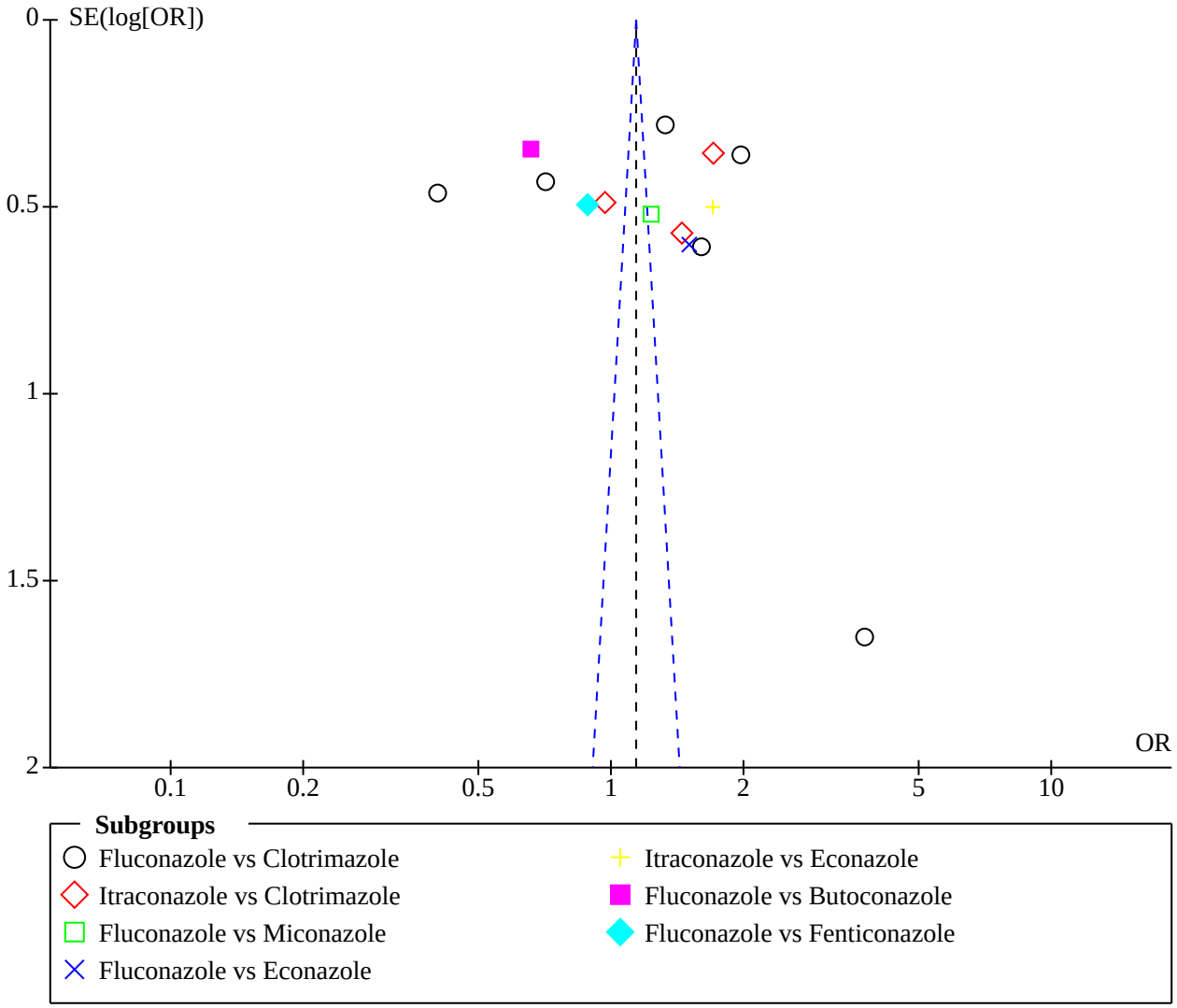


Figure 5. Funnel plot of comparison: 1 Oral vs Intra-vaginal, outcome: 1.2 Clinical cure (long term).

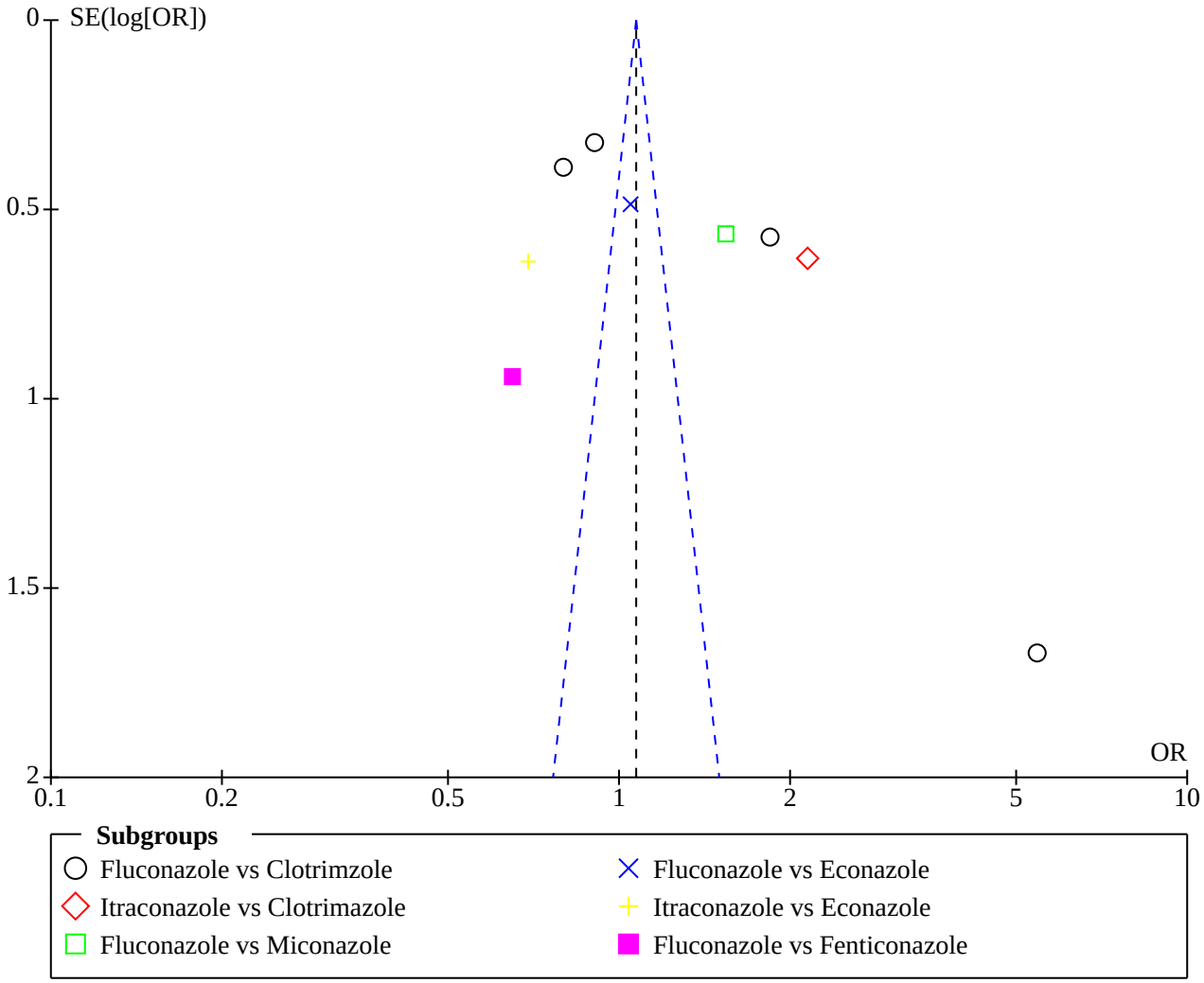


Figure 6. Funnel plot of comparison: 1 Oral vs Intra-vaginal, outcome: 1.3 Mycological cure (short term).

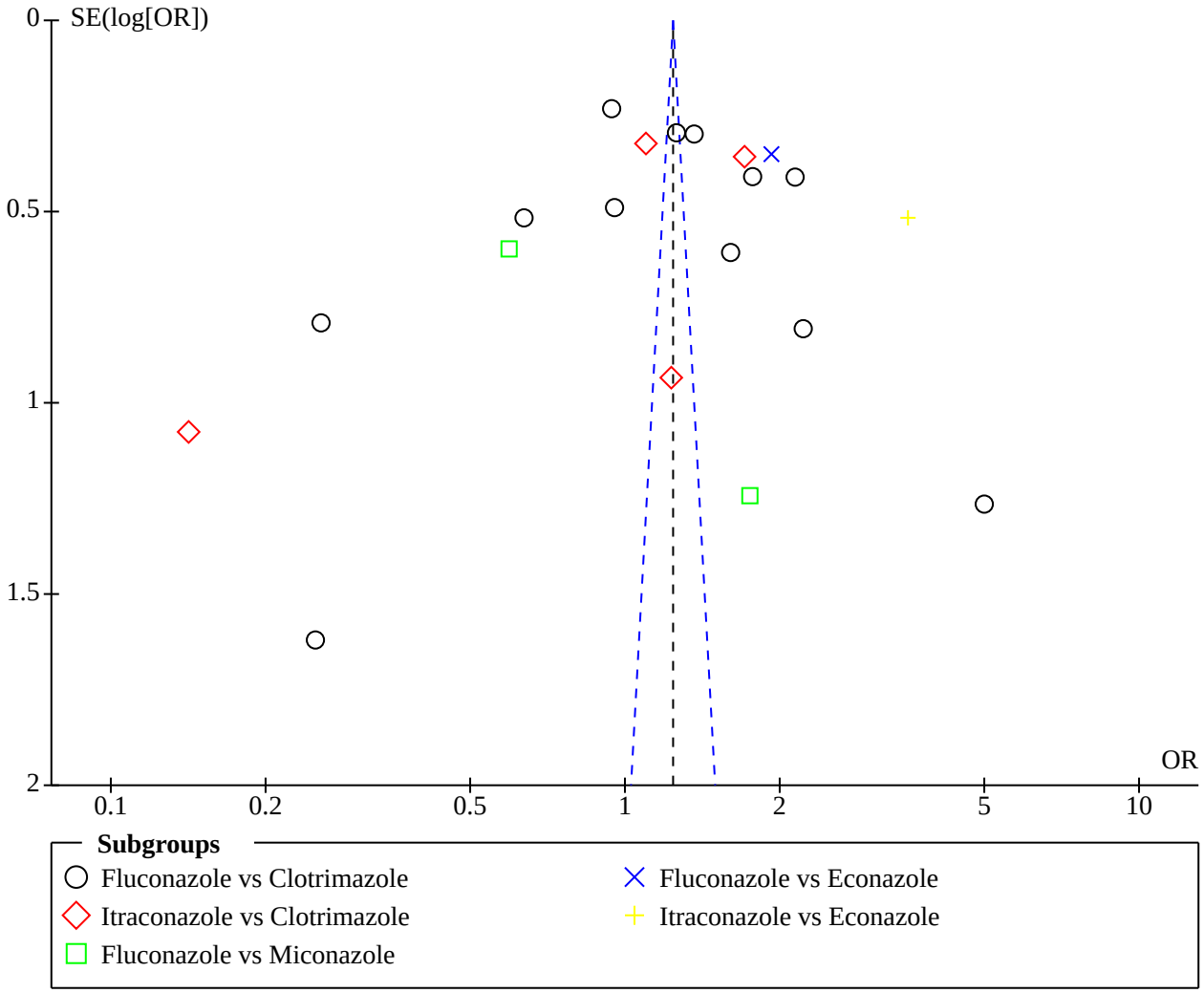


Figure 7. Funnel plot of comparison: 1 Oral vs Intra-vaginal, outcome: 1.4 Mycological cure (long term).

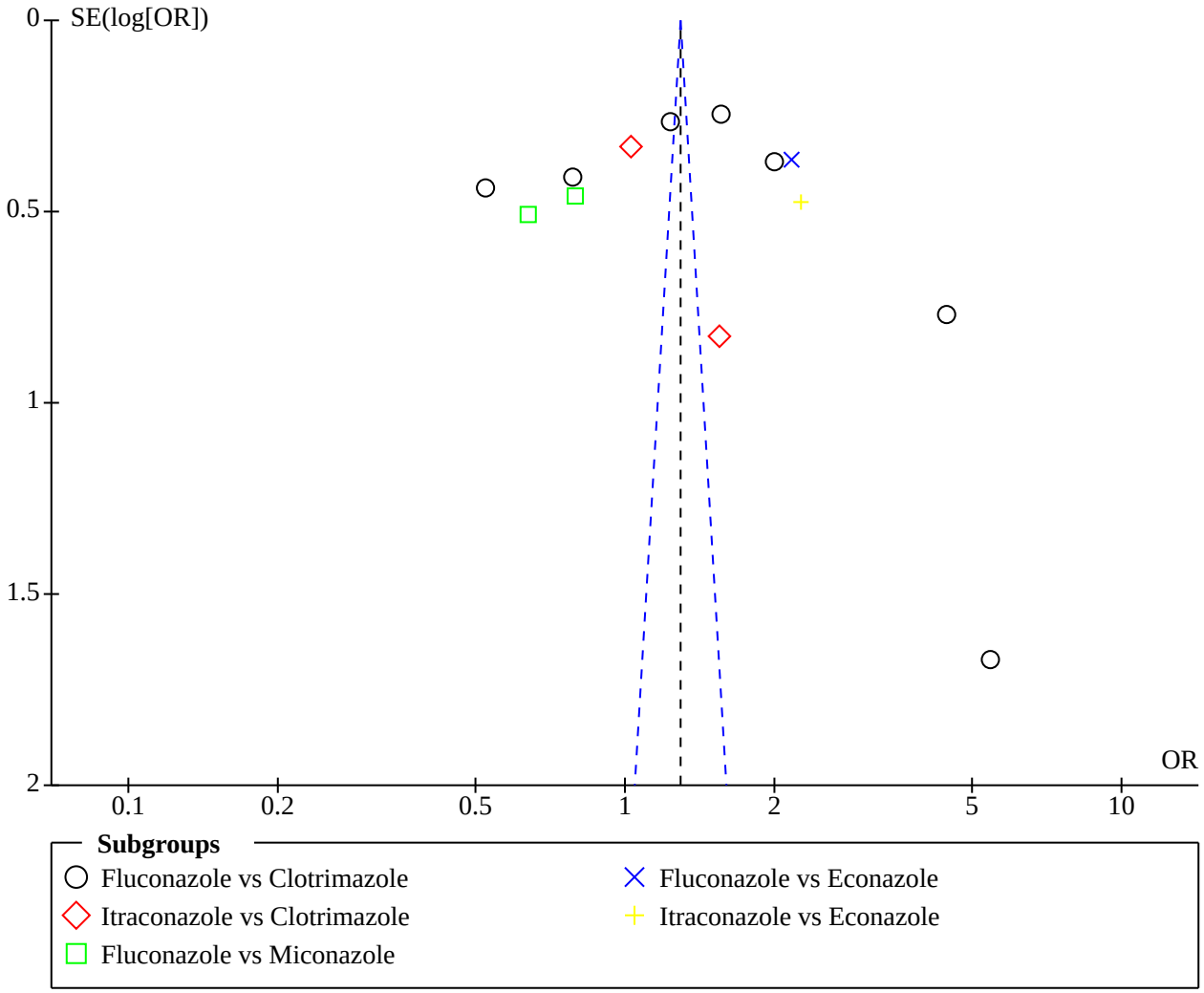
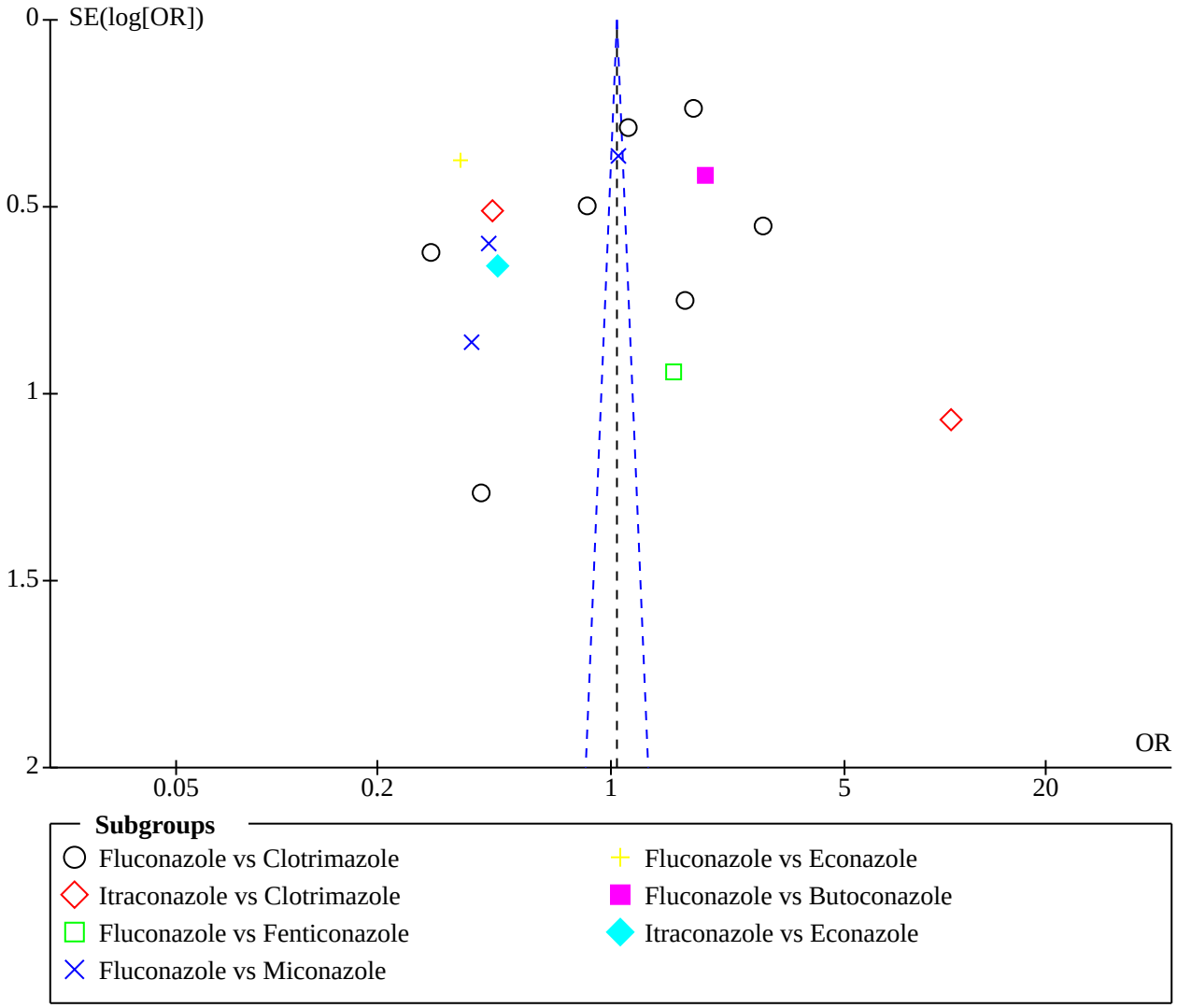


Figure 8. Funnel plot of comparison: 1 Oral vs Intra-vaginal, outcome: 1.6 Side effects.



DISCUSSION

Summary of main results

This review compared the relative effectiveness and safety of oral versus intra-vaginal anti-fungals for the treatment of uncomplicated vulvovaginal candidiasis. We identified 26 trials published between 1989 and 2012 that examined the effectiveness of eight anti-fungals: two oral treatments (fluconazole and itraconazole), and six intra-vaginal treatments (butoconazole, clotrimazole, econazole, miconazole, sertaconazole and terconazole).

There was probably little or no difference between oral and intra-vaginal antifungals for short- and long-term clinical cure. Both routes of administration achieved clinical cure in over 70% of participants. Similar proportions were observed with short-term mycological cure. Our confidence in the evidence is moderate, and this research provides a good indication of the likely effect.

Six trials reported compliance checks. It is possible that non-compliance could have contributed to therapeutic failure (clinical and/or mycological) with some participants.

It is possible that the proportion of women who did not experience clinical cure following anti-fungal therapy (approximately 20% of participants participating in the trials included in this review), had vaginitis due to other causes. Most trials excluded participants with concomitant vaginal infections (e.g. chlamydia, *Trichomonas*). It is possible that some participants may have had an undiagnosed urogenital infection or condition which, in addition to their fungal infection, contributed to their clinical symptoms. Other factors may have influenced unresponsive women's symptoms, including chemical irritants (e.g. perfumed products, detergents) and physical damage (e.g. due to tampons, sexual intercourse).

Oral treatment probably improves mycological cure in the short- and long-term follow-up over intra-vaginal treatment. While our confidence in the evidence is moderate, and this research provides a good indication of the likely effect, the short-term cure rate of

83% and 80% for oral and intra-vaginal preparations, respectively, requires consideration, i.e. what were the causes of therapeutic failure in approximately 20% of women treated? Therapeutic failure may have been due to the presence of fungal species outside the spectrum of the anti-fungals used, or, resistance to specific anti-fungals. The prevalence of non-albicans species has increased rapidly in recent years (Spinillo 1997). Non-albicans *Candida* species are associated with vaginitis but these organisms are more resistant to conventional anti-fungal therapy (Sobel 1993). There is evidence that *C. glabrata* and *C. krusei* are resistant to fluconazole and itraconazole (Rex 2000).

The decrease in mycological cure at long-term follow-up may be explained to some extent by the re-growth of normal *Candida* species as part of the vaginal flora. The higher long-term clinical cure rates support this theory (i.e. the number of women who were mycologically cured decreased between short- and long-term follow-up, however, a corresponding reduction in clinical cure for these time points was not shown). Other factors may contribute to the reduction in mycological cure. Women may have been exposed to risk factors associated with vaginal candidiasis following their entry into a study. Fluctuations in hormone balance (e.g. menstruation, contraceptive use), drug use (e.g. antibiotics, corticosteroids), and changes in hygiene, diet or sexual behaviour, may result in Candidal colonisation (Reed 1992, Sobel 1993, Anonymous 1999). Undiagnosed diabetes may also be a contributory factor to recurrent infection (Anonymous 1999).

There was probably little or no difference between single-dose oral anti-fungal treatment and multiple-dose intra-vaginal regimens. This contrasts with the results of a review of the treatment of vaginal candidiasis in pregnancy that showed multiple dose treatment to be more effective than single-dose anti-fungal therapy (Young 2001).

Withdrawal due to adverse drug effects was used as a measure of anti-fungal safety. There was a low risk of withdrawals due to adverse drug effects for either treatment. Three of 22 studies reported one withdrawal each: two from the intra-vaginal group and one from the oral treatment group. While having few withdrawals appears to demonstrate a low risk, we are not sure which treatment has less risk. The certainty of the evidence was high.

There was little or no difference between treatments in terms of side effects. The certainty of the evidence is low and it is possible that with additional research, the effects could change. Intuitively, the oral administration of any drug, anti-fungal or otherwise, is more likely to be associated with a greater proportion of adverse drug reactions than the intra-vaginal administration of a drug from the same therapeutic category. Furthermore, adverse reactions resulting from anti-fungals given systemically may be more severe or have more serious consequences than those occurring with intra-vaginal administration.

Patient treatment preference for route of anti-fungal administration was assessed as a secondary outcome measure. Data for this outcome were poorly reported and our confidence in the evidence is low. The majority of trials which included this outcome presented percentages of participants who preferred oral treatment and percentages who preferred intra-vaginal treatment, but the denominator was often not reported, and neither were data on whether participants had previous experience of oral and/or intra-vaginal anti-fungal therapy. Despite this shortcoming, the oral route was consistently the preferred route of administration for anti-fungals in trials included in this review. It should be bourne in mind, however, that oral preparations are usually more expensive than intra-vaginal treatments and the systemic side effects associated with oral treatment are likely to be of a more serious nature than intra-vaginal anti-fungals.

We found that there was little or no difference that oral treatments were faster than intra-vaginal treatments for symptom relief (time to first relief) as reported by participants. There was considerable variation in the methods used to derive this outcome and in the way the data were reported. As the certainty of the evidence is low, it is possible that with future research this effect could change.

We were unable to determine the impact of oral versus intra-vaginal treatment on costs. Few data were present in the included trials that could be used in a cost-effectiveness analysis. Generally, oral anti-fungal treatment is more expensive than intra-vaginal therapies. Whether it is the woman or her health system who pays for her anti-fungal treatment will have implications in terms of the difference in costs between the two options for route of administration.

Overall completeness and applicability of evidence

A variety of anti-fungals are available worldwide for the treatment of this infection. In some countries, these drugs can be purchased without a prescription enabling customers to self-medicate. Our search strategies included all the generic names of identifiable anti-fungals that are available world-wide and which are licensed for the treatment of uncomplicated vulvovaginal candidiasis. We identified 26 trials published between 1989 and 2012 that examined the effectiveness of eight anti-fungals (two oral treatments; fluconazole and itraconazole,and six intra-vaginal treatments; butoconazole, clotrimazole, econazole, miconazole, sertaconazole and terconazole). All but three trials included participants with acute vulvovaginal candidiasis. Trials were conducted mainly in high-income countries. The duration of follow-up varied between trials. We were able to identify one unpublished trial through the searches (ACCELERATE 2002). Despite contacting the manufacturers of anti-fungal preparations in the UK for the original review (Nurbhai 2007), we did not locate any others and did not contact manufacturers for this update. We did not limit the search strategies to English language publications, reducing the risk of publication bias (Egger 1997a,Egger 1997b, Moher 1996).

Trials either used a defined range of age limits for their inclusion criteria, were open ended**,** or did not specify the ages of the participants, thus it was difficult to get a clear picture of the full range of ages of the participants from the trials. One trial stated an age range of 15 to 50 years (Roongpisuthipong 2010). While this age range was outside our pre-specified inclusion criteria (16 years or over), we included this trial in our analyses because only eight participants were in the 15 to 19 year age range. Two additional trials included in our analysis had a lower age limit of 15 years old in their age criteria, however the participants were all aged 16 years and over (Adetoro 1990; Osser 1991). Lastly, four trials did not report the age of participants (Boag 1991, Coric 2006, Goode 1992, Mendling 2004), and one only presented median age for participants by trial group (26 years in one treatment group and 25 years in the other) (Murina 2012).

We did not include trials of oral ketoconazole or intra-vaginal ketoconazole in this review due to previous concerns regarding its safety profile. This drug is available in some countries for the treatment of vaginal candidiasis, however, it was not included in this review. The authors of future updates of this review might wish to consider the inclusion of trials of intra-vaginal formulations of ketoconazole.

Quality of the evidence

We identified 26 randomised controlled trials involving 5007 women between the ages of 15 and 65 (where reported). Twenty-three trials included women with acute vulvovaginal candidiasis and three trials included women with chronic vulvovaginal candidiasis. There were eight anti-fungals studied: two oral treatments and six intra-vaginal treatments.

The certainty of the evidence ranged from low to high. The main reason for downgrading was due to serious concern with regards to risk of bias followed by substantial heterogeneity across and within subgroups. There were inconsistencies associated with reporting and we were unable to determine precise effects for some outcomes.

Overall, the risk of bias of the included trials was high. Allocation concealment was poorly reported in all but one trial. Outcome assessment was not blinded in many trials and may have resulted in performance bias in terms of clinical cure. However, all women received active treatment which suggests that this should have been balanced between groups and might not necessarily represent a form of bias unless there was an interaction between treatment preference and treatment received. The denominator could not be calculated for a number of trials because of the poor reporting of data.

Pharmaceutical industry support was reported in 10 trials. It is possible that of the remaining trials, some also had pharmaceutical industry involvement that was not reported. Pharmaceutical sponsorship may be associated with publication bias in randomised trials of drug comparisons (Rochon 1994).

Potential biases in the review process

Using the denominator based upon the number of participants randomised instead of those who were mycologically positive for yeast altered the findings of the review: no statistically significant differences were shown between oral and intra-vaginal treatments when this denominator was used. It should be borne in mind that using the former denominator may overestimate the anti-fungal effect because a proportion of women randomised on the basis of their clinical symptoms will have a negative yeast culture. Using the number of women who had a positive yeast culture as the denominator will underestimate the number of women experiencing clinical cure if recruitment and randomisation has been performed on the basis of these clinical symptoms.

Agreements and disagreements with other studies or reviews

A total of 41 RCTs were included in a recent Bayesian network meta-analysis of the efficacy of anti-fungal medicines for the treatment of vaginal candidiasis (Qin 2018). Seven of the antifungals tested were shown to be more effective than placebo and of these, fluconazole was deemed to be most effective. This study also included studies of ketoconazole as well as non-azole antifungals, and did not restrict comparisons to oral versus intra-vaginal.

AUTHORS' CONCLUSIONS

Implications for practice

There is little or no difference between oral and intra-vaginal anti-fungals in terms of clinical cure. Oral antifungal treatment achieved slightly higher mycological cure rates than intra-vaginal administration of these agents. The decision to prescribe or recommend the purchase of an anti-fungal for oral or intra-vaginal administration should take into consideration: cost, treatment preference, and contraindications.

Unless there is a previous history of adverse reaction to one route of administration or contraindications, women who are purchasing their own treatment should be given full information about the characteristics and costs of treatment to make their own decision. If health services are paying the treatment cost, decision-makers should weigh up the higher cost of oral anti-fungal administration with the marginal gain in mycological cure.

Implications for research

It is questionable whether further trials need to be conducted comparing oral and intra-vaginal anti-fungals. If further trials are conducted, however, they need to incorporate measures of methodological quality specified in this review, robust methods of assessing and reporting treatment preference, and, full health economic assessments of the treatment options under investigation. Further trials need to address outcomes that are useful to the patients for example time to first relief of symptoms (Seidman 2005), adverse events and patient preferences.

Adequate methods of allocation concealment should be used to avoid bias (Schulz 1995).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACCELERATE 2002

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: 91.3% completed study, 82.9% included in efficacy evaluable sample
Participants	Age: 18 years or older Country: USA Setting: 24 centres (Obstetic/Gyncology OPD) Diagnosis: vulvovaginal candidiasis by positive 10% potassium hydroxide wet preparation Characteristics: non-pregnant, non-nursing, with negative wet mount for trichomonas and clue cells and total vulvovaginal signs/symptoms score of 4 or more. Enrolled: 310 (305 evaluable)
Interventions	Group 1: fluconazole oral 150 mg (single dose (n = 150); Group 2: miconazole nitrate, 1200 mg vaginal suppository plus external vulvar 2% cream (Monistat© combination pack) single dose (n = 160) Duration: 11 April to 23 October 2002
Outcomes	Assessed at: 2, 4, 6, 12, 16, 24, 36, 48, 60, and 72 hours following first administration of the MONISTAT External Cream and/or OVULE Insert, or ingestion of the oral tablet. Follow-up: posttherapy telephone contact approximately seven to 10 days following. **Efficacy**

ACCELERATE 2002 *(Continued)*

	Mycological cure: not reported Mycological improvement: not reported Clinical cure: not reported Safety: reported Quote:"one subject (04506) was withdrawn for a clinically significant adverse event". Side effects: reported Drug 1: 17 (11.4%) participants reported at least one treatment-emergent adverse event during the study Drug 2: 17 (10.9%) participants reported at least one treatment-emergent adverse event during the study Treatment preference: not assessed Time to first relief: reported. Time to first relief: (itching, burning, irritation) self-report using diary/worksheet. Based on change in total symptom scores. Primary efficacy parameter was to be the first recorded time of symptom relief, defined as the length of time between the first dose of study drug and the time first relief was noted OR the length of time between the first dose of study drug and the time first relief was noted on the diary. The time to overall symptom relief was to be based on the maximum time to relief of any of the symptoms of itching, burning, or irritation. Other: change in symptom score from baseline, consumer satisfaction (Consumer Satisfaction Questionnaire) adverse events (stated - preferred form of therapy) Costs: not assessed
Notes	Compliance check: yes. At the Posttherapy Telephone Contacts (seven to 10 days following the first dose of study medication), the use of the study medication was confirmed. A total of 303 (99.3%)participants in the safety population were considered compliant Pharmaceutical industry support: study sponsored by Personal Products Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization sequence provided by Personal Products Company (PPC)" Quote: "Eligible subjects were to be equally randomized in strict sequential order to one of two treatment regimens according to a randomization schedule generated by PPC. There was no blinding in this study."
Allocation concealment (selection bias)	High risk	No description of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "There was no blinding in this study"
Blinding of outcome assessment (detection bias)	High risk	Quote: "There was no blinding in this study". Patient self-report.

ACCELERATE 2002 *(Continued)*

Time to First Relief		
Blinding of outcome assessment (detection bias) Mycological Cure	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Mycological Improvement	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Clinical Cure	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Clinical Improvement	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Side Effects	High risk	Quote: "There was no blinding in this study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% lost to follow-up and close in both groups.
Selective reporting (reporting bias)	Low risk	Protocol available, see section 7.2 in protocol, page 111.
Other bias	Low risk	None identified, no baseline imbalance.

Adetoro 1990

Study characteristics	
Methods	Study design: randomised trial Follow-up: 100%
Participants	Age: 17-30 years old Country: Africa/Nigeria Setting: Gynaecological and "special treatment" clinics at the University of Ilorin Teaching Hospital Diagnosis: mycological culture, positive microscopic smear and clinical symptoms. Characteristics: non-lactating Enrolled: 43
Interventions	Group 1: fluconazole (oral) 15 0mg single dose (n = 23) Group 2: clotrimazole 500 mg vaginal tablet single dose (n = 20) Duration: May 1, 1989 to October 31, 1989
Outcomes	Assessed at 8 and 32 days. **Efficacy** Mycological cure: negative culture and negative microscopy Clinical Improvement: cure or, persistence of *C. albicans* and absence of symptoms.

Adetoro 1990 *(Continued)*

	Safety: no withdrawals due to side effects reported Side effects: number of side effects reported. Treatment preference: reported Time to first relief: assessed, but no specific data reported Costs: not assessed
Notes	Compliance checks: not specified Pharmaceutical industry support: yes: Pfizer Products Limited The results do not distinguish between clinical and mycological cure Actual participant numbers not presented for mycological outcome - only percentage values given. This trial had a lower age limit of 15 years old in their age criteria, however the participants were all aged 16 years and over.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined randomisation code, probably random.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, all participants completed study.

Adetoro 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration described.
Other bias	Low risk	None identified, no baseline imbalance.

Andersen 1989

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: 82.7%
Participants	Age: > 18 Country: Europe (Denmark, Finland, France, Germany, Norway, the Netherlands) Setting: not specified (16 centres in various European countries) Diagnosis: mycological culture and microscopy Characteristics: non-lactating Enrolled: 372 enrolled: 369 randomised
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 188) Group 2: clotrimazole 200 mg vaginal tablets for 3 days. (n = 181) Duration: not specified
Outcomes	Assessed at 5 -16 days and 27-62 days. **Efficacy** Clinical improvement: response/relief from symptoms and elimination of signs of vaginal infection.Quote: "Favourable" clinical response if cured or improved. Mycological cure: eradication of Candida (negative culture and microscopy) Safety: no withdrawals due to side effects reported Side effects: participant reported side effects. Treatment preference: reported for one study centre. Time to first relief: reported - median time to first relief Costs: not assessed
Notes	Compliance checks: not specified Pharmaceutical industry support: yes - Pfizer Central Research, Sandwich, England % follow-up calculated based on number randomised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, probably random.
Allocation concealment (selection bias)	High risk	No description but high risk due to block size of four.
Blinding of participants and personnel (performance bias)	High risk	Not possible, given nature of intervention.

Andersen 1989 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible given nature of intervention and symptoms.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Greater than 10% without data (13 one group, 17 in other) with no reason given.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	None identified, no baseline imbalance.

Boag 1991

Study characteristics	
Methods	Study design: randomised trial Follow-up: 90.9%
Participants	Age: not specified Country: UK Setting: Genito-urinary medicine clinic (London) Diagnosis: mycological culture and clinical symptoms Characteristics: non-lactating Enrolled: 23 (22 evaluable)
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 11) Group 2: clotrimazole 500 mg pessary (single dose) (n = 11) Duration: not specified
Outcomes	Assessed at 2, 4, 6 and 10 days after treatment. **Efficacy**

Boag 1991 *(Continued)*

	Mycological cure: no yeasts isolated Clinical cure: not assessed Safety: not assessed Side effects: not assessed Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: done E (nurse-administered) all 22 (100%) patients were compliant with treatment. Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one of 23 patients lost to follow-up.

Boag 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Unclear risk	Baseline data not reported.

Coric 2006

Study characteristics	
Methods	Study design: randomised trial Follow-up: 100%
Participants	Age: not specified Pregnancy status: not specified Country: Croatia Ethnicity: unspecified Setting: O&G OPD, University of Zagreb Diagnosis: mycological Enrolled: 119
Interventions	Group 1: fluconazole (oral) (n = 60) 150 mg single dose Group 2: clotrimazole vaginal tablet 200 mg once daily for 3 days (n = 59) Duration: September 2004 to July 2005
Outcomes	Assessed at 24 hours and 14 days **Efficacy** Mycologocal cure: negative culture Clinical cure: complete relief of symptoms. Safety: not assessed Side effects: not assessed Treatment preference: reported (oral) Time to first relief: reported - onset of symptomatic relief in the first 24 hours of treatment Costs: not assessed
Notes	Compliance: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Coric 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and subjective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had outcome measures
Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Unclear risk	None identified, but unable to assess baseline imbalance

Goode 1992

Study characteristics	
Methods	Study design: randomised trial Follow-up: 42.9% (16 of 28 participants were excluded due to negative culture at baseline. All remaining participants were followed up.)
Participants	Age: not specified Country: USA Setting: not specified Diagnosis: mycological culture

Goode 1992 *(Continued)*

	Characteristics: not specified Enrolled: n = 28 (12 evaluable)
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 14) Group 2: clotrimazole vaginal tablets 100 mg for 7 days.(n = 14) Duration: seven days (not otherwise specified)
Outcomes	Assessed at 2 and 4 weeks. **Efficacy** Clinical cure - complete relief of symptoms Mycological cure - quote: "mycological efficacy" Safety: no withdrawals reported Side effects: specific data not reported Treatment preference: not assessed/reported Time to first relief: not assessed Costs: not assessed
Notes	Compliance checks: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified.
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Unclear risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias)	High risk	Not possible to avoid risk given nature of intervention, and self-report.

Goode 1992 *(Continued)*
Clinical Improvement

Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High number of dropouts but justified in text.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Possible baseline imbalance, unclear of impact.

Mendling 2004

Study characteristics	
Methods	Study design: randomised trial Follow-up: 472 out of 679 (69.5%) participants were included in the per-protocol population. Reasons for the exclusions were not provided.
Participants	Age: not specified Country: Germany Setting: not specified outpatient multi-centre Diagnosis: visual examination, KOH, mycological culture Characteristics: not specified Enrolled: 679 (472 evaluable)
Interventions	Group 1: clotrimazole 500 mg vaginal tablet single dose n = 226 Group 2: clotrimazole 10% vaginal cream in a single dose applicator n = 226 Group 3: fluconazole (oral) 15 0mg single dose n = 227 Duration: not specified
Outcomes	Assessed at 2, 4 and 8 weeks **Efficacy** Mycological cure: mycological culture results Clinical cure: unclearly reported Safety: no withdrawals due to side effects reported Side effects: reported Treatment preference: not assessed Time to first relief: reported - median time to onset of meaningful symptom relief Costs: not assessed
Notes	Compliance checks: not specified Pharmaceutical industry support: not specified
Risk of bias	

Mendling 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Over 25% lost to follow-up in all groups with no explanation. However, ITT data also reported.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Unclear risk	No baseline data presented.

Mikamo 1995

Study characteristics	
Methods	Study design: randomised trial Follow-up: no description of number of participants lost to follow-up
Participants	Age: 18-54 Country: Japan Setting: O&G OPD (single centre)

Mikamo 1995 *(Continued)*

	Diagnosis: mycological culture Characteristics: non-pregnant and non-lactating Enrolled: 150
Interventions	Group 1: fluconazole (oral) 150 mg single dose (N = 50) Group 2: clotrimazole (vaginal) 100 mg for 6 days. (N = 50) Group 3: fluconazole (oral) 50 mg daily for 6 days (n = 50 women)
Outcomes	Assessed at 5-15 days and 30-60 days. **Efficacy** Clinical cure - complete disappearance of presenting signs and symptoms Mycological cure: negative culture and microscopy for Candida species Safety: no withdrawals due to adverse drug reaction. Side effects: quote: "No adverse drug effects were noted" Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance checks: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias)	High risk	Not possible to avoid risk given nature of intervention, and self-report.

Mikamo 1995 *(Continued)*
Clinical Improvement

Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description of number of participants lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Baseline data shows that age varies by 5 years, minimal difference in weight.

Murina 2012

Study characteristics	
Methods	Study design: randomised trial Follow-up: 100%
Participants	Age: median of 26 years in the oral treatment group and 25 years in the intra-vaginal treatment group Country: Italy Setting: not specified Diagnosis: lab test, reported symptoms Characteristic: non-pregnant Enrolled: 80
Interventions	Group 1; fluconazole oral 150 mg repeat dose (N = 40) Group 2: fenticonazole (intra-vaginal) 600 mg (N = 40) repeat dose on day 3 Duration: not specified
Outcomes	Assessed at day 7 and 30 +/- 5 days **Efficacy** Mycological cure: bot assessed Clinical cure: responders Safety: Reported - quote: “no patient belonging to the two groups had to suspend treatment due to the presence of severe side effects.” Side effects: reported - quote: "Three women reported transient nausea after taking fluconazole, while two patients showed burning sensation short vaginal discharge after insertion vaginal fenticonazole." Treatment preference: not assessed Time to first relief: reported mean time to first relief of vulvovaginal pruritus Costs: not assessed

Murina 2012 *(Continued)*

Notes	Compliance checks: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Mycological Improvement	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had outcome measures.
Selective reporting (reporting bias)	Unclear risk	No culture data. No protocol described.
Other bias	Low risk	None identified, no baseline imbalance.

O-Prasertsawat 1995

Study characteristics

Methods	Study design: randomised trial

O-Prasertsawat 1995 *(Continued)*

	Follow-up: 95.1%
Participants	Age: 25-43 years Country: Thailand (Bangkok) Setting: Hospital obstetrics and gynaecology out-patient department (single centre) Diagnosis: visual examination, mycological culture and clinical symptoms Enrolled: 110 (103 evaluable)
Interventions	Group 1: fluconazole (oral)150 mg single dose (n = 53) Group 2: clotrimazole vaginal tablets 200 mg for 3 days. (n = 50) Duration: June 1, 1993 to September 30. 1993
Outcomes	Assessed at 1 and 4 weeks. **Efficacy** Clinical cure: not reported Mycological cure - failure to grow Candida species. Safety: no withdrawals due to side effects reported Side effects: reported side effects (nausea. dizziness, vaginal burning) Treatment preference: not reported Time to first relief: not assessed Costs:not assessed
Notes	Compliance Check: yes - participant questioned regarding use of anti-fungal drugs. No other data reported. Pharmaceutical industry support: not specified The denominator for each outcome was based upon the number randomised as the authors did not indicate at what stage the patient withdrawals from the study occurred.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each patient chose one of two identical boxes, investigator not aware of which treatment patient chose.
Allocation concealment (selection bias)	Low risk	Each patient chose one of two identical boxes, investigator not aware of which treatment patient chose.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.

O-Prasertsawat 1995 *(Continued)*

Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Low risk	Only age comparison provided.

Osser 1991

Study characteristics	
Methods	Study design: randomised trial Follow-up: 91.1%
Participants	Age: 16-60 years old Country: Sweden Setting: multi-centre O&G OPD Diagnosis: Visual examination, KOH, mycological culture, clinical symptoms. Characteristics: Non-pregnant Enrolled: 258 (235 evaluable)
Interventions	Group 1: Econazole 150mg vaginal depot tablet, single dose. (n = 130) (114 evaluable) Group 2: Fluconazole (oral) 150mg single dose. (n = 128) (121 evaluable) Duration: August 1989 to February 1990
Outcomes	Measured at 7-10 days, 28-35 days and 80-100 days. **Efficacy** Mycological cure - mycological culture - absence of yeast fungi Clinical cure. - absence of symptoms Safety: no withdrawals due to side effects reported Side effects: participant reported side effects (gastro-intestinal symptoms, introital burning, vaginal discharge) Treatment preference:reported

Osser 1991 *(Continued)*

	Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: yes - questioning at 7-10 day follow-up. 235 participants (100%) were compliant with treatment. Pharmaceutical industry support: yes - Pfizer AB 19 fluconazole and 14 econazole participants had experienced at least 3 episodes of VVC in the previous 12 months. This trial had a lower age limit of 15 years old in their age criteria, however the participants were all aged 16 years and over.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small percentage of dropout < 10%.
Selective reporting (reporting bias)	Unclear risk	No protocol described.

Osser 1991 *(Continued)*

Other bias	Low risk	Baseline data comparable.

Roongpisuthipong 2010

Study characteristics	
Methods	Study design: randomised trial Follow-up: 94.1%
Participants	Age: 15-50 years old Country: Thailand (Bangkok) Setting: single centre Hospital O&G OPD Diagnosis: mycologic, KOH Characteristics: non pregnant Enrolled: 188 (177 evaluable)
Interventions	Group 1: fluconazole 150mg (oral), single dose (n = 67) Group 2: Other - Sertaconozole 500 mg (intra-vaginal), single dose (n = 66) Group 3: clotrimazole 100 mg, (intra-vaginal), single dose once a day for six consecutive days (n = 55) Duration: August 31, 2004 to January 30, 2006
Outcomes	Accessed at 1 week and 4 weeks **Efficacy** Mycological cure - no yeast growth Clinical cure - not assessed Safety: no withdrawals due to adverse events reported Side effects: quote: "Results showed minimal side effect without adverse event" Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: not specified Pharmaceutical industry support: yes - Pacific Healthcare (Thailand) Co., Ltd This study was included despite the lower age limit being less than the inclusion criteria for this review (16 years) because only 8/188 participants were in the 15-19 year age range in this trial.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Roongpisuthipong 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer randomised does not indicate random order, but likely random.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Clinical Improvement	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 total lost to follow-up, evenly distributed. Reasons for lost to follow-up were not presented. Less than 10% overall.
Selective reporting (reporting bias)	Unclear risk	No clinical outcome events reported.
Other bias	Low risk	Groups roughly comparable. Not sure about funding, but possible funding influence showing in other criteria.

Sanam 2009

Study characteristics	
Methods	Study design: randomised trial Follow-up: 7 from the itraconazole group and 5 from the clotrimazole group were excluded because they were not referred for examination and culture in 10 days after treatment (< 10%).
Participants	Age: mean 28.1 ±4.8 (itraconazole group) and 28 ±5.8 (clotrimazole group)

Sanam 2009 *(Continued)*

	Country: Iran Setting: single centre O&G OPD Gynecological outpatient clinic of the University Hospital Amir, Semnan Diagnosis: mycologic, KOH, visual examination Characteristics: non-pregnant Enrolled: 264 (252 evaluable)
Interventions	Group 1: itraconazole (oral) 400 mg two divided dose in a day (n = 132) Group 2: 1% clotrimazole (intra-vaginal) 5 g daily for 6 days (n = 132) Duration: 1st of June 2006 and 31st of June 2007.
Outcomes	Accessed at day 10 **Efficacy** Mycological cure: complete eradication Clinical cure: no clinical signs and symptoms Safety: no withdrawals due to side effects reported Side effects: reported (frequency of micturition, dyspareunia) Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention..
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.

Sanam 2009 *(Continued)*

Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 lost to follow-up (7 and 5) which is < 10% and comparable in both groups.
Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Low risk	Only age provided as a baseline characteristic.

Seidman 2005

Study characteristics	
Methods	Study design: randomised trial Follow-up: unclear
Participants	Age: 18 years and over Country: USA Setting: multi-centre; 13 Research facilities (not specified type) across the USA) Diagnosis: visual examination, KOH, patient report of signs and symptoms, severity score Characteristics: non-pregnant Enrolled: 181
Interventions	Group 1: butoconazole 5 g vaginal cream (2% site release) single dose (n = 93) Group 2: fluconazole (oral) 150 mg single dose (n = 88) Duration: May to November 2003
Outcomes	Assessed hourly by patient report **Efficacy** Clinical cure: time to total relief of symptoms (measured in hours) Mycological cure: not assessed Safety: no withdrawals due to adverse events reported Side effects: participant reported a range of adverse events (drug and non drug related) Treatment preference: not assessed

Seidman 2005 *(Continued)*

	Time to first relief: reported - median time to first relief (measured in hours) and proportion of patients reporting first relief at 12 and 24 hours post-treatment Costs: not assessed
Notes	Compliance checks: yes - administered in investigator's office; 100% compliance. Pharmaceutical industry support: not specified Patients were provided with a diary and requested to record the date and time they first started to feel relief of symptoms and the date and time they had complete relief of symptoms. Outcomes were calculated using the dosing time and the time reported for each by the patient

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Mycological Improvement	Unclear risk	Outcome not assessed
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described.
Selective reporting (reporting bias)	Unclear risk	No culture data.
Other bias	Low risk	No baseline differences.

Sekhavat 2011

Study characteristics	
Methods	Study design: randomised trial Follow-up: 91.0%
Participants	Age: over 15 years of age Country: Iran Setting: single centre O&G OPD at the University Shahid Sadoughi hospital in Yazd, Iran Diagnosis: mycological, clinical symptoms Characteristics: non-pregnant Enrolled: 156 (142 evaluable)
Interventions	Group1: fluconazole (oral) 150 mg, single dose (n = 72) Group2: clotrimazole (intra-vaginal) 200 mg for 7 days (n = 70) Duration: July 2006 and May 2008
Outcomes	Accessed at 7 days and 1 month **Efficacy** Mycological cure - mycological absence of yeast Clinical cure - absence of signs and symptoms Safety: no withdrawals due to side effects reported Side effects: reported Treatment preference: reported (oral) Time to first relief: not assessed Costs: not assessed
Notes	Compliance: Not specified Pharmaceutical industry support: Not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.

Sekhavat 2011 *(Continued)*

Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 lost to follow-up, unclear which group they were part of, but less than10%.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	None identified, no baseline imbalance.

Slavin 1992

Study characteristics	
Methods	Study design; randomised trial Follow-up: 95.4%
Participants	Age: 18-60 years Country: USA Setting: Obstetrics and gynaecology out-patient department Diagnsosis: microscopic evidence of hyphae from wet mount with gram stain Characteristics: non-lactating. Enrolled: 23 (22 evaluable)
Interventions	Group 1: fluconazole (oral) 200 mg single dose (n = 12) Group 2: terconazole 80 mg intra-vaginal suppository daily for 3 days. (n = 10) Duration: November 1990 through February 1991
Outcomes	Assessed at 7-14 days and 28-34 days. **Efficacy** Mycological cure - negative gram stain and wet mount. Clinical Improvement - favourable clinical response (mycologic cure or improved symptoms.

Slavin 1992 *(Continued)*

	Safety: quote: "No adverse drug events were noted" Side effects: quote: "No adverse drug events were noted" Treatment preference: reported (oral) Time to first relief: reported - median and mean time to first relief Costs: not assessed
Notes	Compliance check: yes - participant questioned at 7-14 day follow-up visit). Assessment of "medication-counts" at the early evaluation was considered 100% compliant. Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	High risk	Not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol described

Slavin 1992 *(Continued)*

Other bias	High risk	Baseline data imbalances reported

Sobel 1995

Study characteristics	
Methods	Study design: randomised trial Follow-up: 93.8%
Participants	Age: 17- 64 years Country: USA Setting: multi-centre (12 centres across the USA); type of setting not specified Diagnosis: KOH, mycological culture and clinical symptoms. Characteristics: non-lactating Enrolled: 429 (358 evaluable)
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 218) Group 2: clotrimazole vaginal tablets (one tablet, strength not stated) for 7 days (n = 214) Duration: not specified
Outcomes	Assessed at 14 and 35 days. **Efficacy** Mycological cure - no mycological colonisation Clinical cure - absence of signs and symptoms of vaginitis. Safety: no patient discontinued therapy Side effects: participant reported side effects Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: done - participant history and pill count. Quote: "No patient discontinued therapy"; 100% compliance. Pharmaceutical industry support: yes Participants had acute or recurrent vaginal candidiasis. Only the results for acute cases are presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.

Sobel 1995 *(Continued)*

Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% dropout, roughly equal in both groups
Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Low risk	Baseline data comparable.

Stein 1991

Study characteristics	
Methods	Study design: randomised trial Follow-up: 93.0%
Participants	Age: 18-65 years Country: USA Setting: multi-centre; Primary Care Clinics Diagnosis: visual examination, KOH and mycological culture Enrolled: 227 (214 evaluable)
Interventions	Group 1: fluconazole (oral) 50 mg for 3 days (n = 111) Group 2: clotrimazole intra-vaginal tablets 200 mg for 3 days. (n = 116) Duration: not specified
Outcomes	Assessed at 7-10 days and 30-35 days. **Efficacy** Mycological cure - absence of candida species Clinical cure - complete resolution of signs and symptoms

Stein 1991 *(Continued)*

	Safety: reported - quote: "One patient discontinued treatment after she developed diarrhea while receiving fluconazole" Side effects: participant reported side effects Treatment preference: not reported. Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: not specified Pharmaceutical industry support: yes - Pfizer Central Research, Groton,CT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined code, likely random
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five of 95 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Groups comparable at baseline.

Stein 1993

Study characteristics	
Methods	Study design: randomised trial (three arm) Follow-up: 94.7% follow-up at first evaluation time point and 63.2% follow-up at second evaluation time point
Participants	Age: 18 years and over Country: USA Setting: not specified Diagnosis: KOH and clinical symptoms and mycological culture. Enrolled: 95 (90 evaluable)
Interventions	Group 1: itraconazole (oral) 200 mg for 3 days (n = 50 Group 2: clotrimazole vaginal tablets 200 mg for 3 days (n = 23) Group 3: placebo: n = 22 Duration: not specified
Outcomes	Assessed at 1 and 4 weeks. **Efficacy** Mycological cure - absence of Candida species Clinical cure - complete resolution of signs and symptoms Safety: quote: "No patients enrolled in this study discontinued treatment because of an adverse event" Side effects: reported Treatment preference: reported. Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: not reported Pharmaceutical industry support: yes - Research Foundation, Piscataway, N.J.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.

Stein 1993 *(Continued)*

Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 60/95 or 63.2% of participants were assessed at four week follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Baseline data comparable.

Timonen 1992a

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: not calculable
Participants	Age: 18 years and over Country: Finland Setting: non-specified multi-centre setting - possibly gynaecologist/physician office/practice Diagnosis: mycological culture and clinical symptoms Enrolled: 125 (63 fluconazole and 62 miconazole) 20 patients were negative for yeast culture after randomisation and removed) 105 evaluable
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 56) Group 2: miconazole 400 mg pessary for 3 days (n = 49) Duration: not specified
Outcomes	Assessed at 1 week and 1 month **Efficacy** Mycologicalcure - negative yeast culture Clinical cure - asymptomatic Safety: quote: "One patient discontinued the treatment because of a severe burning sensation in the vagina" - miconazole group

Timonen 1992a *(Continued)*

	Side effects: reported Treatment preference: reported Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: not reported Pharmaceutical industry support: not reported Results calculated from percentages quoted by authors. Five itraconazole and eight econazole participants had chronic vaginal candidiasis (i.e. 3 or more episodes in previous 12 months) - results not reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not calculable.

Timonen 1992a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Groups comparable at baseline.

Timonen 1992b

Study characteristics	
Methods	Study design: randomised trial Follow-up: not calculable
Participants	Age: 20 to 58 years Country: Finland Setting: multi-centre; three outpatient sites (not specified) Diagnosis: mycological culture Enrolled: 81
Interventions	Group 1: itraconazole 200 mg for 3 days. (n = 40) Group 2: econazole 150 mg for 3 days. (n = 41) Duration: Two years (not specified)
Outcomes	Assessed at 1 and 2 weeks **Efficacy** Mycological cure - negative gram stain and wet mount. Clinical Improvement - favourable clinical response (mycologic cure or improved symptoms. Safety: quote: "None of the patients discontinued treatment because of an adverse event" Side effects: reported Treatment preference: reported Time to first relief: reported - proportion of patients reporting alleviation of symptoms each day post-treatment Costs: not assessed
Notes	Compliance check: not reported Pharmaceutical industry support: yes - Orion Pharmaceutica, Espoo, Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial (double-dummy).

Timonen 1992b *(Continued)*

Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Self-report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not calculable.
Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Low risk	Baseline data was comparable.

Tobin 1992

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: 68.7%
Participants	Age: 18 years and over Country: UK Setting: Genito-urinary medicine clinics in 17 hospitals across UK Diagnosis: visual examination, mycological culture and clinical symptoms (vulvitis, vaginitis). Enrolled: 262 (214 evaluable)
Interventions	Group 1: itraconazole 200 mg two times a day for one day (n = 109) Group 2: clotrimazole 500 mg - Single dose (n = 105) Duration: not specified
Outcomes	Assessed at 5-10 days and 30-40 days: **Efficacy** Clinical cure: not assessed

Tobin 1992 *(Continued)*

	Mycological cure: negative culture for Candida species. Safety: no withdrawals due to adverse events Side effects: not reported Treatment preference: reported Time to first relief: reported - mean time to first relief Costs: not reported
Notes	Compliance Check: not reported Pharmaceutical industry support: yes - Janssen Pharmaceutical Limited, Oxford, UK Participants permitted to use quote: "bland soothing agent" and to record use in diary.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided
Allocation concealment (selection bias)	Unclear risk	No description provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Twenty per cent lost to follow-up.

Tobin 1992 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol described
Other bias	Unclear risk	Baseline data not reported.

Van Heusden 1990

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: 93.9%
Participants	Age: 18-60 years Country: the Netherlands Setting: Out-patients - multi-centre department or centres not specified Diagnosis: mycological culture and clinical symptoms Characteristics: non-lactating Enrolled: 99 (93 evaluable)
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 49) Group 2: Miconazole 1200mg intra-vaginal single dose (n = 50) Duration: Not specified
Outcomes	Assessed at 6-10 days (short-term) and 22-60 days (long-term) follow-up. **Efficacy** Mycological cure - complete absence of Candida species at follow-up. Clinical cure - physician subjective global assessment. Safety: no withdrawals due to side effects reported Side effects: participant reported side effects. Treatment preference: reported Time to first relief: not assessed Costs: not reported
Notes	Compliance check: not reported Pharmaceutical industry support: not specified

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial (double-dummy).

Van Heusden 1990 *(Continued)*

Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small number but all in one group,< 10%
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Comparable groups at baseline.

Van Heusden 1994

Study characteristics	
Methods	Study design: randomised trial (multi-centre) Follow-up: not-calculable
Participants	Age: 18-65 years Country: the Netherlands Setting: Obstetrics and Gynaecology Out-Patient Department and General Practices Diagnosis: mycological culture and clinical symptoms Characteristics: non-lactating Enrolled: 741 (693 evaluable)
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = not clearly reported) Group 2: clotrimazole intra-vaginal tablets 500 mg single dose (n = not clearly reported) Duration: Not specified
Outcomes	Assessed at 7 and 28 days **Efficacy** Mycological cure: complete absence of Candida species

Van Heusden 1994 *(Continued)*

	Clinical cure: signs and symptoms scored by patient and overall efficacy rated by both physician and patient Safety: No withdrawals due to side effects reported Side effects: reported. Treatment preference: reported Time to first relief: not reported Costs: not reported
Notes	Compliance check: not reported Pharmaceutical industry support: not specified Results calculated from percentages quoted by authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute- generated list, likely random.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 6.4% lost to follow-up.

Van Heusden 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Unclear risk	Baseline data not reported.

Woolley 1995

Study characteristics	
Methods	Study design: randomised trial Follow-up: 100%
Participants	Age: 16-53 years Country: UK Setting: Genito-urinary Medicine Clinic Diagnosis: mycological and/or microscopic. Enrolled: 229
Interventions	Group 1: clotrimazole pessary 500 mg (single dose) and 1% cream. (n = 82) Group 2: fluconazole (oral) 150 mg single dose (n = 72) Group 3: itraconazole (oral) 200 mg (single dose) (n = 75) Duration: Not specified
Outcomes	Assessed at 7-10 days. **Efficacy** Mycological cure - negative culture and tests for Candida Clinical cure - assessed by physician Safety: not reported Side effects: not reported Treatment preference: not reported Time to first relief: not reported Costs: not reported
Notes	Compliance check: not reported Pharmaceutical industry support: not specified

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias)	High risk	not possible given nature of intervention

Woolley 1995 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) Time to First Relief	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Mycological Cure	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Mycological Improvement	Low risk	Testing done by lab cultures, which are objective outcomes, not influenced by blinding.
Blinding of outcome assessment (detection bias) Clinical Cure	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	High risk	Not possible to avoid risk given nature of intervention, and self-report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Low risk	Baseline data comparable.

Škerk V 2006

Study characteristics	
Methods	Study design: randomised trial Follow-up:uUnclear, insufficient data presented.
Participants	Age: 18 - 45 years Country; Croatia Settings: General Practice (not specified) Diagnosis: visual examination, clinical symptoms, confirmed microscopically Characteristics: not specified Enrolled: 246 episodes (of thrush) 83 participants
Interventions	Group 1: fluconazole (oral) 150 mg single dose (n = 71 episodes) Group 2: clotrimazole (intra-vaginal) 200 mg daily for 3 days (n = 55 episodes)

Škerk V 2006 *(Continued)*

	Duration: June 1, 2006 until July 31, 2006,
Outcomes	Assessed up to 2 months following treatment allocation. **Efficacy** Clinical cure: successful treatment, recurrent VVC as reported by patients Mycological cure: not reported Safety: no withdrawals due to side effects reported Side effects: reported: quote: "There were no side effects of the doctor trial" (per our translation) Treatment preference: not assessed Time to first relief: not assessed Costs: not assessed
Notes	Compliance check: not specified Pharmaceutical industry support: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided.
Allocation concealment (selection bias)	Unclear risk	No description provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to avoid risk given nature of intervention.
Blinding of outcome assessment (detection bias) Time to First Relief	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Mycological Cure	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Mycological Improvement	Unclear risk	Outcome not assessed.
Blinding of outcome assessment (detection bias) Clinical Cure	Unclear risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Clinical Improvement	Unclear risk	Not possible to avoid risk given nature of intervention, and self-report.
Blinding of outcome assessment (detection bias) Side Effects	Unclear risk	Not possible to avoid risk given nature of intervention, and self-report.

Škerk V 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers in group not specified.
Selective reporting (reporting bias)	Unclear risk	No protocol described.
Other bias	Unclear risk	No data provided for baseline values. See table 1 for baseline imbalance.

ITT: intention-to-treat
O&G OPD = Obstetrics and Gynaecology Out-Patient Department
KOH = potassium hydroxide
VVC: vulvovaginal candidiasis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
EUCTR2005-001360-31-IT	Contacted Abiogen Pharma July 12, 2018 and October 8, 2018 using online contact form to enquire about the open treatment arm to determine eligibility. Study has been completed. Acknowledgment of contact received only; no response to query received. Website: https://www.abiogen.it/en/
Fan 2015	Did not meet inclusion criteria (involved women with complicated vulvovaginal candidiasis)
Fong 1992	Did not meet inclusion criteria (involved women with complicated vulvovaginal candidiasis)
Herzog 1989	Random allocation not specified.
Li 2015	Did not meet inclusion criteria (involved women with complicated vulvovaginal candidiasis).
Lopez Olmos 1994	Random allocation not specified.
Mikamo 1998	The review authors believe that the some of the participants reported in this trial were reported in a previous included trial Mikamo 1995). This trial has been excluded to avoid duplicate use of data.
Wermeling 1992	Abstract only - insufficient information provided.
Zhou 2016	Did not meet inclusion criteria (involved women with complicated vulvovaginal candidiasis).

DATA AND ANALYSES

Comparison 1. Oral versus Intra-vaginal

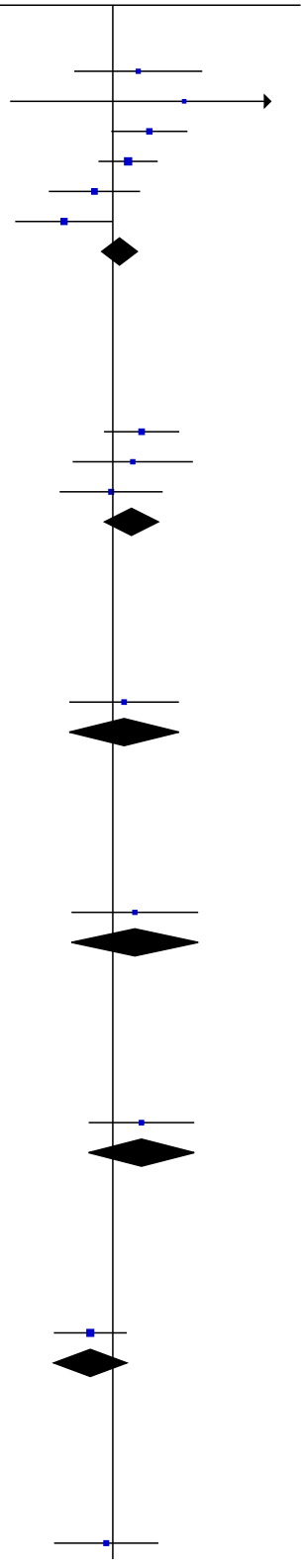
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical cure (short term)	13	1859	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.91, 1.43]
1.1.1 Fluconazole vs Clotrimazole	6	809	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.81, 1.58]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1.2 Itraconazole vs Clotrimazole	3	436	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.86, 2.33]
1.1.3 Fluconazole vs Miconazole	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.45, 3.42]
1.1.4 Fluconazole vs Econazole	1	230	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.46, 4.89]
1.1.5 Itraconazole vs Econazole	1	75	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.64, 4.55]
1.1.6 Fluconazole vs Butoconazole	1	136	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.33, 1.30]
1.1.7 Fluconazole vs Fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.33]
1.2 Clinical cure (long term)	9	1042	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.77, 1.50]
1.2.1 Fluconazole vs Clotrimzole	4	564	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.65, 1.57]
1.2.2 Itraconazole vs Clotrimazole	1	53	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [0.63, 7.37]
1.2.3 Fluconazole vs Miconazole	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.51, 4.66]
1.2.4 Fluconazole vs Econazole	1	177	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.40, 2.72]
1.2.5 Itraconazole vs Econazole	1	75	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.20, 2.41]
1.2.6 Fluconazole vs Fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.10, 4.11]
1.3 Mycological cure (short term)	19	3057	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [1.03, 1.50]
1.3.1 Fluconazole vs Clotrimazole	12	1927	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.93, 1.49]
1.3.2 Itraconazole vs Clotrimazole	4	631	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.71]
1.3.3 Fluconazole vs Miconazole	2	194	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.26, 2.06]
1.3.4 Fluconazole vs Econazole	1	230	Odds Ratio (M-H, Fixed, 95% CI)	1.93 [0.97, 3.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.5 Itraconazole vs Econazole	1	75	Odds Ratio (M-H, Fixed, 95% CI)	3.55 [1.29, 9.77]
1.4 Mycological cure (long term)	13	1661	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [1.05, 1.60]
1.4.1 Fluconazole vs Clotrimazole	7	1015	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [1.00, 1.71]
1.4.2 Itraconazole vs Clotrimazole	2	200	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.98]
1.4.3 Fluconazole vs Miconazole	2	194	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.40]
1.4.4 Fluconazole vs Econazole	1	177	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [1.06, 4.42]
1.4.5 Itraconazole vs Econazole	1	75	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.89, 5.74]
1.5 Safety - number of withdrawals due to adverse events	23		Other data	No numeric data
1.6 Side effects	16	3155	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
1.6.1 Fluconazole vs Clotrimazole	7	1753	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.97, 1.74]
1.6.2 Itraconazole vs Clotrimazole	2	320	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.37]
1.6.3 Fluconazole vs Fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.24, 9.75]
1.6.4 Fluconazole vs Miconazole	3	505	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.31]
1.6.5 Fluconazole vs Econazole	1	235	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.74]
1.6.6 Fluconazole vs Butoconazole	1	181	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [0.85, 4.33]
1.6.7 Itraconazole vs Econazole	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.13, 1.66]
1.7 Treatment preference	12		Other data	No numeric data
1.8 Time to first relief	10		Other data	No numeric data

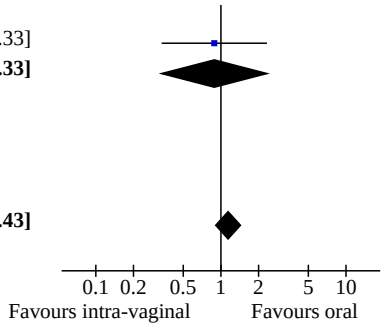
Analysis 1.1. Comparison 1: Oral versus Intra-vaginal, Outcome 1: Clinical cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Fluconazole vs Clotrimazole						
Coric 2006	33	38	37	46	3.2%	1.61 [0.49 , 5.28]
Goode 1992	3	3	6	9	0.3%	3.77 [0.15 , 95.82]
Sekhavat 2011	53	72	41	70	7.9%	1.97 [0.97 , 4.00]
Sobel 1995	108	139	97	134	15.9%	1.33 [0.77 , 2.30]
Stein 1991	76	90	84	95	9.2%	0.71 [0.30 , 1.66]
Woolley 1995	45	72	33	41	11.4%	0.40 [0.16 , 1.00]
Subtotal (95% CI)		**414**		**395**	**47.8%**	**1.13 [0.81 , 1.58]**
Total events:	318		298			
Heterogeneity: Chi² = 9.66, df = 5 (P = 0.09); I² = 48%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.1.2 Itraconazole vs Clotrimazole						
Sanam 2009	110	125	103	127	8.8%	1.71 [0.85 , 3.44]
Stein 1993	35	48	13	20	3.6%	1.45 [0.47 , 4.43]
Woolley 1995	60	75	33	41	6.1%	0.97 [0.37 , 2.53]
Subtotal (95% CI)		**248**		**188**	**18.6%**	**1.41 [0.86 , 2.33]**
Total events:	205		149			
Heterogeneity: Chi² = 0.88, df = 2 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						
1.1.3 Fluconazole vs Miconazole						
Van Heusden 1990	35	43	39	50	4.8%	1.23 [0.45 , 3.42]
Subtotal (95% CI)		**43**		**50**	**4.8%**	**1.23 [0.45 , 3.42]**
Total events:	35		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
1.1.4 Fluconazole vs Econazole						
Osser 1991	113	118	105	112	3.3%	1.51 [0.46 , 4.89]
Subtotal (95% CI)		**118**		**112**	**3.3%**	**1.51 [0.46 , 4.89]**
Total events:	113		105			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.1.5 Itraconazole vs Econazole						
Timonen 1992b	28	38	23	37	4.4%	1.70 [0.64 , 4.55]
Subtotal (95% CI)		**38**		**37**	**4.4%**	**1.70 [0.64 , 4.55]**
Total events:	28		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
1.1.6 Fluconazole vs Butoconazole						
Seidman 2005	33	69	39	67	14.9%	0.66 [0.33 , 1.30]
Subtotal (95% CI)		**69**		**67**	**14.9%**	**0.66 [0.33 , 1.30]**
Total events:	33		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.1.7 Fluconazole vs Fenticonazole						
Murina 2012	28	40	29	40	6.3%	0.89 [0.34 , 2.33]



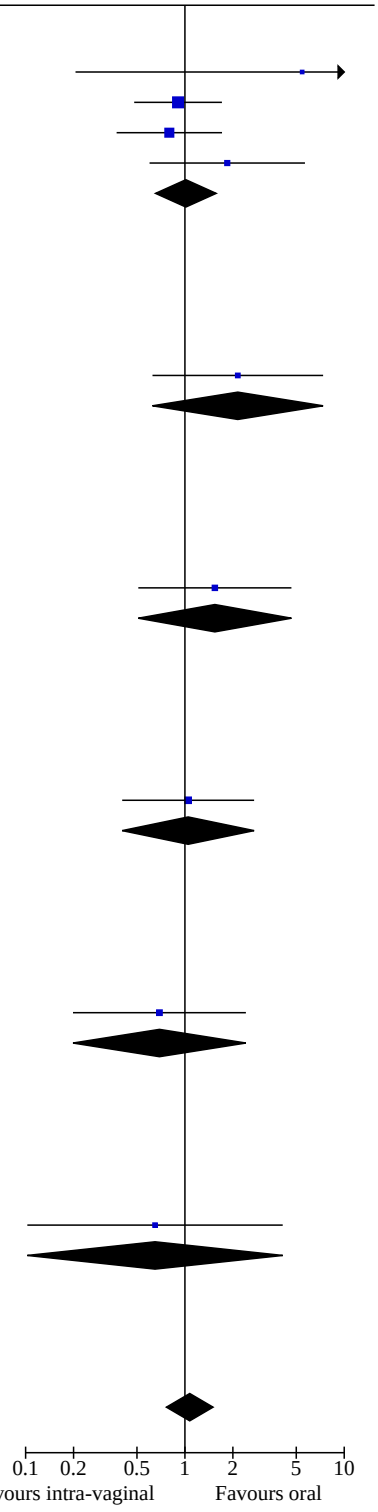
Analysis 1.1. (Continued)

1.1.7 Fluconazole vs Fenticonazole						
Murina 2012	28	40	29	40	6.3%	0.89 [0.34 , 2.33]
Subtotal (95% CI)		**40**		**40**	**6.3%**	**0.89 [0.34 , 2.33]**
Total events:	28		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		**970**		**889**	**100.0%**	**1.14 [0.91 , 1.43]**
Total events:	760		682			
Heterogeneity: Chi² = 14.90, df = 13 (P = 0.31); I² = 13%						
Test for overall effect: Z = 1.14 (P = 0.26)						
Test for subgroup differences: Chi² = 4.39, df = 6 (P = 0.62), I² = 0%						



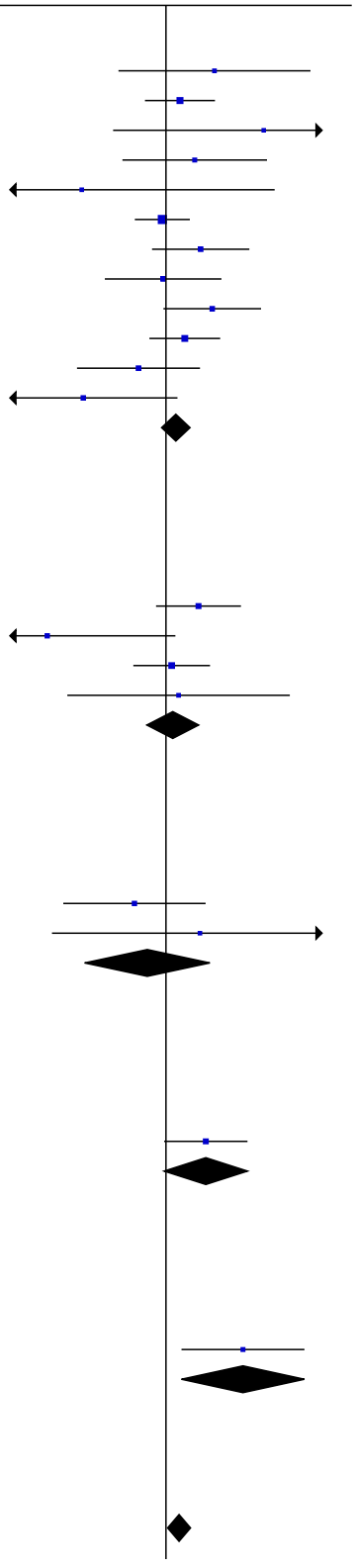
Analysis 1.2. Comparison 1: Oral versus Intra-vaginal, Outcome 2: Clinical cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Fluconazole vs Clotrimzole						
Goode 1992	3	3	4	7	0.6%	5.44 [0.21 , 144.10]
Sobel 1995	106	131	103	125	30.8%	0.91 [0.48 , 1.71]
Stein 1991	68	86	71	86	22.7%	0.80 [0.37 , 1.71]
Škerk V 2006	65	71	47	55	6.8%	1.84 [0.60 , 5.67]
Subtotal (95% CI)		**291**		**273**	**60.9%**	**1.01 [0.65 , 1.57]**
Total events:	242		225			
Heterogeneity: Chi² = 2.60, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.2.2 Itraconazole vs Clotrimazole						
Stein 1993	27	35	11	18	5.1%	2.15 [0.63 , 7.37]
Subtotal (95% CI)		**35**		**18**	**5.1%**	**2.15 [0.63 , 7.37]**
Total events:	27		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
1.2.3 Fluconazole vs Miconazole						
Van Heusden 1990	37	43	40	50	7.9%	1.54 [0.51 , 4.66]
Subtotal (95% CI)		**43**		**50**	**7.9%**	**1.54 [0.51 , 4.66]**
Total events:	37		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
1.2.4 Fluconazole vs Econazole						
Osser 1991	85	95	73	82	12.6%	1.05 [0.40 , 2.72]
Subtotal (95% CI)		**95**		**82**	**12.6%**	**1.05 [0.40 , 2.72]**
Total events:	85		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.2.5 Itraconazole vs Econazole						
Timonen 1992b	31	38	32	37	9.1%	0.69 [0.20 , 2.41]
Subtotal (95% CI)		**38**		**37**	**9.1%**	**0.69 [0.20 , 2.41]**
Total events:	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.2.6 Fluconazole vs Fenticonazole						
Murina 2012	37	40	38	40	4.4%	0.65 [0.10 , 4.11]
Subtotal (95% CI)		**40**		**40**	**4.4%**	**0.65 [0.10 , 4.11]**
Total events:	37		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**542**		**500**	**100.0%**	**1.07 [0.77 , 1.50]**
Total events:	459		419			
Heterogeneity: Chi² = 5.08, df = 8 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 2.45, df = 5 (P = 0.78), I² = 0%						



Analysis 1.3. Comparison 1: Oral versus Intra-vaginal, Outcome 3: Mycological cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Fluconazole vs Clotrimazole						
Adetoro 1990	20	23	15	20	1.1%	2.22 [0.46 , 10.79]
Andersen 1989	143	169	131	161	10.6%	1.26 [0.71 , 2.24]
Boag 1991	10	11	6	9	0.3%	5.00 [0.42 , 59.66]
Coric 2006	33	38	37	46	2.3%	1.61 [0.49 , 5.28]
Goode 1992	2	3	8	9	0.7%	0.25 [0.01 , 5.98]
Mendling 2004	117	154	245	318	19.7%	0.94 [0.60 , 1.48]
Mikamo 1995	82	100	36	50	4.4%	1.77 [0.80 , 3.95]
O-Prasertsawat 1995	42	53	40	50	4.4%	0.95 [0.37 , 2.49]
Sekhavat 2011	60	72	49	70	4.3%	2.14 [0.96 , 4.79]
Sobel 1995	113	139	102	134	10.0%	1.36 [0.76 , 2.44]
Stein 1991	80	90	88	95	4.9%	0.64 [0.23 , 1.75]
Woolley 1995	60	72	39	41	4.3%	0.26 [0.05 , 1.21]
Subtotal (95% CI)		**924**		**1003**	**66.9%**	**1.18 [0.93 , 1.49]**
Total events:	762		796			
Heterogeneity: Chi² = 12.78, df = 11 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.36 (P = 0.17)						
1.3.2 Itraconazole vs Clotrimazole						
Sanam 2009	110	125	103	127	6.3%	1.71 [0.85 , 3.44]
Stein 1993	35	48	19	20	3.7%	0.14 [0.02 , 1.17]
Tobin 1992	73	99	69	96	9.5%	1.10 [0.58 , 2.07]
Woolley 1995	72	75	39	41	1.0%	1.23 [0.20 , 7.68]
Subtotal (95% CI)		**347**		**284**	**20.5%**	**1.12 [0.73 , 1.71]**
Total events:	290		230			
Heterogeneity: Chi² = 5.11, df = 3 (P = 0.16); I² = 41%						
Test for overall effect: Z = 0.52 (P = 0.61)						
1.3.3 Fluconazole vs Miconazole						
Timonen 1992a	45	54	42	47	3.8%	0.60 [0.18 , 1.92]
Van Heusden 1990	42	43	48	50	0.5%	1.75 [0.15 , 20.00]
Subtotal (95% CI)		**97**		**97**	**4.4%**	**0.74 [0.26 , 2.06]**
Total events:	87		90			
Heterogeneity: Chi² = 0.61, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.3.4 Fluconazole vs Econazole						
Osser 1991	102	118	86	112	6.1%	1.93 [0.97 , 3.83]
Subtotal (95% CI)		**118**		**112**	**6.1%**	**1.93 [0.97 , 3.83]**
Total events:	102		86			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
1.3.5 Itraconazole vs Econazole						
Timonen 1992b	30	38	19	37	2.1%	3.55 [1.29 , 9.77]
Subtotal (95% CI)		**38**		**37**	**2.1%**	**3.55 [1.29 , 9.77]**
Total events:	30		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.46 (P = 0.01)						
Total (95% CI)		**1524**		**1533**	**100.0%**	**1.24 [1.03 , 1.50]**
Total events:	1271		1221			



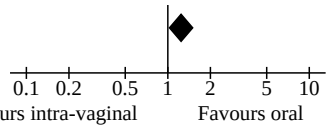
Analysis 1.3. (Continued)

Total (95% CI)	**1524**	**1533**	**100.0%**	**1.24 [1.03 , 1.50]**	
Total events:	1271	1221			

Heterogeneity: Chi² = 25.22, df = 19 (P = 0.15); I² = 25%

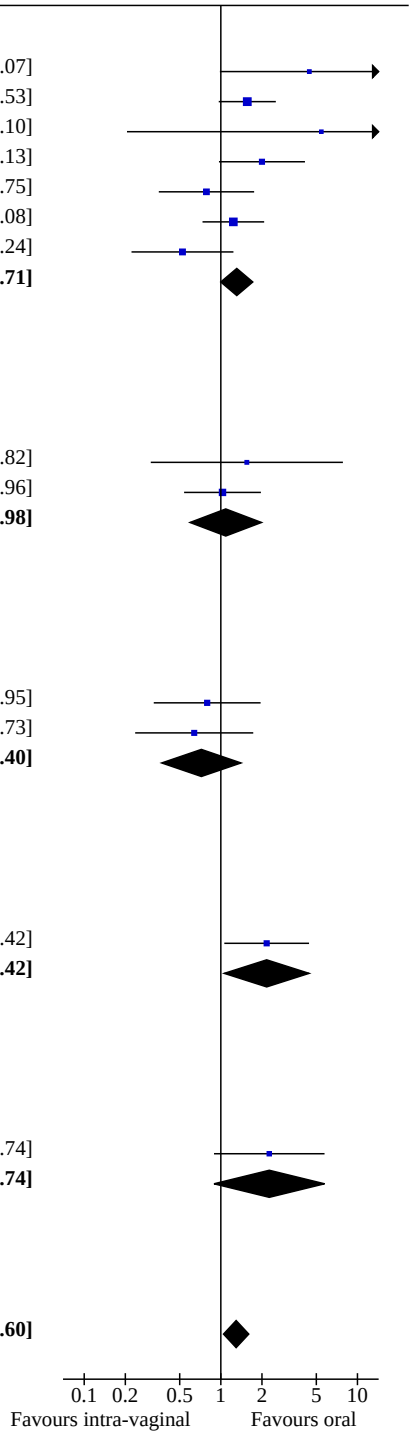
Test for overall effect: Z = 2.24 (P = 0.02)

Test for subgroup differences: Chi² = 7.16, df = 4 (P = 0.13), I² = 44.1%



Analysis 1.4. Comparison 1: Oral versus Intra-vaginal, Outcome 4: Mycological cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Fluconazole vs Clotrimazole						
Adetoro 1990	20	23	12	20	1.1%	4.44 [0.98 , 20.07]
Andersen 1989	115	160	90	145	17.8%	1.56 [0.97 , 2.53]
Goode 1992	3	3	4	7	0.3%	5.44 [0.21 , 144.10]
Mikamo 1995	75	100	30	50	6.7%	2.00 [0.97 , 4.13]
O-Prasertsawat 1995	32	53	33	50	9.0%	0.78 [0.35 , 1.75]
Sobel 1995	90	131	80	125	17.2%	1.23 [0.73 , 2.08]
Stein 1991	57	74	64	74	9.8%	0.52 [0.22 , 1.24]
Subtotal (95% CI)		**544**		**471**	**61.9%**	**1.31 [1.00 , 1.71]**
Total events:	392		313			
Heterogeneity: Chi² = 11.06, df = 6 (P = 0.09); I² = 46%						
Test for overall effect: Z = 1.96 (P = 0.05)						
1.4.2 Itraconazole vs Clotrimazole						
Stein 1993	31	35	15	18	1.5%	1.55 [0.31 , 7.82]
Tobin 1992	36	71	38	76	12.1%	1.03 [0.54 , 1.96]
Subtotal (95% CI)		**106**		**94**	**13.6%**	**1.09 [0.60 , 1.98]**
Total events:	67		53			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.4.3 Fluconazole vs Miconazole						
Timonen 1992a	39	54	36	47	7.2%	0.79 [0.32 , 1.95]
Van Heusden 1990	32	43	41	50	6.5%	0.64 [0.24 , 1.73]
Subtotal (95% CI)		**97**		**97**	**13.7%**	**0.72 [0.37 , 1.40]**
Total events:	71		77			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.4.4 Fluconazole vs Econazole						
Osser 1991	79	95	57	82	6.9%	2.17 [1.06 , 4.42]
Subtotal (95% CI)		**95**		**82**	**6.9%**	**2.17 [1.06 , 4.42]**
Total events:	79		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
1.4.5 Itraconazole vs Econazole						
Timonen 1992b	25	38	17	37	3.9%	2.26 [0.89 , 5.74]
Subtotal (95% CI)		**38**		**37**	**3.9%**	**2.26 [0.89 , 5.74]**
Total events:	25		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**880**		**781**	**100.0%**	**1.29 [1.05 , 1.60]**
Total events:	634		517			
Heterogeneity: Chi² = 18.04, df = 12 (P = 0.11); I² = 33%						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: Chi² = 6.67, df = 4 (P = 0.15), I² = 40.0%						

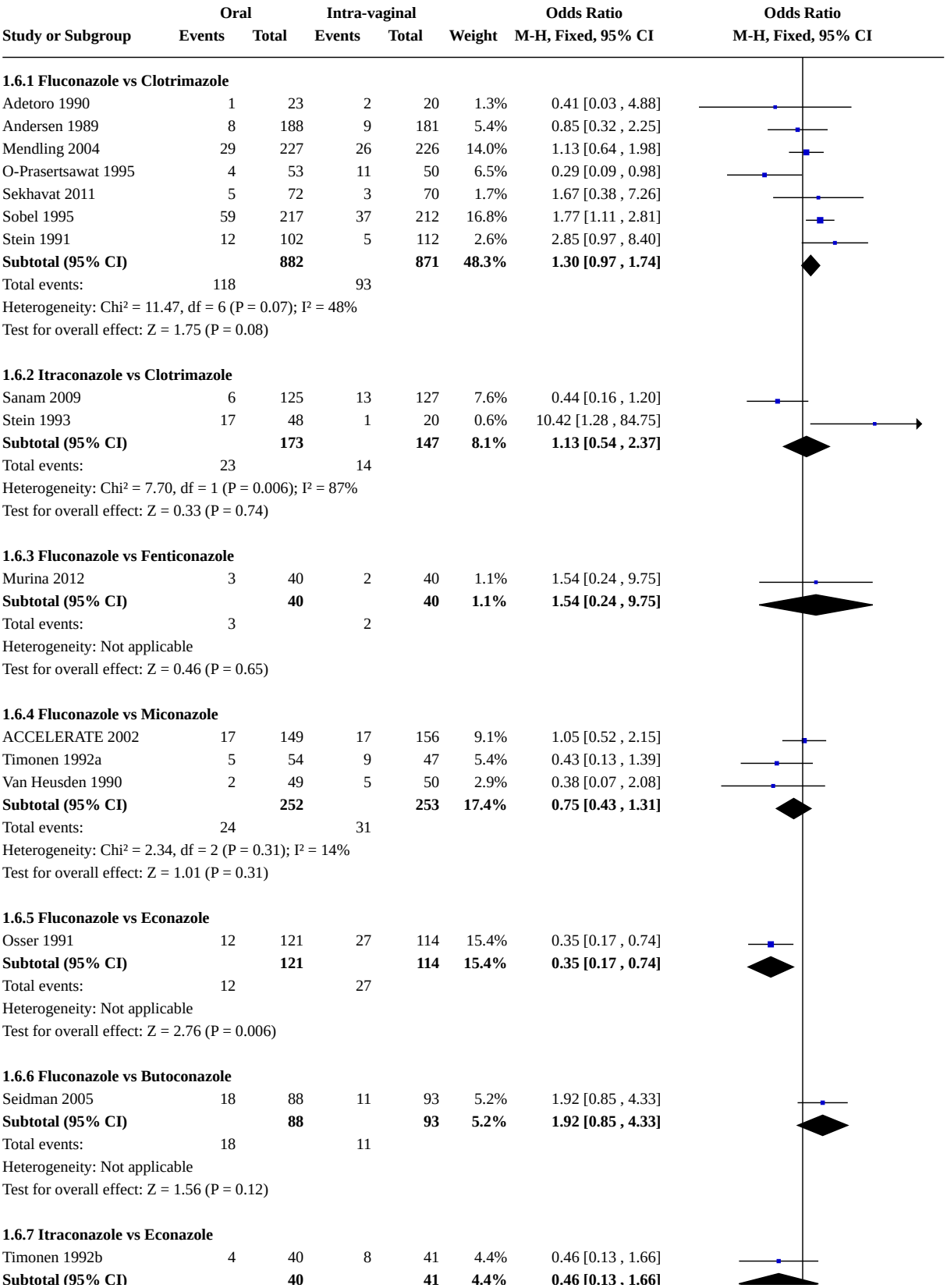


Analysis 1.5. Comparison 1: Oral versus Intra-vaginal, Outcome 5: Safety - number of withdrawals due to adverse events

Safety - number of withdrawals due to adverse events

Study	Any participants withdrew due to adverse effects	Comments
ACCELERATE 2002	Yes	"One subject experienced severe vulvovaginal itching, burning, and irritation and was withdrawn from the study" - MONISTAT-1 Combination Pack treatment group
Adetoro 1990	No	"Both treatments were well-tolerated. One patient receiving fluconazole and two patients receiving clotrimazole reported mild, self-limiting side effects". There were no withdrawals in this study.
Andersen 1989	No	"Both treatments proved to be well tolerated and safe"
Goode 1992	No	"Reported side effects were minimal in both treatment groups"
Mendling 2004	No	"Serious or unexpected events were not observed in any of the treatment groups."
Mikamo 1995	No	"Neither adverse side effects to the drug nor abnormal laboratory values were noted during the treatment or observation periods"
Murina 2012	No	Translation from Italian - no patient belonging to the two groups had to suspend treatment due to the presence of severe side effects
O-Prasertsawat 1995	No	"All side effects were minimal".
Osser 1991	No	No withdrawals due to side effects were reported
Roongpisuthipong 2010	No	"Results showed minimal side-effect without adverse event"
Sanam 2009	No	No withdrawals due to side effects were reported
Seidman 2005	No	No withdrawals due to adverse events were reported
Sekhavat 2011	No	No withdrawals due to side effects were reported
Slavin 1992	No	"No adverse drug effects were noted"
Sobel 1995	No	"No patient discontinued therapy"
Stein 1991	Yes	"One patient discontinued treatment after she developed diarrhea while receiving fluconazole"
Stein 1993	No	"No patients enrolled in this study discontinued treatment because of an adverse event"
Timonen 1992a	Yes	"One patient discontinued the treatment because of a severe burning sensation in the vagina" - miconazole group
Timonen 1992b	No	"None of the patients discontinued treatment because of an adverse event"
Tobin 1992	No	The reasons for withdrawals were reported and adverse effects was not one reported as a reason
Van Heusden 1990	No	"The incidence of side effects was low."No withdrawals due to side effects were reported
Van Heusden 1994	No	No withdrawals due to side effects were reported
Škerk V 2006	No	"There were no side effects of treatment"

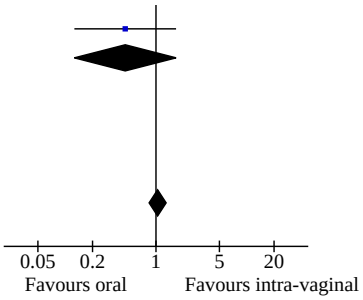
Analysis 1.6. Comparison 1: Oral versus Intra-vaginal, Outcome 6: Side effects



Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Fluconazole vs Clotrimazole						
Adetoro 1990	1	23	2	20	1.3%	0.41 [0.03 , 4.88]
Andersen 1989	8	188	9	181	5.4%	0.85 [0.32 , 2.25]
Mendling 2004	29	227	26	226	14.0%	1.13 [0.64 , 1.98]
O-Prasertsawat 1995	4	53	11	50	6.5%	0.29 [0.09 , 0.98]
Sekhavat 2011	5	72	3	70	1.7%	1.67 [0.38 , 7.26]
Sobel 1995	59	217	37	212	16.8%	1.77 [1.11 , 2.81]
Stein 1991	12	102	5	112	2.6%	2.85 [0.97 , 8.40]
Subtotal (95% CI)		**882**		**871**	**48.3%**	**1.30 [0.97 , 1.74]**
Total events:	118		93			
Heterogeneity: Chi² = 11.47, df = 6 (P = 0.07); I² = 48%						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.6.2 Itraconazole vs Clotrimazole						
Sanam 2009	6	125	13	127	7.6%	0.44 [0.16 , 1.20]
Stein 1993	17	48	1	20	0.6%	10.42 [1.28 , 84.75]
Subtotal (95% CI)		**173**		**147**	**8.1%**	**1.13 [0.54 , 2.37]**
Total events:	23		14			
Heterogeneity: Chi² = 7.70, df = 1 (P = 0.006); I² = 87%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.6.3 Fluconazole vs Fenticonazole						
Murina 2012	3	40	2	40	1.1%	1.54 [0.24 , 9.75]
Subtotal (95% CI)		**40**		**40**	**1.1%**	**1.54 [0.24 , 9.75]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
1.6.4 Fluconazole vs Miconazole						
ACCELERATE 2002	17	149	17	156	9.1%	1.05 [0.52 , 2.15]
Timonen 1992a	5	54	9	47	5.4%	0.43 [0.13 , 1.39]
Van Heusden 1990	2	49	5	50	2.9%	0.38 [0.07 , 2.08]
Subtotal (95% CI)		**252**		**253**	**17.4%**	**0.75 [0.43 , 1.31]**
Total events:	24		31			
Heterogeneity: Chi² = 2.34, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.6.5 Fluconazole vs Econazole						
Osser 1991	12	121	27	114	15.4%	0.35 [0.17 , 0.74]
Subtotal (95% CI)		**121**		**114**	**15.4%**	**0.35 [0.17 , 0.74]**
Total events:	12		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.76 (P = 0.006)						
1.6.6 Fluconazole vs Butoconazole						
Seidman 2005	18	88	11	93	5.2%	1.92 [0.85 , 4.33]
Subtotal (95% CI)		**88**		**93**	**5.2%**	**1.92 [0.85 , 4.33]**
Total events:	18		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						
1.6.7 Itraconazole vs Econazole						
Timonen 1992b	4	40	8	41	4.4%	0.46 [0.13 , 1.66]
Subtotal (95% CI)		**40**		**41**	**4.4%**	**0.46 [0.13 , 1.66]**

Analysis 1.6. (Continued)

Timonen 1992b	4	40	8	41	4.4%	0.46 [0.13 , 1.66]
Subtotal (95% CI)		**40**		**41**	**4.4%**	**0.46 [0.13 , 1.66]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						
Total (95% CI)		**1596**		**1559**	**100.0%**	**1.04 [0.84 , 1.29]**
Total events:	202		186			
Heterogeneity: Chi² = 36.82, df = 15 (P = 0.001); I² = 59%						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: Chi² = 15.66, df = 6 (P = 0.02), I² = 61.7%						



Analysis 1.7. Comparison 1: Oral versus Intra-vaginal, Outcome 7: Treatment preference

Treatment preference

Study	Prefer oral n (%)	Prefer vaginal n (%)	Notes	n	Soft vote count
Adetoro 1990			No numbers provided. Comment in paper: "It was also noted that virtually all treated patients preferred oral treatment to the more conventional intravaginal therapy."	43	Oral
Andersen 1989	25 (65.8)	0 (0)	Data were from only one treatment group (fluconazole treated group) at only one centre.	45	Oral
Coric 2006	93 (78.2)	26 (21.8)		119	Oral
Osser 1991	Fluconazole group (68.3) Econazole group (38.8%)	Fluconazole group (13.8) Econazole group (25.6%)	17.9% of the women administered fluconazole expressed no opinion. 35.6% of the women administered econazole expressed no opinion.	235	Oral
Sekhavat 2011			Comment in paper: "More than 97% patients enrolled in the study would prefer oral fluconazole treatment compared to topical clotrimazole 68.6% (p = 0.001)."	142	Oral
Slavin 1992			Comment in paper: "Seventy-three percent of the study patients preferred oral therapy compared to intravaginal for the treatment of candida vaginitis."	22	Oral
Stein 1993			No numbers provided. Comment in paper: "Itraconazole therapy was highly favored over therapy with clotrimazole in our survey of patients".	95	Oral
Timonen 1992a	Fluconazole group 50 (92.6) Miconazole group 33 (70.2) (80.2)	Fluconazole group 1 (1.9) Miconazole group 3 (6.4) (4.9)	No preference: Fluconazole group 3 (5.6) Miconazole group 11 (23.4) I think the numbers are 65 and 6, but not given in paper. 15% did not state a preference	101	Oral

Timonen 1992b	(80.2)	(4.9)	15% did not state a preference	81	Oral
Tobin 1992			Provides data on whether participants preferred the study treatment (itraconazole or clotrimazole) to previous treatments received, but it is not recorded whether the previous treatments were oral or vaginal.	180	N/A
Van Heusden 1990	43 (46.2)	4 (4.3)	46 (49.5%) had no preference	93	No preference
Van Heusden 1994	(52)	(17)	In addition, 26% had no preference, and 5% said 'other' preference.	471	Oral

Analysis 1.8. Comparison 1: Oral versus Intra-vaginal, Outcome 8: Time to first relief

Time to first relief

Study	Data reported	Results	Notes
ACCELERATE 2002	Median time to initial relief Proportion of patients at timepoints	Miconazole (intravaginal) treatment group = 1.0 hour for individual symptoms and 4.0 hours for all symptoms combined. Fluconazole (oral) treatment group = 4.0 hours for individual symptoms and 16.0 hours for all symptoms combined. Miconazole treatment group = Initial relief was reported by 16.0% of subjects at 20 minutes following dosing, by 30.7% at 40 minutes, and by 96.0% of subjects at 72 hours. Fluconazole treatment group = Initial relief was reported by 5.0% of subjects at 20 minutes following dosing, by 11.9% of subjects at 40 minutes, and by 90.1% of subjects at 72 hours.	favours intravaginal for individual and all symptoms combined
Adetoro 1990	No specific data reported		"The rate or response to treatment suggest that patients receiving fluconazole (oral) or clotrimazole (intravaginal) experienced symptomatic relief after one or two days of treatment, respectively.
Andersen 1989	Median time to initial relief	1 day for fluconazole (oral) and 2 days for clotrimazole (intravaginal) (P<0.001).	favors oral
Coric 2006	Proportion of patients at timepoints	The onset of symptomatic relief in the first 24 h of treatment was significantly higher in the fluconazole (oral) (41 out of 60) than in the clotrimazole (intravaginal) group (9 out of 59).	favors oral
Mendling 2004	Median time to initial relief	Time to first relief was similar in all three treatment groups = 3 days.	no difference
Murina 2012	Mean time to initial relief	Fenticonazole group = 2.3 days. Fluconazole = 4.5 days.	Vulvovaginal pruritus only. favors intravaginal
Seidman 2005	Median time to initial relief Proportion of patients at timepoints	Butoconazole (intravaginal) group = 17.5 hours. Fluconazole (oral) group = 22.9 hours. (p<0.001). By 12- and 24-h post-treatment, 44.4% and 72.8% of patients in the butoconazole treatment group reported first relief of symptoms versus 29.1% and 55.7% of patients in the fluconazole group (p= 0.044 and p= 0.024 respectively).	favors intravaginal
Slavin 1992	Median time to initial relief Mean time to initial relief	Terconazole (intravaginal) median = 1. Fluconazole (oral) median = 2.	favors intravaginal

		Terconazole mean = 1.80 (SD 1.87). Fluconazole mean = 2.42 (SD 1.73).	
Timonen 1992a	Proportion of patients at timepoints	46.8% of the miconazole (intravaginal) group had reported alleviation of symptoms on the first day, compared to 51.9% of the fluconazole (oral) group. 97.9% of the miconazole group had reported alleviation of symptoms by the third day, compared to 85.2% of the fluconazole group. There was no statistical difference between the two groups.	alleviation of symptoms favors oral (day 1) and intravaginal (day 3)
Tobin 1992	Mean time to initial relief	Clotrimazole (intravaginal) group = 5.5 days. Intraconazole (oral) group = 3.8 days. (p=0.069).	favors oral

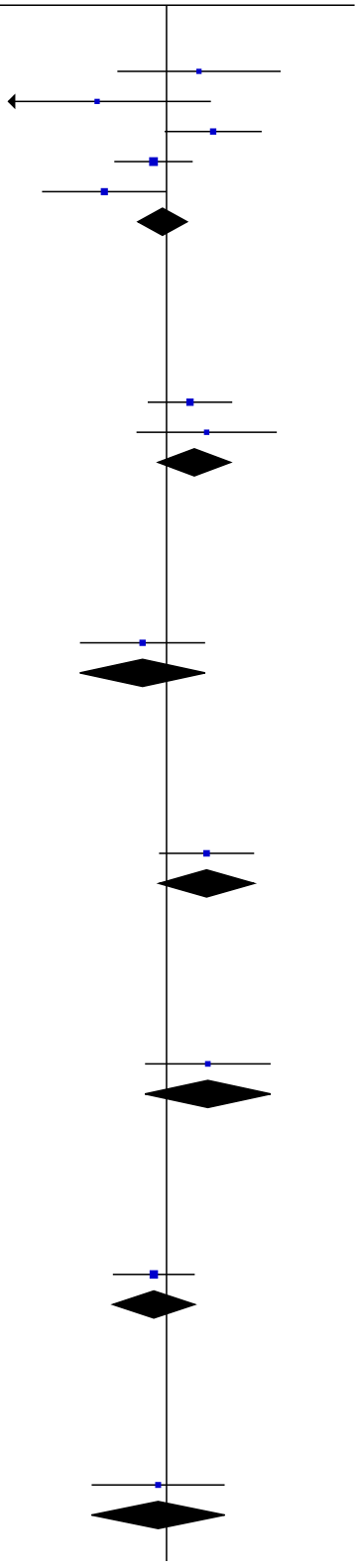
Comparison 2. Oral versus Intra-vaginal (no. randomised)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical cure (short term)	12	1630	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.88, 1.38]
2.1.1 Fluconazole vs Clotrimazole	5	594	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.35]
2.1.2 Itraconazole vs Clotrimazole	2	337	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.88, 2.54]
2.1.3 Fluconazole vs Miconazole	1	99	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.28, 1.76]
2.1.4 Fluconazole vs Econazole	1	258	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.90, 3.59]
2.1.5 Itraconazole vs Econazole	1	81	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.73, 4.56]
2.1.6 Fluconazole vs Butoconazole	1	181	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.51]
2.1.7 Fluconazole vs Fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.33]
2.2 Clinical cure (long term)	8	972	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.88, 1.56]
2.2.1 Fluconazole vs Clotrimzole	3	381	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.72]
2.2.2 Itraconazole vs Clotrimazole	1	73	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.48, 3.44]
2.2.3 Fluconazole vs Miconazole	1	99	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.30, 1.99]
2.2.4 Fluconazole vs Econazole	1	258	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.93, 2.56]
2.2.5 Itraconazole vs Econazole	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.34, 2.76]
2.2.6 fuconazole vs fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.10, 4.11]
2.3 Mycological cure (short term)	16	2343	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.96, 1.40]
2.3.1 Fluconazole vs Clotrimazole	10	1443	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.29]
2.3.2 Itraconazole vs Clotrimazole	2	337	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.65, 1.92]
2.3.3 Fluconazole vs Miconazole	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.44, 1.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.4 Fluconazole vs Econazole	1	258	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [1.14, 3.53]
2.3.5 Itraconazole vs Econazole	1	81	Odds Ratio (M-H, Fixed, 95% CI)	3.47 [1.35, 8.92]
2.4 Mycological cure (long term)	10	1378	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [1.09, 1.68]
2.4.1 Fluconazole vs Clotrimazole	5	742	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.99, 1.78]
2.4.2 Itraconazole vs Clotrimazole	1	73	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.31, 2.44]
2.4.3 Fluconazole vs Miconazole	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.45, 1.38]
2.4.4 Fluconazole vs Econazole	1	258	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [1.26, 3.39]
2.4.5 Itraconazole vs Econazole	1	81	Odds Ratio (M-H, Fixed, 95% CI)	2.35 [0.96, 5.74]
2.5 Side effects	4	796	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.55, 1.50]
2.5.1 Fluconazole vs Clotrimazole	1	142	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.38, 7.26]
2.5.2 Itraconazole vs Clotrimazole	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.18]
2.5.3 Fluconazole vs Fenticonazole	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.24, 9.75]
2.5.4 Fluconazole vs Miconazole	1	310	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.53, 2.19]

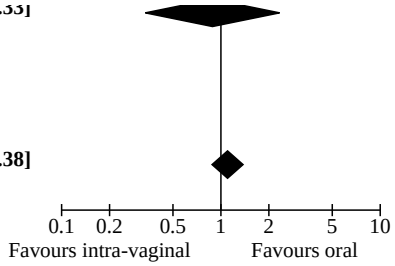
Analysis 2.1. Comparison 2: Oral versus Intra-vaginal (no. randomised), Outcome 1: Clinical cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Fluconazole vs Clotrimazole						
Coric 2006	33	38	37	46	3.0%	1.61 [0.49 , 5.28]
Goode 1992	3	14	6	14	3.2%	0.36 [0.07 , 1.91]
Sekhavat 2011	53	72	41	70	7.5%	1.97 [0.97 , 4.00]
Stein 1991	76	111	84	116	17.7%	0.83 [0.47 , 1.46]
Woolley 1995	45	72	33	41	10.7%	0.40 [0.16 , 1.00]
Subtotal (95% CI)		**307**		**287**	**42.1%**	**0.94 [0.66 , 1.35]**
Total events:	210		201			
Heterogeneity: Chi² = 9.77, df = 4 (P = 0.04); I² = 59%						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.1.2 Itraconazole vs Clotrimazole						
Sanam 2009	110	132	103	132	11.7%	1.41 [0.76 , 2.61]
Stein 1993	35	50	13	23	3.6%	1.79 [0.65 , 4.99]
Subtotal (95% CI)		**182**		**155**	**15.3%**	**1.50 [0.88 , 2.54]**
Total events:	145		116			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
2.1.3 Fluconazole vs Miconazole						
Van Heusden 1990	35	49	39	50	7.5%	0.71 [0.28 , 1.76]
Subtotal (95% CI)		**49**		**50**	**7.5%**	**0.71 [0.28 , 1.76]**
Total events:	35		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
2.1.4 Fluconazole vs Econazole						
Osser 1991	113	128	105	130	8.3%	1.79 [0.90 , 3.59]
Subtotal (95% CI)		**128**		**130**	**8.3%**	**1.79 [0.90 , 3.59]**
Total events:	113		105			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.1.5 Itraconazole vs Econazole						
Timonen 1992b	28	40	23	41	4.6%	1.83 [0.73 , 4.56]
Subtotal (95% CI)		**40**		**41**	**4.6%**	**1.83 [0.73 , 4.56]**
Total events:	28		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
2.1.6 Fluconazole vs Butoconazole						
Seidman 2005	33	88	39	93	16.2%	0.83 [0.46 , 1.51]
Subtotal (95% CI)		**88**		**93**	**16.2%**	**0.83 [0.46 , 1.51]**
Total events:	33		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.1.7 Fluconazole vs Fenticonazole						
Murina 2012	28	40	29	40	5.9%	0.89 [0.34 , 2.33]
Subtotal (95% CI)		**40**		**40**	**5.9%**	**0.89 [0.34 , 2.33]**
Total events:	28		29			



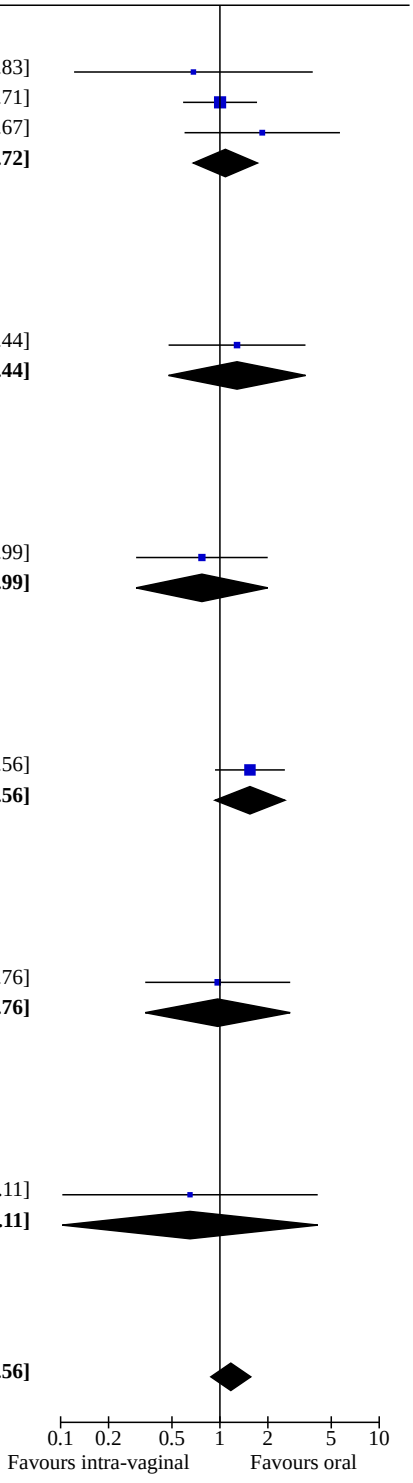
Analysis 2.1. (Continued)

Subtotal (95% CI)	**40**	**40**	**5.9%**	**0.89 [0.34 , 2.33]**	
Total events:	28	29			
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Total (95% CI)	**834**	**796**	**100.0%**	**1.10 [0.88 , 1.38]**	
Total events:	592	552			
Heterogeneity: Chi² = 16.89, df = 11 (P = 0.11); I² = 35%					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Chi² = 7.08, df = 6 (P = 0.31), I² = 15.3%					



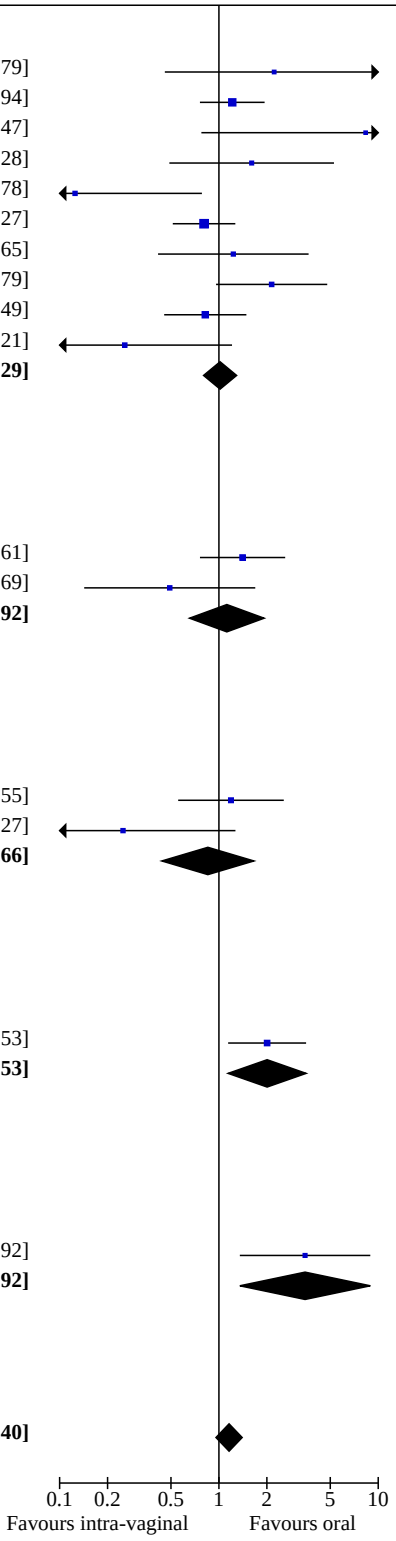
Analysis 2.2. Comparison 2: Oral versus Intra-vaginal (no. randomised), Outcome 2: Clinical cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Fluconazole vs Clotrimzole						
Goode 1992	3	14	4	14	3.7%	0.68 [0.12 , 3.83]
Stein 1991	68	111	71	116	31.5%	1.00 [0.59 , 1.71]
Škerk V 2006	65	71	47	55	5.2%	1.84 [0.60 , 5.67]
Subtotal (95% CI)		**196**		**185**	**40.4%**	**1.08 [0.68 , 1.72]**
Total events:	136		122			
Heterogeneity: Chi² = 1.22, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
2.2.2 Itraconazole vs Clotrimazole						
Stein 1993	27	50	11	23	8.1%	1.28 [0.48 , 3.44]
Subtotal (95% CI)		**50**		**23**	**8.1%**	**1.28 [0.48 , 3.44]**
Total events:	27		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
2.2.3 Fluconazole vs Miconazole						
Van Heusden 1990	37	49	40	50	11.3%	0.77 [0.30 , 1.99]
Subtotal (95% CI)		**49**		**50**	**11.3%**	**0.77 [0.30 , 1.99]**
Total events:	37		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.2.4 Fluconazole vs Econazole						
Osser 1991	85	128	73	130	28.5%	1.54 [0.93 , 2.56]
Subtotal (95% CI)		**128**		**130**	**28.5%**	**1.54 [0.93 , 2.56]**
Total events:	85		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
2.2.5 Itraconazole vs Econazole						
Timonen 1992b	31	40	32	41	8.3%	0.97 [0.34 , 2.76]
Subtotal (95% CI)		**40**		**41**	**8.3%**	**0.97 [0.34 , 2.76]**
Total events:	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
2.2.6 fuconazole vs fenticonazole						
Murina 2012	37	40	38	40	3.3%	0.65 [0.10 , 4.11]
Subtotal (95% CI)		**40**		**40**	**3.3%**	**0.65 [0.10 , 4.11]**
Total events:	37		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**503**		**469**	**100.0%**	**1.17 [0.88 , 1.56]**
Total events:	353		316			
Heterogeneity: Chi² = 3.78, df = 7 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 2.56, df = 5 (P = 0.77), I² = 0%						



Analysis 2.3. Comparison 2: Oral versus Intra-vaginal (no. randomised), Outcome 3: Mycological cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Fluconazole vs Clotrimazole						
Adetoro 1990	20	23	15	20	1.0%	2.22 [0.46 , 10.79]
Andersen 1989	143	188	131	181	16.0%	1.21 [0.76 , 1.94]
Boag 1991	10	11	6	11	0.3%	8.33 [0.78 , 89.47]
Coric 2006	33	38	37	46	2.2%	1.61 [0.49 , 5.28]
Goode 1992	2	14	8	14	3.4%	0.13 [0.02 , 0.78]
Mendling 2004	59	114	129	226	20.9%	0.81 [0.51 , 1.27]
Mikamo 1995	38	50	18	25	2.9%	1.23 [0.41 , 3.65]
Sekhavat 2011	60	72	49	70	4.1%	2.14 [0.96 , 4.79]
Stein 1991	80	111	88	116	12.0%	0.82 [0.45 , 1.49]
Woolley 1995	60	72	39	41	4.1%	0.26 [0.05 , 1.21]
Subtotal (95% CI)		**693**		**750**	**67.0%**	**1.02 [0.80 , 1.29]**
Total events:	505		520			
Heterogeneity: Chi² = 18.06, df = 9 (P = 0.03); I² = 50%						
Test for overall effect: Z = 0.14 (P = 0.89)						
2.3.2 Itraconazole vs Clotrimazole						
Sanam 2009	110	132	103	132	8.6%	1.41 [0.76 , 2.61]
Stein 1993	35	50	19	23	3.9%	0.49 [0.14 , 1.69]
Subtotal (95% CI)		**182**		**155**	**12.5%**	**1.12 [0.65 , 1.92]**
Total events:	145		122			
Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 0.42 (P = 0.68)						
2.3.3 Fluconazole vs Miconazole						
Timonen 1992a	45	63	42	62	6.1%	1.19 [0.56 , 2.55]
Van Heusden 1990	42	49	48	50	3.4%	0.25 [0.05 , 1.27]
Subtotal (95% CI)		**112**		**112**	**9.4%**	**0.85 [0.44 , 1.66]**
Total events:	87		90			
Heterogeneity: Chi² = 2.92, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 0.47 (P = 0.64)						
2.3.4 Fluconazole vs Econazole						
Osser 1991	102	128	86	130	8.7%	2.01 [1.14 , 3.53]
Subtotal (95% CI)		**128**		**130**	**8.7%**	**2.01 [1.14 , 3.53]**
Total events:	102		86			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
2.3.5 Itraconazole vs Econazole						
Timonen 1992b	30	40	19	41	2.3%	3.47 [1.35 , 8.92]
Subtotal (95% CI)		**40**		**41**	**2.3%**	**3.47 [1.35 , 8.92]**
Total events:	30		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**1155**		**1188**	**100.0%**	**1.16 [0.96 , 1.40]**
Total events:	869		837			
Heterogeneity: Chi² = 33.48, df = 15 (P = 0.004); I² = 55%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 10.84, df = 4 (P = 0.03), I² = 63.1%						



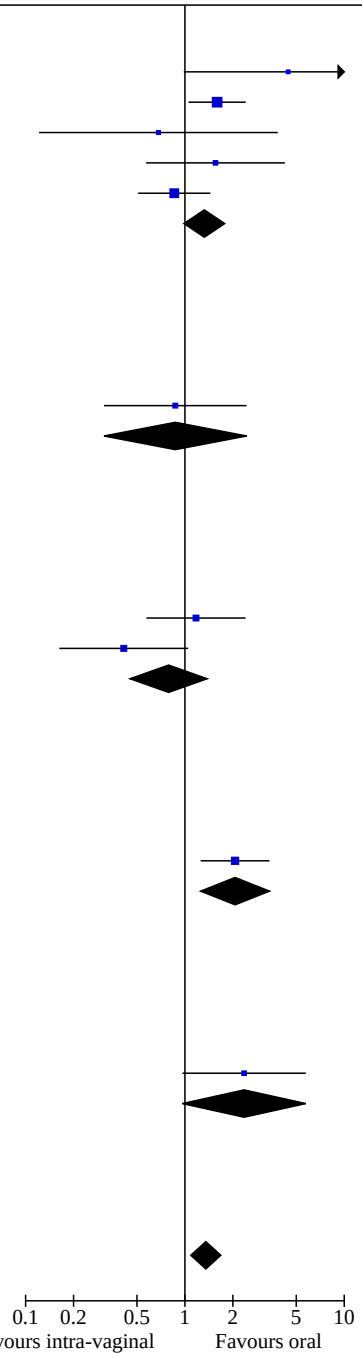
Analysis 2.3. (Continued)

Test for overall effect: Z = 1.52 (P = 0.13) Favours intra-vaginal Favours oral

Test for subgroup differences: Chi² = 10.84, df = 4 (P = 0.03), I² = 63.1%

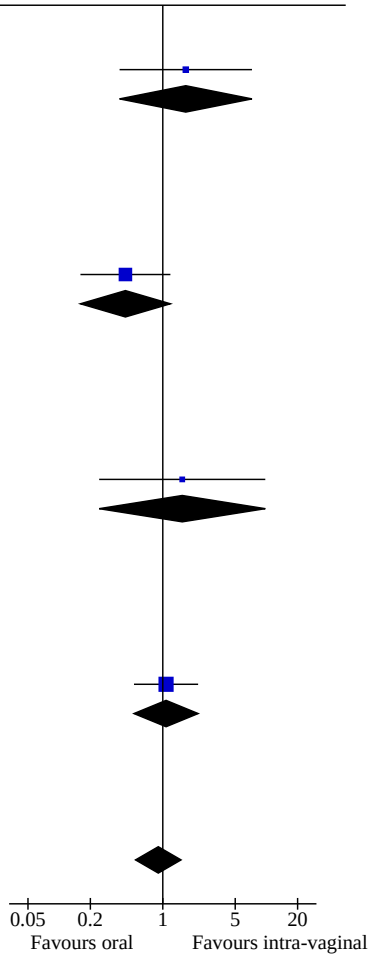
Analysis 2.4. Comparison 2: Oral versus Intra-vaginal (no. randomised), Outcome 4: Mycological cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 Fluconazole vs Clotrimazole						
Adetoro 1990	20	23	12	20	1.2%	4.44 [0.98 , 20.07]
Andersen 1989	115	188	90	181	25.3%	1.59 [1.05 , 2.41]
Goode 1992	3	14	4	14	2.2%	0.68 [0.12 , 3.83]
Mikamo 1995	35	50	15	25	4.3%	1.56 [0.57 , 4.24]
Stein 1991	57	111	64	116	21.7%	0.86 [0.51 , 1.45]
Subtotal (95% CI)		**386**		**356**	**54.7%**	**1.32 [0.99 , 1.78]**
Total events:	230		185			
Heterogeneity: Chi² = 6.57, df = 4 (P = 0.16); I² = 39%						
Test for overall effect: Z = 1.87 (P = 0.06)						
2.4.2 Itraconazole vs Clotrimazole						
Stein 1993	31	50	15	23	5.6%	0.87 [0.31 , 2.44]
Subtotal (95% CI)		**50**		**23**	**5.6%**	**0.87 [0.31 , 2.44]**
Total events:	31		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
2.4.3 Fluconazole vs Miconazole						
Timonen 1992a	39	63	36	62	9.8%	1.17 [0.57 , 2.40]
Van Heusden 1990	32	49	41	50	10.0%	0.41 [0.16 , 1.05]
Subtotal (95% CI)		**112**		**112**	**19.9%**	**0.79 [0.45 , 1.38]**
Total events:	71		77			
Heterogeneity: Chi² = 3.04, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.83 (P = 0.41)						
2.4.4 Fluconazole vs Econazole						
Osser 1991	79	128	57	130	15.4%	2.06 [1.26 , 3.39]
Subtotal (95% CI)		**128**		**130**	**15.4%**	**2.06 [1.26 , 3.39]**
Total events:	79		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
2.4.5 Itraconazole vs Econazole						
Timonen 1992b	25	40	17	41	4.5%	2.35 [0.96 , 5.74]
Subtotal (95% CI)		**40**		**41**	**4.5%**	**2.35 [0.96 , 5.74]**
Total events:	25		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
Total (95% CI)		**716**		**662**	**100.0%**	**1.35 [1.09 , 1.68]**
Total events:	436		351			
Heterogeneity: Chi² = 17.95, df = 9 (P = 0.04); I² = 50%						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Chi² = 8.57, df = 4 (P = 0.07), I² = 53.3%						



Analysis 2.5. Comparison 2: Oral versus Intra-vaginal (no. randomised), Outcome 5: Side effects

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 Fluconazole vs Clotrimazole						
Sekhavat 2011	5	72	3	70	8.9%	1.67 [0.38 , 7.26]
Subtotal (95% CI)		**72**		**70**	**8.9%**	**1.67 [0.38 , 7.26]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.5.2 Itraconazole vs Clotrimazole						
Sanam 2009	6	132	13	132	39.2%	0.44 [0.16 , 1.18]
Subtotal (95% CI)		**132**		**132**	**39.2%**	**0.44 [0.16 , 1.18]**
Total events:	6		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
2.5.3 Fluconazole vs Fenticonazole						
Murina 2012	3	40	2	40	5.8%	1.54 [0.24 , 9.75]
Subtotal (95% CI)		**40**		**40**	**5.8%**	**1.54 [0.24 , 9.75]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.5.4 Fluconazole vs Miconazole						
ACCELERATE 2002	17	150	17	160	46.0%	1.08 [0.53 , 2.19]
Subtotal (95% CI)		**150**		**160**	**46.0%**	**1.08 [0.53 , 2.19]**
Total events:	17		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**394**		**402**	**100.0%**	**0.90 [0.55 , 1.50]**
Total events:	31		35			
Heterogeneity: Chi² = 3.26, df = 3 (P = 0.35); I² = 8%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi² = 3.26, df = 3 (P = 0.35), I² = 7.9%						



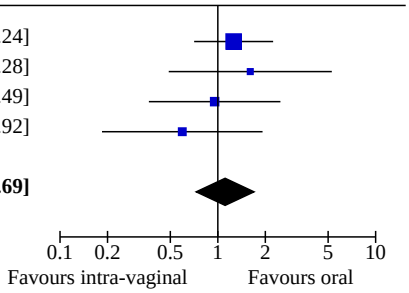
Comparison 3. Single-dose oral therapy versus 3 days intra-vaginal therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mycological cure (short term)	4	618	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.73, 1.69]
3.2 Mycological cure (long term)	3	509	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.82, 1.73]

Analysis 3.1. Comparison 3: Single-dose oral therapy versus 3 days intra-vaginal therapy, Outcome 1: Mycological cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andersen 1989	143	169	131	161	50.3%	1.26 [0.71 , 2.24]
Coric 2006	33	38	37	46	10.7%	1.61 [0.49 , 5.28]
O-Prasertsawat 1995	42	53	40	50	20.8%	0.95 [0.37 , 2.49]
Timonen 1992a	45	54	42	47	18.2%	0.60 [0.18 , 1.92]
Total (95% CI)		**314**		**304**	**100.0%**	**1.11 [0.73 , 1.69]**
Total events:	263		250			

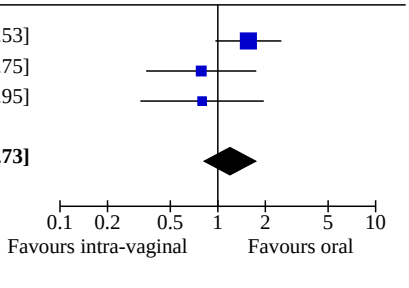
Heterogeneity: Chi² = 1.74, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Single-dose oral therapy versus 3 days intra-vaginal therapy, Outcome 2: Mycological cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andersen 1989	115	160	90	145	52.4%	1.56 [0.97 , 2.53]
O-Prasertsawat 1995	32	53	33	50	26.5%	0.78 [0.35 , 1.75]
Timonen 1992a	39	54	36	47	21.1%	0.79 [0.32 , 1.95]
Total (95% CI)		**267**		**242**	**100.0%**	**1.19 [0.82 , 1.73]**
Total events:	186		159			

Heterogeneity: Chi² = 3.03, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



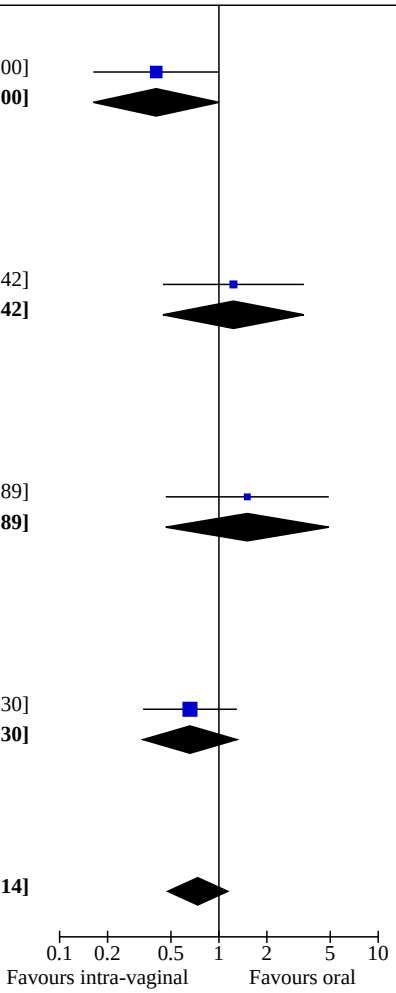
Comparison 4. Single-dose oral anti-fungal therapy versus single-dose intra-vaginal anti-fungal therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Clinical cure (short term)	4	572	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.14]
4.1.1 Fluconazole vs Clotrimazole	1	113	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.16, 1.00]
4.1.2 Fluconazole vs Miconazole	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.45, 3.42]
4.1.3 Fluconazole vs Econazole	1	230	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.46, 4.89]
4.1.4 Fluconazole vs Butoconazole	1	136	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.33, 1.30]
4.2 Clinical cure (long term)	2	270	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.60, 2.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.1 Fluconazole vs Miconazole	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.51, 4.66]
4.2.2 Fluconazole vs Econazole	1	177	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.40, 2.72]
4.3 Mycological cure (short term)	6	737	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.77, 1.74]
4.3.1 Fluconazole vs Clotrimazole	4	414	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.50, 1.42]
4.3.2 Fluconazole vs Miconazole	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [0.15, 20.00]
4.3.3 Fluconazole vs Econazole	1	230	Odds Ratio (M-H, Fixed, 95% CI)	1.93 [0.97, 3.83]

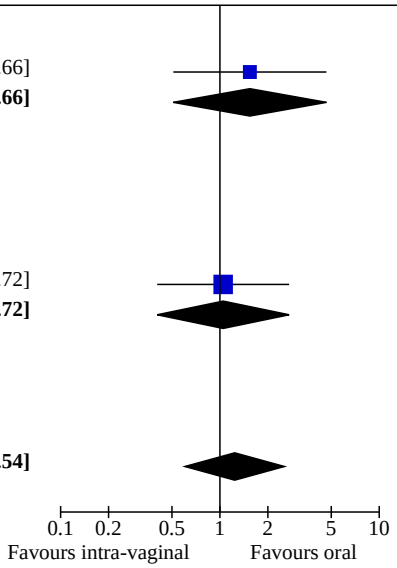
Analysis 4.1. Comparison 4: Single-dose oral anti-fungal therapy versus single-dose intra-vaginal anti-fungal therapy, Outcome 1: Clinical cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Fluconazole vs Clotrimazole						
Woolley 1995	45	72	33	41	33.1%	0.40 [0.16 , 1.00]
Subtotal (95% CI)		**72**		**41**	**33.1%**	**0.40 [0.16 , 1.00]**
Total events:	45		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
4.1.2 Fluconazole vs Miconazole						
Van Heusden 1990	35	43	39	50	14.1%	1.23 [0.45 , 3.42]
Subtotal (95% CI)		**43**		**50**	**14.1%**	**1.23 [0.45 , 3.42]**
Total events:	35		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
4.1.3 Fluconazole vs Econazole						
Osser 1991	113	118	105	112	9.6%	1.51 [0.46 , 4.89]
Subtotal (95% CI)		**118**		**112**	**9.6%**	**1.51 [0.46 , 4.89]**
Total events:	113		105			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
4.1.4 Fluconazole vs Butoconazole						
Seidman 2005	33	69	39	67	43.3%	0.66 [0.33 , 1.30]
Subtotal (95% CI)		**69**		**67**	**43.3%**	**0.66 [0.33 , 1.30]**
Total events:	33		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**302**		**270**	**100.0%**	**0.74 [0.48 , 1.14]**
Total events:	226		216			
Heterogeneity: Chi² = 4.19, df = 3 (P = 0.24); I² = 28%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Test for subgroup differences: Chi² = 4.19, df = 3 (P = 0.24), I² = 28.4%						

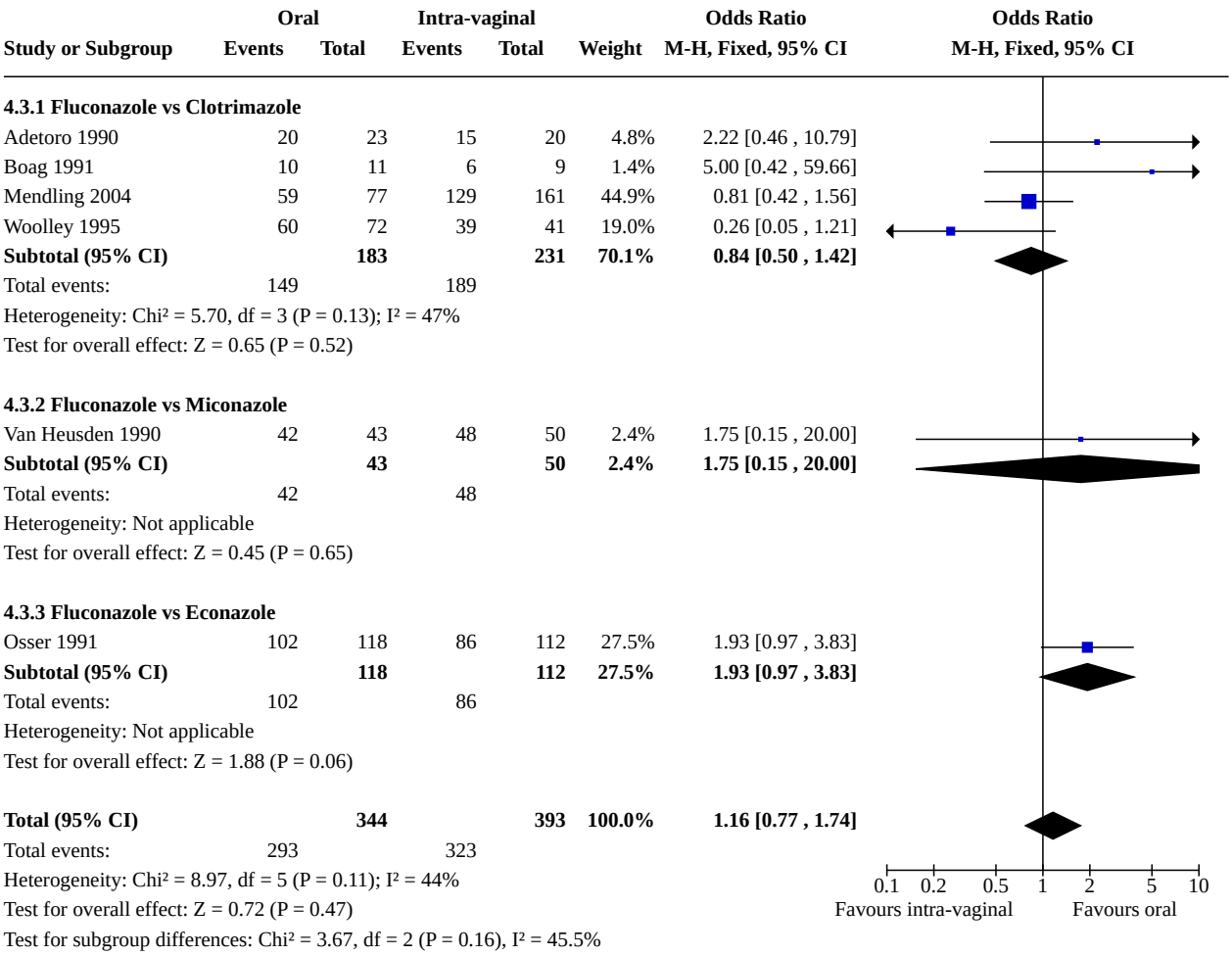


Analysis 4.2. Comparison 4: Single-dose oral anti-fungal therapy versus single-dose intra-vaginal anti-fungal therapy, Outcome 2: Clinical cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Fluconazole vs Miconazole						
Van Heusden 1990	37	43	40	50	38.5%	1.54 [0.51 , 4.66]
Subtotal (95% CI)		**43**		**50**	**38.5%**	**1.54 [0.51 , 4.66]**
Total events:	37		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
4.2.2 Fluconazole vs Econazole						
Osser 1991	85	95	73	82	61.5%	1.05 [0.40 , 2.72]
Subtotal (95% CI)		**95**		**82**	**61.5%**	**1.05 [0.40 , 2.72]**
Total events:	85		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**138**		**132**	**100.0%**	**1.24 [0.60 , 2.54]**
Total events:	122		113			
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						



Analysis 4.3. Comparison 4: Single-dose oral anti-fungal therapy versus single-dose intra-vaginal anti-fungal therapy, Outcome 3: Mycological cure (short term)



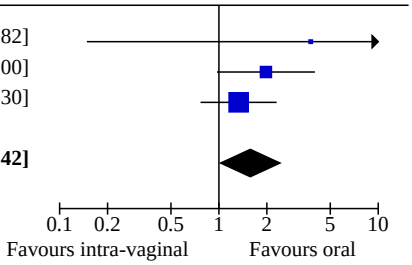
Comparison 5. Single-dose oral therapy versus 6-7 day intra-vaginal therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Clinical cure (short term)	3	427	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [1.03, 2.42]
5.2 Clinical cure (long term)	2	266	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.54, 1.83]
5.3 Mycological cure (short term)	4	527	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.97, 2.21]
5.4 Mycological cure (long term)	3	366	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.88, 2.10]
5.5 Side effects	1	142	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.38, 7.26]

Analysis 5.1. Comparison 5: Single-dose oral therapy versus 6-7 day intra-vaginal therapy, Outcome 1: Clinical cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goode 1992	3	3	6	9	1.4%	3.77 [0.15 , 95.82]
Sekhavat 2011	53	72	41	70	32.8%	1.97 [0.97 , 4.00]
Sobel 1995	108	139	97	134	65.8%	1.33 [0.77 , 2.30]
Total (95% CI)		**214**		**213**	**100.0%**	**1.57 [1.03 , 2.42]**
Total events:	164		144			

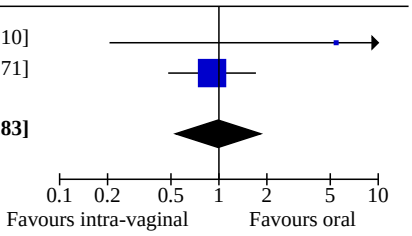
Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Single-dose oral therapy versus 6-7 day intra-vaginal therapy, Outcome 2: Clinical cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goode 1992	3	3	4	7	1.8%	5.44 [0.21 , 144.10]
Sobel 1995	106	131	103	125	98.2%	0.91 [0.48 , 1.71]
Total (95% CI)		**134**		**132**	**100.0%**	**0.99 [0.54 , 1.83]**
Total events:	109		107			

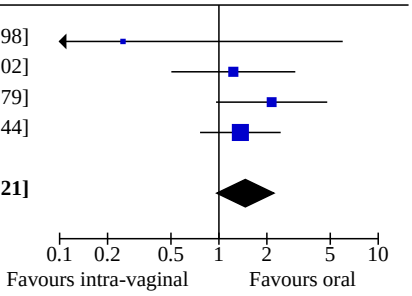
Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Single-dose oral therapy versus 6-7 day intra-vaginal therapy, Outcome 3: Mycological cure (short term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goode 1992	2	3	8	9	3.5%	0.25 [0.01 , 5.98]
Mikamo 1995	38	50	36	50	22.9%	1.23 [0.50 , 3.02]
Sekhavat 2011	60	72	49	70	22.0%	2.14 [0.96 , 4.79]
Sobel 1995	113	139	102	134	51.6%	1.36 [0.76 , 2.44]
Total (95% CI)		**264**		**263**	**100.0%**	**1.47 [0.97 , 2.21]**
Total events:	213		195			

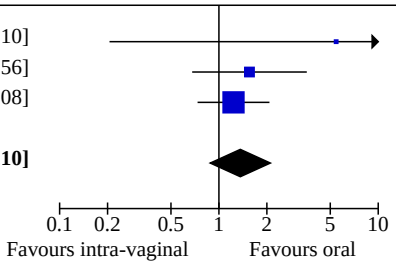
Heterogeneity: Chi² = 2.25, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Single-dose oral therapy versus 6-7 day intra-vaginal therapy, Outcome 4: Mycological cure (long term)

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goode 1992	3	3	4	7	1.1%	5.44 [0.21 , 144.10]
Mikamo 1995	35	50	30	50	25.7%	1.56 [0.68 , 3.56]
Sobel 1995	90	131	80	125	73.2%	1.23 [0.73 , 2.08]
Total (95% CI)		**184**		**182**	**100.0%**	**1.36 [0.88 , 2.10]**
Total events:	128		114			

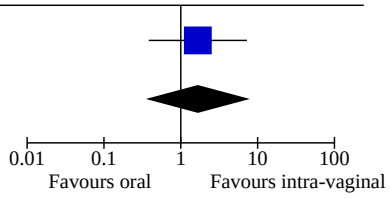
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Single-dose oral therapy versus 6-7 day intra-vaginal therapy, Outcome 5: Side effects

Study or Subgroup	Oral Events	Oral Total	Intra-vaginal Events	Intra-vaginal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sekhavat 2011	5	72	3	70	100.0%	1.67 [0.38 , 7.26]
Total (95% CI)		**72**		**70**	**100.0%**	**1.67 [0.38 , 7.26]**
Total events:	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



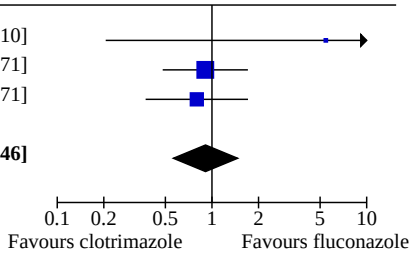
Comparison 6. Fluconazole versus Clotrimazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Long term clinical cure	3	438	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.56, 1.46]
6.2 Long term mycological cure	7	940	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.94, 1.65]

Analysis 6.1. Comparison 6: Fluconazole versus Clotrimazole, Outcome 1: Long term clinical cure

Study or Subgroup	Fluconazole Events	Fluconazole Total	Clotrimazole Events	Clotrimazole Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goode 1992	3	3	4	7	1.1%	5.44 [0.21 , 144.10]
Sobel 1995	106	131	103	125	56.9%	0.91 [0.48 , 1.71]
Stein 1991	68	86	71	86	42.0%	0.80 [0.37 , 1.71]
Total (95% CI)		**220**		**218**	**100.0%**	**0.91 [0.56 , 1.46]**
Total events:	177		178			

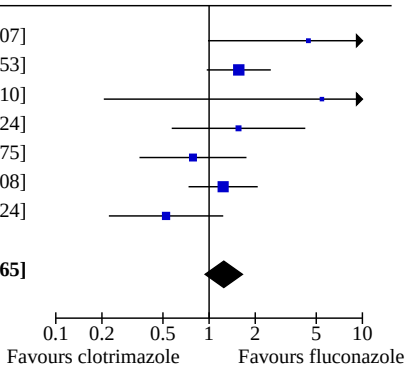
Heterogeneity: Chi² = 1.26, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Fluconazole versus Clotrimazole, Outcome 2: Long term mycological cure

Study or Subgroup	Fluconazole Events	Fluconazole Total	Clotrimazole Events	Clotrimazole Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Adetoro 1990	20	23	12	20	1.9%	4.44 [0.98 , 20.07]
Andersen 1989	115	160	90	145	30.0%	1.56 [0.97 , 2.53]
Goode 1992	3	3	4	7	0.4%	5.44 [0.21 , 144.10]
Mikamo 1995	35	50	15	25	6.8%	1.56 [0.57 , 4.24]
O-Prasertsawat 1995	32	53	33	50	15.2%	0.78 [0.35 , 1.75]
Sobel 1995	90	131	80	125	29.0%	1.23 [0.73 , 2.08]
Stein 1991	57	74	64	74	16.6%	0.52 [0.22 , 1.24]
Total (95% CI)		**494**		**446**	**100.0%**	**1.25 [0.94 , 1.65]**
Total events:	352		298			

Heterogeneity: Chi² = 9.73, df = 6 (P = 0.14); I² = 38%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Duration of follow-up (for primary and/or secondary outcome measures)

Study	T1	T2	T3	T4
ACCELERATE 2002	7 - 10 days			
Adetoro 1990	8 days	32 days		
Andersen 1989	5 - 16 days	27 - 62 days		
Boag 1991	1 - 3 days	4 - 5 days	6 - 8 days	9 -12 days
Coric 2006	24 hours	14 days		
Goode 1992	2 weeks	4 weeks		
Mendling 2004	2 weeks	4 weeks	8 weeks	
Mikamo 1995	5 - 15 days	30 - 60 days		
Murina 2012	7days	30 - 35		
O-Prasertsawat 1995	1 week	4 weeks		
Osser 1991	7 - 10 days	28 - 35 days	80 - 100 days	
Roongpisuthipong 2010	7 days	28 days		
Sanam 2009	10 days			
Seidman 2005	hourly			
Sekhavat 2011	7 days	1 month		

Table 1. Duration of follow-up (for primary and/or secondary outcome measures) *(Continued)*

Škerk V 2006	up to 2 months	
Slavin 1992	7 - 14 days	28 - 34 days
Sobel 1995	14 days	35 days
Stein 1991	1 week	4 weeks
Stein 1993	7 - 10 days	30 - 35 days
Timonen 1992a	1 week	2 weeks
Timonen 1992b	1 week	1 month
Tobin 1992	5 - 10 days	30 - 40 days
Van Heusden 1990	6 - 10 days	22 - 60 days
Van Heusden 1994	7 days	28 days
Woolley 1995	7 - 10 days	

Table 2. Sensitivity Analyses

Outcome Measure	All comparisons	Selection Bias	Blinded Outcome Assessor	Incomplete Outcome Data
Clinical cure (short)	14 comparisons, OR 1.14, 95% CI [0.91, 1.43]	0/14 comparisons	1/14 comparisons, OR 1.70, 95% CI [0.64, 4.55]	12/14 comparisons, OR 1.22, 95% CI [0.95, 1.56]
Clinical cure (long)	9 comparisons, OR 1.07, 95% CI [0.77, 1.50]	0/9 comparisons	1/9 comparisons, OR 0.69, 95% CI [0.20, 2.41]	7/9 comparisons, OR 0.95, 95% CI [0.66, 1.38]
Mycological cure (short)	20 comparisons, OR 1.24, 95% CI [1.03, 1.50]	1/20 comparisons, OR 0.95, 95% CI [0.37, 2.49]	1/20 comparisons, OR 3.55, 95% CI [1.29, 9.77]	15/20 comparisons, OR 1.41, 95% CI, [1.09, 1.82]
Mycological cure (long)	13 comparisons, OR 1.29, 95% CI [1.05, 1.60]	1/13 comparisons, OR 0.78, 95% CI [0.35, 1.75]	1/13 comparisons, OR 2.26, 95% CI [0.89, 5.74]	9/13 comparisons, OR 1.19, 95% CI [0.90, 1.56],

OR - odds ratio
95% CI - 95% percent confidence interval
Comparisons had to be rated as low risk of bias for both random allocation and allocation concealment to be included in the selection bias sensitivity analysis. Comparisons for blinded outcome assessor and incomplete outcome data had to be rated as low risk of bias in the respective categories. All sensitivity analyses are reported as odds ratio with 95% confidence intervals.

APPENDICES

Appendix 1. MEDLINE, Embase and CENTRAL search strategy update (2015-2018)

Database	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update
Platform	Ovid
Search date	23/05/2018
Range of search date	2015 - 2018
Language Restrictions	None
Other Limits	Randomized clinical trials
Search strategy (results)	1 exp Imidazoles/ (251315) 2 exp Triazoles/ (33299) 3 exp Antifungal Agents/ (155439) 4 (butoconazole or clotrimazole or econazole).tw. (2981) 5 (fenticonazole or fluconazole or isoconazole).tw. (10938) 6 (itraconazole or miconazole or omoconazole).tw. (10034) 7 (oxiconazole or terconazole or tioconazole).tw. (345) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (420014) 9 exp Candidiasis, Vulvovaginal/ (3314) 10 ((vagina$ adj5 candidosis) or (vulvovagina$ adj5 candidosis) or (vagina$ adj5 mycoses) or (vagina$ adj5 candidiasis) or (vulvovagina$ adj5 candidiasis) or (vagina$ adj5 mycoses) or (vagina$ adj5 thrush)).tw. (2281) 11 9 or 10 (4141) 12 randomized controlled trial.pt. (462300) 13 controlled clinical trial.pt. (92438) 14 (randomized or randomised).ti,ab. (531453) 15 placebo.ti,ab. (194698) 16 clinical trials as topic.sh. (183855) 17 randomly.ti,ab. (292138) 18 trial.ti. (183315) 19 (crossover or cross-over or cross over).tw. (76612) 20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1217979) 21 exp animals/ not humans.sh. (4463161) 22 20 not 21 (1122279)

(Continued)

	23 8 and 11 and 22 (390) 24 limit 23 to yr="2015 -Current" (28)
Number of references identified	28

Database	EMBASE
Platform	EMBASE.com
Search date	23/05/2018
Range of search date	2015-2018
Language Restrictions	None
Other Limits	Randomized clinical trials
Search strategy (results)	1. 'imidazole derivative'/exp (777386) 2. 'triazole derivative'/exp (147637) 3. 'antifungal agent'/exp (332564) 4. butoconazole:ab,ti OR clotrimazole:ab,ti OR econazole:ab,ti (3908) 5. fenticonazole:ab,ti OR fluconazole:ab,ti OR isoconazole:ab,ti (15085) 6. itraconazole:ab,ti OR miconazole:ab,ti OR omoconazole:ab,ti (13381) 7. oxiconazole:ab,ti OR terconazole:ab,ti OR tioconazole:ab,ti (504) 8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 (1064410) 9. 'vagina candidiasis'/exp (4869) 10. ((vagina* NEAR/5 candidosis):ab,ti) OR ((vulvovagina* NEAR/5 candidosis):ab,ti) OR ((vagina* NEAR/5 candidiasis):ab,ti) OR ((vulvovagina* NEAR/5 candidiasis):ab,ti) OR ((vagina* NEAR/5 mycoses):ab,ti) OR ((vagina* NEAR/5 thrush):ab,ti) (3134) 11. #9 OR #10 (5771) 12. 'randomized controlled trial'/de (497851) 13. 'controlled clinical study'/de (426369) 14. random*:ti,ab (1288799) 15. 'randomization'/de (77741) 16. 'intermethod comparison'/de (234226) 17. placebo:ti,ab (269265) 18. compare:ti OR compared:ti OR comparison:ti (472043) 19. (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab) (1726872)

(Continued)

	20. (open NEAR/1 label):ti,ab (63503) 21. ((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab (207173) 22. 'double blind procedure'/de (148746) 23. (parallel NEXT/1 group*):ti,ab (21432) 24. crossover:ti,ab OR 'cross over':ti,ab (91765) 25. ((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab (279205) 26. assigned:ti,ab OR allocated:ti,ab (327361) 27. (controlled NEAR/7 (study OR design OR trial)):ti,ab (291068) 28. volunteer:ti,ab OR volunteers:ti,ab (222766) 29. trial:ti249242 30. 'human experiment'/de (404507) 31. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 (4260415) 32. #8 AND #11 AND #31 (646) 33. #8 AND #11 AND #31 AND [embase]/lim AND [2015-2018]/py (109)
Number of references identified	109

Database	Cochrane Central Register of Controlled Trials
Platform	Ovid
Search date	23/05/2018
Range of search date	2015-2018
Language Restrictions	None
Other Limits	None
Search strategy (results)	1 exp Imidazoles/ (17051) 2 exp Triazoles/ (2174) 3 exp Antifungal Agents/ (6176) 4 (butoconazole or clotrimazole or econazole).tw. (476) 5 (fenticonazole or fluconazole or isoconazole).tw. (918) 6 (itraconazole or miconazole or omoconazole).tw. (997) 7 (oxiconazole or terconazole or tioconazole).tw. (76) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (24607)

(Continued)

	9 exp Candidiasis, Vulvovaginal/ (259) 10 ((vagina$ adj5 candidosis) or (vulvovagina$ adj5 candidosis) or (vagina$ adj5 mycoses) or (vagina$ adj5 candidiasis) or (vulvovagina$ adj5 candidiasis) or (vagina$ adj5 mycoses) or (vagina$ adj5 thrush)).tw. (380) 11 9 or 10 (459) 12 8 and 11 (341) 13 limit 12 to yr="2015 -Current" (33)
Number of references identified	33

Appendix 2. MEDLINE, Embase and CENTRAL search strategy update (2018-2019)

Database	§ MEDLINE § MEDLINE In-Process & Other Non-Indexed Citations § MEDLINE Daily Update
Platform	Ovid
Search date	29/08/2019
Range of search date	2018-2019
Language Restrictions	None
Other Limits	None
Search strategy (results)	1. (recurr$ adj5 herpes).tw. (1960) 2. exp Herpes Genitalis/ (4594) 3. exp Herpes Simplex/ (23809) 4. herpe$.tw. (80739) 5. hsv$.tw. (23822) 6. or/2-5 (88021) 7. recurr$.tw. (480861) 8. 6 and 7 (5095) 9. 1 or 8 (5095) 10. (short adj5 therapy).tw. (8549) 11. (short adj5 treatment).tw. (20480) 12. (short adj5 course).tw. (8582) 13. (short adj5 term).tw. (201653) 14. (short adj5 regimen).tw. (901)

(Continued)

15. (short adj5 cycle).tw. (1619)

16. (short adj5 strategy).tw. (1011)

17. (episodic adj5 therapy).tw. (175)

18. (episodic adj5 treatment).tw. (518)

19. (episodic adj5 course).tw. (215)

20. (episodic adj5 regimen).tw. (10)

21. (episodic adj5 cycle).tw. (26)

22. (episodic adj5 strategy).tw. (31)

23. or/10-22 (221262)

24. randomized controlled trial.pt. (487300)

25. controlled clinical trial.pt. (93205)

26. randomized.ab. (400631)

27. placebo.ab. (184378)

28. clinical trials as topic.sh. (188022)

29. randomly.ab. (275513)

30. trial.ti. (178802)

31. 24 or 25 or 26 or 27 or 28 or 29 or 30 (1130737)

32. exp animals/ not humans.sh. (4610034)

33. 31 not 32 (1031704)

34. 9 and 23 and 33 (55)

35. limit 34 to yr="2015 -Current" (3)

Number of references identified	7

Database	EMBASE
Platform	EMBASE.com
Search date	29/08/2019
Range of search date	2018-2019
Language Restrictions	None
(Other Limits	None
Search strategy (results)	1. 'imidazole derivative'/exp (853556)
	2. 'triazole derivative'/exp (159845)

(Continued)

3. 'antifungal agent'/exp (355627)

4. butoconazole:ab,ti OR clotrimazole:ab,ti OR econazole:ab,ti (4113)

5. fenticonazole:ab,ti OR fluconazole:ab,ti OR isoconazole:ab,ti (16491)

6. itraconazole:ab,ti OR miconazole:ab,ti OR omoconazole:ab,ti (14377)

7. oxiconazole:ab,ti OR terconazole:ab,ti OR tioconazole:ab,ti (533)

8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #71161419

9. 'vagina candidiasis'/exp (5196)

10. ((vagina* NEAR/5 candidosis):ab,ti) OR ((vulvovagina* NEAR/5 candidosis):ab,ti) OR ((vagina* NEAR/5 candidiasis):ab,ti) OR ((vulvovagina*NEAR/5 candidiasis):ab,ti) OR ((vagina* NEAR/5 mycoses):ab,ti) OR ((vagina* NEAR/5 thrush):ab,ti) (3366)

11. #9 OR #10 (6135)

12. 'randomized controlled trial'/de (564076)

13. 'controlled clinical study'/de (427613)

14. random*:ti,ab (1438163)

15. 'randomization'/de (83269)

16. 'intermethod comparison'/de (252074)

17. placebo:ti,ab (292650)

18. compare:ti OR compared:ti OR comparison:ti (508934)

19. (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab) (1963716)

20. (open NEAR/1 label):ti,ab (72969)

21. ((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab (223924)

22. 'double blind procedure'/de (164124)

23. (parallel NEXT/1 group*):ti,ab (23905)

24. crossover:ti,ab OR 'cross over':ti,ab (99844)

25. ((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab (310834)

26. assigned:ti,ab OR allocated:ti,ab (364001)

27. (controlled NEAR/7 (study OR design OR trial)):ti,ab (327118)

28. volunteer:ti,ab OR volunteers:ti,ab (238808)

29. trial:ti (283135)

30. 'human experiment'/de (462873)

31. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29OR #30 (4735963)

32. #8 AND #11 AND #31 (684)

#8 AND #11 AND #31 AND [embase]/lim AND [2018-2019]/py (55)

(Continued)

Number of references identified	55

Database	CENTRAL
Platform	OVID
Search date	29/08/2019
Range of search date	2018-2019
Language Restrictions	None
Other Limits	None
Search strategy (results)	1. exp Imidazoles/ (19488) 2. exp Triazoles/ (2412) 3. exp Antifungal Agents/ (7650) 4. (butoconazole or clotrimazole or econazole).tw. (607) 5. (fenticonazole or fluconazole or isoconazole).tw. (1193) 6. (itraconazole or miconazole or omoconazole).tw. (1271) 7. (oxiconazole or terconazole or tioconazole).tw. (89) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (28893) 9. exp Candidiasis, Vulvovaginal/ (307) 10. ((vagina$ adj5 candidosis) or (vulvovagina$ adj5 candidosis) or (vagina$ adj5 mycoses) or (vagina$ adj5 candidiasis) or (vulvovagina$ adj5 candidiasis) or (vagina$ adj5 mycoses) or (vagina$ adj5 thrush)).tw. (541) 11. 9 or 10 (627) 12. 8 and 11 (440) 13. 13 limit 12 to yr="2018 -Current" (22)
Number of references identified	22

Appendix 3. Worksheets for grading the certainty of the evidence

No of studies	Design	Risk of bias	Inconsistency	Indirectness[1]	Imprecision	Other[2]	Certainty (overall score)[3]
Outcome: Clinical cure - short term							
15	RCT	Agreed: main high risk is due to lack of blinding of participants and outcomes Downgrade by -1 for serious concerns.	Agreed: low concern. While some heterogeneity around Analysis 1.1.1, the result is no effect, which is the overall result of the whole analysis.	Agreed: no concerns and no downgrading.	Agreed: minor concern and no downgrading. While the confidence intervals are wide, they do not extend into a very high or very low odds ratio (OR) range. The number of people in the analysis is large.	None	Downgrade -1 to moderate certainty
Outcome: Clinical cure - long term							
9	RCT	Agreed - same issues as above downgrade -1	Agreed: low heterogeneity, no concerns.	Agreed: no concerns and no downgrading	Agreed: same as above.Minor concern and no downgrading	None	Downgrade -1 to moderate certainty
Outcome: Mycological cure - short term							
19	RCT	Agreed: minor concerns and no downgrading. This is more of an objective measure and blinding may be less important. There are also some minor concerns about allocation concealment and selective reporting.	Agreed: although there is some heterogeneity present here, it seems to be mainly explained by the different drugs in the comparisons. Because there is a plausible explanation for the heterogeneity, note as minor concerns.	Agreed: no concerns and no downgrading	Agreed:there are a lot of people in this analysis, but the confidence interval includes values that suggest almost no effect to values that suggest 50% more likely to favour oral. This is somewhat imprecise and downgrade by -1.	None	Downgrade -1 to moderate certainty
Outcome: Mycological cure - long term							

(Continued)

13	RCT	Agreed: same as above	Agreed: minor concern - Analyisis 1.4.1 shows quite a bit of heterogeneity within the same drug comparison, but not a serious concern	Agreed: no concerns and no downgrading	Agreed: same as above	None	Downgrade -1 to moderate certainty
Outcome: Safety - withdrawals							
3	RCT	Agreed: the number of withdrawals is small and was the choice of health professionals. No serious concerns	Agreed: no forest plot, but majority of studies had no withdrawals, and the two that did only had a very small number of withdrawals, thus no concerns	Agreed: no concerns and no downgrading	Agreed: no CIs to assess	None	No downgrading - high certainty
Outcome: Side effects							
17	RCT	Agreed: side effects are poorly defined in the studies, and assessment was highly subjective meaning it could have been influenced by the lack of blinding. Downgrade -1 for serious concerns.	Agreed: substantial heterogeneity across and within subgroups. Serious concerns, downgrade by -1.	Agreed: no concerns and no downgrading	Agreed: while the confidence intervals are wide, they do not extend into a very high or very low odds ratio (OR) range. The number of people in the analysis is large. Only minor concerns, not serious. Don't downgrade.	None	Downgrade by -2 to low certainty
Outcome: Treatment preference							
12	RCT	Agreed: this is self-report outcome and overall ROB for the studies (5 high, 5 unclear and 2 low). If we ignore the assessments fo the blinding of the other outcomes we still have the high and unclear judgments - serious concerna and downgrade -1	Agreed: no forest plot, but the majority of studies found the same result of preference for oral treatment over intra-vaginal, no concerns here.	Agreed: no concerns and no downgrading	Agreed: no CIs to assess. Self-report and inconsistencies with reporting the preferred route of administration limit the use of these data. Downgrade -1	None	Downgrade -2 to low certainty
Outcome: Time to first relief							

(Continued)

10	RCT	Agreed: assessment was highly subjective meaning it could have been influenced by the lack of blinding. Downgrade -1 for serious concerns	Agreed: difficult to assess due to differences in reporting of data. Inconsistencies can likely be explained by the differences in how side effects were assessed and recorded between studies. Because there is a plausible explanation for the heterogeneity, Don't downgrade but note as minor concerns.	Agreed: no concerns and no downgrading	Agreed: no CIs to assess. Unable to determine precise effects. Downgrade -1	None	Downgrade -2 to low certainty
Outcome: Costs							
0	-	-	-	-	-	-	-

[1] Indirectness includes consideration of:

- · Indirect (between study) comparisons
- · Indirect (surrogate) outcomes
- · Applicability (study populations, interventions or comparisons that are different than those of interest)

[2] Other considerations for downgrading include publication bias. Other considerations for upgrading include a strong association with no plausible confounders, a dose response relationship, and if all plausible confounders or biases would decrease the size of the effect (if there is evidence of an effect), or increase it if there is evidence of no harmful effect (safety)

[3]

Score 4 **High certainty**= This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different** is low.

Score 3 **Moderate certainty** = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different** is moderate.

Score 2 **Low** certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different** is high.

Scpre 1 **Very low** certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different** is very high.

** Substantially different = a large enough difference that it might affect a decision

WHAT'S NEW

Date	Event	Description
29 August 2019	New search has been performed	This is the second update of the original review. The methods and searches have been updated to current Cochrane standards. There have been changes to the authorship with the addition of six new authors. We searched for studies to 29 August 2019 and identified seven new trials (ACCELERATE 2002; Coric 2006; Murina 2012; Roongpisuthipong 2010; Sanam 2009; Sekhavat 2011; Škerk V 2006). This review includes 26 trials.
29 August 2019	New citation required but conclusions have not changed	The addition of new evidence does not change the conclusions of the review. The results of this review should be considered stable in terms of the antifungal medicines included. The frequency of future updates should be limited. No further updates are planned.

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 1, 2001

Date	Event	Description
20 October 2015	Amended	Final updated version submitted to STI group
15 September 2015	Amended	An additional outcome, time to first relief, was added.
30 June 2015	New search has been performed	The review was updated with data identified from searches conducted on 18th June 2015. A new statistically significant differ-

Date	Event	Description
		ence was shown with long term mycological cure as a result of the inclusion of the new studies.
11 November 2008	Amended	Converted to new review format.
22 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JMG is the guarantor for this review

HD, JW, MCW and MES undertook duplicate screening and data abstraction

AM, HD, JW and MES completed the risk of bias assessment

CR, HD, JW and SR performed the GRADE assessment

AM, CB, HD, JMG, JW, MCW, MES contributed to the preparation of the review manuscript

The original review was conceived by Margaret C Watson (MCW), Jeremy M Grimshaw (JMG) and Christine Bond (CB).The views expressed in this review are those of the authors and may not be shared by the funding organisation.

DECLARATIONS OF INTEREST

HD: None known

JW: None known

CMB: Has received editor honoraria from Wiley and The Canadian Journal of Hospital Pharmacy; occasional fees from multiple (non pharma) organisations for speaking at meetings, reviewing book proposals; and reimbursement of expenses for travel to meetings

JMG: None known

AM: None known

CR: None known

SR: Awarded internship by University of Aberdeen to work on this project.

MES: None known

MCW: None known

SOURCES OF SUPPORT

Internal sources

- Health Services Research Unit, University of Aberdeen, UK
- Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, Canada

  (Salary support for Julia Worswick)
- Centre of Academic Primary Care, University of Aberdeen, UK

External sources

- JMG holds a Tier 1 Canadian Research Chair in Knowledge Transfer and Uptake, Canada
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the 2020 update we updated the review methods to align with current Cochrane standards and these are now different from those of the published protocol and the last published version of the review (Nurbhai 2007). We used a fixed-effect model only for the meta-analyses. We also added safety and side effects outcomes and have revised the review objective to reflect this. For the 'Risk of bias' assessment, we increased the follow-up requirement from 80% to 90% for the incomplete outcome data (attrition bias) criterion. There have been changes to the authorship with the addition of the following new authors: Hayley Denison, Alain Mayhew, Shakila Gnani Ramadoss, Clare Robertson, Mary Ellen Schaafsma and Julia Worswick. Munira Nurbhai, Jill Mollison and Anne Ludbrook did not participate in this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Intravaginal; Administration, Oral; Antifungal Agents [*administration & dosage] [economics]; Azoles [*administration & dosage] [economics]; Bias; Candidiasis, Vulvovaginal [*drug therapy]; Cost-Benefit Analysis; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans