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Antiamoebic drugs for treating amoebic colitis (Review)

Gonzales MLM, Dans LF, Sio-Aguilar J

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[Intervention Review]

Antiamoebic drugs for treating amoebic colitis

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ABSTRACT

Background

Infection with the protozoan *Entamoeba histolytica* is common in low- and middle-income countries, and up to 100,000 people with severe disease die every year. Adequate therapy for amoebic colitis is necessary to reduce illness, prevent development of complicated disease and extraintestinal spread, and decrease transmission.

Objectives

To evaluate antiamoebic drugs for treating amoebic colitis.

Search methods

We searched the available literature up to 22 March 2018. We searched the Cochrane Infectious Diseases Group Specialised Register, CENTRAL, MEDLINE, Embase, LILACS, *m*RCT, and conference proceedings. We contacted individual researchers, organizations, and pharmaceutical companies, and we checked reference lists.

Selection criteria

Randomized controlled trials of antiamoebic drugs given alone or in combination, compared with placebo or another antiamoebic drug, for treating adults and children with a diagnosis of amoebic colitis.

Data collection and analysis

Two review authors independently assessed the eligibility and methodological quality of trials and extracted and analysed the data. We calculated clinical and parasitological failure rates and rates of relapse and adverse events as risk ratios (RRs) with 95% confidence intervals (CIs), using a random-effects model. We determined statistical heterogeneity and explored possible sources of heterogeneity using subgroup analyses. We carried out sensitivity analysis by using trial quality to assess the robustness of reported results.

Main results

In total, 41 trials (4999 participants) met the inclusion criteria of this review. In this update, we added four trials to the 37 trials included in the first published review version. Thirty trials were published over 20 years ago. Only one trial used adequate methods of randomization and allocation concealment, was blinded, and analysed all randomized participants. Only one trial used an *E histolytica* stool antigen test, and two trials used amoebic culture.

Tinidazole may be more effective than metronidazole for reducing clinical failure (RR 0.28, 95% CI 0.15 to 0.51; 477 participants, eight trials; low-certainty evidence) and is probably associated with fewer adverse events (RR 0.65, 95% CI 0.46 to 0.92; 477 participants, 8 trials; moderate-certainty evidence). Compared with metronidazole, combination therapy may result in fewer parasitological failures (RR 0.36, 95% CI 0.15 to 0.86; 720 participants, 3 trials; low-certainty evidence), but we are uncertain which combination is more effective than another. Evidence is insufficient to allow conclusions regarding the efficacy of other antiamoebic drugs.

Authors' conclusions

Compared with metronidazole, tinidazole may be more effective in reducing clinical failure and may be associated with fewer adverse events. Combination drug therapy may be more effective for reducing parasitological failure compared with metronidazole alone. However, these results are based mostly on small trials conducted over 20 years ago with a variety of poorly defined outcomes. Tests that detect *E histolytica* more accurately are needed, particularly in countries where concomitant infection with other bacteria and parasites is common.

11 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (22 Mar, 2018) were included and two ongoing studies have been identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Antiamoebic drugs for treating amoebic colitis

What is the aim of this review?

This Cochrane Review aims to determine the effectiveness and safety of drugs used to treat people with amoebic colitis, which is an infection of the large intestines caused by the parasite, *Entamoeba histolytica*. Cochrane researchers searched for all relevant studies to answer this question and included 41 relevant studies in this review.

Key messages

Tinidazole may be more effective than metronidazole for reducing clinical symptoms and may be associated with fewer adverse events. Combination therapy resulted in fewer parasitological failures than occurred with metronidazole alone. Evidence is insufficient to allow conclusions regarding the efficacy of other antiamoebic drugs. Better quality randomized trials using accurate diagnostic methods and standardized outcomes are needed to evaluate the efficacy of drugs for treating individuals with amoebic colitis.

What was studied in the review?

Entamoeba histolytica is distributed throughout the world and is commonly acquired by ingestion of contaminated food or water. An estimated 40 to 50 million people infected with *E histolytica* develop amoebic colitis or extraintestinal abscesses, resulting in up to 100,000 deaths per year.

Metronidazole is currently the standard therapy for treating adults and children with invasive amoebiasis, but it may not be sufficient to eliminate amoebic cysts from the intestine. Some unpleasant adverse effects have been associated with metronidazole, and the possibility of parasite resistance to metronidazole has led to the development of alternative drugs. Combinations of metronidazole with other drugs that eradicate surviving cysts in the intestines have been recommended, so evidence to support this approach needs to be assessed.

This review compares different drugs used against amoebic colitis, alone or in combination, and also assesses single-dose regimens versus longer regimens.

What are the main results of the review?

This review included 41 studies, most of which were conducted in countries considered to be highly endemic for amoebiasis. Most trials were old: 30 were conducted before 1998. Trials varied in the inclusion criteria used to enrol participants and in the definition and timing of measured outcomes. Stool microscopy with direct wet saline smear was the method used most often to detect the presence of *E histolytica* in stools. Study participants ranged in age from seven months to 80 years. Included trials reported a variety of comparisons and involved 25 individual drugs, two herbal products, and 15 different combinations.

The review shows that in individuals with amoebic colitis, tinidazole may be better for reducing clinical symptoms (low-certainty evidence) and probably results in fewer adverse events when compared with metronidazole (moderate-certainty evidence). However, we do not know whether it is more effective for eradicating amoebae from the stools. Combination drug therapy may be more effective than metronidazole alone for eradicating amoebae (low-certainty evidence), but we are uncertain which drug combination is most effective, and if combination

treatment will lead to more rapid resolution of clinical symptoms or in more adverse events (very low-certainty evidence). Evidence is insufficient to allow conclusions regarding efficacy of the other antiamoebic drugs.

How up-to-date is this review?
The review authors searched for studies that had been published up to 22 March 2018.

Summary of findings for the main comparison. Summary of findings table 1

Tinidazole compared with metronidazole as treatment for amoebic colitis

Patient or population: adults and children with amoebic colitis

Settings: low- and middle-income countries

Intervention: tinidazole

Comparison: metronidazole

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Metronidazole	Tinidazole				
Clinical failure	**1 to 14 days after end of treatment**	**5 per 100**	**1 per 100** (< 1 to 7)	**RR 0.17** (0.02 to 1.30)	285 (2 studies)	⊕⊕⊖⊖ LOW[a-d] due to risk of bias and imprecision	Tinidazole may be more effective than metronidazole for reducing clinical failure
	15 to 60 days after end of treatment	**21 per 100**	**6 per 100** (3 to 11)	**RR 0.28** (0.15 to 0.51)	477 (8 studies)	⊕⊕⊖⊖ LOW[e-h] due to risk of bias	Tinidazole may be more effective than metronidazole for reducing clinical failure
Parasitological failure Method: stool microscopy demonstrating *E histolytica* cysts or trophozoites	**1 to 14 days after end of treatment**	**48 per 100**	**48 per 100** (28 to 84)	**RR 1.01** (0.58 to 1.74)	285 (2 studies)	⊕⊕⊖⊖ LOW[a,c,d,i] due to risk of bias and imprecision	Comparing tinidazole and metronidazole treatment, there may be little or no difference in number of parasitological failures
	15 to 60 days after end of treatment	**14 per 100**	**9 per 100** (4 to 23)	**RR 0.64** (0.25 to 1.64)	507 (9 studies)	⊕⊖⊖⊖ VERY LOW[d,e,g,j]	It is uncertain whether the number of parasitological failures differs comparing tinidazole or metronidazole treatment

						due to imprecision, risk of bias, and inconsistency	
Adverse events	**Until 30 days after start of treatment**	**45 per 1000**	**29 per 100** (21 to 41)	**RR 0.65** (0.46 to 0.92)	477 (8 studies)	⊕⊕⊕⊖ MODERATE[g,k-m] due to risk of bias	Tinidazole is probably associated with fewer adverse events than metronidazole

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; *E histolytica*:*Entamoeba histolytica*; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by 1 for serious risk of bias: the two trials that assessed outcomes 1 to 14 days after end of treatment were unclear regarding randomization, allocation concealment, and blinding. Both trials used only stool microscopy to diagnose and assess parasitological outcomes, and misclassification of diagnosis and eradication of *E histolytica* in stools is possible.

[b]Heterogeneity could not be assessed because only one trial contributed data.

[c]No serious indirectness: studies were conducted in countries endemic for amoebiasis: India (Joshi 1975) and Kenya (Chunge 1989). Trials included participants with unspecified intestinal amoebiasis or amoebic colitis, and results could be applied to other populations for whom amoebic colitis is endemic and who have similar clinical presentation.

[d]Downgraded by 1 for imprecision: total sample size and number of events are small. The 95% confidence interval around pooled estimates includes both no effect and appreciable benefit or appreciable harm for tinidazole.

[e]Downgraded by 2 for very serious risk of bias: trials were at high risk of selection bias because of unclear randomization and allocation concealment and inadequate blinding of outcome assessors. In four trials (Misra 1974; Joshi 1975; Mathur 1976; Swami 1977), treatment was extended to 10 days if there was persistence of clinical symptoms or presence of *E histolytica* in stools at the end of the planned treatment duration, but outcomes were analysed regardless of duration of treatment. It is also possible that Misra 1978 is a duplicate of the study Misra 1977. All trials used only stool microscopy to diagnose and assess parasitological outcomes, and misclassification of diagnosis and eradication of *E histolytica* in stools is possible.

[f]No serious inconsistency: there was no statistical heterogeneity (I^2 is 0% and the P value for heterogeneity is greater than 0.10). Effect sizes in these trials all seem to favour tinidazole.

[g]No serious indirectness: eight trials were conducted in endemic areas (seven trials in India and one trial in Bangladesh), and one trial was conducted in an industrialized country (Sweden). All trials included patients with unspecified intestinal amoebiasis or amoebic colitis, and study results could be applied to other populations for whom amoebic colitis is endemic and who have similar clinical presentation.

[h]No serious imprecision: these studies are adequately powered to detect 50% reductions in clinical and parasitological failure. The result is statistically significant.

[i]No serious inconsistency: there was no statistical heterogeneity (I^2 is 10% and the P value for heterogeneity is greater than 0.10). Confidence intervals in trials overlap, and the point estimate indicates both benefit and harm for tinidazole.

[j]Downgraded by 1 for inconsistency: statistical heterogeneity was high (I^2 is 64% and the P value for heterogeneity is less than 0.10), which could be explained by differences in populations. All studies indicate that tinidazole is comparable with metronidazole, except Pehrson 1984, which favours metronidazole.

[k]Downgraded by 1 for serious risk of bias: trials had inadequate or unclear blinding of outcome assessors for adverse events. Procedures for reporting adverse events and for monitoring laboratory test results were not standardized and were inadequately reported.

[l]No serious inconsistency: statistical heterogeneity was not significant (I^2 is 48% and the P value for heterogeneity is 0.10), except for one trial (Swami 1977); all trials consistently show lower risk of adverse events among those given tinidazole compared with those given metronidazole. Adverse effects reported were predominantly gastrointestinal, such as nausea, vomiting, anorexia, bitter or metallic taste, and abdominal discomfort.

[m]No serious imprecision: studies are adequately powered to detect 50% difference in adverse events between the two groups. The result is statistically significant.

Summary of findings 2. Summary of findings table 2

Combination therapy compared with metronidazole alone as treatment for amoebic colitis

Patient or population: adults and children with amoebic colitis

Settings: low- and middle-income countries

Intervention: combination therapy

Comparison: metronidazole alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combination therapy	Metronidazole alone				
Clinical failure 1 to 14 days after end of treatment	**71 per 100**	**23 per 100** (8 to 70)	**RR 0.33** (0.11 to 0.98)	1025 (3 studies)	⊕⊝⊝⊝ VERY LOW[a-d] due to risk of bias, inconsistency, and indirectness	It is uncertain whether clinical failure differs between combination therapy or metronidazole treatment
Parasitological failure 1 to 14 days after end of treatment Method: stool microscopy demonstrating *E histolytica* cysts or trophozoites	**13 per 100**	**5 per 100** (2 to 11)	**RR 0.36** (0.15 to 0.86)	720 (3 studies)	⊕⊕⊝⊝ LOW[a,c-e] due to risk of bias and indirectness	Combination therapy may result in fewer parasitological failures compared with metronidazole
Adverse events	Adverse events were incompletely reported and could not be combined in a meta-analysis			1025 (3 studies)	⊕⊝⊝⊝ VERY LOW[c,f]	It is uncertain whether the number of adverse events differs with combina-

			due to indirectness and risk of bias	tion therapy or metronidazole treatment

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; *E histolytica*:*Entamoeba histolytica*; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by 1 for serious risk of bias: all three trials included for this outcome had unclear randomization and allocation concealment, and two trials had inadequate blinding. Prasad 1985 was at high risk of selective reporting bias because of inadequate reporting of the method used for outcome evaluation and variable treatment duration ranging from 5 to 10 days. All trials used only stool microscopy to diagnose and assess parasitological outcomes, and misclassification of diagnosis and eradication of *E histolytica* in stools is possible.

[b]Downgraded by 1 for inconsistency: heterogeneity was statistically significant (I^2 is 71% and the P value for heterogeneity is less than 0.05). Heterogeneity could be explained by differences in severity of illness and variable drug combinations used.

[c]Downgraded by 1 for indirectness: trials were conducted in countries that are endemic for amoebiasis (India - Asrani 1995 and Prasad 1985 - and South Africa - Rubidge 1970) but used various drug combinations. Studies using different combination of drugs would need to be studied. Some of these drugs are no longer marketed, and it is not known whether the results could be applied to other combinations.

[d]No serious imprecision: these studies are adequately powered to detect 50% reductions in clinical and parasitological failure 15 to 60 days after end of treatment. The result is statistically significant.

[e]No serious inconsistency: statistical heterogeneity was moderate with I^2 of 42% and P value for heterogeneity of 0.18). The CIs overlap, and the pooled estimate shows significant benefit favouring combination therapy.

[f]Downgraded by 2 for very serious risk of bias: blinding was inadequate, and reporting of the frequency and type of adverse events in trials was incomplete.

BACKGROUND

Description of the condition

Amoebiasis is a parasitic disease caused by *Entamoeba histolytica*, a protozoan parasite that is found worldwide. An estimated 40 to 50 million people infected with *E histolytica* develop amoebic colitis or extraintestinal abscess, which results in up to 100,000 deaths annually (Bercu 2007; Choudhuri 2012). Amoebic colitis is a leading cause of severe diarrhoea worldwide, particularly in children below five years of age living in low- and middle-income countries (LMICs) (Shirley 2018). The greatest burden of amoebiasis occurs in LMICs in Asia, the sub-Saharan and tropical regions of Africa, and in Central and South America (Choudhuri 2012; Shirley 2018). In these areas, prevalence rates vary with the population studied and differ between countries and areas with different socioeconomic and sanitary conditions and with the diagnostic test used.

Seroprevalence studies have detected antibodies ranging from 12% to 65% among those living in highly endemic areas in Asia and Latin America, including asymptomatic individuals (Braga 1996; Haque 1999; Haque 2001; Barwick 2002; Gatti 2002). Antibodies that develop after invasive infection can be measured by several immunological tests, but these tests will differentiate past infection from current or active amoebiasis. Studies using more sensitive tests that can differentiate pathogenic *E histolytica* from non-pathogenic species, such as enzyme-linked immunosorbent assay (ELISA) stool antigen detection or polymerase chain reaction (PCR), reported that the incidence of intestinal amoebiasis in highly endemic areas ranged from 13% to 67% among individuals with diarrhoea (Haque 1997; Abd-Alla 2002; Tanyuksel 2005; Rivera 2006; Samie 2006), and from 1.0% to 13.8% among asymptomatic individuals (Haque 1997; Braga 1998; Rivera 1998; Ramos 2005). A prospective study conducted in asymptomatic schoolchildren two to five years of age living in an urban slum in Bangladesh showed that 90% were infected with *E histolytica* at least once, as determined by stool antigen detection, and that repeat infection occurred in 68% of 162 children who completed 8.2 years of observation (Petri 2009).

Infection is commonly acquired by ingestion of food or water contaminated with cysts of *E histolytica*, but transmission also occurs through oral and anal sex and via contaminated enema apparatuses (Haque 2003; Stanley 2003; Shirley 2018). In high-income countries, infection occurs primarily among returning travellers or recent immigrants from endemic regions, homosexuals engaging in oral-anal sexual practices, immunosuppressed people, and institutionalized individuals (Salit 2009; Petri 2010; Herbinger 2011; Shirley 2018). HIV infection was shown to be a common coexisting condition with amoebiasis among USA residents who died (Gunther 2011), and *E histolytica* remains an important diagnostic consideration for those presenting with bloody diarrhoea (Petri 2010). Studies have documented increased prevalence of amoebiasis among HIV-positive men who have sex with men in several Asia Pacific countries (Tsai 2006; Chen 2007; Park 2007; Hung 2008; James 2010; Nagata 2012; Zhou 2013), with higher risk of developing invasive disease reported in this population (Hung 2008; Stark 2008; Watanabe 2011).

About 90% of people infected with *E histolytica* have no symptoms of disease and spontaneously clear their infection, while the remaining 10% develop invasive disease (Haque 2002; Stanley 2003; Choudhuri 2012). The underlying factors responsible for variable clinical outcomes of infection by *E histolytica* remain largely unknown and may be determined by a complex interaction between host factors, parasite genotype, and environmental factors (Ralston 2011; Wilson 2012; Shirley 2018).

Amoebic colitis is a manifestation of intestinal amoebiasis that commonly presents as ulcers and inflammation of the colon. This results in a complete spectrum of colonic signs and symptoms ranging from non-bloody diarrhoea to dysentery (acute diarrhoea with bloody stools), and to necrotizing colitis (severe inflammation of the colon) with intestinal perforation and peritonitis (infection of abdominal cavity membranes) (Ravdin 2005; Shirley 2018).

Based on clinical manifestation, amoebic colitis may be classified as amoebic dysentery or non-dysenteric amoebic colitis (Bercu 2007; Petri 2010; Ximenez 2011; Choudhuri 2012). Amoebic dysentery is acute diarrhoea with visible blood and mucus in stools and the presence of haematophagous trophozoites (trophozoites with ingested red blood cells) in stools or tissues. Non-dysenteric amoebic colitis presents as recurrent bouts of diarrhoea with or without mucus but with no visible blood and the presence of *E histolytica* cysts or non-haematophagous trophozoites (trophozoites with no ingested red blood cells) in the stools. The sigmoidoscopic examination of the colon originally described in the Report of the WHO Expert Committee on Amoebiasis showed inflamed mucosa with discrete ulcers in amoebic dysentery but usually normal results in the nondysenteric type (WHO 1969). However, recent studies have documented mucosal inflammation with small colonic ulcers or erosions on colonoscopy even in those with mild or nonspecific symptoms of non-dysenteric colitis (Okamoto 2005; Lee 2015).

The most severe complication of amoebic colitis is fulminant or necrotizing colitis, occurring in 0.5% of cases (Haque 2003; Choudhuri 2012; Shirley 2018). Necrotizing colitis occurs with profuse bloody diarrhoea, fever, and widespread abdominal pain, frequently progressing to severe injury of the bowel wall, intestinal haemorrhage, or perforation with peritonitis (Haque 2003; Stanley 2003; Choudhuri 2012; Shirley 2018). Among people with this condition, the case-fatality rate ranges from 40% to 89% (Choudhuri 2012; Shirley 2018). Young children, malnourished individuals, pregnant women, immunocompromised individuals, and those receiving corticosteroids are at higher risk for invasive disease (Stanley 2003; Petri 2010; Shirley 2016). Extraintestinal complications of amoebic infection include abscess in various organs, empyema (accumulation of pus around the lungs), and pericarditis (inflammation of membranes surrounding the heart) (Petri 2010; Choudhuri 2012). For treatment of necrotizing colitis and extraintestinal amoebiasis, surgery and additional antibiotics may be required, aside from specific antiamoebic drugs (Petri 2010; Choudhuri 2012; Shirley 2018).

In many countries where amoebiasis is endemic, amoebic colitis is commonly diagnosed by identifying cysts or motile trophozoites in a saline wet mount of a stool specimen. Finding in the stool trophozoites that contain ingested red blood cells is considered by many to be diagnostic of invasive intestinal amoebiasis (Tanyuksel 2003; Choudhuri 2012; Talamas-Lara 2014). Stool microscopy is incapable of differentiating *E histolytica* from non-pathogenic species such as *Entamoeba dispar* or *Entamoeba moshkovskii*, and the accuracy of microscopic methods is highly dependent on the competence of the diagnostic laboratory (Haque 2003;

Petri 2010). When a definitive diagnosis by microscopy is not possible, the presence of the *E histolytica*/*E dispar* complex should be reported (WHO 1997; Haque 1998; CDC 2010). Culture followed by isoenzyme analysis will differentiate *E histolytica* from *E dispar* but is technically difficult and is associated with significant false-negative rates (Fotedar 2007). Currently, specific and sensitive means to detect *E histolytica* in stools include stool antigen detection testing and PCR techniques based on amplification of the target parasite RNA and DNA (Haque 1998; Nesbitt 2004; Fotedar 2007; Petri 2010; Choudhuri 2012; Shirley 2018). Ideally, stool samples positive for*E histolytica* on microscopy should be confirmed with stool antigen or PCR before treatment starts. Unfortunately, in resource-limited countries, where the incidence of amoebiasis is highest, these tests are not routinely used and are not widely available for the diagnosis of amoebic colitis.

Description of the intervention

The goals of treatment for individuals with amoebic colitis are to treat invasive disease and to eradicate intestinal carriage of the organism (Haque 2003; Kappagoda 2011). *E histolytica* may be found in the bowel lumen, in the bowel wall, and in tissues, including the liver (Choudhuri 2012; Shirley 2018). Antiamoebic drugs vary in efficacy at the three sites where parasites commonly exist and generally are divided into two classes based on their main site of activity. Luminal amoebicides act principally in the bowel lumen, and tissue amoebicides act principally in the bowel wall and in the liver. See Table 1 for examples.

Among the antiamoebic drugs listed in the table, nitazoxanide is the most recent addition. Nitazoxanide is a nitrothiazole derivative whose structure is similar to metronidazole; however, it has greater antiparasitic activity against various intestinal protozoal and parasitic infections when compared with metronidazole (Fox 2005; Ochoa 2005; Parashar 2005). Effectiveness of nitazoxanide and its major metabolite, tizoxanide against both luminal and invasive forms have been demonstrated (Adagu 2002; Cedillo-Rivera 2002; Petri 2003; Shirley 2018), but further studies are needed to determine if this can be recommended as treatment for amoebic colitis.

Metronidazole is considered standard therapy for treating people with invasive amoebiasis (WHO 2005; The Medical Letter 2013; AAP 2015). The recommended regimen of metronidazole for treatment of amoebic colitis is 500 to 750 mg given three times daily in adults, and 30 to 50 mg/kg/day given for five to 10 days in children (WHO 2005; The Medical Letter 2013; AAP 2015). Although this dose may have sufficient activity against both trophozoites and cysts (WHO 1994; Li 1996), the predominant belief is that metronidazole alone is not reliably effective for eliminating cysts in the colonic lumen due to its failure to reach adequate therapeutic concentrations in the large intestines (Haque 2003; Stanley 2003). This results in persistence of the parasites in the intestine in as many as 40% to 60% of patients (Haque 2003; Stanley 2003; Petri 2010). Thus, the general recommendation is that patients with invasive amoebiasis should receive a luminal amoebicide after treatment with a tissue amoebicide, to eliminate any surviving organisms in the colon (Kappagoda 2011; Choudhuri 2012; The Medical Letter 2013; AAP 2015). This recommendation is based on the assumption that drugs acting on different protozoal processes may enhance the effects of other drugs. However, evidence to support combination therapy has not been reviewed, and it is not known whether drug combinations reduce clinical symptoms or eradicate parasites more effectively than tissue amoebicides given alone. Controversy surrounds the need for cyst eradication following metronidazole or tinidazole treatment, especially in endemic areas, where re-infection is frequent. Furthermore, the increased complexity of combination regimens, additional drug costs, and potentially increased adverse events, combined with the unavailability of luminal agents on the market, act as major deterrents to compliance with combination therapy.

Adverse effects may occur even with conventional doses of metronidazole and include headache, loss of appetite, metallic taste, nausea, and vomiting (Petri 2003; The Medical Letter 2013), the last two of which may be exacerbated by drinking alcohol. Dizziness, convulsions, poor co-ordination, and numbness of the extremities are less common but more serious adverse effects that warrant discontinuation of metronidazole (Petri 2003). Other nitroimidazole drugs with longer half-lives, such as tinidazole, ornidazole, and secnidazole, allow shorter periods of treatment and appear to be better tolerated than metronidazole. These drugs have been used successfully when administered in shorter courses and have been recommended as alternative antiamoebic drugs to metronidazole (Haque 2003; Stanley 2003; WHO 2005; The Medical Letter 2013; AAP 2015).

Treatment failure has been reported with metronidazole, and most of these cases have been attributed to incorrect diagnosis, selection of an unsuitable drug, or failure to observe certain principles of treatment, rather than to drug resistance (Wassman 1999; Stanley 2003). However, induction of metronidazole-resistant *E histolytica* strains in the laboratory suggests that indiscriminate use of antiamoebic drugs can result in an increased minimum inhibitory concentration against *E histolytica* (Samarawickrema 1997; Wassman 1999; Bansal 2006; Nagpal 2012). Furthermore, continued morbidity and higher mortality seen among those who develop complicated severe disease, despite the availability of antiamoebic drugs such as metronidazole, not only imply delayed diagnosis and inappropriate treatment but also suggest that current therapeutic options may be insufficient (Haque 2003; Ralston 2011; Hayat 2016).

Why it is important to do this review

In addition to being a potentially fatal disease, invasive amoebiasis has important social and economic consequences. Amoebic colitis is a temporarily incapacitating disease that may require hospitalization for some individuals presenting with severe diarrhoea or dysentery. Amoebic colitis affecting adults in the wage-earning group may require several weeks of hospitalization and up to two to three months for full recovery (WHO 1985; Walsh 1986). Pregnant and postpartum women appear to have increased risk of severe disease and death (Stanley 2003; Petri 2010). Persistent infection can impair physical and mental growth and can affect the nutrition and general development of children. Children with *E histolytica*-associated diarrhoea during the first two years of life were three times more likely to be malnourished and were five times more prone to be stunted (Mondal 2006; Verkere 2012). Other studies have demonstrated that malnutrition and amoebic dysentery were associated with cognitive deficiencies, particularly in preschool children (Tarleton 2006; Petri 2009).

Adequate therapy for amoebic colitis is necessary to reduce severity of illness, prevent development of complicated disease and extraintestinal spread, and decrease infectiousness and

transmission to others. In LMICs where amoebiasis is common and most patients are treated in private practice or as hospital outpatients, the aim of treatment should be to provide an effective, safe, and simple regimen that can be given on an outpatient basis.

A reliable summary of the evidence is needed to determine the best treatment for people with amoebic colitis. Rapid relief of diarrhoea and other gastrointestinal symptoms associated with intestinal amoebiasis is an important concern of the individual with the disease, and eradication of the parasite is important to prevent further invasion with damage to the intestinal mucosa and possible extraintestinal spread. Treatment failure and unpleasant adverse effects associated with metronidazole in some patients and the possibility of overt clinical resistance of *E histolytica* to metronidazole make it imperative that alternative treatments are investigated. The benefits of using combination regimens over monotherapy and single-dose regimens over longer regimens remain to be determined. Furthermore, the effectiveness of newly discovered antiamoebic drugs must be ascertained.

OBJECTIVES

To evaluate antiamoebic drugs for treating amoebic colitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs). We excluded quasi-RCTs.

Types of participants

We included trials with adults and children with clinical symptoms of amoebic colitis (as previously described) and demonstration of *E histolytica* cysts or trophozoites in a stool sample, or *E histolytica* trophozoites in a tissue biopsy or ulcer scraping by histopathology. We included individuals with positive *E histolytica*/*E dispar* on stool examination confirmed by *E histolytica* antigen detection testing or PCR.

We excluded trials including only individuals with asymptomatic infection and those requiring surgery or additional antibiotic therapy, such as those with fulminant or necrotizing colitis; peritonitis, intestinal perforation, or haemorrhage; or with evidence of extraintestinal amoebiasis including hepatic amoebiasis.

Types of interventions

Interventions

Antiamoebic drugs, administered alone or in combination.

Controls

Placebo or another antiamoebic drug.

Types of outcome measures

Primary outcomes

- Clinical failure, defined as absence of *E histolytica* in stools or scrapings but with little or no relief of signs or symptoms, or with persistent rectal ulcerations on sigmoidoscopy
- Parasitological failure, defined as persistence of *E histolytica* cysts or trophozoites in stools or colonic ulcer scrapings, with or without the presence of symptoms or rectal ulcers
- Relapse, defined as reappearance of cysts or trophozoites of *E histolytica* after their initial disappearance, with or without recurrence of clinical signs or symptoms of amoebic colitis after completion of treatment
- Serious adverse events (death, life-threatening events, hospitalization required or duration of hospitalization prolonged, development of a persistent or significant disability or incapacity, having offspring with a congenital anomaly or birth defect, or development of cancer)

Secondary outcomes

- Adverse events resulting in discontinuation of treatment
- Other adverse events including gastrointestinal adverse events, systemic symptoms such as weakness or fatigue, central nervous system effects such as headache or dizziness, and dermatological effects such as skin rashes

Search methods for identification of studies

We searched for all publications that described RCTs on antiamoebic drugs for treating amoebic colitis, regardless of language or publication status.

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2018, Issue 1); MEDLINE (1966 to March 2018); Embase (1974 to March 2018); and Latin American Caribbean Health Sciences Literature (LILACS) (1982 to March 2018). Using 'amoebic,' 'amoeba', and 'amoebiasis' as search terms, we also searched the *meta*Register of Controlled Trials (*m*RCT; latest search February 2018), the WHO International Clinical Trials Registry Platform (ICTRP search portal; latest search February 2018), and the United Kingdom Clinical Trials Gateway (UKCTG; last searched February 2018).

Searching other resources

Conference proceedings

We searched electronic databases of the conference proceedings listed in Appendix 2 for relevant abstracts.

Organizations and pharmaceutical companies

To help identify unpublished and ongoing trials, we contacted researchers working for the organizations listed in Appendix 3, as well as the pharmaceutical companies and associated databases listed in Appendix 4.

Reference lists

We checked the reference lists and bibliographies of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (MLMG, LFD) independently assessed results of the literature search to determine whether the title or abstract of each trial described an RCT. We retrieved full reports for all trials considered by one or both review authors to be potentially relevant, as well as for those whose relevance was unclear. We used a standard eligibility form based on the inclusion criteria to assess trials independently. We contacted trial authors for clarification if necessary and resolved disagreements through discussion or by consultation with the third review author (JSA in this update).

We included RCTs assessing the effectiveness of antiamoebic drugs given alone or in combination for treatment of amoebic colitis, and for which outcomes were measured in both experimental and control populations. We excluded quasi-randomized trials (e.g. those utilizing alternate allocation), animal studies, duplicate publications, reviews, abstracts with no full report, and studies describing only results without providing detailed background and methods.

Data extraction and management

For this update, two review authors (MLMG, JSA) independently extracted data from study reports using pre-tested data extraction forms. We collected details regarding inclusion and exclusion criteria for participants, treatment interventions given, total numbers randomized, number of participants in each group for all outcomes, dropouts and withdrawals, and numbers experiencing each outcome. For dichotomous data, we extracted the number of participants who experienced the event of interest and the number of participants randomized and analysed in each treatment group. We resolved disagreements by referring to the trial report and holding discussions. When data were insufficient or missing, we made attempts to contact the trial authors. Review author MLM Gonzales entered data for analysis.

For each study, we collected the following data: study methods (study design, sequence generation. allocation sequence concealment, blinding), participants (total number, age, sex, type of amoebic colitis, diagnostic method used, presence of concomitant infection with other intestinal parasites, duration of follow-up), interventions (total number of intervention groups and specific interventions including dosage, route, and duration), setting, and funding source. For each outcome, we recorded the number of participants allocated to each intervention group, the proportion of participants with the outcome, methods or tests used to measure the outcome, and timing of outcome measurement.

Assessment of risk of bias in included studies

Two review authors (MLMG, LFD) independently assessed risk of bias in each trial using a prepared form. We resolved disagreements through discussion between review authors and with the third review author (JSA) if needed.

We assessed risk of bias for each of the included trials and evaluated sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other sources of bias', using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For each item, we provided a description of what was reported to have happened in the study along with a subjective judgement regarding protection from bias ('Yes' for low risk of bias, 'No' for high risk of bias, 'Unclear' otherwise). For sequence generation and allocation concealment, we described for each included study the method used, and we made subjective judgements on the adequacy of the procedure to protect against possible bias. For blinding, we assessed who was blinded, such as trial participants, care providers, or outcome assessors, for both clinical and parasitological outcomes and for adverse events. We prepared separate reports for outcomes evaluated 1 to 14 days after end of treatment and those evaluated 15 to 60 days after end of treatment. We stated numbers included in the analysis compared with the total number of randomized participants, whether attrition and exclusions were reported, reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. For selective reporting bias, we described for each included trial whether it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported. For 'other sources of bias', we described for each included study any important concerns identified that could be possible sources of bias, such as study design, method of diagnosing amoebic infection, and presence of concomitant parasitic or protozoal infection.

We recorded all assessments in risk of bias tables and produced an overall pictorial summary of the risk of bias assessment.

For trials that were at high risk of bias according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact the findings. We explored the impact of the level of bias by performing sensitivity analyses.

Measures of treatment effect

We used risk ratios (RRs) with 95% confidence intervals (CIs) to compare dichotomous data. When available, we recorded continuous data, such as time until resolution of clinical symptoms and disappearance of amoeba parasites in the stools, as mean value and standard deviation or as median with range of outcome measurements.

Unit of analysis issues

For trials with more than two intervention groups (e.g. two or more experimental interventions, different doses or preparations of the same drug), we combined multiple treatment arms as appropriate into one group and compared them collectively with the standard or control group to avoid counting placebo or control participants more than once in the same meta-analysis.

Dealing with missing data

If we noted a discrepancy between the number randomized and the number analysed, we calculated the percentage lost to follow-up for each treatment group and reported this information. We performed an available-case analysis, wherein only available data were analysed and no assumptions were made regarding missing data.

Assessment of heterogeneity

We calculated summary RRs from meta-analysis using both a fixed-effect model (Mantel-Haenszel method), which assumes trial

homogeneity, and a random-effects model (DerSimonian and Laird method), which accounts for trial heterogeneity.

We reported results using the random-effects model when we noted differences between trials that may potentially influence the size of the treatment effect, or when we detected significant statistical heterogeneity. We determined the presence of statistical heterogeneity among the same interventions by inspecting forest plots for overlapping confidence intervals and by applying the Chi^2 test for heterogeneity ($P < 0.10$ considered statistically significant) and the I^2 statistic to quantify inconsistency across trials ($I^2 >$ 50% used to denote substantial heterogeneity). If we detected heterogeneity but still considered it clinically meaningful to combine trial data, we explored potential sources of heterogeneity by conducting subgroup analysis. We presented subtotals for each subgroup only if pooled results showed significant heterogeneity.

Assessment of reporting biases

When at least 10 trials were included in the meta-analysis, we determined publication bias by looking for asymmetry in a funnel plot. The presence of asymmetry in the funnel plot suggests possible publication bias but may also indicate heterogeneity or poor methodological quality of trials.

Data synthesis

We analysed data collected using Review Manager 5 (RevMan 5) (RevMan 2014). For dichotomous outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). We did not perform meta-analysis of continuous data because of inconsistency of trial reporting, but we described and summarized outcomes in a table.

The main comparisons were between any single antiamoebic drug and metronidazole (current standard therapy), any antiamoebic drug and placebo, combination regimens and monotherapy, and any single-dose regimen and longer regimens. We included but did not pool data from other trials that compared any antiamoebic drug with another antiamoebic drug, and we did not address any particular pharmacological or clinical questions relevant to this review.

For trials reporting results at multiple or varying time points, we performed separate analyses for outcomes measured from end of treatment to 14 days and 15 to 60 days after end of treatment. For trials comparing drugs with different treatment durations, we measured the time point in relation to the last day of the longest treatment period. We did not consider outcomes that were measured during treatment or before completion of treatment. Likewise, we did not include outcomes measured beyond two months because this could indicate re-infection rather than true failure or relapse.

Certainty of the evidence

We assessed the certainty of the evidence for important outcomes using the GRADE approach (GRADE 2004), and we presented this information in 'Summary of fIndings' tables.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis for the time of outcome measurements (from end of treatment to 14 days and 15 to 60 days after end of treatment) and for subgroups that may influence treatment response, such as clinical categories (amoebic dysentery, non-dysenteric amoebic colitis, or unspecified amoebic colitis) and participant age (adults 15 years of age or older, and children younger than 15 years). We could not undertake subgroup analysis based on diagnostic tests as planned because only one trial used a stool *E histolytica* ELISA test.

Potential sources of heterogeneity explored for the primary outcome measures involved the methodological quality of studies. Other sources of heterogeneity included in the post hoc subgroup analysis were type of intestinal infection (*E histolytica* infection alone or mixed intestinal infection) and criteria for determining outcomes (based on WHO 1969 criteria or other criteria).

Sensitivity analysis

We performed sensitivity analysis to assess the robustness of overall estimates by calculating the results using all trials and then excluding trials of lower methodological quality (i.e. trials with inadequate generation of allocation sequence, allocation concealment, or blinding, or trials that analysed < 90% of randomized participants), and by excluding trials that were sponsored by pharmaceutical companies. Although pharmaceutical industry-sponsored trials may publish only when demonstrating positive treatment effects, it is possible that pharmaceutical industry-sponsored trials were conducted with better methodological quality because they received adequate funds. We determined the effect of the date of publication on the overall pooled effect in a sensitivity analysis when we noted large differences in the publication dates. It is unclear whether two trials reported the same results, and our attempts to contact trial authors for clarification were not successful (Misra 1977; Misra 1978). We entered these two trials as separate trials and carried out sensitivity analysis to determine whether exclusion of the latter trial would have an effect on the overall estimate.

RESULTS

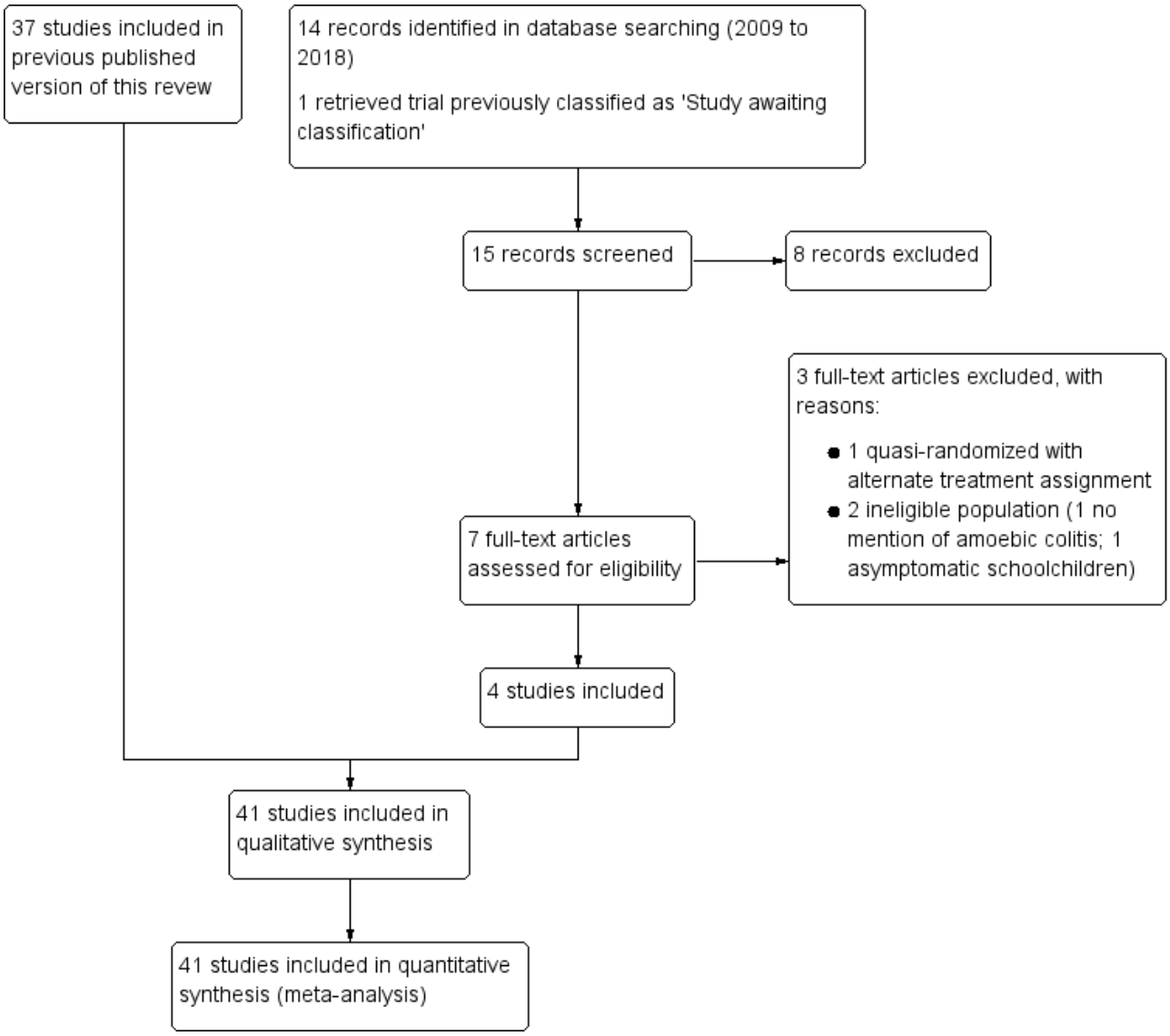
Description of studies

We have presented a summary of included studies in Table 2, and we have listed further study details in the 'Characteristics of included studies' table.

Results of the search

Thirty-seven trials met the inclusion criteria of the first published version of this review (Gonzales 2009). We retrieved one trial previously classified under 'Studies awaiting classification' following the initial search (Guevara 1980), and we assessed 14 additional studies identified in updated searches conducted from the time of publication of the review in 2009 until 22 March 2018. Of these, we retrieved the full-text articles of six studies, of which we excluded three for the following reasons: one was quasi-randomized with alternate treatment assignment (Dinleyici 2009), and two included an ineligible population: one enrolled patients with bacillary dysentery with no mention of amoebic colitis (Sharif 2017); one with asymptomatic schoolchildren (Speich 2013)). See Figure 1 and the 'Characteristics of excluded studies' table for studies detected by the search specifications but excluded from this review.

Figure 1. Study flow diagram.



We included four new RCTs in this review update. Guevara 1980 was previously classified as awaiting classification and compared quinfamide with teclozan for treatment of adults with non-dysenteric amoebiasis. One trial compared a probiotic, *Saccharomyces boulardii*, in addition to metronidazole versus metronidazole alone (Savas-Erdeve 2009). Two trials compared various herbal products versus a combination of metronidazole and diloxanide furoate - as in Siddiqui 2015 - or metronidazole alone - as in Shah 2016. We identified two ongoing RCTs: one trial will determine the efficacy of auranofin, a gold-containing chemical salt oral drug, for treating adults with amoebiasis or giardiasis (NIAID 2016), and the other is a non-randomized trial that will determine the safety and efficacy of paromomycin for treating individuals with intestinal amoebiasis (Pfizer 2016). See Characteristics of ongoing studies.

Thus, we included 41 trials in total in this review update. All trial reports were published in English, except Huggins 1982 (Portuguese), Karabay 1999 (Turkish), and Donckaster 1964 and Guevara 1980 (Spanish). Trials included in this review were published between 1964 and 2016; 27 were conducted between 1964 and 1989, three between 1990 and 1997, and eleven between 1998 and 2016 (see the 'Characteristics of included studies' table and Table 2).

Included studies

Locations

A total of 39 trials were conducted in 16 different countries (see details in Appendix 5), 15 of which are considered to be highly endemic for amoebiasis: India (12), Indonesia (5), Mexico (3), Turkey (3), Colombia (2), Brazil (2), Pakistan (2), Kenya (2), Egypt (2), Bangladesh (1), Nigeria (1), South Africa (1), Chile (1), Iran (1), and Iraq (1). The remaining two trials were conducted in Sweden.

Trials were conducted in a variety of settings (see details in Appendix 6): hospital (14), outpatient clinic (15), community (1), and school (1). Eight trials did not state the study setting. One trial treated most participants as outpatients but treated a few with severe symptoms in the hospital (Toppare 1994). In another trial,

patients were initially hospitalized for one day, then were followed up as outpatients (Guevara 1980).

Source of funding

Twenty-one trials did not state the source of funding. Seventeen trials reported that a pharmaceutical company provided funding (Nnochiri 1967; Batra 1972; Naoemar 1973; Pudjiadi 1973; Panggabean 1980; Sitepu 1982; Tripathi 1986; Chunge 1989; Pamba 1990; Rossignol 2001; Rossignol 2007), or supplied study drugs (Kapadia 1968; Rubidge 1970; Misra 1974; Joshi 1975; Singh 1977; Davila 2002). Two trials reported that at least one trial author was connected with the pharmaceutical company manufacturing the study drug (Asrani 1995; Salles 1999), although study authors did not describe the level of involvement of the company. One trial was funded by the university at which study authors were affiliated (Siddiqui 2015).

Participants

A total of 4999 participants were enrolled in the trials; 17 trials included 1200 adults, 11 trials included 1185 children, 11 trials included 2474 children and adults, and two trials did not mention the age of participants. Included trials used different inclusion criteria for study participants.

- Acute amoebic dysentery in 12 trials (Nnochiri 1967; Rubidge 1970; Batra 1972; Naoemar 1973; Pudjiadi 1973; Panggabean 1980; Sitepu 1982; Soedin 1985; Mohammed 1998; Karabay 1999; Mansour-Ghanaei 2003; Savas-Erdeve 2009).
- Chronic or vague abdominal symptoms compatible with non-dysenteric amoebic colitis, without bloody diarrhoea or other signs of intestinal invasion, in five trials (Guevara 1980; Huggins 1982; Pehrson 1983; Pehrson 1984; Padilla 2000).
- Acute amoebic dysentery and non-dysenteric amoebic colitis among enrolled participants and analysed separately in five trials.
  - Three trials stratified participants during the analysis of outcomes into those with acute amoebic dysentery and those with non-dysenteric amoebic colitis (Botero 1974; Botero 1977; Swami 1977).
  - Two trials classified participants as having invasive trophozoite forms and non-invasive cyst forms based on stool microscopy findings and analysed the two groups separately (Kapadia 1968; Pamba 1990).
- Clinical symptoms of intestinal amoebiasis, with no differentiation between amoebic dysentery and non-dysenteric amoebic colitis in 19 trials.
  - Two trials categorized participants as having acute amoebic dysentery, subacute amoebiasis, or chronic amoebiasis based on severity of symptoms and whether trophozoites or cysts of *E histolytica* were present but analysed participants as one group (Joshi 1975; Mathur 1976).
  - Two trials classified participants as having acute or chronic amoebiasis based on duration of symptoms but analysed study participants as one group (Misra 1974; Tripathi 1986).
  - Fifteen trials recruited and analysed participants with symptoms of intestinal amoebiasis or amoebic colitis, regardless of whether or not they presented with dysentery.

Participant age ranged from seven months to 80 years; see Appendix 7 for details. Seventeen trials enrolled only adults, and 11 trials recruited only children. The remaining 11 trials recruited both adults and children. Two trials did not state participant age (Kapadia 1968; Batra 1972).

Methods used to diagnose amoebic colitis

Trials used stool microscopy with direct wet saline smear as the predominant method for determining the presence of *E histolytica* cysts or trophozoites in stools (details in Appendix 8). In addition to direct smears, researchers used other methods - various staining methods (10 trials), concentration methods such as formalin or formol-ether (12 trials), zinc sulphate centrifugal flotation technique (four trials), or an unspecified concentration method (four trials) - for better detection of cysts; one trial used polyvinyl alcohol fixative for detection of trophozoites. Two trials used National Institute of Health (NIH) media to culture stools for *E histolytica,* in addition to stool microscopy to evaluate parasitological response (Batra 1972; Tripathi 1986), but one trial did not use this as an inclusion criterion (Batra 1972). In addition to stool examination, 11 trials performed rectosigmoidoscopy whenever possible to determine the appearance of the bowel mucosa and the presence of ulcers but did not use this as the sole criterion for enrolling participants or evaluating outcomes. Only one trial used stool antigen-based ELISA testing (Rossignol 2007). One trial used antibody detection testing in addition to stool microscopy to confirm amoebiasis infection (Shah 2016).

Concomitant infection with other intestinal parasites

Aside from *E histolytica,* 10 trials identified concomitant infection with other intestinal parasites: giardiasis (Singh 1977; Prasad 1985; Tripathi 1986; Rossignol 2001); intestinal helminth infection (Pudjiadi 1973; Panggabean 1980; Sitepu 1982); and other intestinal protozoal and helminth infections (Pehrson 1983; Salles 1999; Davila 2002). Six trials explicitly stated that stool bacterial culture was done before enrolment; five trials included only those found to be negative for pathogenic bacteria (Toppare 1994; Karabay 1999; Rossignol 2001; Rossignol 2007; Savas-Erdeve 2009), and one trial analysed those found to be positive for *Shigella* separately from those positive for *E histolytica* (Nnochiri 1967). The remaining trials did not examine or mention concomitant infection with other intestinal pathogens or bacteria. Because clinical symptoms may not have been exclusively caused by amoebiasis in those with concomitant intestinal parasites, and given that the effect of concomitant infection on eradication of *E histolytica* by antiamoebic drugs is not known, we used data for *E histolytica* infection alone in assessing outcomes, except for trials that did not separate the data for those with single infection from those with mixed infection. Three trials performed separate analyses for clinical outcomes among those with *E histolytica* alone and those with concomitant infection with *Giardia* and *E histolytica* (Prasad 1985; Rossignol 2001; Davila 2002).

Drug comparisons

Included trials reported a variety of comparisons that involved over 30 individual drugs and combinations. As shown in Appendix 9, we grouped trials into the following categories (some trials are included in more than one category).

- **Single-agent alternative versus metronidazole (17 trials):** 10 trials on tinidazole versus metronidazole; three on ornidazole versus metronidazole; and one each on secnidazole versus

metronidazole, panidazole versus metronidazole, satranidazole versus metronidazole, and praziquantel versus metronidazole.

- **Any antiamoebic drug versus placebo (four trials):** two trials on nitazoxanide versus placebo; one on quinfamide versus placebo; and one on 10 different drugs belonging to six drug classes versus placebo.
- **Combination regimen versus monotherapy (seven trials):** three trials on various combinations (dehydroemetine plus oral tetracycline and diloxanide furoate, metronidazole and diiodohydroxyquinolone, metronidazole and furazolidone) versus metronidazole alone; one on nimorazole and aminosidine or nimorazole and etofamide or etofamide and aminosidine versus nimorazole or aminosidine or etofamide monotherapy; and one each on tetracycline and clioquinol versus secnidazole, quinfamide and mebendazole versus nitazoxanide, and tinidazole and diloxanide furoate versus tinidazole.
- **Single-dose regimens versus longer regimens (five trials):** one trial each on quinfamide (one dose) versus quinfamide (two or three doses); secnidazole (one dose) versus tetracycline and clioquinol (five days); secnidazole (one dose) versus tinidazole (two days); quinfamide (one dose) versus nitazoxanide (three days); and secnidazole (one dose) versus metronidazole (10 days).
- **Other amoebic drug comparisons (13 trials):** two trials on ornidazole versus tinidazole; 11 trials using different drug comparisons, with one trial reporting on each of the following: ornidazole versus secnidazole, chlorhydroxyquinoline versus diiodohydroxyquinoline, MK-910 low dose (0.5 mg/kg and 1 mg/kg) versus MK-910 high dose (2 mg/kg and 3 mg/kg), quinfamide versus secnidazole, quinfamide versus teclozan, quinfamide versus nitazoxanide, metronidazole and iodoquinol with *Saccharomyces boulardii* versus metronidazole and iodoquinol, metronidazole and iodoquinol with *Saccharomyces boulardii* versus metronidazole alone, herbal drug versus metronidazole, fixed-drug combination of metronidazole and diloxanide furoate versus herbal product, and fixed-drug combination of diloxanide furoate and tetracycline with chloroquine versus fixed-drug combination of diloxanide furoate and tetracycline without chloroquine.

Six trials compared more than two interventions. Four trials compared different doses of the same drug using standard or control groups: three dosages of quinfamide with teclozan (Guevara 1980); three dosages of quinfamide with placebo (Huggins 1982); two treatment durations of tinidazole with metronidazole (Awal 1979); and four dosages of MK-910 (Batra 1972). Donckaster 1964 compared 10 different treatment groups with placebo, and Pamba 1990 compared three drugs used alone or in three different combinations. One trial compared two brands of tinidazole and two brands of metronidazole (Chunge 1989). For trials with more than two intervention groups, we combined multiple treatment arms as appropriate into one group and compared them collectively with the standard or control group. This is the recommended approach to avoid a unit of analysis error by not counting placebo or control participants more than once in the same meta-analysis (Higgins 2008). For the trial comparing two brands of tinidazole and two brands of metronidazole (Chunge 1989), the two brands of tinidazole were combined as one group and were compared with the two brands of metronidazole used in the other group.

Duration of follow-up

The follow-up period varied considerably between trials. Seven trials followed participants only until the end of the treatment period (Kapadia 1968; Batra 1972; Pudjiadi 1973; Prasad 1985; Chunge 1989; Asrani 1995; Shah 2016). Duration of follow-up was less than 15 days and ranged from 7 to 14 days in 10 trials (Huggins 1982; Sitepu 1982; Toppare 1994; Mohammed 1998; Padilla 2000; Rossignol 2001; Davila 2002; Rossignol 2007; Savas-Erdeve 2009; Siddiqui 2015). Seventeen trials had a duration of follow-up of about four weeks, and two of about three weeks. Five trials had a follow-up period longer than four weeks and ranging from 40 days to 12 months after treatment (Donckaster 1964; Nnochiri 1967; Rubidge 1970; Panggabean 1980; Pamba 1990).

Outcome measures

The primary outcomes in this review were clinical failure, parasitological failure, and relapse. Thirty-three trials evaluated both clinical and parasitological outcomes, and six evaluated parasitological outcomes only (Donckaster 1964; Nnochiri 1967; Pehrson 1983; Pehrson 1984; Padilla 2000; Davila 2002). One trial based the final evaluation on parasitological outcomes (Guevara 1980), and it is unclear whether clinical outcomes were evaluated after treatment. The definition of clinical and parasitological cure or failure varied between trials. Nine trials - Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979; Tripathi 1986 - used the definitions set by the WHO Expert Committee on Amoebiasis (WHO 1969), which defined 'cure' as symptom-free, ulcers healed, stools negative for *E histolytica;* 'probable failure' as persistent symptoms and rectal ulcerations despite disappearance of *E histolytica* from stools or ulcer scrapings; and 'failure' as positive *E histolytica* with or without symptoms and rectal ulcers. For this review, review authors interpreted 'probable failure' as clinical failure, and 'failure' as parasitological failure, based on the definitions given. Most trials presented data for clinical and parasitological outcomes as dichotomous data.

Nine trials presented the duration of time from start of treatment until resolution of diarrhoea and other clinical symptoms but measured this in a variety of ways: range in hours (Batra 1972), number of days (Naoemar 1973; Pudjiadi 1973; Karabay 1999), mean duration in days and standard deviation (Mansour-Ghanaei 2003), median and range in days (Toppare 1994; Savas-Erdeve 2009), median time in days (Rossignol 2001), and survival analysis of time from first dose to passage of last unformed stools (Rossignol 2007). Two trials reported the duration of time from start of treatment to disappearance of *E histolytica* from stools (Naoemar 1973; Pudjiadi 1973). Four trials reported on the number of stools passed at different periods: during treatment (Savas-Erdeve 2009); after treatment (Pudjiadi 1973); and during treatment and on follow-up after treatment (Botero 1977; Tripathi 1986), while another reported average daily frequency of stools on admission and at the end of days 5 and 10 of treatment (Asrani 1995). One trial assessed clinical and parasitological outcomes jointly as 'cure' (Prasad 1985); only dichotomous outcomes were included in the analysis because of inconsistency in reporting continuous data (see Table 3).

Two trials reported relapse or recurrence; both compared ornidazole with metronidazole (Naoemar 1973; Botero 1974). Another trial reported the proportion of participants who

developed recurrence, but we could not include the data because researchers did not report the actual number of participants followed up (Pamba 1990).

Measurements of clinical and parasitological outcomes were made at different time points. Fifteen trials reported outcomes between end of treatment and 14 days, and 16 trials reported outcomes from 18 to 30 days after end of treatment. Nine trials measured outcomes repeatedly, and six trials reported outcomes measured at two time points (Donckaster 1964; Nnochiri 1967; Naoemar 1973; Joshi 1975; Soedin 1985; Karabay 1999). Three trials reported results at only one time point because of high dropout rates during the other follow-up periods (Panggabean 1980; Sitepu 1982; Pamba 1990).

A total of 37 trials reported adverse events, and four trials did not ascertain adverse events (Sitepu 1982; Chunge 1989; Karabay 1999; Mansour-Ghanaei 2003). Seventeen trials provided incomplete data: Five reported specific adverse events but not the number of participants who developed any adverse event (Batra 1972; Pamba 1990; Asrani 1995; Padilla 2000; Rossignol 2007); two reported only the number of participants with adverse events severe enough to cause discontinuation of drug treatment (Pehrson 1983; Pehrson 1984); five did not report the actual number of participants who developed any adverse event (Kapadia 1968; Prasad 1985; Soedin 1985; Toppare 1994; Davila 2002); two mentioned that one or more adverse events were reported but did not specify the treatment groups affected (Nnochiri 1967; Rossignol 2001); two reported adverse events only for the experimental group (Mohammed 1998; Savas-Erdeve 2009); and one reported serious adverse events and allergic reactions severe enough to result in discontinuation of treatment but did not specify the treatment groups affected (Shah 2016).

Excluded studies

We have described in the 'Characteristics of excluded studies' table trials identified by specifications from initial and updated searches but excluded from the review.

Risk of bias in included studies

Review authors prepared a risk of bias assessment for each trial with clinical and parasitological outcomes as outcome measures. Only one trial reported using appropriate procedures to minimize or eliminate bias in allocation concealment; generation of the allocation sequence; blinding of care providers, participants, and outcome assessors; and inclusion of all randomized participants (Rossignol 2007). Many trials provided little information on which to make any assessment other than 'unclear' for most criteria.

We assessed eight trials as having low risk of bias for at least three criteria (Nnochiri 1967; Naoemar 1973; Pudjiadi 1973; Misra 1974; Awal 1979; Padilla 2000; Rossignol 2001; Rossignol 2007). Many trials had high risk for bias for one or more criteria, most commonly lack of blinding and selective outcome reporting. Most trials had unclear risk of bias for random sequence generation and allocation concealment. Many trials also had the potential risk of misclassification of amoebic colitis because the diagnosis of amoebiasis was based solely on stool microscopy in most trials, except in one that used *E histolytica* stool antigen testing to confirm the diagnosis (Rossignol 2007), and in two trials that used NIH stool culture for *E histolytica* to monitor response (Batra 1972; Tripathi 1986).

We have provided an overall pictorial summary of the risk of bias assessment in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

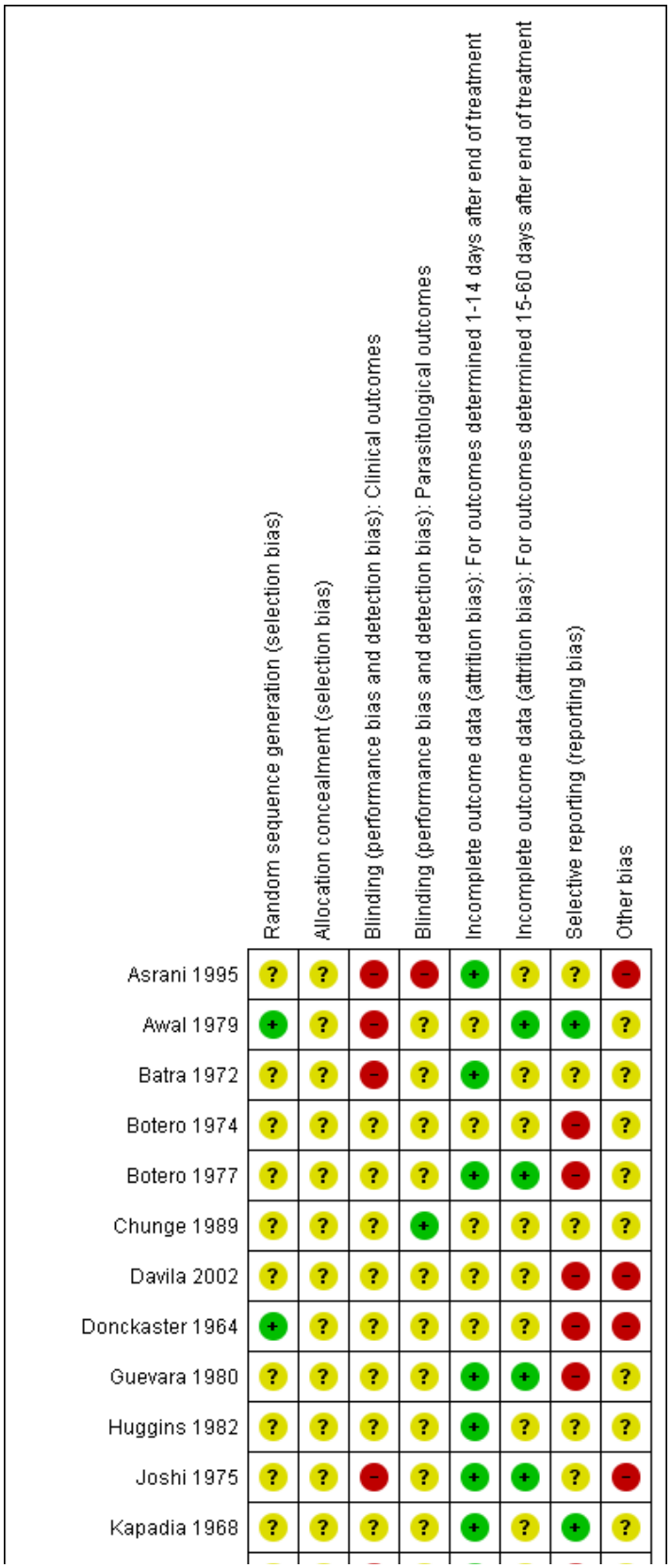
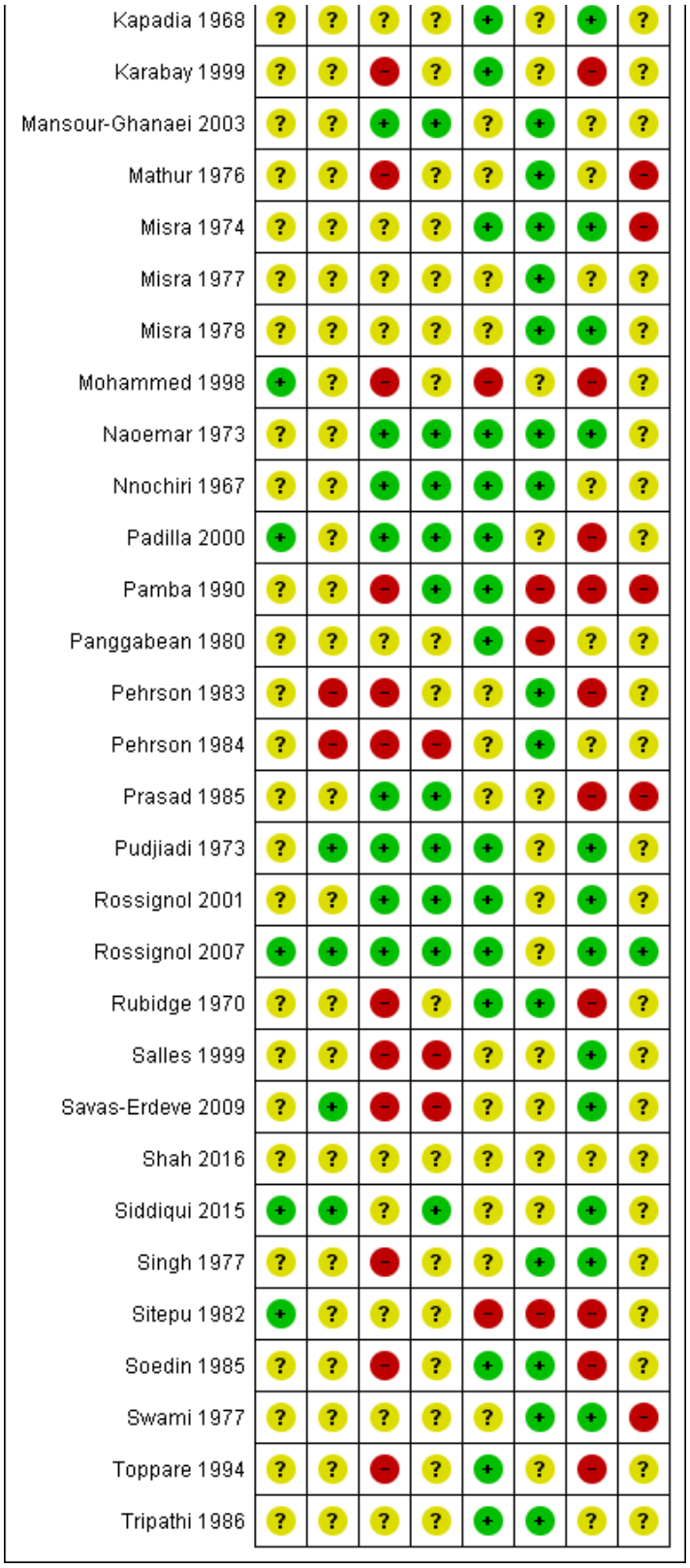


Figure 2. (Continued)



Allocation

Generation of allocation sequence

Only seven trials reported adequate generation of the allocation sequence: Four trials used a random numbers table (Donckaster 1964; Awal 1979; Sitepu 1982; Mohammed 1998), and one trial each used computer-generated randomization (Rossignol 2007), coin toss (Padilla 2000), and random selection of papers marked with the treatment assignment (Siddiqui 2015). Other trials did not describe the method used.

Allocation concealment

Four trials reported adequate allocation concealment: Two trials used sequentially numbered coded drug containers prepared independently by a person or at a site remote from the study site (Pudjiadi 1973; Rossignol 2007); one trial used sealed opaque envelopes prepared by another person (Savas-Erdeve 2009); and another trial used random selection of papers marked with the treatment assignment by another person independent of the study team (Siddiqui 2015). Two trials had inadequate allocation concealment as communicated by the primary author (Pehrson 1983; Pehrson 1984). The remaining 35 trials did not report on this.

Blinding

Only eight trials reported blinding of participants, care providers, and outcome assessors (Nnochiri 1967; Naoemar 1973; Pudjiadi 1973; Prasad 1985; Padilla 2000; Rossignol 2001; Mansour-Ghanaei 2003; Rossignol 2007). One trial reported blinding of participants and the microscopist assessing stool specimens but did not mention blinding of the outcome assessor for clinical outcomes (Chunge 1989), and another reported blinding only of the microscopist assessing stool specimens but not of care providers or outcome assessors for clinical outcomes (Pamba 1990). Eleven trials were reported to be ‘double-blind', but most of these (nine trials) did not describe the procedure for blinding, the person(s) blinded, similarity of the appearance of drugs, or the use of placebo (Donckaster 1964; Botero 1974; Botero 1977; Guevara 1980; Huggins 1982; Sitepu 1982; Tripathi 1986; Davila 2002; Shah 2016). One trial mentioned blinding only of participants and care providers but was unclear about blinding of outcome assessors for clinical and parasitological outcomes (Panggabean 1980), and one trial mentioned blinding only of laboratory personnel assessing the stool specimens (Siddiqui 2015). One trial was reported as ‘single-blind', but it is unclear who was blinded (Misra 1974). Four trials were open trials (Pehrson 1984; Asrani 1995; Salles 1999; Savas-Erdeve 2009), and three were unclear regarding blinding (Kapadia 1968; Misra 1977; Misra 1978). We assessed the other 12 trials as being at high risk of performance and detection bias because researchers used different dosages and regimens of study drugs and did not mention blinding procedures.

Incomplete outcome data

The number of participants followed up was adequate (≥ 90%) for at least one outcome (clinical or parasitological failure) in 34 trials. Of these 34 trials with adequate follow-up, three trials had missing data owing to incomplete follow-up of participants and lack of reporting of the treatment group to which participants were randomized (Botero 1974; Prasad 1985; Asrani 1995), and another trial did not mention the reason for incomplete data (Salles 1999). Four trials reported loss of participants greater than 10% (Panggabean 1980; Sitepu 1982; Pamba 1990; Mohammed 1998), and three trials reported only the number included in the final analysis and did not report the actual number initially randomized (Donckaster 1964; Chunge 1989; Davila 2002).

Selective reporting

Fourteen trials reported all relevant outcomes, 17 were at high risk for selective outcome reporting, and 10 were at unclear risk for selective reporting bias. Selective outcome reporting was noted in the following 17 trials: Five trials assessed parasitological outcomes but not clinical outcomes (Donckaster 1964; Guevara 1980; Pehrson 1983; Pehrson 1984; Davila 2002); four trials provided incomplete clinical assessment for some patients (Botero 1974; Botero 1977; Sitepu 1982; Soedin 1985); one trial reported only the "average days of clearance of symptoms" but did not report the number of participants analysed for clinical outcomes (Karabay 1999); three trials did not pre-specify the method or timing used for outcome assessment or criteria for clinical cure (Rubidge 1970; Prasad 1985; Toppare 1994); one trial did not mention the timing of assessment of clinical and parasitological outcomes (Mohammed 1998); one trial did not report the number of participants remaining in the study at specified time points and reported parasitological cure as cumulative clearance of amoebic forms from stools, which was not pre-specified (Pamba 1990); one trial included only specific adverse effects but did not mention the number of participants who showed clinical improvement (Padilla 2000); and one trial incompletely reported on adverse events (Shah 2016). Three trials did not report the number of participants who developed adverse events (Sitepu 1982; Chunge 1989; Karabay 1999), and five trials incompletely reported adverse events (Pehrson 1984; Pamba 1990; Mohammed 1998; Davila 2002; Shah 2016). The presence of selective reporting bias was unclear in 10 trials owing to the following: Three trials did not report results of rectosigmoidoscopy, even if this was pre-specified as a criterion for enrolment and/or clinical cure (Joshi 1975; Mathur 1976; Misra 1977); one trial reported outcomes only as duration from start of treatment until disappearance of blood or parasites from the stools (Batra 1972); and six trials provided incomplete reporting of adverse events (Nnochiri 1967; Huggins 1982; Tripathi 1986; Chunge 1989; Asrani 1995; Mansour-Ghanaei 2003). In addition, two trials included an analysis that was not pre-specified: frequency of loose stools per day and rate of disappearance of parasites in stools (Tripathi 1986); and time from first dose to passage of last unformed stools shown on a survival analysis graph (Rossignol 2007).

Other potential sources of bias

Duration of treatment was variable in six trials and could be extended up to 10 days if there was persistence of clinical symptoms or *E histolytica* in stools at the end of five-day treatment (Misra 1974; Joshi 1975; Mathur 1976; Prasad 1985; Asrani 1995), or at the end of three-day treatment (Swami 1977). In two trials, the number of participants for whom treatment was extended was greater among those given metronidazole than among those given tinidazole (Joshi 1975; Swami 1977). In both trials, clinical and parasitological cure was greater in the tinidazole group, despite the longer treatment duration reported in more patients given metronidazole. The effect could be greater if the outcome was assessed before treatment was extended. Two other trials did not report the number of participants in each group for which treatment was extended (Prasad 1985; Asrani 1995), and bias could favour those given longer treatment. One trial studied 10 different antiamoebic drugs and one placebo and randomized participants

to another treatment after poor response to the first treatment but did not mention who among the participants received additional drugs (Donckaster 1964). Another trial compared various treatment regimens (Davila 2002): For those randomized to the nitazoxanide group, nitazoxanide alone was given regardless of the type of parasitosis, while for those in the second group, participants could receive quinfamide alone, mebendazole alone, or both quinfamide and mebendazole depending on the types of parasites seen. Treatment types received by the two groups were very different, and this may represent a potential source of bias. One group stopped recruitment early owing to adverse events (Pamba 1990). Another trial administered different dosages and duration of treatment for adults (five days) and for children (seven days) but analysed these data together (Naoemar 1973).

Exept for Rossignol 2007, which used *E histolytica* stool antigen testing to confirm the diagnosis of intestinal amoebiasis, diagnosis of amoebiasis in the included trials was based on stool microscopy, and non-pathogenic *Entamoeba* species were not differentiated by more sensitive tests such as PCR and stool antigen testing. Two trials used amoebic stool culture (Batra 1972; Tripathi 1986), but one of these did not mention whether all patients had a positive stool culture on admission (Batra 1972). Most trials did not identify *E histolytica* as the true cause of colitis or diarrhoea; this could lead to overestimation of the treatment effect if infection is due to non-pathogenic*Entamoeba* species and resolves spontaneously. In addition, many studies did not mention whether concomitant infection with other protozoa, such as giardiasis or other helminth parasites, was determined. Many of the symptoms of giardiasis and intestinal parasites may be seen in intestinal amoebiasis, and not all trials identified *E histolytica* as the single cause for the intestinal symptoms; therefore, assessment of clinical outcomes may be biased if persistent symptoms after treatment were caused by these other infections.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table 1; **Summary of findings 2** Summary of findings table 2

We have shown in Appendix 9 details of the comparisons and interventions included in this review. We have presented 'Summary of findings' tables for two important outcomes: tinidazole compared with metronidazole as treatment for amoebic colitis (Summary of findings for the main comparison); and combination therapy compared with metronidazole alone as treatment for amoebic colitis (Summary of findings 2).

1. Single alternative drug versus metronidazole

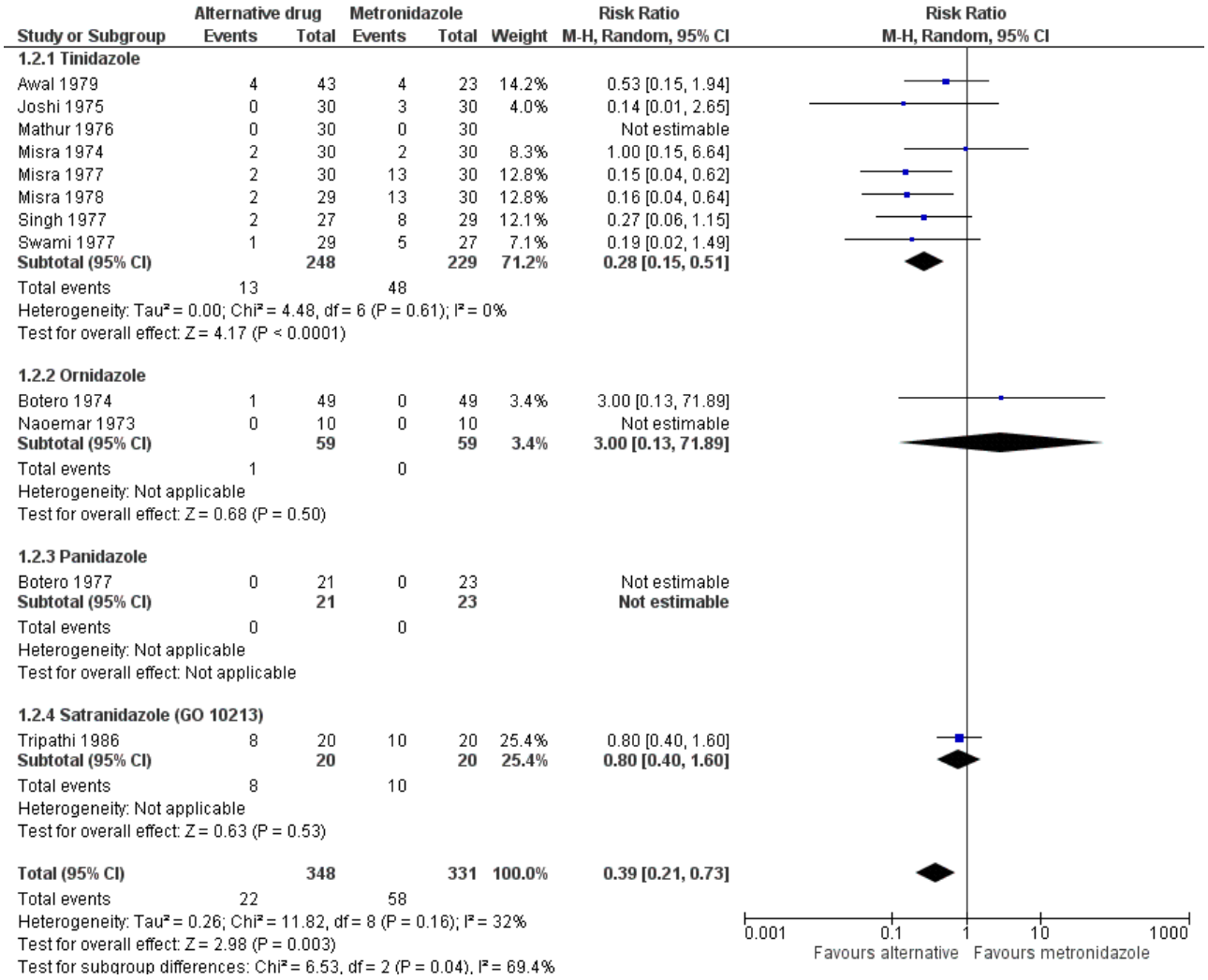
Sixteen trials compared alternative nitroimidazoles versus metronidazole, and one trial compared praziquantel versus metronidazole (Mohammed 1998).

1.1. Tinidazole versus metronidazole

Ten trials compared tinidazole versus metronidazole, with two trials evaluating clinical and parasitological failure 1 to 14 days after end of treatment (Joshi 1975; Chunge 1989); eight trials evaluating clinical failure 15 to 60 days after end of treatment (Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979); and nine trials evaluating parasitological failure 15 to 60 days after end of treatment (Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979; Pehrson 1984). We graded the overall certainty of evidence as low because of serious risk of bias (see Summary of findings for the main comparison): All trials had unclear allocation concealment and randomization except Awal 1979; five trials were not blinded for clinical outcomes and were unclear on blinding for parasitological outcomes (Joshi 1975; Mathur 1976; Singh 1977; Awal 1979; Pehrson 1984); and four trials had variable duration of treatment with treatment extended to 10 days for persistence of clinical symptoms or *E histolytica* in the stools at the end of planned treatment (Misra 1974; Joshi 1975; Mathur 1976; Swami 1977). In addition, all trials used only stool microscopy for diagnosis and assessment of parasitological outcomes, hence misclassification of diagnosis and eradication of *E histolytica* in stools is possible. Nine trials were conducted in countries endemic for amoebiasis (eight in India, one in Bangladesh). For clinical failure 1 to 14 days after end of treatment, results showed imprecision probably due to small sample sizes and few events (RR 0.17, 95% CI 0.02 to 1.30; 285 participants, 2 trials; low-certainty evidence; Analysis 1.1).

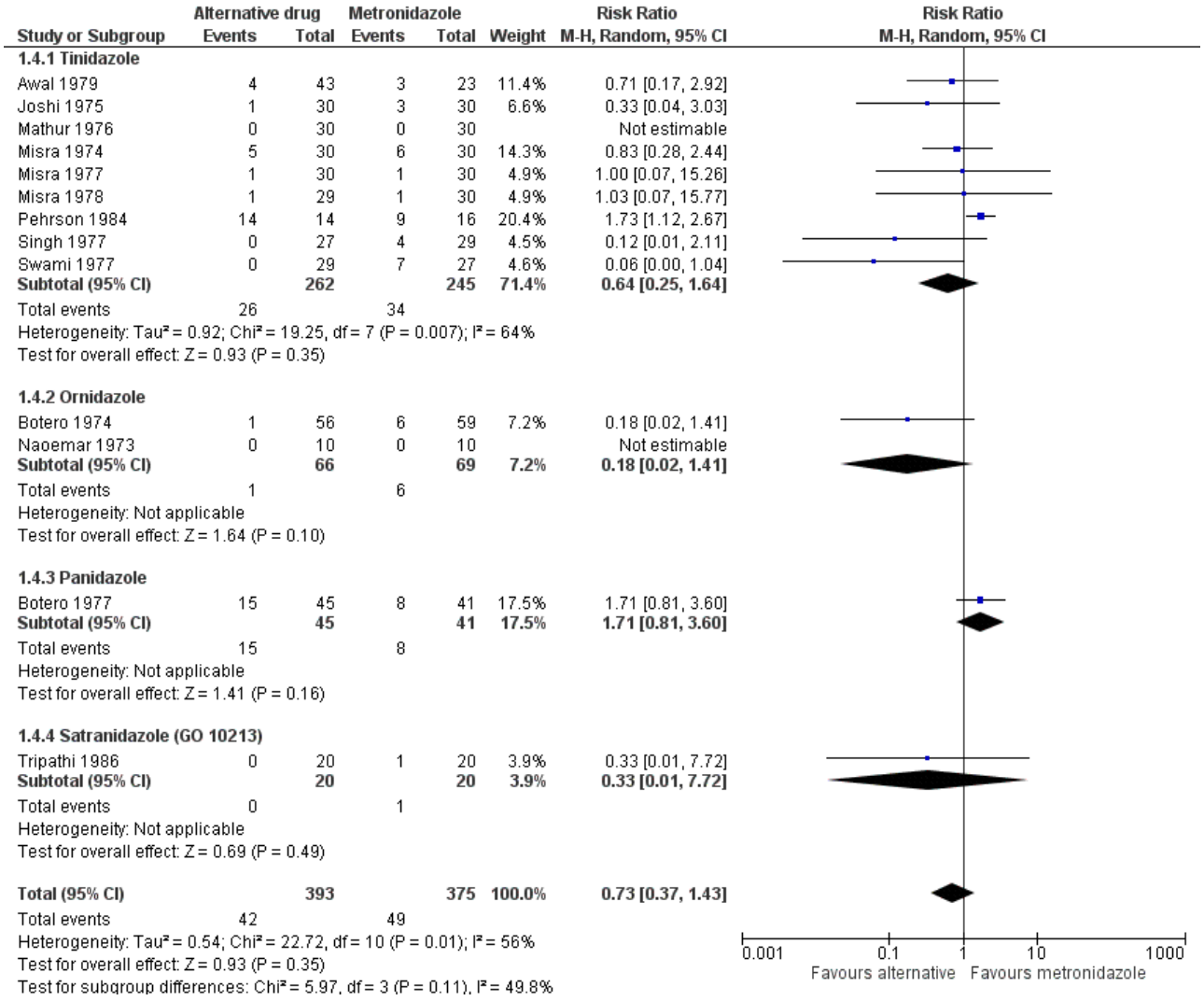
For clinical failure 15 to 60 days after end of treatment, tinidazole reduced clinical failure by 72% compared with metronidazole (RR 0.28, 95% CI 0.15 to 0.51; 477 participants, 8 trials; low-certainty evidence; Analysis 1.2 and Figure 3). A sensitivity analysis evaluating quality in relation to allocation concealment and blinding was not possible. We noted no significant change in the overall result when we excluded Misra 1978, which may be a duplicate publication of an earlier trial - Misra 1977 (RR 0.31, 95% CI 0.16 to 0.61; 418 participants, 7 trials; low-certainty evidence; Analysis 12.1). Excluding four trials funded by pharmaceutical companies also did not affect the overall result (RR 0.24, 95% CI 0.11 to 0.50; 241 participants, 4 trials; low-certainty evidence; Analysis 12.2) (Misra 1974; Joshi 1975; Mathur 1976; Singh 1977).

Figure 3. Alternative drug versus metronidazole: clinical failure 15 to 60 days after end of treatment.



Results for parasitological failure did not show that tinidazole was more effective than metronidazole in eradicating *E histolytica* 1 to 14 days after end of treatment (RR 1.01, 95% CI 0.58 to 1.74; 285 participants, 2 trials; low-certainty evidence; Analysis 1.3) or 15 to 60 days after end of treatment (RR 0.64, 95% CI 0.25 to 1.64; 507 participants, 9 trials; very low-certainty evidence; Analysis 1.4 and Figure 4). Heterogeneity was significant in trials that evaluated parasitological failure 15 to 60 days after end of treatment. Subgroup analysis conducted to investigate possible sources of heterogeneity showed reduced heterogeneity in trials with non-dysenteric amoebic colitis and unspecified amoebic colitis (Analysis 6.1), as well as in trials that used the WHO criteria (Analysis 6.4). Age and the presence or absence of other concomitant intestinal infection did not explain heterogeneity (Analysis 6.2 and Analysis 6.3). Subgroup analysis showed greater treatment effects of tinidazole in those given the higher dose of 2 grams in a single dose for three days compared with lower doses of tinidazole at 600 mg twice daily for five days. although this was significant only for clinical improvement (RR 0.24, 95% CI 0.13 to 0.47; 297 participants, 5 trials; low-certainty evidence; Analysis 11.1) - not for parasitological response (Analysis 11.2).

Figure 4. Alternative drug versus metronidazole: parasitological failure 15 to 60 days after end of treatment.



Researchers reported no data on relapse.

Eight trials reported adverse events (Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979). We graded the certainty of evidence for this outcome as moderate because of serious risk of bias due to lack of blinding or unclear blinding in all trials, and lack of standardization in reporting of both clinical and laboratory adverse events. Four trails reported no blinding of outcome assessors for adverse events (Joshi 1975; Mathur 1976; Singh 1977; Awal 1979), and in the other four trials, this was unclear (Misra 1974; Misra 1977; Swami 1977; Misra 1978). Participants in seven trials voluntarily reported adverse events, but one trial did not specify the method used to solicit adverse events (Misra 1974). Five trials monitored adverse events for 30 days from start of treatment, but two trials did not mention the duration of monitoring (Misra 1974; Misra 1978). All eight trials reported no abnormalities seen on haematological, biochemical, and urine analyses, and two trials reported no abnormalities on electrocardiographic studies (Misra 1974; Misra 1977). All trials conducted laboratory tests before treatment, but trials repeated testing at different time points during and after treatment. No trials reported that serious adverse events or adverse events necessitated drug withdrawal. Other non-serious adverse events appeared to be less common among those given tinidazole than among those given metronidazole (RR 0.65, 95% CI 0.46 to 0.92; 477 participants, 8 trials; moderate-certainty evidence; Analysis 1.6); nausea, vomiting, decreased appetite, and altered taste or metallic taste were the most common (see Appendix 10 for other details).

1.2. Other nitroimidazole drugs versus metronidazole

Other alternative drugs tested were ornidazole (155 participants, 3 trials; Naoemar 1973; Pudjiadi 1973; Botero 1974), secnidazole (44 participants, 1 trial; Karabay 1999), panidazole (86 participants, 1 trial; Botero 1977), and satranidazole (40 participants, 1 trial; Tripathi 1986). The number of participants in these trials comparing other nitroimidazoles versus metronidazole was inadequate to allow detection of any significant difference in clinical failure or parasitological failure 1 to 14 days after end of treatment (Analysis 1.1 and Analysis 1.3), or 15 to 60 days after end of treatment (Analysis 1.2 and Analysis 1.4). Researchers reported no differences in time to resolution of clinical symptoms and eradication of *E histolytica* in stools between intervention and control groups (see Table 3).

For relapse, the data reported in two small trials, both comparing ornidazole versus metronidazole (Naoemar 1973; Botero 1974), were of very low certainty because of inadequate description of the randomization process and allocation concealment, and additionally in one trial for unclear blinding procedures (Botero 1974). In these trials, more relapses were evident among those given ornidazole than among those given metronidazole (RR 4.74, 95% CI 1.07 to 20.99; 135 participants, 2 trials; very low-certainty evidence; Analysis 1.5), but data are insufficient to allow definitive conclusions because of the small numbers of events reported.

Three trials comparing ornidazole versus metronidazole reported adverse events (Naoemar 1973; Pudjiadi 1973; Botero 1974), as did one trial comparing panidazole with metronidazole - Botero 1977 - and another trial comparing satranidazole with metronidazole - Tripathi 1986. No trials reported serious adverse events or withdrawals resulting from adverse events, except one - Botero 1974 - in which one participant given ornidazole developed temporary numbness of the hands and tongue with difficulty speaking that disappeared after treatment was stopped. In another trial (Naoemar 1973), the dosage of two participants each in the ornidazole group and the metronidazole group had to be reduced because of dizziness or nausea. No abnormalities in laboratory tests were seen in trials that conducted these tests (see Appendix 10 for other details). There seems to be no difference in adverse events among those given ornidazole, panidazole, and satranidazole compared with metronidazole (Analysis 1.6).

2. Any antiamoebic drug versus placebo

Four studies involved comparison of any antiamoebic drug versus placebo: nitazoxanide (167 participants, 2 trials; Rossignol 2001; Rossignol 2007) and quinfamide (96 participants, 1 trial; Huggins 1982); and versus 10 different drugs belonging to six drug classes (367 participants, 1 trial; Donckaster 1964).

Compared with placebo, both quinfamide and nitazoxanide reduced clinical and parasitological failure rates 1 to 14 days after end of treatment (Analysis 2.1 and Analysis 2.2). However, heterogeneity among trials was significant, even in the two trials that evaluated nitazoxanide. Subgroup analysis using clinical categories did not explain heterogeneity (Analysis 7.1), but such heterogeneity was reduced in trials that included adult participants only (Analysis 7.2 and Analysis 7.3). Excluding the single trial that used stool antigen-based ELISA testing to confirm *E histolytica* - Rossignol 2007 - also reduced heterogeneity in the remaining trials (Analysis 7.4 and Analysis 7.5). Sensitivity analysis using concealment and blinding was not possible because only one trial was concealed - Rossignol 2007 - and only two trials were blinded - Rossignol 2001 and Rossignol 2007.

Researchers reported no data on relapse.

No trial reported serious adverse events or withdrawals due to adverse events. Also no trials reported differences in adverse events among those given antiamoebic drugs compared with placebo (530 participants, 3 trials; Analysis 2.3), although the results could be biased because of a great imbalance in the numbers of those given active drugs versus placebo. The most common adverse events were mild gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and headache. One individual given diiodohydroxyquinoline presented with severe intestinal colic (see Appendix 11 for details).

3. Combination regimen versus monotherapy

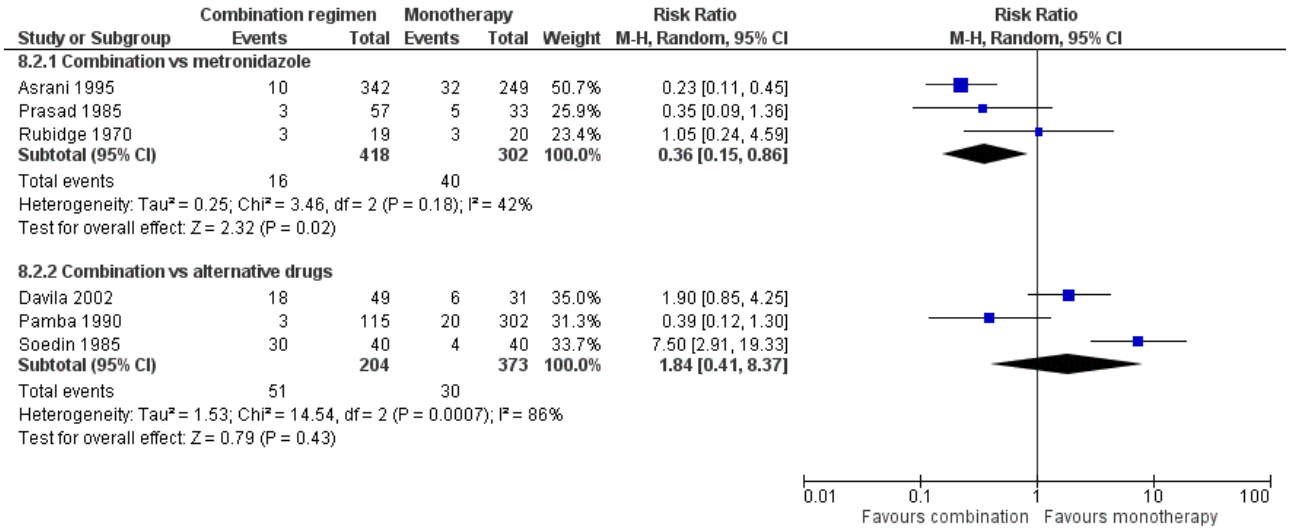
Three trials compared various combination regimens versus metronidazole alone (Rubidge 1970; Prasad 1985; Asrani 1995), and four trials compared other combination regimens versus alternative single drugs (Pehrson 1983; Soedin 1985; Pamba 1990; Davila 2002).

3.1. Combination regimen versus metronidazole alone

We graded the overall certainty of evidence as very low for the outcome of clinical failure 1 to 14 days after end of treatment (Summary of findings 2). All three trials did not describe the randomization process and allocation concealment, and blinding was lacking in two trials (Rubidge 1970; Asrani 1995). Prasad 1985 was at high risk of selective reporting bias because researchers did not adequately describe the method used for outcome evaluation and researchers analysed participants after different treatment durations ranging from 5 to 10 days, depending on severity of disease and response to therapy. All three trials were conducted in countries endemic for amoebiasis and used only stool microscopy to assess parasitological outcomes, hence misclassification of eradication of *E histolytica* from stools is possible. The pooled result shows that compared with metronidazole alone, combination therapy reduced clinical failure 1 to 14 days after end of treatment by 67% (RR 0.33, 95% CI 0.11 to 0.98; 1025 participants, 3 trials; very low-certainty evidence; Analysis 8.1). However, significant heterogeneity seen in these trials could be due to the various combination regimens used: a combination of dehydroemetine, tetracycline, and diloxanide furoate (Rubidge 1970); a fixed-drug combination suspension of metronidazole and furazolidone (Prasad 1985); and a fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline (Asrani 1995). Heterogeneity could also be explained by differences in clinical disease, because exclusion of the trial that included only children with amoebic dysentery resulted in greater effect favouring combination therapy in patients with unspecified intestinal amoebiasis (RR 0.17, 95% CI 0.12 to 0.25; 986 participants, 2 trials; very low-certainty evidence; Analysis 9.1) (Rubidge 1970). This could be attributed to additional luminal drugs (diiodohydroxyquinoline in Asrani 1995 and furazolidone in Prasad 1985) that may be more effective against cyst forms in patients with unspecified intestinal amoebiasis.

For parasitological failure 1 to 14 days after end of treatment, we graded the overall certainty of evidence as low because of lack of allocation concealment and blinding, selective reporting, and indirectness as described above. Results showed a 64% reduction in parasitological failure 1 to 14 days after end of treatment among those given the combination compared with those given metronidazole alone (RR 0.36, 95% CI 0.15 to 0.86; 720 participants, 3 trials; low-certainty evidence; Analysis 8.2). We noted no significant heterogeneity among trials (Figure 5). Subgroup analysis showed that excluding the trial on children with amoebic dysentery showed greater benefit for those with unspecified intestinal amoebiasis (RR 0.25, 95% CI 0.13 to 0.46; 681 participants, 2 trials; low-certainty evidence; Analysis 9.2).

Figure 5. Combination regimen versus monotherapy: parasitological failure 1 to 14 days after end of treatment, subgrouped by intervention.



For both clinical and parasitological failure, the overall results were driven by one trial, which analysed a large number of participants (896 participants analysed for clinical failure; 591 participants analysed for parasitological failure) compared with the other two trials (Asrani 1995). This was an open-label trial with unclear allocation concealment and method of randomization, hence the high possibility of bias. This trial also may have been funded by a pharmaceutical company because one of the study authors is connected with the company that provided the study drug - a fixed-drug combination of metronidazole and diiodohydroxyquinoline. A sensitivity analysis performed while excluding this trial reduced heterogeneity and significantly changed the overall results for both clinical and parasitological outcomes (i.e. no benefit in giving combination therapy compared with giving metronidazole alone) (RR 0.58, 95% CI 0.20 to 1.73; 129 participants, 2 trials; low-certainty evidence; Analysis 13.1; Analysis 13.2).

Researchers reported no data on relapse.

The three trials reported no serious adverse events but indicated that one participant given a fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline developed an unspecified allergic reaction on the first day, necessitating withdrawal from the trial. Two trials did not blind outcome assessors for adverse events (Asrani 1995; Rubidge 1970). One trial reported that tolerance of both regimens was excellent and noted no toxicity (Rubidge 1970); another trial reported no difference in the overall incidence of side effects between the two groups but did not report on the number who developed adverse events (Asrani 1995). The most frequently reported adverse events in both groups were metallic taste, abdominal pain, and nausea. Only one trial reported a higher incidence of side effects with metronidazole compared with the fixed-drug combination suspension of furazolidone and metronidazole but did not report the specific adverse events and the number who developed adverse events (Prasad 1985). See Appendix 12 for details.

3.2. Combination regimen versus other single-drug regimens

Four trials studied the efficacy of combination regimens compared with other single-drug regimens. Two trials compared combination regimens with other nitroimidazoles: a combination of tetracycline and clioquinol versus secnidazole alone (80 participants, 1 trial; Soedin 1985); and a combination of tinidazole and diloxanide furoate versus tinidazole alone (41 participants, 1 trial; Pehrson 1983). The third trial compared three different combinations (nimorazole and aminosidine, nimorazole and etophamide, and etophamide and aminosidine) versus the same drugs given as monotherapy (400 participants, 1 trial; Pamba 1990). The fourth trial compared quinfamide and mebendazole versus nitazoxanide (80 participants, 1 trial; Davila 2002).

Trials could not be pooled because they performed different drug comparisons, but we have presented the data for clinical failure (Analysis 3.1) and parasitological failure (Analysis 3.2). Trials did not show any difference in clinical or parasitological failure rates between combination regimens and single-drug regimens, except in two comparisons. Soedin 1985 showed that secnidazole alone resulted in greater resolution of clinical symptoms and greater eradication of *E histolytica* when compared with the combination of tetracycline and clioquinol on day 28 of treatment (80 participants, 1 trial; Analysis 3.1; Analysis 3.2). Pehrson 1983, another small trial, showed that the combination of tinidazole and diloxanide furoate resulted in greater eradication of *E histolytica* compared with tinidazole alone one month after end of treatment (41 participants, 1 trial). Both trials reported wide confidence intervals; thus no definitive conclusions regarding these regimens can be made.

Researchers reported no data on relapse.

Trials incompletely reported adverse events. Pamba 1990 discontinued recruitment of participants in the combination etophamide-aminosidine group because of the high incidence of severe diarrhoea. Soedin 1985 and Davila 2002 reported that both treatment regimens were well tolerated with only a few side effects but did not report the specific adverse events and the number of participants who developed any adverse events.

Pehrson 1983 reported that no serious adverse events necessitated discontinuation of treatment but provided no details. See Appendix 12 for details.

4. Single-dose regimen versus longer or multiple-dose regimens

Five trials compared a single-dose regimen versus longer duration of therapy or multiple-dose regimens. Three trials compared longer duration of other drugs versus single-dose secnidazole (Soedin 1985; Karabay 1999; Salles 1999), and two trials compared longer duration of other drugs versus single-dose quinfamide (Huggins 1982; Davila 2002).

4.1. Single-dose secnidazole versus longer or multiple-dose regimens

Salles 1999 compared single-dose secnidazole versus tinidazole for two days (303 participants, 1 trial), Karabay 1999 compared single-dose secnidazole versus metronidazole for 10 days (44 participants, 1 trial), and Soedin 1985 compared single-dose secnidazole versus a combination of tetracycline and clioquinol for five days (80 participants, 1 trial). These trials were unclear on allocation concealment and were not blinded.

Soedin 1985 showed that single-dose secnidazole resulted in greater resolution of clinical symptoms at end of treatment compared with five days of tetracycline and clioquinol (RR 0.12, 95% CI 0.03 to 0.48; 80 participants, 1 trial; low certainty evidence; Analysis 4.1). Salles 1999 did not show any difference in clinical failure 19 days after end of treatment between single-dose secnidazole and two-day tinidazole treatment (275 participants, 1 trial; Analysis 4.2). We could not pool results for clinical failure because of a difference between the two trials in the time of evaluation of clinical outcomes (Analysis 4.1 and Analysis 4.2).

Single-dose secnidazole may result in lower parasitological failure 1 to 14 days after end of treatment compared with multi-dose regimens (Soedin 1985; Karabay 1999) (RR 0.14, 95% CI 0.06 to 0.35; 124 participants, 2 trials; low-certainty evidence; Analysis 4.3 and Analysis 10.1). Although no heterogeneity was evident, the antiamoebic drugs compared with secnidazole were different; secnidazole was compared with metronidazole in one trial (Karabay 1999), and with a combination of tetracycline and clioquinol in another trial (Soedin 1985). Both trials were small with unclear allocation concealment and blinding of the microscopist examining the stools. Another trial compared single-dose secnidazole versus tinidazole and suggested that secnidazole may be more effective than tinidazole for eradication of amoebae from the stools 19 days after end of treatment (RR 0.61, 95% CI 0.43 to 0.88; 300 participants, 1 trial; low-certainty evidence; Analysis 4.4) (Salles 1999). As this was an open trial, Salles 1999 appears to be at high risk of bias.

Researchers reported no data on relapse.

Only Salles 1999 reported on adverse events. Researchers reported no serious adverse events or withdrawals for adverse events. Adverse events most commonly reported were bitter taste, nausea, vomiting, and abdominal pain, with no difference in frequency between those given single-dose secnidazole compared with tinidazole for two days. Soedin 1985 did not report the proportion of participants who developed adverse events but mentioned that side effects were few and treatment was well tolerated regardless of the regimen received (see Appendix 12 for details).

4.2. Single-dose quinfamide versus multiple doses of quinfamide or longer duration of another drug

Investigators compared single-dose quinfamide versus two or three doses of quinfamide (72 participants; Huggins 1982), and they compared single-dose quinfamide versus nitazoxanide for three days (25 participants; Analysis 4.1; Analysis 4.3) (Davila 2002).

Huggins 1982 showed no difference in clinical failure between those given one dose compared with two or three doses of quinfamide (72 participants; Analysis 4.1).

For parasitological failure 1 to 14 days after end of treatment, pooling of results from two trials revealed a trend favouring more doses compared with single-dose quinfamide for eradicating *E histolytica* (RR 2.13, 95% CI 1.02 to 4.46; 97 participants; two trials; low-certainty evidence; Analysis 10.1) (Huggins 1982; Davila 2002). Both trials were unclear regarding generation of the allocation sequence, concealment, and blinding. Results were not heterogeneous, but numbers of trials and participants were too small to permit any definitive conclusions.

Researchers reported no data on relapse.

Only Huggins 1982 reported on adverse events; these reports were based on only two symptoms - nausea and headache. None of those given single-dose quinfamide developed adverse effects, but 12 among those who received two or three doses of quinfamide developed nausea and headache. Davila 2002 reported that both quinfamide and nitazoxanide were well-tolerated but mentioned no specific adverse effects (see Appendix 12 for details).

5. Other antiamoebic drug comparisons

Thirteen trials studied different drug comparisons (see Appendix 9 for details). Only two trials were adequately concealed (Savas-Erdeve 2009; Siddiqui 2015). Blinding was not done or was unclear in all except two trials (Nnochiri 1967; Padilla 2000). Dropout rates were high in two trials, with one trial analysing only 62.5% of those initially randomized (Panggabean 1980), and the other trial analysing 82% (Sitepu 1982).

Eight trials assessed clinical failure 1 to 14 days after end of treatment (Kapadia 1968; Batra 1972; Panggabean 1980; Sitepu 1982; Toppare 1994; Savas-Erdeve 2009; Siddiqui 2015; Shah 2016). Kapadia 1968 showed chlorhydroxyquinoline to be probably more effective than diiodohydroxyquinoline in reducing clinical failure (RR 0.24, 95% CI 0.11 to 0.53; 100 participants, 1 trial). Two trials reported no difference in clinical failure rates when comparing the other antiamoebic drugs: ornidazole versus tinidazole (66 participants, 2 trials; Panggabean 1980; Sitepu 1982). Other trials reported no difference in clinical failure rates when comparing ornidazole versus secnidazole (102 participants, 1 trial; Toppare 1994), a fixed combination of metronidazole and diloxanide furoate versus an herbal product composed of several different natural products (153 participants, 1 trial; Siddiqui 2015), and metronidazole versus an herbal product (184 participants, 1 trial; Shah 2016). Two trials reported no clinical failures when comparing respectively four dosage regimens of MK-910 (40 participants, 1 trial) and *Saccharomyces boulardii* probiotic added to metronidazole versus metronidazole alone (85 participants, 1

trial; Analysis 5.1) (Batra 1972; Savas-Erdeve 2009). Two trials evaluated the effect of added *S boulardii* on duration of clinical symptoms; one trial reported this outcome as the mean (Mansour-Ghanaei 2003), and the other trial as median and range (Savas-Erdeve 2009). One trial evaluating resolution of diarrhoea and abdominal pain showed significantly shorter mean duration among those given *S boulardii* in addition to metronidazole and iodoquinol (Mansour-Ghanaei 2003), but another trial did not show a difference in median and range for this outcome when *S boulardii* was added to metronidazole (Savas-Erdeve 2009). See Table 3.

Ten trials assessed parasitological failure one to 14 days after end of treatment (Kapadia 1968; Batra 1972; Panggabean 1980; Sitepu 1982; Toppare 1994; Padilla 2000; Davila 2002; Savas-Erdeve 2009; Siddiqui 2015; Shah 2016). Two trials assessed parasitological failure approximately one month after treatment (Guevara 1980; Mansour-Ghanaei 2003), and another trial assessed parasitological failure during two time periods - 1 to 14 days and 15 to 60 days after treatment (Nnochiri 1967). One trial showed that chlorhydroxyquinoline probably was more effective than diiodohydroxyquinoline in reducing parasitological failure 1 to 14 days after end of treatment (RR 0.53, 95% CI 0.35 to 0.80; 100 participants, 1 trial; low-certainty evidence; Analysis 5.3) (Kapadia 1968). Researchers reported no difference in eradication of amoebae from the stools in trials comparing ornidazole versus other nitroimidazoles: ornidazole versus tinidazole (74 participants, 2 trials; Panggabean 1980; Sitepu 1982); and ornidazole versus secnidazole (102 participants, 1 trial; Toppare 1994). Single-dose quinfamide appeared to result in better parasitological eradication when compared with single-dose secnidazole in one trial (RR 0.57, 95% CI 0.34, 0.96; 239 participants, 1 trial - Padilla 2000; low-certainty evidence; Analysis 5.3) but not when compared with nitazoxanide in another trial (25 participants, 1 trial - Davila 2002; Analysis 5.3). Another trial comparing three doses of quinfamide versus teclozan reported no differences between the two groups (37 participants, 1 trial - Guevara 1980; Analysis 5.4). Batra 1972 noted no difference in parasitological failure when comparing low-dosage regimens of MK-910 versus higher dosages (≥ 2 mg/kg/d) of the same drug (40 participants, 1 trial). Two trials evaluated the efficacy of adding the probiotic *S boulardii* to metronidazole and found a trend toward increased parasitological eradication in the group given *S boulardii* in addition to metronidazole and iodoquinol (54 participants, 1 trial - Mansour-Ghanaei 2003; Analysis 5.3), and in addition to metronidazole alone (85 participants, 1 trial - Savas-Erdeve 2009; Analysis 5.2), but the results were not statistically significant. Another trial showed a non-significant increase in both clinical and parasitological failure at end of treatment among those given an herbal product compared with those given a fixed-drug combination of metronidazole and diloxanide furoate (154 participants, 1 trial - Siddiqui 2015; Analysis 5.1 and Analysis 5.2). One trial showed no significant difference in parasitological failure at end of treatment between an herbal drug product and metronidazole (184 participants, 1 trial; Shah 2016). A small trial that compared a fixed-drug combination of diloxanide furoate, tetracycline, and chloroquine versus the fixed-drug combination without chloroquine showed no difference in parasitological failure between the two groups at end of treatment (59 participants, 1 trial; Analysis 5.2) but showed a significant advantage for the combination containing chloroquine on follow-up seven weeks after end of treatment (RR 0.29, 95% CI 0.09 to 0.92; 58 participants, 1 trial; low-certainty evidence; Analysis 5.3) (Nnochiri 1967).

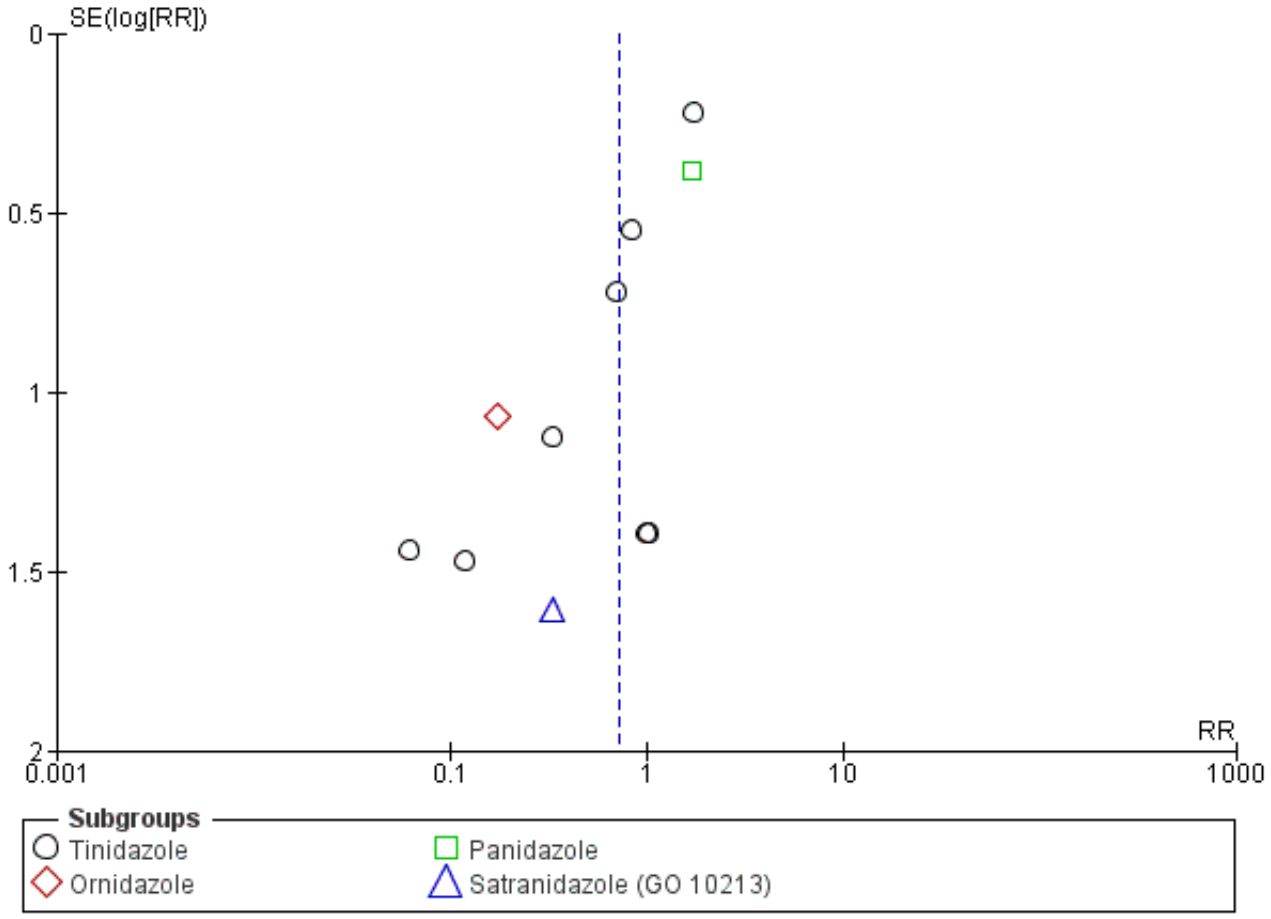
Researchers reported no data on relapse.

One trial reported that the higher dosage regimen of MK-910 resulted in nausea, vomiting, and abdominal pain severe enough to require withdrawal from treatment for two participants (Batra 1972). Gastrointestinal adverse effects occurred more frequently in the secnidazole group than in the quinfamide group (Padilla 2000). Mild vomiting occurred in one participant given ornidazole, but none occurred among those given tinidazole (Panggabean 1980). Those given a fixed-drug combination of metronidazole and diloxanide furoate had significantly greater gastrointestinal adverse effects compared with those given the herbal product (Siddiqui 2015). One trial reported no difference in adverse effects between those given quinfamide or teclozan (Guevara 1980). Three trials mentioned that participants reported no side effects but provided no further details (Toppare 1994; Davila 2002; Savas-Erdeve 2009). One trial reported that 57.4% of those given metronidazole developed mild side effects, including nausea and vomiting, but did not report any adverse effects of the herbal drug (Shah 2016). Two trials reported only on specific adverse events - not on the number of participants with adverse events (Nnochiri 1967; Batra 1972); and three trials did not report on clinical adverse effects (Kapadia 1968; Sitepu 1982; Mansour-Ghanaei 2003). See Appendix 12 for details.

Funnel plot

We constructed a funnel plot with 10 trials for one outcome measure and examined it visually for possible bias or heterogeneity: any antiamoebic drug versus metronidazole and measuring parasitological failure 15 to 60 days after end of treatment (13 trials; Figure 6). This included nine trials that compared tinidazole with metronidazole. Asymmetry in the funnel plot may indicate the presence of publication bias but may also indicate inadequate trial methodological quality or heterogeneity resulting from differences in study populations, interventions, outcome measurements, and trial design.

Figure 6. Funnel plot. Alternative drug versus metronidazole: parasitological failure 15 to 60 days after end of treatment.



DISCUSSION

See Summary of findings for the main comparison and Summary of findings 2.

Tinidazole versus metronidazole

In patients with amoebic colitis, treatment with tinidazole reduced clinical failure by 72% compared with treatment with metronidazole for outcomes evaluated 15 to 60 days after end of treatment and may be as effective as metronidazole in eradicating *Entamoeba histolytica* from stools. The incidence of mild to moderate gastrointestinal complaints also appeared to be lower among those given tinidazole. These results must be interpreted with caution because most trials are old (8 of the 10 trials were conducted between 1974 and 1978), the overall certainty of trial evidence is very low, and standardization in enrolment, diagnosis, treatment, and outcome assessment is lacking. None of the trials used *E histolytica* antigen detection or culture for diagnosis, and none determined the presence of infection with other pathogenic organisms, so uncertainty surrounds the diagnosis of amoebic colitis and the decision of whether clinical symptoms are due to amoebic colitis alone. Differences in clinical responses could also be due to lack of standardization of dosage, interval, and duration of drug treatments given. Other studies have shown that tinidazole is better when given as a single dose than in divided doses because of its longer half-life of approximately 12 to 14 hours, resulting in longer concentrations in the body (Monro 1974; Looke 1987), whereas metronidazole has a shorter half-life of about 6 to 10 hours and is better given in divided doses. Also, longer courses may lead to re-excretion through the bile, resulting in higher concentrations within the bowel lumen (Tracy 2001). This is supported by the summary report of nine trials conducted in India, which reported that tinidazole given as a single dose daily was more effective than divided doses, and was more effective and was associated with fewer gastrointestinal adverse events when compared with metronidazole given once daily (Bakshi 1978).

The risk difference for clinical failure among those given tinidazole and those given metronidazole is 0.16, yielding a number needed to treat for an additional beneficial outcome (NNTB) of 6.25. Thus, seven people will have to be treated with tinidazole for clinical failure to be reduced in one more individual. However, this finding cannot be applied to parasitological failure, as no significant difference in eradication of *E histolytica* is apparent between those given tinidazole and those given metronidazole.

Other nitroimidazole drugs versus metronidazole

Ornidazole and secnidazole are promising alternative antiamoebic drugs because they share the same mechanism of action as metronidazole against amoebae but remain longer in the blood. Compared with metronidazole, ornidazole remains in the blood around 1.7 times longer (with half-life ranging from 11 to 14 hours), and secnidazole remains in the blood around three times longer (with half-life ranging from 17 to 28 hours) (Lamp 1999). This review shows that evidence is insufficient at the moment to demonstrate advantage of these drugs over metronidazole for treating individuals with amoebic colitis. More high-quality trials in larger populations will be needed to determine whether or not these other nitroimidazole agents will be significantly more effective than metronidazole in reducing clinical signs of amoebiasis and in preventing persistence of amoebae in the stools.

Antiamoebic drugs versus placebo

The general recommendation is to give antiamoebic treatment to all individuals with definitive *E histolytica* infection, including those who have no symptoms of disease (WHO 1997; The Medical Letter 2013; AAP 2015). Approximately 3% to 10% of infected individuals may develop symptoms of invasive amoebiasis if left untreated (Haque 2001; Haque 2002; Blessman 2003). However, it is not known who among these asymptomatic individuals with *E histolytica* infection will develop symptomatic disease. Therefore, unless the diagnosis of *E histolytica* infection is uncertain for an asymptomatic individual, use of placebo as a comparison drug, particularly in patients with symptoms of invasive disease, is not appropriate. This review shows that antiamoebic drugs were more effective than placebo in reducing clinical symptoms of amoebic colitis and in eradicating *E histolytica* from the stools, although trials were of very low quality and heterogeneity was significant. Heterogeneity could be attributed to differences in participant characteristics or to the varied antiamoebic drugs used. The disappearance of parasites in 50 out of 133 (38%) individuals taking placebo may be explained by spontaneous eradication of *E histolytica* or infection with non-pathogenic amoebae. Studies have shown that up to 90% of individuals with untreated *E histolytica* infection spontaneously clear their infection within one year (Gathiram 1987; Haque 2001; Haque 2002; Blessman 2003; Stanley 2003; Choudhuri 2012). It may also be possible that patients were actually infected with non-pathogenic amoebae because stool microscopy was the only diagnostic test utilized.

Combination regimen versus metronidazole alone

For all forms of invasive disease, including amoebic colitis, the standard recommendation is to give a tissue amoebicide followed by a luminal amoebicide to eliminate surviving cysts in the bowel lumen (WHO 1995; WHO 1997; The Medical Letter 2013; AAP 2015). Compared with metronidazole alone, combination therapy resulted in a reduction of about 60% for both clinical and parasitological failure. The advantage of combination therapy is attributed to the distinct activities of different drugs against cysts and trophozoites found at the different sites (WHO 1995; Tracy 2001; The Medical Letter 2013). This was consistent with the greater effect of combination therapy for those with unspecified intestinal amoebiasis when both invasive and cyst forms could be present compared with individuals with amoebic dysentery alone. However, interpretation of these results is complicated because trials used different combinations of drugs in comparison with metronidazole: fixed-drug combination of diiodohydroxyquinoline and metronidazole (Asrani 1995); fixed-drug combination suspension of furazolidone and metronidazole (Prasad 1985); and combination of subcutaneous dehydroemetine plus oral tetracycline and diloxanide furoate (Rubidge 1970). No conclusions can be drawn regarding the most effective combination antiamoebic drug regimen because none of the included trials were of sufficient size to reveal this. Some of these drugs are no longer marketed, and it is not known whether these results could be applied to other combinations. It is also not known whether combination therapy would lead to increased adverse events, because this information was incompletely reported.

Single-dose regimen compared with longer-duration or other single-dose regimens

The advantages of single-dose regimens are numerous, including ease of administration, convenience, better patient compliance, and reduced cost with no evidence of increased adverse effects. Two antiamoebic drugs - secnidazole and quinfamide - were evaluated as single-dose therapy: Results were inconclusive owing to the small sample size and the low methodological quality of trials. More trials are needed to determine the clinical and parasitological efficacy of single-dose regimens of secnidazole or quinfamide and of other antiamoebic drugs that can be given for a shorter duration than other drugs, including the current standard antiamoebic drug, metronidazole.

Other antiamoebic drug comparisons

Available data are insufficient to establish the efficacy and safety of the other antiamoebic drugs for treating amoebic colitis. More recently, interest in the effect of non-traditional therapy against amoebiasis has been increasing. Two trials evaluated the effect of adding *Saccharomyces boulardii,* a probiotic fungal organism, to metronidazole therapy. Probiotics are live micro-organisms that confer a health benefit on the host, including prevention and treatment of diarrhoea. Reviews on the efficacy of probiotics support clinical benefit in preventing *Clostridium difficile*-associated diarrhoea (Goldenberg 2013), as well as in reducing the duration and severity of acute infectious diarrhoea in children (Allen 2010). In general, this beneficial effect has been shown to be dose-dependent and strain-dependent. Probiotics may have the potential to restore the normal gut flora, although the exact mechanism of the antiamoebic effect of *S boulardii* remains to be elucidated. Two studies included in this review reported conflicting results: In one study, the addition of *S boulardii* to the combination of metronidazole and iodoquinol reduced stool frequency and duration of illness in adults with acute amoebic colitis (Mansour-Ghanaei 2003), whereas the second study, which enrolled children, did not show a significant decrease in symptoms nor in eradication of amoebae from stools when *S boulardii* was added to metronidazole (Savas-Erdeve 2009). Two other studies evaluated the effects of herbal products and suggested that herbal products may be as effective as or superior to conventional antiamoebic therapy with fewer adverse effects (Siddiqui 2015; Shah 2016). Potential use of probiotics or herbal products in combination with antiamoebic drugs includes situations in which single-drug therapy does not result in satisfactory clinical and parasitological cure rates, additional antiamoebic drugs such as luminal antiamoebic drugs are warranted but are not available, and adverse reactions to additional or higher doses of antiamoebic

drugs may arise. Further studies are needed to determine the role of these natural products in treating people with amoebic colitis.

Summary of main results

This review shows that for individuals with amoebic colitis, tinidazole may be better in reducing clinical symptoms and may result in fewer adverse events compared with metronidazole, but we do not know if it will be more effective in eradicating amoebae from the stools. Combination drug therapy may be more effective than metronidazole alone for eradicating amoebae, but we do not know which drug combination will be most effective, and if this will lead to more rapid resolution of clinical symptoms or to an increase in adverse events. Evidence is insufficient to allow conclusions regarding the efficacy of other antiamoebic drugs. Two trials comparing ornidazole versus metronidazole evaluated relapse and showed higher occurrence of relapse among those given ornidazole, but we are uncertain about this result. Randomized controlled trials of better quality and using standardized outcomes are needed to evaluate the efficacy of drugs for treating patients with amoebic colitis.

Overall completeness and applicability of evidence

This review was limited to symptomatic individuals with uncomplicated amoebic colitis. The effects of antiamoebic drugs on those with severe amoebic colitis, complicated disease, or extraintestinal amoebiasis were not studied. The potential effect of malnutrition, immune suppression, or AIDS on treatment is not known. Studies have demonstrated that severity of disease outcomes following *E histolytica* infection are determined by host susceptibility, which can be dependent on genetic factors or on environmental factors, such as malnutrition, and therefore may vary among different populations and geographical locations (Morfl 2012). Although asymptomatic infection with *E histolytica* is more common than symptomatic disease, treatment of these individuals remains controversial because most will clear their infection within one year, and only about 3% to 10% will manifest invasive disease (Gathiram 1987; Haque 2001; Haque 2002; Blessman 2003).

The limited availability of many antiamoebic drugs must be addressed in the light of reports that newer nitroimidazole drugs may be as effective as, and better tolerated than, metronidazole, and that clinical and parasitological failures may be fewer when luminal agents are given in conjunction with tissue amoebicides. Metronidazole is widely used and may be the only available antiamoebic drug in many countries. Tinidazole and the other nitroimidazole drugs, such as ornidazole and secnidazole, and luminal agents, such as diloxanide furoate, iodoquinol, and paromomycin, are not widely available and may be purchased only from certain pharmaceutical companies or requested from government agencies. Although tinidazole was shown in this review as probably more effective and better tolerated than metronidazole, the limitations of currently available evidence and the limited availability of tinidazole in many regions would make a widespread recommendation for its use impractical. Similarly, evidence by which combination therapy can be recommended is inadequate, and the limited availability of luminal agents in the market poses a major deterrent to compliance with the recommendation for combination therapy.

Certainty of the evidence

We used the GRADE approach in assessing the certainty of trial evidence. Limitations in study quality, imprecise or sparse data for some outcomes, important inconsistencies across trials, and a high probability of reporting or publication bias decrease the certainty of evidence. Therefore the conclusions of this review should be interpreted with caution. More than half of the included studies were conducted before 1990, and the very low quality of trials included for primary outcomes implies uncertainty in the results. Inaccurate diagnosis of *E histolytica* infection by stool microscopy, absence of standardized classification of the various categories of amoebic colitis (particularly non-dysenteric amoebic colitis), and variable timing and definitions of outcome measurements would lead to inaccuracy in assessing treatment effects. In areas highly endemic for amoebiasis, true treatment failure or relapse would be difficult to differentiate from re-infection without the benefit of finger typing or genotyping. Incomplete reporting may lead to an inaccurate assessment of adverse events.

Potential biases in the review process

This systematic review included data from a large number of small, randomized, low-quality trials comparing all eligible treatments, making it difficult to draw an overall conclusion about the best treatment for amoebic colitis. Asymmetry in the funnel plot for an outcome with a sufficient number of studies indicates the presence of publication bias, as well as possible overestimation of intervention effects in smaller trials of poor methodological quality.

An advanced approach to meta-analysis of multiple treatments, such as a network meta-analysis, may be conducted in the future to incorporate information from a combination of all relevant direct and indirect treatment comparisons and to generate a ranking scheme of different drugs according to best treatment outcomes (Caldwell 2005; Catalla-Lopez 2014).

Agreements and disagreements with other studies or reviews

A systematic review published in *Clinical Evidence* summarized the effects of different drug treatments for amoebic dysentery in endemic areas (Dans 2006). This systematic review included 12 randomized controlled trials and concluded that ornidazole, secnidazole, and tinidazole were likely to be beneficial in treating amoebic dysentery, but that metronidazole was unlikely to be beneficial. Trial results were not combined, and no formal statistical methods were performed to determine summary measures of drug effectiveness. Updates to the *Clinical Evidence* review - Mackey-Lawrence 2011 and Marie 2013 - mainly summarized findings from the previous version of this current Cochrane review on antiamoebic drugs and performed GRADE evaluation of the certainty of evidence for applied interventions (Gonzales 2009). Authors of the *Clinical Evidence* reviews recognized the generally poor quality of the included trials, largely due to methodological flaws and limitations of diagnostic tests for amoebic infection.

An earlier systematic review on amoebic dysentery published in *Clinical Evidence* concluded that metronidazole was "unlikely to be beneficial" in that some trials demonstrated ineffectiveness or associated harm, and that ornidazole, secnidazole, and tinidazole were "likely to be beneficial" because other trials demonstrated effectiveness of these drugs with no increased harm (Dans 2006). This review used the *Clinical Evidence* search strategy and included

12 randomized controlled trials, defined therapeutic failure as persistence of symptoms or persistence of parasites or both, analysed outcomes reported together for different time points, and did not pool data to generate an overall summary measure. Subsequent updates of this *Clinical Evidence* review - Mackey-Lawrence 2011 and Marie 2013 - mainly summarized findings of the previous version of the earlier published Cochrane review on antiamoebic drugs and included a GRADE evaluation of the certainty of evidence for interventions (Gonzales 2009). Review authors concluded that compared with placebo, ornidazole may be more effective in clearing parasites, and that secnidazole, tinidazole, and metronidazole may be as effective as ornidazole in curing amoebic dysentery. They also concluded that metronidazole may be less effective than tinidazole in reducing clinical symptoms but may be as effective in clearing parasites. For the other antiamoebic drugs, nitazoxanide was found more effective than placebo for reducing clinical failure but not for preventing parasitological failure. As described in this Cochrane review, the authors of the *Clinical Evidence* review recognized the generally poor quality of trials included in the systematic review, largely due to methodological flaws such as lack of blinding, sparse data, and lack of directness due to uncertainty of the diagnosis of amoebic dysentery.

We have made no changes to the conclusions of this updated version of the earlier review (Gonzales 2009). We conclude that although tinidazole may be more effective than metronidazole in reducing clinical failure and was probably associated with fewer adverse effects, it did not show any significant advantage over metronidazole in reducing parasitological failure. Data were also insufficient to show the efficacy of other antiamoebic drugs compared with metronidazole or other drugs. Compared with metronidazole, combination therapy may result in fewer parasitological failures, although the optimal combination of antiamoebic drugs cannot be determined by this review. More high-quality trials including sufficient numbers of participants and using more accurate diagnostic tests are needed to determine the most effective antiamoebic drug or combination of drugs for treating amoebic colitis.

AUTHORS' CONCLUSIONS

Implications for practice

Antiamoebic drugs are indicated for treating individuals with amoebic colitis. Metronidazole has been the standard therapy for treating amoebic colitis owing to its history of long use and availability. Compared with metronidazole, tinidazole may be more effective in reducing clinical failure and probably has fewer adverse effects, but evidence is insufficient to show whether it is more effective in eradicating amoebic parasites from the stools. Combination drug therapy may be more effective than metronidazole alone in reducing parasitological failure, but data are insufficient for recommendation of a specific combination or to show whether this will lead to more rapid resolution of clinical symptoms or to increased adverse effects. Trials were generally inadequate or unclear in the key components measuring methodological quality, and most used stool microscopy alone for diagnosis and evaluation of parasitological outcomes. Thus, evidence is insufficient for review authors to be certain about study results. No definitive conclusions can be drawn regarding the efficacy of other antiamoebic drugs when compared with metronidazole or other drugs. Many antiamoebic drugs are not available in all countries; therefore, the choice of antiamoebic drugs for treatment would depend largely on availability of, and accessibility to, drugs for treatment.

Implications for research

More randomized controlled trials on the efficacy of drugs for treating amoebic colitis, reporting better methodological quality and using standardized definitions for evaluating outcomes, are needed. The diagnosis of amoebic colitis should not rely solely on stool microscopy but should be confirmed by a reliable test that differentiates *E histolytica* from non-pathogenic amoebae. The most cost-effective and accurate diagnostic test that can be used in LMICs must be identified. Investigations on possible interactions of other intestinal pathogens affecting treatment response for *E histolytica* are needed, especially in areas where mixed infections along with other intestinal pathogens and helminths are common. Randomized controlled trials are also needed to determine which luminal agent would be most effective when used in conjunction with metronidazole, or another nitroimidazole, for eradicating *E histolytica* from the intestine and for decreasing relapse. Finally, additional trials are needed to compare single-dose or shorter regimens versus multiple-dose or longer duration of therapy. A network meta-analysis to compare multiple treatments may reveal the best treatment for all or for a subgroup of patients with amoebic colitis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Asrani 1995

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100% for parasitological assessment; 93.4% (898/961) for clinical assessment
Participants	*Numbers:* 961 enrolled, 898/961 (93.4%) included in analysis of clinical outcome; 591/591 (100%) positive for *E histolytica* on stool examination at baseline included in analysis of parasitological outcome *Inclusion criteria:* male and non-pregnant female patients > 12 years of age with clinical symptoms of intestinal amoebiasis and/or presence of trophozoites or cysts of*E histolytica* in stool specimens *Exclusion criteria:* history of alcohol abuse; hypersensitivity or contraindications to any of the study drugs; systemic amoebiasis; severe illness; and/or persistent vomiting
Interventions	• Metronidazole: 400 mg thrice daily orally for 5 days • Metronidazole and diiodohydroxyquinoline: fixed-drug combination of metronidazole (200 mg) plus diiodohydroxyquinoline (325 mg) (Qugyl by Sil Pharma, Bombay, India) given as 2 tablets thrice daily for 5 days Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to clear the stools of *E histolytica*
Outcomes	• Parasitological cure: clearance of *E histolytica* from stool specimens at end of treatment • Clinical cure: remission of clinical symptoms on days 5 and 10 after start of treatment • Adverse events: clinical adverse events monitored by study personnel during treatment *Not included in this review:* average daily frequency of stools on admission and on day 5 and day 10 of treatment; overall clinical response (rated as "poor" if < 25% relief and not tolerated, "fair" if 25% to 49% relief and not well tolerated, "poor" if 50% to 74% relief and well tolerated, or "excellent" if 75% to 100% relief and well tolerated)

Asrani 1995 *(Continued)*

Notes	*Location:* various cities (not specified) in India *Date:* 1995 (date of publication only; actual study period not reported) *Source of funding:* not stated; one of the study authors (Dr SJ Phaterpekar) is connected with Searle (India) Limited, Bombay, India Several attempts were made to inquire about study methods, but no response was obtained from the primary author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomization schedule was prepared for a group of 120 patients in advance. Each co-ordinator used the same randomization schedule" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Reported to be an open-label study
Blinding (performance bias and detection bias) Parasitological outcomes	High risk	Reported to be an open-label study
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	5 days after end of treatment (day 10): For clinical assessment, 63/961 (6.6%) lost to follow-up or were protocol violators (33/421 in metronidazole group, 30/540 in combination therapy group); 1 participant in the combination group withdrawn from the study owing to allergic reaction on the first day of treatment. Missing patients were those lost to follow-up, who received other antiamoebic drugs or met exclusion criteria and were not included for efficacy analysis, but actual numbers in the 2 groups were not specified. In addition, 1 participant in the combination group developed an allergic reaction on the first day of treatment and was withdrawn from the study. Total number of participants analysed overall for clinical evaluation was 93.3% (898/961). For parasitological evaluation, no data were missing among the 249 in the metronidazole group and no data were missing among the 342 in the combination group whose stools were positive for*E histolytica* on admission. "Patients whose stool samples could not be examined were excluded from the parasitological efficacy assessment." Total number of participants analysed overall for parasitological evaluation was 591/591 (100%)
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Unclear risk	Published report included pre-specified outcomes, although data on adverse effects included only those with specific adverse effects and did not report the number of participants in whom adverse effects were observed in both treatment groups

Asrani 1995 *(Continued)*

Other bias	High risk	Diagnosis of intestinal amoebiasis was based on presence of clinical symptoms and those "suspected to be suffering from amoebiasis". Not all participants had stool exams positive for *E histolytica*. Stools were examined by microscopy, but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA test or PCR From the report, those with persistent *E histolytica* at the end of 5 days' treatment were advised to continue the same treatment for another 5 days and were examined again at the end of 10 days' therapy. The number of cases that required treatment extension to 10 days was not mentioned, and there was only 1 analysis regardless of duration of treatment It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Awal 1979

Methods	*Generation of allocation sequence:* random numbers table *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 66 enrolled and analysed *Inclusion criteria:* adults and children with clinical signs and symptoms of intestinal amoebiasis and motile haematophagous trophozoites of *E histolytica* in fresh stool specimens and on sigmoidoscopy *Exclusion criteria:* antiamoebic treatment during previous 4 weeks; pregnant women; dehydrated patients; those with evidence of hepatic or renal dysfunction
Interventions	• Tinidazole: 2 g single oral dose daily for 3 days • Tinidazole: 2 g single oral dose daily for 2 days • Metronidazole: 2 g single dose for 2 days
Outcomes	• Parasitological cure: eradication of *E histolytica* from stools on day 30 from start of therapy • Clinical cure: resolution of baseline symptoms of intestinal amoebiasis on day 30 from start of therapy • Adverse events: voluntary reporting of side effects by participants; laboratory tests monitored before and after treatment including complete blood count, serum bilirubin, alkaline phosphatase, and liver transaminase (SGOT)
Notes	*Location:* hospital in Bangladesh *Date:* 1979 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to any one of the three treatment regimens by a prearranged randomization table" Comment: Randomization table probably refers to a table of random numbers

Awal 1979 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (tinidazole 2 g for 2 or 3 days; metronidazole 2 g for 2 days) and blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not determined
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	28 days after end of treatment (day 30): No outcome data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	Unclear risk	Trial enrolled only those who showed haematophagous trophozoites of *E histolytica* in the stools, but diagnosis of intestinal amoebiasis was based only on stool microscopy and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa or helminth parasites was determined

Batra 1972

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 40 enrolled; 40 analysed; 2 withdrawn from treatment because of severe gastrointestinal adverse effects *Inclusion criteria:* acute amoebic dysentery and stool specimens positive for trophozoites of *E histolytica* by saline and iodine smears *Exclusion criteria:* pregnant women; critically ill patients; those with neurological and cardiac abnormalities or disturbed renal function
Interventions	MK-910: Each arm used 1-methyl-2-(4'fluorophenyl)-5-nitroimidazole (MK-910) at different daily dosages, all given in 3 divided doses orally for 10 days

Batra 1972 *(Continued)*

- 0.5 mg/kg body weight
- 1.0 mg/kg body weight
- 2.0 mg/kg body weight
- 3.0 mg/kg body weight

Outcomes	• Parasitological response: disappearance of *E histolytica* from stools on day 5 and day 10 of treatment, both on saline and iodine smear examination and on stool culture using NIH medium • Clinical response: reduction in clinical signs and symptoms (tenesmus, diarrhoea, bloody stools) • Time (range in hours) until disappearance of *E histolytica* cysts and trophozoites from stools • Adverse events: monitored by study personnel during treatment; laboratory tests monitored before and on day 5 and day 11 of treatment including complete blood count, platelet count, urinalysis, blood urea, blood sugar, serum bilirubin, alkaline phosphatase, liver transaminases (SGOT, SGPT), thymol turbidity tests, and 12-lead electrocardiogram *Not included in this review:* disappearance of colonic ulcers on sigmoidoscopic examination on day 5 and at end of treatment on day 10
Notes	*Location:* hospital in New Delhi, India *Date:* 1972 (date of publication only; actual study period not reported) *Source of funding:* Merck, Sharp, and Dohme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The allocation was randomized on the basis of a pre-planned schedule" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages of MK-910 were used (daily doses of 0.5 mg/kg,1.0 mg/kg, 2.0 mg/kg, and 3.0 mg/kg in 3 divided doses for 10 days), and blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment (day 10): 2/20 in the high-dose group (1 participant each in the 2-mg/kg and 3-mg/kg groups) had to be dropped from the study because of severe adverse effects, but it is unclear whether they were excluded from the analysis of outcomes
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined

Batra 1972 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Clinical outcome was measured by determining duration in hours from start of treatment until relief of symptoms, cessation of unformed stools, and disappearance of blood and mucus from stools. Parasitological outcome was reported as duration in hours from start of treatment to disappearance of *E histolytica* from the stools
Other bias	Unclear risk	Diagnosis of acute amoebic dysentery was based on stool microscopy demonstrating trophozoites of *E histolytica* and sigmoidoscopic examination, but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR. The stool was cultured for *E histolytic*a but only on the fifth and tenth days of treatment, not at baseline It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Botero 1974

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors not described *Inclusion of all randomized participants:* 95.8% (115/120)
Participants	*Numbers:* 120 enrolled; 115 analysed; 5 lost to follow-up; 1 participant in Ro 7-0207 terminated treatment after day 6 because of adverse effects *Inclusion criteria:* adult males with clinical symptoms of intestinal amoebiasis confirmed by the presence of *E histolytica* in the stools examined by direct smear and Ritchie formalin-ether concentration methods *Exclusion criteria:* not stated
Interventions	• Ro 7-0207 (ornidazole): 2 × 250-mg capsules twice daily for 10 days • Metronidazole: 2 × 250-mg capsules twice daily for 10 days
Outcomes	• Parasitological response: clearance of *E histolytica* from stools at end of treatment and at weekly intervals on follow-up for at least 1 month • Relapse: reappearance of *E histolytica* in the stools within 1 month after becoming negative at end of treatment • Clinical response: disappearance of or improvement in clinical signs and symptoms on day 5, at end of treatment, and at weekly intervals during follow-up for at least 1 month • Adverse events: clinical adverse events monitored for all participants but cardiovascular, neurological, and laboratory monitoring only for the first 20 participants (laboratory tests not specified)
Notes	*Location:* hospital in Medellin, Colombia *Date:* 1974 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Botero 1974 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to one of two treatment groups..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported as "double-blind", but it is unclear who was blinded. Both Ro 7-0207(ornidazole) and metronidazole were given 1 g daily, administered as two 250-mg capsules twice daily for 10 days, but the appearance of the 2 drugs was not described Comment: It is not specifically mentioned who among the participants, study personnel, and clinical outcome assessors was blinded
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not specifically mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	At end of treatment (day 10 after onset of treatment): Total number analysed was 115/120 (95.8%). 5 out of the 120 participants enrolled in the trial left the hospital after treatment, did not complete follow-up, and were not included in the analysis. The type of intestinal amoebiasis (acute or chronic amoebiasis), treatment groups to which the 5 were randomized, and reasons for non-compliance with follow-up were not specified
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	30 days after end of treatment: Total number analysed was 115/120 (95.8%) at complete follow-up, and they were not included in the analysis. Type of intestinal amoebiasis (acute or chronic amoebiasis), treatment groups to which the 5 were randomized, and reasons for non-compliance with follow-up were not reported
Selective reporting (reporting bias)	High risk	No clinical assessment was done for those with chronic intestinal amoebiasis, even if on enrolment, it is mentioned that all participants had symptomatic intestinal amoebiasis
Other bias	Unclear risk	Separate analysis was carried out for those with acute dysenteric intestinal amoebiasis and those with chronic intestinal amoebiasis, but this was not prespecified Diagnosis of intestinal amoebiasis was based on demonstration of *E histolytica* on stool microscopy (direct smear and concentration technique), but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Botero 1977

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors was not described

Botero 1977 *(Continued)*

	Inclusion of all randomized participants: 100%
Participants	*Number:* 100 enrolled and 100 analysed *Inclusion criteria:* adult males with clinical symptoms of intestinal amoebiasis and stools positive for *E histolytica* examined by direct smear and Ritchie formalin-ether concentration methods *Exclusion criteria:* not stated *Concomitant intestinal infection:* 26 participants in panidazole group and 27 participants in metronidazole group had concomitant infection with other enteric protozoa and intestinal helminths (*Entamoeba coli, Endolimax nana, Iodamoeba butschlii, Ascaris lumbricoides, Trichuris trichiura, Necator americanus, Strongyloides stercoralis*)
Interventions	• Panidazole: 2 × 250-mg tablets (500 mg), 4 times daily for 6 days • Metronidazole: 2 × 250-mg tablets (500 mg), 4 times daily for 6 days
Outcomes	• Parasitological cure: eradication of parasites in any of the post-treatment laboratory examinations • Clinical response: improvement in or disappearance of symptoms during weekly follow-up until 4 weeks after treatment • Adverse events: clinical adverse events monitored during treatment and on follow-up; laboratory tests monitored before and after treatment including complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, liver transaminases, urinalysis, and electrocardiogram *Not included in this review:* number of stools passed in 24 hours on day 3 and day 6 of treatment and on days 7 and 21 after treatment; clearance of *E histolytica* in 14 asymptomatic carriers
Notes	*Location:* Colombia *Date:* 1977 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "study was performed in 100 adult male patients randomly assigned to receive one of the two drugs..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported as "double-blind trial", but it is unclear who was blinded. Both panidazole and metronidazole were administered in 250-mg tablets at a dose of 2 grams per day (500 mg QID), but the appearance of the 2 drugs was not described Comment: It is not specifically mentioned who among participants, study personnel, and clinical outcome assessors was blinded
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not specifically mentioned
Incomplete outcome data (attrition bias)	Low risk	One to 4 weeks after therapy: no missing data from 45 in the panidazole group and 41 in the metronidazole group with diagnosis of acute dysentery and non-dysenteric amoebiasis

Botero 1977 *(Continued)*

For outcomes determined 1-14 days after end of treatment		
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	4 weeks after end of treatment: no missing data from 45 in the panidazole group and 41 in the metronidazole group with diagnosis of acute dysentery and non-dysenteric amoebiasis
Selective reporting (reporting bias)	High risk	Published report did not completely report data for clinical outcomes in those with chronic non-dysenteric amoebiasis, so data could not be included. "Most of the intestinal symptoms due to amoebiasis improved or disappeared even in cases which did not obtain a complete parasitological cure"
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating cysts or trophozoites of *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR Number of cases with concomitant infection with other protozoa such as *Entamoeba coli, Endolimax nana,* and *Iodamoeba butschlii* was similar in the 2 groups (26 in the panidazole group and 27 in the metronidazole group). Other helminth parasites were also identified *(Ascaris lumbricoides, Trichuris trichiura, Necator americanus, Strongyloides stercoralis*), but exact numbers in each group were not reported

Chunge 1989

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* Only participants and laboratory staff examining stools were blinded; unclear whether those assessing clinical outcomes were blinded *Inclusion of all randomized participants:* unclear; only those who completed the required stool examinations were included (225 participants), and the number initially randomized was not stated
Participants	*Numbers:* number enrolled and randomized not stated, 225 analysed *Inclusion criteria:* adults and children presenting with at least any 4 of the following symptoms of intestinal amoebiasis: abdominal pain, diarrhoea, constipation, mucoid stools, malaise, flatulence, nausea, fever, tenesmus, and stool specimens positive for trophozoites or cysts of *E histolytica* by direct smear or formol-ether concentration technique *Exclusion criteria:* pregnant women
Interventions	• Tinidazole (Fasigyn): 2 g single oral dose daily for 3 days • Tinidazole (Tynazole): 2 g single oral dose daily for 3 days • Metronidazole (Flagyl): 400 mg thrice daily orally for 5 days • Metronidazole (Metrozol): 400 mg thrice daily orally for 5 days
Outcomes	• Parasitological cure: absence of trophozoites or cysts from stool specimens on day 6 after start of treatment • Clinical cure: absence of any 4 of the symptoms initially present at day 6 after start of treatment
Notes	*Location:* outpatient departments of 3 district hospitals in Kiambo, Kilifi, and Machakos in Kenya

Chunge 1989 *(Continued)*

Date: 1989 (date of publication only; actual study period not reported)

Source of funding: Farmitalia Carlo Erba

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: Patients were "randomly allocated to 4 treatment groups receiving different treatment schedules" Comment: no information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Different dosages and regimens were used (tinidazole single dose for 3 days; metronidazole thrice daily for 5 days), and although participants were reported to be unaware of the treatment regimen used, blinding of study personnel and clinical outcome assessors was not mentioned Comment: insufficient information about blinding of study personnel and clinical outcome assessors
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Quote: "Neither the laboratory staff examining the specimens, nor the patients knew the various treatment regimens being tried"
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	1 day after end of treatment (day 6): Only those who completed required stool examinations were included in the final analysis of results; 225 treated patients were evaluated. However, the total number initially randomized was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Unclear risk	Published report included pre-specified outcomes. Adverse effects were not reported
Other bias	Unclear risk	Diagnosis of Intestinal amoebiasis was based only on stool microscopy (direct smear and concentration technique) demonstrating cysts or trophozoites of *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Davila 2002

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear

Davila 2002 *(Continued)*

	Blinding: unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors was not described *Inclusion of all randomized participants:* unclear; no mention of how many were randomized; children who did not complete treatment or did not provide post-treatment faecal sample were not included in the final analysis
Participants	*Numbers:* 275 enrolled with various helminthic and protozoal intestinal infections; 105/275 (38%) had *E histolytica* or *E dispar* infection (25 single infections and 80 mixed infections with other intestinal parasites) and were included in the review and analysed *Inclusion criteria:* children with stool specimens positive for *E histolytica*/*E dispar* and/or other intestinal parasites by direct smear or Kato-Katz technique *Exclusion criteria:* not stated
Interventions	• Nitazoxanide: 100 mg/5 mL twice daily orally for 3 days • Quinfamide: 100 mg/5 mL single oral dose; mebendazole 100 mg/5 mL twice daily orally for 3 days was added to quinfamide when another parasite other than *E histolytica*/*E dispar* was observed Not stated whether placebo was used
Outcomes	• Parasitological cure: eradication of *E histolytica/E dispar* on stool examination 14 days after treatment • Adverse events: only tolerance to the drugs reported Data for parasitological cure were presented separately for nitazoxanide versus quinfamide for single infections and for nitazoxanide versus quinfamide plus mebendazole for mixed infections, and were included in a separate meta-analysis
Notes	*Location:* 3 communities in Colima, Mexico *Date:* 2002 (date of publication only; actual study period not reported) *Source of funding:* Instituto Mexicano del Seguro Social (IMSS); nitazoxanide was provided by Laboratories Columbia, S.A. de C.V., Mexico, D.F., Mexico Several attempts made to contact the primary author were not successful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "children were randomly assigned to one of the 2 treatment groups in a double-bind design" Comment: no information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to have a "double blind design", but it is unclear who was blinded. Different dosages and regimens were used (nitazoxanide 100 mg/5 mL, given as 10 mL twice daily for 3 days; quinfamide 100 mg/5 mL given as 5 mL single dose given for 3 days). Those randomized to the quinfamide group could be given quinfamide alone or both quinfamide and mebendazole when mixed parasitosis was detected Comment: insufficient information on how blinding of participants, study personnel, or clinical outcome assessors was ensured

Davila 2002 *(Continued)*

Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	14 days after treatment: Of 105 with *E histolytica/E dispar* infection, 25 had *E histolytica/E dispar* infection alone and 80 had concomitant *Giardia* or helminth infection. Trial reports that children who did not complete treatment or did not provide post-treatment faecal sample were not included in the final analysis, but no further information was provided
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	Study report did not include clinical response and adverse effects that would be expected to be reported for such a study. Only tolerance to the drugs was reported; adverse effects were not reported
Other bias	High risk	Study design involves giving varied treatment regimens; type of treatment received by the 2 groups is too different and may be a potential source of bias: For those randomized to the nitazoxanide group, nitazoxanide alone was given regardless of type of parasitosis, and for those in the second group, participants could receive quinfamide alone, mebendazole alone, or both quinfamide and mebendazole depending on the type of parasites seen. The trial author reported that parasite identification was exclusively morphological because only stool microscopy was used to diagnose intestinal amoebiasis, so differentiation of pathogenic *E histolytica* from non-pathogenic species such as *E dispar* was not possible

Donckaster 1964

Methods	*Generation of allocation sequence:* random numbers table *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors not described *Inclusion of all randomized participants:* unclear; no mention of how many were randomized
Participants	*Number:* 346 were treated initially; 21 cases who failed after administration of the primary drugs were randomized a second time to receive a different drug and were analysed twice under 2 different groups *Inclusion criteria:* adults and children with clinical symptoms of intestinal amoebiasis and stool specimens positive for cysts and/or trophozoites of *E histolytica* examined by the modified Telemann concentration technique (centrifugation with saline formol and ether) for cysts and polyvinyl alcohol with fixative of Schaudinn for trophozoites *Exclusion criteria:* those without a source of potable water at home; unable to dispose of their excrement properly; or with other non-parasitic infections and taking other medications for these infections
Interventions	• Dimethychlortetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 15 mg/kg and adults 900 mg • Oxytetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 25 mg/kg and adults 1500 mg

Donckaster 1964 *(Continued)*

	• Tetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 25 mg/kg and adults 1500 mg • Chlorphenoxamide: once daily after meals for 10 days at the following oral daily doses – children 125 mg for every 2 years of age and adults 1500 mg • Chlorbetamide: once daily after meals for 10 days at the following oral daily doses – children 100 mg/kg and adults 4000 mg • Racemic dehydroemetine: once daily after meals for 10 days at the following oral daily doses – children 5 mg for every 2 years of age and adults 40 mg • Diiodohydroxyquinoline: once daily after meals for 21 days at the following oral daily doses – children 200 mg for every 2 years of age and adults 1800 mg • Phenanthridinone: once daily after meals for 10 days at the following oral daily doses – children 25 mg for every 2 years of age and adults 300 mg • Bismuth glycoarsanilate: once daily after meals for 10 days at the following oral daily doses – children 250 mg for every 2 years of age and adults 2000 mg • Iodochlorhydroxyquinoline: once daily after meals for 21 days at the following oral daily doses – children 125 mg for every 2 years of age and adults 1000 mg • Placebo (starch): once daily after meals for 10 days at the following oral daily doses – children 250 mg for every 2 years of age and adults 1500 mg Not stated which among the drugs, if any, were identical in appearance to placebo
Outcomes	• Parasitological failure: presence of cysts and/or trophozoites in stool examinations done 10 and 40 days after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants every 3 days during treatment and every 10 to 15 days after treatment
Notes	*Location:* outpatient clinic of the University of Chile in Santiago, Chile *Date:* 1964 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From English translation: "Randomized table of distribution" was used Comment: probably refers to a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported as "double-blind", but it is unclear who was blinded. There were 10 treatment groups and 1 placebo group. All medications were given once daily orally but at different times and at different durations of therapy: Antibiotics with antiamoebic activity were not given with meals or with milk, and the other antiamoebic drugs and placebo were given with or after meals. Durations of therapy were different, with quinolones given for 21 days and all other antiamoebic drugs given for 10 days Comment: insufficient information on how blinding of participants, study personnel, and clinical outcome assessors was ensured
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned

Donckaster 1964 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	10 to 12 days after start of treatment: There was no report of loss to follow-up or dropouts, but there was no mention of how many were initially randomized. 21 cases that failed after administration of the primary drugs were randomized a second time to receive a different drug and were analysed twice under 2 different groups, but outcomes for these 21 were not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	40 days after start of treatment; however, no outcomes were reported. There was no report of loss to follow-up or dropouts, but there was no mention of how many were initially randomized. 21 cases that failed after administration of the primary drugs were randomized a second time to receive a different drug and were analysed twice under 2 different groups, but the outcomes for these 21 were not reported
Selective reporting (reporting bias)	High risk	Published report did not include report of clinical outcomes
Other bias	High risk	Too many antiamoebic drugs were being compared (10 different drugs belonging to 6 different drug classes). Of the 346 enrolled, 346 were analysed initially, but 21 cases that failed after administration of the primary drugs were randomized a second time to receive a different drug and were analysed twice under 2 different groups Diagnosis of Intestinal amoebiasis was based only on stool microscopy demonstrating *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Guevara 1980

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors not described *Inclusion of all randomized participants:* 92.5% (37/40)
Participants	*Numbers:* 40 enrolled; 37/40 (92.5%) analysed; 2 in the quinfamide group and 1 in the teclozan group lost to follow-up *Inclusion criteria:* adults with non-dysenteric amoebiasis with trophozoites of *E histolytica* in recently emitted faecal material and/or in recto-colonic mucosal exudate, recto-colonic lesions suggestive of amoebiasis present or not, and not presenting clinical manifestations of acute amoebic recto-colitis *Exclusion criteria:* those with clinical manifestations of acute amoebic recto-colitis
Interventions	• Quinfamide given at 3 doses in 1 day: 100 mg for 3 doses (300 mg), 200 mg for 3 doses (600 mg), 400 mg for 3 doses (1200 mg) • Teclozan at 3 doses in one day: 500 mg for 3 doses (1500 mg)
Outcomes	• Parasitological failure: persistence of trophozoites in rectal exudates by rectosigmoidoscopy 15 and 30 days after end of treatment and in fresh faecal material 8, 15, and 30 days after treatment

Guevara 1980 *(Continued)*

- Adverse events: Clinical and laboratory tests were monitored on the day after drug administration, then 8, 15, and 30 days after treatment

Notes	*Location:* Patients were hospitalized for 1 day, then were followed up as outpatients *Date:* 1980 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	From the English translation: "The patients were randomly assigned to one of the treatment groups as they were incorporated into the study" Comment: no information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to be a "double-blind study", but it is unclear who was blinded. Different dosages of drugs were given (quinfamide 100 mg, 200 mg, or 300 mg 3 times in 1 day; teclozan 500 mg 3 times in 1 day), and the appearance of the drugs was not described Comment: It is not specifically mentioned who among participants, study personnel, and clinical outcome assessors was blinded
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not specifically mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	8 days after end of treatment: Not more than 2/30 from the quinfamide group and 1/10 from the teclozan group left ("abandoned") the study and were not included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	15 and 30 days after end of treatment: 2/30 from the quinfamide group and 1/10 from the teclozan group left ("abandoned") the study and were not included in the analysis
Selective reporting (reporting bias)	High risk	Final evaluation was based on parasitological outcomes, and it is unclear whether clinical outcomes were evaluated after treatment. Patients selected for enrolment included those with recto-colonic lesions suggestive of amoebiasis, but results of rectosigmoidoscopy were not mentioned in the results. Results of laboratory monitoring for any abnormalities were not reported
Other bias	Unclear risk	Diagnosis of non-dysenteric amoebiasis was based on demonstration of *E histolytica* in stools and rectal exudates taken by rectosigmoidoscopy, but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Huggins 1982

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but blinding of participants, care providers, and outcome assessors not described *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 96 enrolled and analysed *Inclusion criteria:* adults with chronic intestinal amoebiasis and stool specimens positive for *E histolytica* by direct smear with Lugol's stain according to the Telemann-Richter or Hoffman, Pons, and Janer methods *Exclusion criteria:* not stated
Interventions	• Win 40.014 (quinfamide): 100 mg single oral dose • Win 40.014 (quinfamide): 100 mg twice a day orally at 12-hourly intervals for 1 day • Win 40.014 (quinfamide): 100 mg thrice a day orally at 8-hourly intervals for 1 day • Placebo: 300 mg daily dose orally; no information given on the frequency of administration Not stated if Win 40.014 (quinfamide) and placebo tablets were identical in appearance
Outcomes	• Parasitological cure: clearance of amoebae from stools on days 2 and 7 after treatment • Clinical cure: disappearance of the 4 symptoms recorded at baseline (pain, colic, diarrhoea, and constipation) evaluated on days 2 and 7 after treatment • Adverse events: only 2 symptoms (nausea and headache) solicited from participants; laboratory tests were done before and after treatment, but results were not presented
Notes	*Location:* Clinical Hospital of the Federal University of Pernambuco, Brazil *Date:* 1982 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	From the English translation: "The medication was administered according to a previously established routine, based on a randomised double-blind study" Comment: no information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to be a double-blind study, but it is unclear who was blinded. The study drug, WIN 40.014, was given for 1 day at different frequencies: 100 mg as a single dose, every 12 hours, and every 8 hours. No information is provided on frequency of administration of placebo Comment: It is not specifically mentioned who among participants, study personnel, and clinical outcome assessors was blinded
Blinding (performance bias and detection bias)	Unclear risk	Blinding of the microscopist examining the stools was not specifically mentioned

Huggins 1982 *(Continued)*
Parasitological outcomes

Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	7 days after end of treatment (day 7): No data were missing from all treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess whether there is risk for selective outcome reporting. Results of laboratory tests before or after treatment were not presented. Only 2 adverse effects were monitored - nausea and headache; no mention of any other adverse effects monitored
Other bias	Unclear risk	Diagnosis of non-dysenteric amoebic colitis was based on demonstration of *E histolytica* in stools, but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Joshi 1975

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 60 enrolled and analysed *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* *Exclusion criteria:* those who received antiamoebic treatment in the previous 1 month, pregnant women, dehydrated patients, and those with hepatic, renal, haematological, or ECG abnormalities
Interventions	• Tinidazole: 600 mg twice daily orally for 5 days • Metronidazole: 400 or 800 mg thrice daily orally for 5 days Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*
Outcomes	• Parasitological response: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical response: complete or partial relief of symptoms and healing of ulcers on sigmoidoscopy, when carried out • Adverse events: voluntary reporting by participants; laboratory tests monitored before and after treatment including haemogram, urinalysis, serum bilirubin, serum transaminases (SGOT, SGPT), alkaline phosphatase, and blood urea
Notes	*Location:* Ahmedabad, India

Joshi 1975 *(Continued)*

Date: 1975 (date of publication only; actual study period not reported)

Source of funding: not stated

Tinidazole tablets (Fasigyn) were supplied by Pfizer Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "60 cases of symptomatic intestinal amoebiasis...were randomly allocated to treatment with tinidazole or metronidazole" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (tinidazole 600 mg twice daily and metronidazole 400 mg or 800 mg thrice daily), and treatment was extended to 10 days by the assessor when 5 days' treatment failed to relieve symptoms or clear *E histolytica* from the stools. Blinding of participants, study personnel, and clinical outcome assessors is not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	1 to 15 after end of treatment (days 5, 10, and 20 after start of treatment): No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	20 to 25 days after end of treatment (day 30 after start of treatment): No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	The published report mentions that "sigmoidoscopy was carried out wherever possible before and after treatment", but it is not mentioned in how many cases sigmoidoscopy was carried out. Results of sigmoidoscopy were not reported, although healing of ulcers was reported as one of the criteria for cure
Other bias	High risk	Diagnosis of intestinal amoebiasis was based only on stool microscopy demonstrating *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR Duration of treatment was determined by persistence of clinical symptoms or *E histolytica* at end of treatment, and duration of treatment was variable in both groups, which was not considered in the analysis. Among those who showed clinical improvement and cleared *E histolytica* from the stools, 4 of 29 in the tinidazole group and 10 of 24 in the metronidazole group required 10 days' treatment. Participants were analysed together regardless of duration of treatment

Joshi 1975 *(Continued)*

	It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Kapadia 1968

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 100 enrolled and analysed *Inclusion criteria:* clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites and/or cysts of *E histolytica* *Exclusion criteria:* not stated
Interventions	• Chlorhydroxquinoline: 500 mg thrice daily orally for 10 days • Di-diiodohydroxyquinoline: 500 mg thrice daily orally for 10 days Not stated if chlorhydroxyquinoline and di-diiodohydroxyquinoline were identical in appearance
Outcomes	• Parasitological cure: eradication of *E histolytica* from stools at the end of the 10-day treatment period • Clinical cure: improvement or disappearance of symptoms at the end of the 10-day treatment period • Adverse events: clinical adverse events and liver function testing monitored before and after treatment including total bilirubin, serum albumin and globulin, and zinc sulphate
Notes	*Location:* Bombay, India *Date:* 1968 (date of publication only; actual study period not reported) *Source of funding:* not stated Supply of chlorhydroxyquinoline (Quixalin) from Sarabhai Chemicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Two groups of randomly allocated 50 cases of amebiasis were treated by chlorohydroxyquinoline and di-iodohydroxyquinoline...." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	All participants were treated with 2 tablets (250 mg each) of the drug thrice a day for 10 days, but blinding of participants, study personnel, and clinical outcome assessors was not mentioned
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned

Kapadia 1968 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment (day 10): No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Published report includes pre-specified outcomes
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based only on stool microscopy demonstrating *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Karabay 1999

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 44 enrolled and analysed *Inclusion criteria:* acute amoebic dysentery and stool specimens positive for *E histolytica* cysts and/or trophozoites examined by 0.85% saline water, Lugol's solution, and trichrome stain *Exclusion criteria:* received treatment for diarrhoea in the last 10 days; those with pathogenic bacteria identified in stool culture
Interventions	• Secnidazole: 2 g single oral dose • Metronidazole: 750 mg thrice daily orally for 10 days
Outcomes	• Parasitological response: clearance of *E histolytica* from stools on days 14 and 21 • Time (mean number of days) from start of treatment to resolution of clinical symptoms (abdominal pain, diarrhoea, bloody diarrhoea, abdominal distension, tenesmus, fever)
Notes	*Location:* military hospital in Erzurum, Turkey *Date:* July 1998 to November 1998 *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Karabay 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated at random into one or other treatment groups..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (secnidazole 2 g single dose and metronidazole 750 mg thrice daily for 10 days), and blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	Four and 11 days after end of treatment (day 14 and day 21): 1 participant in the metronidazole group missed day 14 follow-up but came back for day 21 follow-up. No losses to follow-up or withdrawals from the secnidazole group. All participants randomized were included in the analysis, even the 3 participants on metronidazole who were non-compliant with medications
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	Clinical outcomes were reported only as "average days of clearance of symptoms", but the number of participants analysed for clinical outcomes was not reported. Adverse effects were not reported or mentioned
Other bias	Unclear risk	Diagnosis of amoebic dysentery was based only on stool microscopy, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Mansour-Ghanaei 2003

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* double (participants, care providers, and outcome assessors – from personal communication with primary author) *Inclusion of all randomized participants:* 94.7% (54/57))
Participants	*Numbers:* 57 enrolled; 54 analysed; 3 non-compliant participants (2 from the group without *S boulardii* and 1 from the group with *S boulardii*) were excluded from analysis

Mansour-Ghanaei 2003 *(Continued)*

	Inclusion criteria: adults with amoebic dysentery presenting with mucous bloody diarrhoea, fever, and abdominal pain; stool specimens positive for haematophagous trophozoites of *E histolytica* (laboratory diagnostic method was not specified) *Exclusion criteria:* pregnant women; those on maintenance haemodialysis, steroids, or chemotherapy
Interventions	• Metronidazole, iodoquinol, and placebo: metronidazole 750 mg and iodoquinol 650 mg given thrice daily orally with placebo tablets for 10 days • Metronidazole, iodoquinol, and *S boulardii*: 750 mg and iodoquinol 650 mg thrice daily orally for 10 days plus lyophilized *S boulardii* 250 mg orally thrice daily for 10 days *S boulardii* and placebo were identical in appearance
Outcomes	• Parasitological failure: persistence of amoebic cysts in stool examinations at 4 weeks after treatment • Mean duration of diarrhoea, abdominal pain, fever, and headache from start of treatment to resolution of symptoms
Notes	*Location:* Shahid Beheshti Educational and Therapeutic Center in Shiraz, Iran *Date:* 21 March 1995 to 21 March 1996 *Source of funding:* not stated The study author was contacted and kindly provided data on method of blinding; however, no response was obtained regarding method of allocation concealment despite several follow-up communications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were then randomized to receive either metronidazole 750 mg and iodoquinol 650 mg thrice a day for 10 days or the same medications plus lyophilized *Saccharomyces boulardii* 250 mg orally thrice a day" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Reported to be double-blind From correspondence with primary author: Placebo capsules were identical in appearance to *S boulardii* capsules Comment: Blinding of participants, study personnel, and clinical outcome assessors was adequate
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Reported to be double-blind, and blinding of the microscopist examining the stools was probably done
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not determined
Incomplete outcome data (attrition bias)	Low risk	4 weeks after end of treatment: 2/29 from the metronidazole and iodoquinol group and 1/28 from the metronidazole and iodoquinol plus *S boulardi*i group were excluded because of non-compliance

Mansour-Ghanaei 2003 *(Continued)*

For outcomes determined 15-60 days after end of treatment		
Selective reporting (reporting bias)	Unclear risk	Published report includes pre-specified outcomes. It is mentioned that participants reported no adverse reactions to *S boulardii*, but adverse effects in the group without *Saccharomyces* were not reported
Other bias	Unclear risk	Diagnosis of amoebic dysentery was based on both clinical presentation and presence of (haematophagous) amoeba trophozoites engulfing red blood cells in diarrhoeal stools. However, differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Mathur 1976

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 60 enrolled and 60 analysed *Inclusion criteria:* adults and adolescents with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* *Exclusion criteria:* received antiamoebic treatment in the previous 1 month; pregnant women; dehydrated patients; and those with hepatic, renal, hematological, or ECG abnormalities
Interventions	• Tinidazole: 600 mg twice daily orally for 5 days • Metronidazole: 400 mg thrice daily orally for 5 days (for acute amoebic dysentery) or 800 mg thrice daily for 5 days (for other cases) Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*
Outcomes	• Parasitological cure: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical cure: relief of presenting clinical signs and symptoms and healing of ulcers on sigmoidoscopy, when carried out • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including haemogram, urinalysis, serum bilirubin, transaminases (SGOT, SGPT), alkaline phosphatase, and blood urea
Notes	*Location:* India *Date:* 1976 (date of publication only; actual study period not reported) *Source of funding:* not stated Tinidazole tablets (Fasigyn) were supplied by Pfizer Ltd
Risk of bias	

Mathur 1976 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "60 cases of symptomatic intestinal amoebiasis were randomly allocated to treatment with tinidazole or metronidazole" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (tinidazole 600 mg twice daily and metronidazole 400 mg or 800 mg thrice daily), and treatment was extended to 10 days by the assessor when 5 days' treatment failed to relieve symptoms or clear *E histolytica* from the stools. Blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	15 to 25 days after end of treatment (day 30): No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	The report mentions that sigmoidoscopy was carried out wherever possible before and after therapy. It is not clear in how many cases sigmoidoscopy was done, even if healing of ulcers was 1 criterion for cure
Other bias	High risk	Diagnosis of intestinal amoebiasis was based only on stool microscopy demonstrating cysts or trophozoites of *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined Duration of treatment was determined by persistent clinical symptoms or presence of *E histolytica* in the stools at end of treatment. Therefore, duration of treatment varied in both groups, which was not considered in the analysis. Four participants in each group required extension of the treatment period to 10 days

Misra 1974

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear

Misra 1974 *(Continued)*

	Blinding: unclear; reported as "single blind", but it is not stated who among participants, care providers, or outcome assessors was blinded *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 60 enrolled and analysed *Inclusion criteria:* adults and children with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* by direct smear or concentration method *Exclusion criteria:* antiamoebic treatment in the preceding 1 month before enrolment; pregnant women; severe anaemia
Interventions	• Tinidazole: 600 mg twice daily orally for 5 days • Metronidazole: 400 mg thrice daily orally for 5 days (for acute amoebic dysentery) or 800 mg thrice daily orally for 5 days (for chronic intestinal amoebiases, if symptoms were longer than 15 days' duration) Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*
Outcomes	• Parasitological cure: eradication of *E histolytica* on follow-up stool examinations or ulcer scrapings on day 30 after start of treatment • Clinical cure: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before and after treatment including complete blood count and platelet count, urinalysis, electrocardiogram, blood urea, serum bilirubin, alkaline phosphatase, and liver transaminases (SGOT, SGPT)
Notes	*Location:* Medical College Hospital in Bhopal, India *Date:* 1974 (date of publication only; actual study period not reported) *Source of funding:* Pfizer Ltd for support and for supply of study drugs tinidazole (Fasigyn) and metronidazole (Flagyl)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Ten groups of 30 cases each were at random administered metronidazole and tinidazole" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported as "single-blind", but it is unclear who was blinded. Different dosages and regimens were used (tinidazole 600 mg twice daily and metronidazole 400 mg thrice daily), and treatment was extended to 10 days when 5 days' treatment failed to relieve symptoms or clear *E histolytica* from the stools Blinding of the clinical outcome assessor was not specifically mentioned
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Reported as "single-blind", but it is unclear if the microscopist examining the stools was blinded
Incomplete outcome data (attrition bias)	Low risk	10 to 15 days after end of treatment (day 20): No data were missing from both treatment groups; all randomized participants were included in the analysis

Misra 1974 *(Continued)*

For outcomes determined 1-14 days after end of treatment		
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	20 to 25 days after end of treatment (day 30): No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	High risk	Diagnosis of Intestinal amoebiasis was based only on stool microscopy (direct smear or concentration technique) demonstrating cysts or trophozoites of *E histolytica,* but differentiation from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined Duration of treatment was determined by persistence of clinical symptoms or *E histolytica* in the stools at end of treatment. Therefore, duration of treatment varied in both groups, which was not considered in the analysis. Treatment had to be extended to 10 days in 4 cases in the tinidazole group and in 5 cases in the metronidazole group, but these were not analysed separately

Misra 1977

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 60 enrolled and analysed *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* by direct smear or formol-ether concentration technique, sigmoidoscopy for colonic ulcers, and parasitological examination of sigmoidoscopic scrapings *Exclusion criteria:* received antiamoebic treatment within the previous 4 weeks; pregnant women; dehydrated patients; evidence of hepatic, renal, haematological, or ECG abnormalities
Interventions	• Tinidazole: 2 g single oral dose daily for 3 days • Metronidazole: 2 g single oral dose daily for 3 days Not stated whether tinidazole and metronidazole were identical in appearance
Outcomes	• Parasitological response: eradication of *E histolytica* from stools or ulcer scrapings on day 30 after start of treatment • Clinical response: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including urinalysis, complete blood count, serum bilirubin, alkaline phosphatase, liver transaminases (SGOT, SGPT), blood urea, and electrocardiogram

Misra 1977 *(Continued)*

Notes	*Location:* hospital in Bhopal, India *Date:* 1977 (date of publication only; actual study period not reported) *Source of funding:* not stated Unclear if Misra 1977 and Misra 1978 reported results for the same group of participants Several attempts were made to contact study authors, but no response was obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Sixty patients with symptomatic intestinal amoebiasis were treated for 3 days with a single dose of 2 g of either tinidazole or metronidazole respectively by random order" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Both tinidazole and metronidazole were administered as 2 g single dose for 3 days, but blinding of the participants, study personnel, and clinical outcome assessors was not mentioned
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	20 to 25 days after end of treatment (day 30): No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Criteria for cure included healing of ulcers seen on sigmoidoscopy, but these results were not mentioned
Other bias	Unclear risk	May be a duplicate of the Misra 1978 trial because of similar methods and numbers of enrolled participants Diagnosis of Intestinal amoebiasis was based on presence of *E histolytica* in the stools and in sigmoidoscopic scrapings using direct smear and concentration techniques and sigmoidoscopy for colonic ulcers. However, differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Misra 1978

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear *Inclusion of all randomized participants:* 98.3% (59/60)
Participants	*Numbers:* 60 enrolled; 59 analysed, 1 randomized to tinidazole group excluded because it was discovered later that he had a history of ulcerative colitis *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites and cysts of *E histolytica* by direct smear or formol-ether concentration technique, sigmoidoscopy for colonic pathology *Exclusion criteria:* received antiamoebic treatment in the previous 4 weeks before enrolment
Interventions	• Tinidazole: 2 g single oral dose daily for 3 days • Metronidazole: 2 g single oral dose daily for 3 days Not stated whether tinidazole and metronidazole were identical in appearance
Outcomes	• Parasitological cure: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical cure: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory monitoring done before and after treatment including complete blood count, urinalysis, and blood chemistry
Notes	*Location:* hospital in Bhopal, India *Date:* 1978 (date of publication only; actual study period not reported) *Source of funding:* not stated Unclear if Misra 1977 and Misra 1978 reported results for the same group of participants Several attempts were made to contact the study author, but no response was obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "According to a predetermined random order, patients were assigned to wither tinidazole or metronidazole" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Blinding of participants, study personnel, and clinical outcome assessors was not mentioned
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned

Misra 1978 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	20 to 25 days after end of treatment (day 30): 1/30 in the tinidazole group was excluded from the analysis because of history of ulcerative colitis; no outcome data were missing in the metronidazole group
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes, including presence of colonic pathology on sigmoidoscopy
Other bias	Unclear risk	May be a duplicate publication of an earlier trial by the same author (Misra 1977) because of the identical number of enrolled participants and methods, although 1 participant in the tinidazole group was excluded from the analysis of the Misra 1978 trial Diagnosis of intestinal amoebiasis was based on presence of cysts or trophozoites of *E histolytica* in the stools using direct smear and concentration tests and sigmoidoscopy for colonic ulcers. However, differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Mohammed 1998

Methods	*Generation of allocation sequence:* random numbers table *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 72.5% (50/69)
Participants	*Numbers:* 69 enrolled; 50 analysed; 19 lost to follow-up (11 in the praziquantel group, 8 in the metronidazole group); 3 in the praziquantel group had their treatment changed to metronidazole because of lack of response *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for vegetative trophozoite forms (acute amoebic dysentery) or cysts of *E histolytica*; those who were cyst passers were treated with praziquantel alone and were not included in the review *Exclusion criteria:* not stated
Interventions	• Praziquantel: 40 mg/kg body weight divided into 2 doses orally and taken 4 to 6 hours apart • Metronidazole: 800 mg thrice daily orally for 5 days
Outcomes	• Parasitological response: disappearance of *E histolytica* from stools 1 week after treatment • Clinical response: disappearance of baseline clinical signs and symptoms at end of treatment • Adverse events: voluntary reporting of clinical adverse events by participants only for praziquantel
Notes	*Location:* outpatients in Iraq

Mohammed 1998 *(Continued)*

Date: 1993 to 1995

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done according to a pre-designed dispensing list (10 patients each) constructed from a table of random numbers..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (praziquantel 40 mg/kg in a single dose and metronidazole 800 mg thrice daily), and blinding of participants, study personnel, or clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	High risk	One week after treatment: 11/37 missing from the praziquantel group and 8/32 missing from the metronidazole group. No reasons for missing data provided
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	The published report mentions that at the end of 28 days, "patients were assessed as per W.H.O. criterion." Frequency of loose stools per day and rate of disappearance of parasites in the stools were also reported but were not prespecified. Incomplete report of adverse effects (no report for metronidazole)
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating trophozoites or cysts of *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Naoemar 1973

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* double (participants, care providers, and outcome assessors)

Naoemar 1973 *(Continued)*

	Inclusion of all randomized participants: 100% at end of treatment and 1 month after end of treatment
Participants	*Numbers:* 20 enrolled, 20 analysed *Inclusion criteria:* adults and children with bloody diarrhoea and stools positive for motile haematophagous trophozoites of *E histolytica* examined by eosin and iodine smears *Exclusion criteria:* anaemia or other diseases but exact conditions not stated
Interventions	• Ro 7-0207 (ornidazole) • Metronidazole Both drugs given as follows: 2 to 6 years of age – 125 mg daily in 3 divided doses for 7 days; 7 to 12 years of age – 250 mg daily in 3 divided doses for 7 days; adults – 1500 mg daily in 3 divided doses for 5 days Ro 7-0207 and metronidazole were identical in appearance (light yellow capsules) and were kept in numbered bottles
Outcomes	• Parasitological response: clearance of *E histolytica* from stools at end of treatment and 1 month after end of treatment • Clinical cure: disappearance of symptoms at end of treatment and at 1 month after end of treatment • Relapse: reappearance of *E histolytica* in stools 1 month after end of treatment • Time (range in days) from start of treatment to clearance of *E histolytica* from stool specimens • Time (range in days) from start of treatment to disappearance of bloody diarrhoea • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before and after end of treatment including complete blood counts, liver transaminase (SGPT), alkaline phosphatase, urinalysis, blood urea, and electrocardiogram
Notes	*Location:* outpatient clinics in Jakarta, Indonesia *Date:* 1973 (date of publication only; actual study period not reported) *Source of funding:* Roche Far East Research Foundation for supply of drugs and support for the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All were given ambulatory treatment with either Ro7-0207 or metronidazole according to a randomized numbering system" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Reported as "double-blind", and drugs were given in identical physical forms (light yellow capsules) kept in bottles that were numbered Comment: Blinding of participants, study personnel, and clinical outcome assessors was adequate
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Reported as "double-blind"; blinding of microscopist examining the stools probably was also done
Incomplete outcome data (attrition bias)	Low risk	At end of treatment: No data were missing from both treatment groups; all randomized participants were included in the analysis

Naoemar 1973 *(Continued)*

For outcomes determined 1-14 days after end of treatment		
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	One month after end of treatment: Outcome for relapse was reported, and no withdrawals or losses to follow-up were mentioned
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Unclear risk	Diagnosis of amoebic dysentery in children was based on presence of bloody stools with actively motile haematophagous *E histolytica* in the stools However, differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, and helminth parasites was determined Children and adults in the trial were given different dosages and duration of treatment (7 days in children, 5 days in adults) but were not analysed separately

Nnochiri 1967

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* double (participants, care providers, and outcome assessors) *Inclusion of all randomized participants:* 100% at end of treatment; 96.7% (58/60) at 7 weeks after end of treatment
Participants	*Numbers:* 60 with acute amoebic dysentery enrolled; 60 analysed at end of treatment, and 58 (96.8%) analysed 7 weeks after end of treatment *Inclusion criteria:* military personnel and their families with diagnosis of acute amoebic dysentery and stool specimens positive for *E histolytica* examined by saline and iodine-stained smears *Exclusion criteria:* not stated
Interventions	• Diloxanide furoate, tetracycline hydrochloride, and chloroquine phosphate (per capsule): diloxanide furoate (187.5 mg), tetracycline hydrochloride (125 mg), and chloroquine phosphate (50 mg) given in 3 dosage regimens of 2 capsules 4 times a day for 5 days, 2 capsules 4 times a day for 7 days, or 2 capsules 4 times a day for 10 days • Diloxanide furoate and tetracycline hydrochloride (per capsule): diloxanide furoate (187.5 mg) and tetracycline hydrochloride (125 mg) given in 3 dosage regimens of 2 capsules 4 times a day for 5 days, 2 capsules 4 times a day for 7 days, or 2 capsules 4 times a day for 10 days The 2 drug combinations with and without chloroquine were identical in appearance
Outcomes	• Parasitological response: clearance of *E histolytica* cysts and trophozoites at end of treatment, then on follow-up 7 weeks from completion of treatment; patients whose stools remained negative 7 weeks after treatment were followed up at 3 and 6 months from completion of treatment

Nnochiri 1967 *(Continued)*

- Clinical response: recurrence of symptoms (reported only for those given 10 days' treatment: 16/34 in the diloxanide furoate-tetracycline hydrochloride-chloroquine phosphate group and 10/26 in the diloxanide furoate-tetracycline hydrochloride group)
- Adverse events: clinical adverse events monitored during treatment and on follow-up; laboratory tests monitored before and after treatment including urine cytology and presence of protein, blood examination for haemoglobin, total erythrocyte and leucocyte counts, and differential count

Not included in this review: results of stool examination at 3, 6, and 12 months after treatment; clearance of *E histolytica* from stools of 36 asymptomatic cyst carriers

Notes	*Location:* Yaba Military Hospital in Lagos, Nigeria *Date:* August 1965 to July 1966 *Source of funding:* Messrs Boots Pure Drug Co Ltd, Nottingham, England

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Sixty patients with acute amoebic dysentery were admitted...and placed in two groups on a randomized basis" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	From the report: "The two furamide combinations...were encapsulated and the capsules were made to look identical" Comment: Blinding of participants, study personnel, and clinical outcome assessors was done
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Although it is not specifically mentioned, blinding of the microscopist examining the stools was probably done
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment: No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	7 weeks after end of treatment: 1/34 from the diloxanide furoate-tetracycline hydrochloride-chloroquine phosphate group and 1/26 from the diloxanide furoate-tetracycline hydrochloride group were missing from the analysis. Reasons for missing data were not reported *Note:* High attrition rates at 3, 6, and 12 months after end of treatment (10 soldiers treated for amoebic dysentery were transferred and were unable to report for 12-month follow-up). Results beyond 7 weeks were not included in the review because re-infection could not be ruled out
Selective reporting (reporting bias)	Unclear risk	Published report included pre-specified outcomes, although data on adverse effects were incomplete and the number of participants for whom adverse effects was ascertained was not specified for treatment groups

Nnochiri 1967 *(Continued)*

Other bias	Unclear risk	Diagnosis of amoebic dysentery was based only on stool microscopy, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Stool specimens from all acute dysenteric cases were cultured in appropriate culture media for enteric organisms, but it is not mentioned whether concomitant infection with other protozoa and helminth parasites was determined

Padilla 2000

Methods	*Generation of allocation sequence:* coin toss *Allocation concealment:* unclear *Blinding:* double-blind (participants and outcome assessors for clinical and parasitological outcomes blinded; unclear whether care provider (main investigator) who administered the medications was blinded) *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 239 enrolled and analysed *Inclusion criteria:* children with clinical symptoms of non-dysenteric amoebic colitis with at least 1 of 3 stool specimens positive for *E histolytica* cysts examined by direct smear using Faust concentration method *Exclusion criteria:* history of sensitivity to clioquinol or to metronidazole and its derivatives; children who had received antibacterial and/or antiparasitic drugs in the 15 days before their entry into the study; those with amoebic dysentery
Interventions	• Secnidazole: 30 mg/kg body weight orally in a single dose • Quinfamide: 4.3 mg/kg body weight orally in a single dose
Outcomes	• Parasitological response: clearance of *E histolytica* cysts on days 5, 6, and 7 after administration of drugs • Adverse events: Clinical adverse events were solicited by investigators through direct questioning for the presence of abdominal pain, nausea, vomiting, headache, diarrhoea, and unpleasant taste in the mouth *Not included in this review:* acceptability of taste
Notes	*Location:* 2 urban federal elementary schools in Celaya, Guanajuato, Mexico (Urban Federal Elementary schools 'Carmen Serdan' and 'Juan Jesus de los Reyes') *Date:* 2000 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation (by tossing a coin) was performed progressively as patients were included in the study"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned

Padilla 2000 *(Continued)*

Blinding (performance bias and detection bias) Clinical outcomes	Low risk	From the report (blinding of participants and study personnel): "The medications were administered by the main investigator, and both patients and their parents were blinded to the antiamoebic drugs administered by removal of the labels from the bottles; however, the flavours and colours of these drugs are very different and this could have led to bias" From the report (blinding of clinical adverse events and acceptability): "A different investigator carried out a clinical evaluation on the fifth day, and she was also blinded to the patient" Comment: Blinding of participants, study personnel, and clinical outcome assessors was adequate
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	From the report: "The laboratory analyst was also blinded to the medication received by the children" *Comment:* Blinding of the microscopist examining the stools was done
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	7 days after end of treatment: No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	Parasitological efficacy was reported, but clinical evaluation included only specific adverse events with no mention of the number and proportion of participants who showed disappearance of or improvement in clinical symptoms after treatment
Other bias	Unclear risk	Diagnosis of amoebic dysentery was based only on stool microscopy with concentration techniques used, but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with bacteria, other protozoa, or helminth parasites was determined

Pamba 1990

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* single (only outcome assessors for parasitological response and rectosigmoidoscopy results were blinded; not stated whether assessors for clinical response were blinded) *Inclusion of all randomized participants:* 95.9% (400/417) at end of treatment for clinical cure only; for stool examination - 100% (417/417) at end of treatment, 88.5% (369/417) 15 days after start of treatment, 67.6% (282/417) 30 days after start of treatment, and 51.3% (214/417) 60 days after start of treatment

Pamba 1990 *(Continued)*

Participants	*Numbers:* 417 enrolled; 369/417 (88.5%) analysed 15 days after start of treatment, 282/417 (67.6%) analysed 30 days after start of treatment, and 214/417 (51.3%) analysed 60 days after start of treatment; recruitment to the etophamide plus aminosidine group was discontinued because of high incidence of diarrhoea; withdrawals not stated for the other groups *Inclusion criteria:* adults and children with clinical symptoms of intestinal amoebiasis with stool specimens positive for *E histolytica* by direct smear and a concentration method (not specified) *Exclusion criteria:* pregnant women; known allergy to the drugs; those with coexisting extraintestinal amoebiasis or other major diseases; treated with antiamoebic drugs in the 30 days before recruitment
Interventions	• Aminosidine (A): 500 mg twice daily orally for adults, 15 mg/kg body weight twice daily orally for children for 5 days • Etophamide (E): 600 mg twice daily orally for adults, 15 mg/kg body weight twice daily orally for children for 5 days • Nimorazole (N): 1 g twice daily orally for adults, 20 mg/kg body weight twice daily orally for children for 5 days • Combination of nimorazole and aminosidine (NA): same doses as above for 5 days • Combination of nimorazole and etophamide (NE): same doses as above for 5 days • Combination of etophamide and aminosidine (EA): same doses as above for 5 days
Outcomes	• Parasitological cure: disappearance of any form of *E histolytica* from stools or ulcer scrapings at end of treatment • Recurrence (relapse): reappearance of *E histolytica* during follow-up on days 15, 30, and 60 after initial disappearance; owing to incomplete data on follow-up, results could not be included in the meta-analysis • Clinical cure: disappearance of all baseline symptoms at end of treatment • Adverse events: clinical adverse events monitored during treatment *Not included in this review:* cumulative daily clearance of *E histolytica* from stools during treatment, at end of treatment, and on days 15, 30, and 60 after start of treatment; evolution of mild and severe amoebic ulcers seen on rectosigmoidoscopy; and anatomical cure (healing of previous ulceration)
Notes	*Location:* 3 district hospitals of Kiambo, Machakos, and Kilifi in Kenya, Africa *Date:* 1990 (date of publication only; actual study period not reported) *Source of funding:* Farmitalia Carlo Erba

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to 6 different treatment groups" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Blinding of participants, study personnel, and clinical outcome assessors was not mentioned. Antiamoebic drugs (aminosidine, etophamide, nimorazole) were given in different dosages, were computed differently for adults and children, and were given singly and in combination. It was reported that "All drugs were administered under direct medical supervision", so the physician administering the drugs probably was not blinded and the clinical outcome assessor was not mentioned

Pamba 1990 *(Continued)*

Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	From the report: "The persons in charge of stool examination and rectosigmoidoscopy were not informed of the drug being taken" Comment: Blinding of the microscopist examining the stools and the person doing the rectosigmoidoscopy was done
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment: 17/115 in the combination group (all given etophamide-aminosidine) were not analysed for clinical cure because of high incidence of diarrhoea; no data were missing for the monotherapy group. For parasitological outcomes, all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	High risk	From the report: "The percentage of patients reporting for recheck was 88.5% at 15 days, 67.6% at 30 days and 51.3% at 60 days", but the exact number of missing participants in each of the treatment groups was not given
Selective reporting (reporting bias)	High risk	Although clinical and parasitological outcomes defined in the methods were reported, the exact numbers of participants remaining in the study at specified time points were not reported. For parasitological cure, results were reported as cumulative daily clearance of amoebic forms from stools, which was not pre-specified. Adverse effects or "drug tolerance" was incompletely reported
Other bias	High risk	Recruitment of participants in one group (etophamide plus aminosidine) was discontinued early owing to increased adverse effects (severe diarrhoea) Stool microscopy and rectosigmoidoscopy were used to diagnose intestinal amoebiasis and to differentiate invasive from non-invasive forms, but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Other protozoal and bacterial infections (e.g. *Campylobacter, Shigella, Balantidium*) were mentioned by the trial author as causing ulcerative lesions in the distal gut indistinguishable from those caused by *E histolytica,* but this was not determined in the trial

Panggabean 1980

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* reported as "double-blind", but only care provider was blinded; blinding of participants and outcome assessors was not described *Inclusion of all randomized participants:* 62.5% (25/40) 1 week after treatment, 42.5% (17/40) 2 weeks after treatment, 27.5% (11/40) 3 weeks after treatment, and 15% (6/40) 4 weeks after treatment
Participants	*Numbers:* 40 enrolled; 25/40 (62.5%) analysed 1 week after treatment, 17/40 (42.5%) analysed 2 weeks after treatment, 11/40 (27.5%) analysed 3 weeks after treatment, and 6/40 (15%) analysed 4 weeks after treatment *Inclusion criteria:* children with amoebic dysentery presenting with bloody stools and motile haematophagous trophozoites of *E histolytica* in stools examined by direct smear method with eosin 2% stain *Exclusion criteria:* not stated

Panggabean 1980 *(Continued)*

	Concomitant intestinal infection: 35 participants included in the analysis had concomitant intestinal helminthic infection, and groups were comparable for numbers and types of concomitant intestinal helminthic infection (tinidazole group: *Ascaris lumbricoides* 10, *Trichuris trichiura* 26, *Ancylostoma* 2; ornidazole group: *Ascaris lumbricoides* 12, *Trichuris trichiura* 12, *Ancylostoma* 3)
Interventions	• Tinidazole: 50 mg/kg body weight in a single oral dose daily for 3 days • Ornidazole: 50 mg/kg body weight in a single oral dose daily for 3 days *Other interventions:* Children with concomitant intestinal helminthic infection were given single-dose pyrantel pamoate 10 mg/kg, and those with trichuriasis were given mebendazole 1 tablet twice daily for 3 consecutive days
Outcomes	• Parasitological cure: disappearance of all forms of *E histolytica* on stool examinations done weekly until 4 weeks after completion of treatment • Re-infection: reappearance of *E histolytica* after the second month • Clinical cure: disappearance of blood and mucus from stools at follow-up examinations done weekly until 4 weeks after completion of treatment • Adverse events: clinical adverse effects reported by participants during treatment
Notes	*Location:* outpatient clinic of the Sub-department of Gastroenterology, Department of Child Health Medical School, General Hospital, Medan, Indonesia *Date:* January 1978 to June 1978 *Source of funding:* PT. Pfizer Indonesia and PT. Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "cases were randomly selected for either one of the groups" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to be a double-blind trial Quote: "The children were treated ambulatorily and the tablets were administered in the hospital daily under the supervision of the authors, without knowing which drug was being given" Comment: Participants and study personnel were blinded, but blinding of the clinical outcome assessor was not mentioned. It is unclear whether those administering the drugs are also the clinical outcome assessors
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment (day 3): 4/20 missing from the tinidazole group (3 did not complete treatment, 1 did not return for follow-up); 3/20 missing from the ornidazole group (1 did not return for follow-up, reasons for 2 were not reported)
Incomplete outcome data (attrition bias)	High risk	Four weeks after treatment: 15/20 missing from the tinidazole group (3 did not complete treatment, 14 did not return for follow-up); 19/20 missing from the

Panggabean 1980 *(Continued)*

For outcomes determined 15-60 days after end of treatment		ornidazole group (17 did not return for follow-up, reasons for 2 were not reported)
Selective reporting (reporting bias)	Unclear risk	Overall clinical and parasitological cure rates were reported until the end of the fourth week of follow-up, but dropout rates for the 2 groups were high, and numbers for those who returned for follow-up visits were decreasing
Other bias	Unclear risk	Trial enrolled only those children with bloody stools who showed motile trophozoites of *E histolytica* containing red blood cells in diarrhoeal stool. However, only stool microscopy was used to diagnose amoebic dysentery, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, and helminth parasites was determined

Pehrson 1983

Methods	*Generation of allocation sequence:* unclear (unrecalled by primary author during personal communication) *Allocation concealment:* inadequate – no attempts to conceal treatment allocation (personal communication with primary author) *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 41 enrolled and analysed *Inclusion criteria:* adults and children with clinical symptoms of intestinal amoebiasis but no signs of invasion (e.g. no fever or acute dysentery) and stool specimens positive for trophozoites or cysts of *E histolytica* by direct smear or formol-ether concentration technique by Ridley and Hawgood; had not received any antiamoebic drug during the previous year *Exclusion criteria:* acute dysenteric amoebiasis; liver abscess *Concomitant intestinal infection:* 17 participants had concomitant infection with other intestinal organisms (*Giardia lamblia* 9, *Campylobacter jejuni* 2, *Hymenolepsis nana* 1, *Ascaris lumbricoides* 1, *Trichuris trichiura* 1, *Salmonella paratyphi A* 1), but the distribution in the 2 groups was not specified
Interventions	• Tinidazole: 40 mg/kg body weight in a single oral dose daily for 5 days • Tinidazole plus diloxanide furoate: tinidazole 40 mg/kg body weight in a single oral dose daily for 5 days plus diloxanide furoate 20 mg/kg body weight divided into 3 daily doses for 10 days
Outcomes	• Parasitological response: clearance of *E histolytica* from any of the 3 stool specimens evaluated 1 month after end of treatment • Adverse events: only adverse events severe enough to result in cessation of therapy
Notes	*Location:* hospital in Stockholm, Sweden *Date:* 1983 (date of publication only; actual study period not reported) *Source of funding:* not reported The study author was contacted and kindly provided further data. Details on method of randomization could not be recalled by the trial author

Pehrson 1983 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In a predetermined, random order, the patients were allocated to two groups..." From correspondence with primary trial author: unrecalled method of randomization
Allocation concealment (selection bias)	High risk	From correspondence with primary trial author: no method used to conceal allocation sequence
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and frequencies were used (tinidazole 40 mg/kg in 1 daily dose for 5 days; combined tinidazole plus diloxanide furoate 20 mg/kg divided into 3 daily doses for 10 days), and blinding of participants and study personnel was not mentioned From correspondence with primary trial author: no method used to blind participants and study personnel
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Unclear if the microscopist examining the stools was blinded
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not determined
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	One month after end of treatment: No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	High risk	Study report does not include results for clinical outcomes that would be expected to be reported for such a study
Other bias	Unclear risk	Diagnosis of non-invasive amoebiasis was based only on presence of *E histolytica* on stool microscopy (direct microscopy and concentration technique), and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Twelve participants had concomitant protozoal or helminth infection (9 with *Giardia lamblia*, 1 with *Hymenolepsis nana*, 1 with *Ascaris lumbricoides,* and 1 with *Trichuris trichiura*) and 5 had concomitant bacterial infection (2 with *Shigella flexneri*, 2 with *Campylobacter jejuni*, 1 with *Salmonella paratyphi A*). It is not specified whether these concomitant organisms were equally distributed in the two groups although the trial author reported that "the presence of parasites did not seem to affect the outcome of the treatment"

Pehrson 1984

Methods	*Generation of allocation sequence:* unclear (unrecalled by primary author during personal communication)

Pehrson 1984 *(Continued)*

	Allocation concealment: inadequate – no attempts to conceal treatment allocation (personal communication with primary author) *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 30 enrolled and analysed *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis but no signs of invasion (e.g. no fever or acute dysentery) and stool specimens positive for trophozoites or cysts of *E histolytica* examined by direct smear or formol-ether concentration technique *Exclusion criteria:* not stated
Interventions	• Tinidazole: 600 mg twice daily orally for 5 days • Metronidazole: 800 mg thrice daily orally for 5 days
Outcomes	• Parasitological cure: clearance of *E histolytica* trophozoites or cysts from any of the 3 stool specimens taken 1 month after end of treatment • Adverse events: only adverse events severe enough to result in cessation of therapy
Notes	*Location:* Stockholm, Sweden *Date:* 1984 (date of publication only; actual study period not reported) *Source of funding:* not reported The study author was contacted and kindly provided further data. Details on method of randomization could not be recalled by the trial author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (from report): "Thirty consecutive, diagnosed cases of noninvasive amoebiasis...were randomly allocated in two groups" From correspondence with primary author: unrecalled method of randomization
Allocation concealment (selection bias)	High risk	From correspondence with primary trial author: No method was used to conceal allocation of treatment assignment
Blinding (performance bias and detection bias) Clinical outcomes	High risk	From correspondence with primary author: No method was used to blind participants and study personnel
Blinding (performance bias and detection bias) Parasitological outcomes	High risk	Stools were "examined by two very experienced laboratory technicians", but blinding of these lab technicians was not mentioned. Given that the study author confirmed that this was an open study, laboratory technicians probably were not blinded
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not determined

Pehrson 1984 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	One month after end of treatment (day 30): No data were missing from both treatment groups; all randomized participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Study report does not include results for resolution of abdominal symptoms or results of specific adverse effects
Other bias	Unclear risk	Diagnosis of non-invasive amoebiasis was based only on demonstration of cysts or trophozoites of *E histolytica* on stool microscopy (direct smear and concentration technique), but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Bacterial causes of diarrhoea ware excluded by cultures; sigmoidoscopy and colon X-ray ware performed to rule out ulcerative colitis

Prasad 1985

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* coded drug containers; code broken only at the end of the trial *Blinding:* double (participants, care providers, and outcome assessors) *Inclusion of all randomized participants:* 91.1% (164/180)
Participants	*Number:* 180 patients with amoebiasis or giardiasis or both were enrolled; 164/180 (91.1%) were analysed, 90 with amoebiasis alone, 47 with giardiasis, and 27 with mixed infection with amoebiasis and giardiasis; 16/180 (8.9%) did not complete treatment and were dropped from the trial, but it is not stated whether those who dropped out had amoebiasis, giardiasis, or mixed infection *Inclusion criteria:* children with clinical symptoms of intestinal amoebiasis or giardiasis (diarrhoea, abdominal pain, dysentery, gastrocolic urgency, etc.) and whose stools were positive for amoebae or *Giardia* *Exclusion criteria:* not stated *Concomitant intestinal infection: Ascaris lumbricoides* present in 20%, *Ancylostoma duodenale* 9.9%, *Enterobius vermicularis* 1.8%, but distribution in the 2 groups not reported
Interventions	• Metronidazole: 100 mg/5 mL suspension, given as 5 mL thrice daily for those 1 to 5 years of age, and as 10 mL thrice daily for those 6 to 15 years of age, for 5 or 10 days depending on severity of disease • Metronidazole plus furazolidone: fixed-drug combination suspension of (per 5 mL) metronidazole 75 mg plus furazolidone 25 mg, given as 5 mL thrice daily for those 1 to 5 years of age, and as 10 mL thrice daily for those 6 to 15 years of age, for 5 or 10 days depending on severity of disease
Outcomes	• Parasitological and clinical response: evaluated jointly on day 7 after start of therapy; overall outcome reported as complete cure, partial cure, and no cure, but these terms were not defined • Adverse events: clinical adverse events reported by participants during treatment *Not included in this review:* clinical and parasitological response in those with mixed amoebiasis and giardiasis infection; 12/63 from the metronidazole group and 15/101 from the fixed-drug combination metronidazole plus furazolidone group had mixed amoebiasis and giardiasis and were not included in this review
Notes	*Location:* paediatric outpatient department of S.N. Medical College, Agra, India

Prasad 1985 *(Continued)*

Date: 1985 (date of publication only; actual study period not reported)

Source of funding: not stated

Attempts made to contact study authors were unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "180 patients who entered the trial were randomly divided into two treatment groups" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Quote: "The codes of the two drugs were broken at the end of the trial..." Comment: Blinding of participants, study personnel, and clinical outcome assessors was not specifically mentioned but was implied
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Although not specifically mentioned, blinding of the microscopist examining the stools was probably done because it is mentioned that the "codes of the two drugs were broken at the end of the trial"
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	At end of treatment (day 7): 16 out of 180 participants enrolled did not complete treatment and were dropped from the trial, but the actual number and treatment groups to which these non-compliant participants were randomized were not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	Method for outcome evaluation was not pre-specified. For those classified as "partial cure", it is unclear whether this pertains to clinical or parasitological outcome
Other bias	High risk	Diagnosis of amoebiasis was based on demonstration of cysts or trophozoites of *E histolytica* on stool microscopy, but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR Participants with both amoebiasis and giardiasis were analysed separately, and only those with single infection with amoebiasis were included in this review Concomitant infection with other helminth parasites (*Ascaris lumbricoides, Ancylostoma duodenale, Enterobius vermicularis*) was determined, but distribution in the 2 groups was not reported Treatment duration was not uniform for all participants because duration of the treatment period ranged "from 5 to 10 days depending on the severity of disease and response to the therapy"

Pudjiadi 1973

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* sequentially numbered coded drug containers supplied by Roche Far East Research Foundation, Hong Kong; sealed envelope containing the list of drugs opened only after the entire trial was finished *Blinding:* double (participants, care providers, and outcome assessors) *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 20 enrolled and analysed *Inclusion criteria:* children with bloody diarrhoea and stools positive for *E histolytica* examined by eosin and Lugol's solution *Exclusion criteria:* not stated *Concomitant intestinal infection: Ascaris lumbricoides* found in faeces of 6 participants, *Trichuris trichiura* found in faeces of 6 participants, but distribution in the 2 groups not specified
Interventions	• Ro 7-0207 (ornidazole): 125-mg capsules • Metronidazole: 125-mg capsules Both drugs were given as follows: up to 2 years of age – 62.5 mg, 2 to 6 years of age – 125 mg, and 6 to 12 years of age - 250 mg daily, divided into 3 daily doses for 7 days
Outcomes	• Parasitological response: clearance of *E histolytica* from stools after 7 days of treatment • Clinical response: disappearance of clinical symptoms after 7 days of treatment • Time (range in days) from start of treatment to disappearance of *E histolytica* from the stools • Time (range in days) from start of treatment to disappearance of bloody diarrhoea • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before, during, and after treatment including complete blood count, urinalysis, electrocardiogram, liver transaminases (SGPT), and alkaline phosphatase
Notes	*Location:* hospital at the Department of Child Health, Medical School University of Indonesia, Jakarta, Indonesia *Date:* 1973 (date of publication only; actual study period not reported) *Source of funding:* Roche Far East Research Foundation for supply of drugs and study grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The list stating which bottles contained Ro 7-0207 or metronidazole was sent by Roche Far East Research Foundation, Hong Kong in a sealed envelope..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "The list stating which bottles contained Ro 7-0207 or metronidazole was sent by Roche Far East Research Foundation, Hong Kong in a sealed envelope and was only opened after the entire trial was finished" Comment: Allocation concealment was adequate
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Quote: "A double-blind set containing ten bottles of Ro 7-0207 125 mg capsules and 10 bottles of metronidazole capsules about 125 mg was supplied by the Roche Far East Research Foundation, Hong Kong. The bottles were num-

Pudjiadi 1973 *(Continued)*

		bered 191-210 and contained either Ro 7-0207 or metronidazole. The first admitted case was treated with capsules from bottle 191, the second with those from bottle 192, etc" Comment: Blinding of participants, study personnel, and clinical outcome assessors was adequate
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Although not specifically mentioned, blinding of the microscopist examining the stools was probably done
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment (after 7 days of treatment): No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Concomitant infection with *Ascaris lumbricoides* and *Trichuris trichiura* was found in 6 cases each, but in which treatment group was not specified Concomitant infection with pathogenic bacteria and other protozoa was not determined

Rossignol 2001

Methods	*Generation of allocation concealment:* unclear *Allocation concealment:* unclear *Blinding:* double (participants, care providers, and outcome assessors) *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 91 enrolled but only 67 (74%) had *Entamoeba histolytica* (53 with single and 14 with mixed *Giardia* and *Entamoeba* infection); 67 analysed *Inclusion criteria:* adults and children with diarrhoea and stool specimens positive for cysts or trophozoites of *E histolytica* and/or *E dispar* alone or with concomitant *Giardia intestinalis* by direct smear, concentration technique, Ziehl-Neelsen stain, and an immunofluorescent assay (MeriFluor Meridian Diagnostics) *Exclusion criteria:* pregnant women; using any drug with antiprotozoal activity within 2 weeks of enrolment; known to have or suspected or acquired immunodeficiency syndrome (AIDS) *Concomitant intestinal infection:* mixed *Entamoeba histolytica* and *Giardia intestinalis* infection in 6/36 (17%) participants in the nitazoxanide group and in 8/31 (26%) in the placebo group

Rossignol 2001 *(Continued)*

Interventions	• Nitazoxanide: 500 mg twice daily orally for 3 days • Placebo tablet (identical): twice daily orally for 3 days
Outcomes	• Parasitological response: clearance of *E histolytica* from 2 stool specimens collected between days 7 and 10 after start of treatment • Clinical response: disappearance of symptoms, resolution of diarrhoea and haematochezia on day 7 after start of treatment • Median duration of diarrhoea (days) • Adverse events: clinical adverse events monitored by study personnel
Notes	*Location:* outpatient clinic of the Department of Hepatology, Gastroenterology, and Infectious Diseases of the Benha University Hospital, governorate of Kalubia, Nile Delta, Egypt *Date:* 2001 (date of publication only; actual study period not reported) *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Reported as a double blind placebo-controlled trial, where "each of the patients received 1 nitazoxanide 500mg yellow film-coated tablets or a matching placebo tablet twice daily for 3 consecutive days" The trial author also reported that patients, personnel assessing clinical response, and laboratory personnel evaluating stool samples were blinded
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Laboratory personnel evaluating stool samples were blinded
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	5 days after end of treatment (day 7): 1/48 in the nitazoxanide group and 1/42 in the placebo group withdrew from the study before taking any study medication and were excluded from the analysis. Of those included in the study, 53 with *E histolytica/E dispar* alone (30 in the nitazoxanide group and 23 in the placebo group) were analysed for clinical cure, and 67 with *E histolytica/E dispar* and *Giardia intestinalis* (36 in the nitazoxanide group and 31 in the placebo group) were analysed for parasitological cure. No data were missing from both treatment groups
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done

Rossignol 2001 *(Continued)*

	Stool culture was done to identify bacterial causes of diarrhoea, but other protozoa or helminth parasites were not identified

Rossignol 2007

Methods	*Generation of allocation sequence:* computer-generated randomization *Allocation concealment:* adequate *Blinding:* double (participants, care providers, outcome assessors) *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 100 enrolled and 100 analysed; 2 participants in the placebo group lost to follow-up and considered treatment failures *Inclusion criteria:* adults and children with diarrhoea; ≥ 1 enteric symptom; *E histolytica*/*E dispar* trophozoites identified in stool by microscopic examination using direct smear and concentration technique; stool positive for *E histolytica* by antigen-based ELISA *Exclusion criteria:* other enteric pathogens identified by Ziehl-Neelsen stain, immunofluorescent assay (MeriFluor Meridian Diagnostics), and stool culture; pregnant and lactating women; using any drug with antiprotozoal activity within 2 weeks of enrolment; and known or suspected to have acquired immunodeficiency syndrome (AIDS) or other immune deficiencies
Interventions	• Nitazoxanide: for 3 days; adults aged ≥ 12 years, 500-mg tablet twice daily; children 100 mg/5 mL suspension – 1 to 3 years received 5 mL twice daily, 4 to 11 years received 10 mL twice daily • Placebo: matching placebo tablet or suspension twice daily for 3 days
Outcomes	• Parasitological response: clearance of *E histolytica* from 2 stool specimens collected between days 7 and 10 after start of treatment • Clinical response: disappearance of symptoms, resolution of diarrhoea and haematochezia on day 7 after start of treatment • Adverse events: monitored by patient diary *Not included in this review:* survival analysis of time from first dose to passage of last unformed stools (survival graph)
Notes	*Location:* outpatient clinic of the Benha University Hospital, Benha, Egypt *Date:* 17 February 2004 to 2 October 2005 *Source of funding:* Romark Laboratories, L.C.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list was used
Allocation concealment (selection bias)	Low risk	Quote: "Upon enrolment, each patient was sequentially assigned a number corresponding to the number on his/her package of study medication" Comment: Allocation concealment was adequate

Rossignol 2007 *(Continued)*

Blinding (performance bias and detection bias) Clinical outcomes	Low risk	Reported as a double-blind placebo-controlled trial, where "patients, principal investigators and their staffs, laboratory personnel and the study monitors were blinded" Trial reports that "packaging of study medications were prepared by the study sponsor" Comment: Blinding of participants, study personnel, and clinical outcome assessors was adequate
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Laboratory personnel evaluating stool samples were blinded
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	5 days after end of treatment (day 7): No data were missing from both treatment groups. Analysis was conducted for all participants randomised to the study and using a modified intention-to-treat population from which participants with no *E histolytica* cysts or trophozoites in their baseline stool sample and those with other identified enteric pathogens in their stool samples were excluded
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were clinical response at day 7 and microbiological response between days 7 and 10. Survival analysis graph showing time from first dose to passage of last unformed stool was not pre-specified
Other bias	Low risk	Study appears to be free of other sources of bias. Only those confirmed to be positive for *E histolytica* by the stool antigen ELISA test were included. Those with other identified enteric pathogens were excluded

Rubidge 1970

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 39 enrolled and analysed *Inclusion criteria:* children with amoebic dysentery presenting with acute onset of diarrhoea with blood, mucus, and actively motile haematophagous trophozoites of *E histolytica* in stool specimens examined by direct smear and zinc sulphate flotation technique *Exclusion criteria:* not stated
Interventions	• Metronidazole: 50 mg per kg body weight orally for 7 days • Dehydroemetine, tetracycline, and diloxanide furoate: dehydroemetine (2 mg/kg body weight daily by subcutaneous injection for 10 days), tetracycline (50 mg/kg body weight daily orally for 7 days), and diloxanide furoate (25 mg/kg body weight daily orally for 10 days)

Rubidge 1970 *(Continued)*

Outcomes	• Parasitological response: clearance of *E histolytica* at end of treatment and on subsequent stool specimens during follow-up until 28 days after start of treatment • Clinical response: disappearance of symptoms at end of treatment and during follow-up until 28 days after start of treatment • Adverse events: only tolerance to drugs reported
Notes	*Location:* hospital in Durban, South Africa *Date:* 1970 (date of publication only; actual study period not reported) *Source of funding:* not stated; metronidazole was supplied by Messrs May and Baker, Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "children were randomly allocated to one of the following two treatment schedules" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (metronidazole for 7 days; combination of dehydroemetine subcutaneous injection plus tetracycline for 7 days and diloxanide furoate for 10 days), and no blinding of participants, study personnel, and clinical outcome assessors was mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	10 to 12 days after end of treatment (day 20 or 22): No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	After day 55: 1/19 in the combination dehydroemetine, tetracycline, and diloxanide furoate group was lost to follow-up. No loss to follow-up was mentioned in the metronidazole group
Selective reporting (reporting bias)	High risk	Outcomes and timing of determination of outcomes were not pre-specified
Other bias	Unclear risk	Trial enrolled only children with amoebic dysentery, defined as acute bloody stools with motile haematophagous trophozoites of *E histolytica* in their stools However, only stool microscopy (using direct smear and zinc sulphate flotation technique) was used to demonstrate *E histolytica* in the stools, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done

Rubidge 1970 *(Continued)*

	It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, and helminth parasites was determined

Salles 1999

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 90.7% (275/303) included in evaluation for clinical efficacy; 99% (300/303) included in evaluation for parasitological efficacy
Participants	*Numbers:* 303 enrolled; 275/303 (90.7%) included in evaluation for clinical efficacy; 300/303 (99%) included in evaluation for parasitological efficacy *Inclusion criteria:* children with clinical symptoms of intestinal amoebiasis with stool specimens positive for *E histolytica* by direct smear using the Faust and Katz method and no history of intolerance to imidazole drugs *Exclusion criteria:* history of vomiting in the past 48 hours; taken antiemetic drugs in the past 24 hours; treated with antiamoebic drugs in the past 15 days; symptoms of extraintestinal amoebiasis *Concomitant intestinal infection:* Groups were comparable for presence of other intestinal parasites (*Ascaris lumbricoides, Tricuris trichiura, Giardia lamblia, Necator americanus, Ancylostoma, Hymenolepsis nana, Schistosoma, Enterobius vermicularis, Endolimax nana*), except *Strongyloides stercoralis,* which was more frequent in the tinidazole group (3 participants) than in the secnidazole group (11 participants)
Interventions	• Secnidazole: 1 mL/kg body weight orally in a single dose • Tinidazole: 0.5 mL/kg body weight once daily orally for 2 days
Outcomes	• Parasitological response: clearance of *E histolytica* from stool specimens collected on days 7, 14, and 21 following treatment • Clinical response: disappearance of all symptoms at the end of the study (day 21) • Adverse events: solicited from the participants or their guardians during follow-up visits
Notes	*Location:* 5 different centres in Brazil *Date:* 1999 (date of publication only; actual study period not reported) *Source of funding:* not stated One study author (Valfredo Costa) is connected with Rhodia Farma Ltd, the manufacturer of Secnidal (secnidazole)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly divided into 2 groups" Comment: insufficient information about the sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned

Salles 1999 *(Continued)*

Blinding (performance bias and detection bias) Clinical outcomes	High risk	Reported to be an open comparative multi-centre study
Blinding (performance bias and detection bias) Parasitological outcomes	High risk	Reported to be an open comparative multi-centre study
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Clinical and laboratory responses were determined on days 7 and 14 (5 or 12 days after end of treatment), but results were not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	19 days after end of treatment (day 21): Proportion remaining in the trial was 99.0% (300/303) for parasitological efficacy: 2/156 missing data from the secnidazole group and 1/147 missing data from the tinidazole group did not complete all 3 stool tests and were not included in the laboratory efficacy analysis. For clinical efficacy, proportion remaining was 90.7% (275/303): 18/156 missing data from the secnidazole group and 10/147 from the tinidazole group; reasons for missing data were not reported. Imbalance in quantity of missing data between the 2 groups and in the proportion of missing outcomes (18/156; 11.5%) compared with observed event risk (10/138; 7.2%) in the secnidazole group may induce clinically relevant bias in the intervention effect estimate
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating *E histolytica* in the stools, but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Other parasites were identified in the 2 groups (*Ascaris lumbricoides, Trichuris trichiura, Giardia lamblia, Strongyloides stercoralis*) and were not statistically different, except *Strongyloides stercoralis,* which was more frequently found in the tinidazole group (P = 0.02). Concomitant infection with pathogenic bacteria or other protozoa was not determined

Savas-Erdeve 2009

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* adequate *Blinding:* open *Inclusion of all randomized participants:* 94.4% (85/90)
Participants	*Numbers:* 90 enrolled; 85/90 (94.4%) analysed; 5 in the metronidazole plus *Saccharomyces boulardii* group excluded because of non-compliance *Inclusion criteria:* children from 1 to 15 years of age who presented with *E histolytica*-associated diarrhoea, defined as presence of compatible clinical presentations (acute diarrhoea, fever, and abdominal pain) and presence of *E histolytica* trophozoite engulfing red blood cells in diarrhoeal stool by light microscopy (fresh and trichrome staining)

Savas-Erdeve 2009 *(Continued)*

	Exclusion criteria: children with severe intercurrent illnesses treated by any other antidiarrhoeal/antibiotics within 2 months, treated by probiotics within 1 week, severely malnourished, or with chronic disease/immune deficiency *Concomitant intestinal infection:* Stool cultures were obtained from all participants, and no positive stool cultures were reported for participants
Interventions	• Metronidazole: 30 to 50 mg/kg/d orally for 10 days (maximum: 500 to 750 mg) • Metronidazole plus *Saccharomyces boulardii* (Reflor,Sanofi-Synthelabo, France): metronidazole 30 to 50 mg/kg/d orally (maximum: 500 to 750 mg) plus lyophilized *S boulardii* 250 mg (includes 5,000,000 living micro-organisms) orally once a day for 10 days
Outcomes	• Parasitological response: clearance of *E histolytica* from stool specimens collected 14 days after end of treatment • Clinical response: disappearance of all symptoms (diarrhoea, bloody diarrhoea, vomiting, fever, abdominal pain) at the end of the study (day 10) • Time (median and range in days) to resolution of diarrhoea, bloody diarrhoea, vomiting, fever, abdominal pain • Adverse events: recorded during the active treatment period *Not included in this review:* survival analysis graph of the number of stools per day during the 10-day treatment period
Notes	*Location:* outpatient in Turkey *Date:* January 2006 to April 2007 *Source of funding:* not stated The study author was contacted and kindly provided data on location (outpatient), type of amoebiasis (amoebic dysentery), randomization (randomly numbered by another person), allocation concealment (sequentially numbered sealed envelopes), and clinical outcomes (all improved by end of 10-day treatment period)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 90 children were randomized into two groups" Comment: insufficient information about the sequence generation process even after correspondence
Allocation concealment (selection bias)	Low risk	From correspondence: "Envelopes were opaque and were prepared by a physician who was blind to the study. After preparation they were randomly numbered by another person" Comment: Allocation concealment was adequate
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Reported to be an "open prospective study"
Blinding (performance bias and detection bias) Parasitological outcomes	High risk	Reported to be an "open prospective study"
Incomplete outcome data (attrition bias)	Unclear risk	14 days after end of treatment: 5/45 from the metronidazole plus *S boulardii* group were excluded because of non-compliance with the study; none were missing from the metronidazole group

Savas-Erdeve 2009 *(Continued)*

For outcomes determined 1-14 days after end of treatment		Comment: Imbalance in quantity of missing data between the 2 groups and in the proportion of missing outcomes (5/45; 11%) compared with observed event risk (3/40; 7.5%) in the group receiving *S boulardii* may induce clinically relevant bias in intervention effect estimate
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes. Safety outcome were not pre-specified, but study authors did not mention in the discussion that no side effects occurred among enrolled participants
Other bias	Unclear risk	Trial enrolled only children with clinical symptoms and presence of *E histolytica* engulfing red blood cells in diarrhoeal stools compatible with amoebic dysentery. However, trial author states as one limitation failure to do more specific diagnostic tests for amoebic dysentery such as stool antigen ELISA test or PCR to differentiate *E histolytica* from non-pathogenic species Other causes of dysentery were ruled out by obtaining stool cultures on enrolment, but the presence of other protozoa or helminth parasites was not determined

Shah 2016

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear *Inclusion of all randomized participants:* 88.5% (184/208); 8 patients did not agree to participate in the clinical trial, 6 patients dropped out owing to poor response, 4 patients were excluded owing to some serious side effects, and 4 were dropped because of allergic reaction
Participants	*Numbers:* 184 patients complied with the criteria for inclusion - 93 in the Herbal drug group and 91 in the metronidazole group *Inclusion criteria:* patients suffering from amoebiasis infection (confirmed by stool microscopy and antibody detection tests); no previous treatment against amoebiasis; living in Bahawalpur and Karachi division *Exclusion criteria:* concurrent physical illness, e.g. uncontrolled hypertension and diabetes mellitus; previous gastrointestinal surgery; any drug interaction or hypersensitivity; pregnant females; chronic diseases such as tuberculosis and cardiac myopathies; hospitalized for any serious disease
Interventions	• Herbal drug Amoebex 400-mg tablet 2 tablets after meal thrice daily; duration was not reported • Metronidazole 400 mg 2 tablets thrice daily for 5 days
Outcomes	• Parasitological response: eradication of *Entamoeba histolytica* from stool specimens at end of treatment • Clinical response: disappearance of sign and symptoms of amoebiasis at end of study *Not included in this review:* improvement in intensity of symptoms

Shah 2016 *(Continued)*

Notes	*Location:* hospital, multi-centre (Shifa-ul-mulk Memorial Hospital, Hamdard University Karachi, Hakeem, Pakistan) Muhammad Said Shaheed Memorial Research Center, Bahawalpur and Bahawalpur Victoria Hospital, Bahawalpur *Date:* March 2010 to February 2012 *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned to receive either herbal medicine or control allopathic treatment" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Described to be a "double blind, multicenter evaluation", but it is unclear who was blinded Comment: insufficient information on how blinding of participants, study personnel, and clinical outcome assessors was ensured
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Described to be a "double blind, multicenter evaluation", but it is unclear who was blinded Comment: insufficient information on how blinding of participants, study personnel, and clinical outcome assessors was ensured
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	At end of treatment: 184 patients who were included were analysed
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Unclear risk	Published report included pre-specified outcomes. Adverse effects were incompletely reported. The treatment group to which the 4 participants who experienced serious side effects and the 4 who developed allergic reactions were assigned is not mentioned. It is reported that 57.4% of participants on metronidazole experienced mild side effects, including nausea and vomiting, but no further details were given. How many in the herbal group experienced adverse effects is not mentioned
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating *E histolytica* in the stools and antibody detection test, but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done. At baseline, not all participants were positive on stool microscopy for amoebiasis

Shah 2016 *(Continued)*

	Concomitant infection with pathogenic bacteria or other protozoa was not determined

Siddiqui 2015

Methods	*Generation of allocation sequence:* adequate *Allocation concealment:* adequate *Blinding:* unclear *Inclusion of all randomized participants:* 89.5% (153/171)
Participants	*Numbers:* 171 enrolled; 153 analysed; 18/171 were not included in the analysis: 8/86 from the combination metronidazole + diloxanide furoate (7 refused to submit a second stool specimen; 1 left the city); 10/85 from the herbal group (8 refused to submit a second stool specimen; 2 changed physicians) *Inclusion criteria:* between the ages of 5 and 60 years with symptoms of amoebiasis (abdominal pain, blood in stool, or diarrhoea) and positive for *E histolytica* cyst or trophozoite by direct smear, Lugol's iodine smear, zinc sulphate floatation preparation, or formalin-ether sedimentation method *Exclusion criteria:* congenital malformation, chronic diseases such as tuberculosis, or comorbid condition such as hypertension and diabetes; known hypersensitivity to study drugs; any other infection as shown by laboratory investigation
Interventions	• Combination of metronidazole 400 mg + diloxanide furoate 500 mg (Entamizole DS, Pakistan) in tablet form given 3 times a day for 5 days • Herbal product (Endemali, Pakistan) available in 4-g sachet containing *Boswellia glabra* 270.9 mg, *Kaolinum ponderosum* 255 mg, *Ocimum pilosum* 580 mg, *Pistacia terbinthus* 116.1 mg, *Plantago ispagula* 812.7 mg, *Vateria indica* 232.2 mg; sweetening agent q.s. Endemali was given 4 times a day for 10 days
Outcomes	• Parasitological response: no *E histolytica* cyst found in the stool 5 days after treatment was stopped • Clinical response: absence (partial or complete) of symptoms after treatment was stopped • Adverse events: Clinical adverse events were reported by participants after they received study drugs, but the method of reporting was not specified; no biochemical tests were monitored
Notes	*Location:* outpatient department of 2 centres in Pakistan (Shifa-Ul-Maluk Hospital, Gadap and Zahida Medical Centre, North Karachi) *Date:* October 2008 to December 2009 *Source of funding:* Hamdard University (Karachi, Pakistan)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Marked papers were prepared by a person who was not part of research team. Half (five) of each block of 10 were marked 'Treatment Group 1' (TR1) and the rest marked as 'Treatment Group 2' (TR2). Each eligible participant was invited to pick blindly, one sheet out of 10 available" Comment: adequate sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "Marked papers were prepared by a person who was not part of research team"

Siddiqui 2015 *(Continued)*

		"These sheets were pulled out by the patient from a drawer at the time of informed consent, so allocation was concealed" Comment: adequate allocation concealment
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to be a randomized double-blind clinical trial Quote: "...physician and laboratory person were also blinded for the type of treatment" Comment: Although the physician was reported to be blinded, the formulations of the 2 study drugs, the regimen, and the duration were very different, and it is unclear how the physician and participants were blinded to the type of treatment received. It is not mentioned whether those administering the drugs were also the clinical outcome assessors. Attempts to contact the primary author for clarification were unsuccessful
Blinding (performance bias and detection bias) Parasitological outcomes	Low risk	Reported to be a randomized double-blind clinical trial Quote: "...physician and laboratory person were also blinded for the type of treatment" Comment: Although the formulations of the 2 study drugs, the regimen, and the duration were very different, the laboratory person examining the stools probably was blinded
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	5 days after end of treatment: 8/86 dropped out from the combination metronidazole + diloxanide furoate group (7 refused to submit a second stool specimen; 1 left the city); and 10/85 dropped out from the herbal group (8 refused to submit a second stool specimen; 2 changed physicians) Overall missing data are 10.5% (18/171). Except for 1 who left the city and 2 who remained symptomatic, 15 were symptom-free but were not included in the analysis of clinical outcomes
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based on stool microscopy demonstrating *E histolytica* in the stools, but differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is unclear whether participants with other intestinal infections were not enrolled

Singh 1977

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open

Singh 1977 *(Continued)*

	Inclusion of all randomized participants: 93.3% (56/60)
Participants	*Numbers:* 60 enrolled; 56 analysed; 3 participants in the tinidazole group and 1 in the metronidazole group did not comply with the regimen and were excluded from analysis *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* by direct smear or formol-ether concentration technique *Exclusion criteria:* received antiamoebic treatment in the previous 4 weeks before enrolment; pregnant women; dehydrated patients; evidence of hepatic, renal, haematological, or ECG abnormalities *Concomitant intestinal infection:* 12 had concomitant giardiasis, 6 in each group
Interventions	• Tinidazole: 500-mg tablets × 4 (2 g) single dose daily for 3 days • Metronidazole: 400-mg tablets × 5 (2 g) single dose daily for 3 days
Outcomes	• Parasitological response: eradication of *E histolytica* on follow-up stool examinations on day 30 after start of treatment • Clinical response: disappearance of presenting clinical signs and symptoms on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including complete blood count, urinalysis, serum bilirubin, alkaline phosphatase, transaminases, and blood urea
Notes	*Location:* medical outpatient department of the Government Medical College and Hospital, Patiala India *Date:* 1977 (date of publication only; actual study period not reported) *Source of funding:* not stated; tinidazole was supplied by Pfizer Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were allocated either to tinidazole or to metronidazole by random order" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different drugs and regimens were used (tInidazole 500 mg × 4 tabs and metronidazole 400 mg × 5 tabs once daily for 3 days), and blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: The appearance of the drugs was not mentioned, and blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not reported

Singh 1977 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	28 days after end of treatment (day 30): 3/30 in the tinidazole group and 1/30 in the metronidazole group did not comply with the treatment regimen and were excluded from analysis
Selective reporting (reporting bias)	Low risk	Published report includes pre-specified outcomes
Other bias	Unclear risk	Diagnosis of Intestinal amoebiasis was based only on demonstration of cysts or trophozoites of *E histolytica* on stool microscopy (direct smear or concentration technique), but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR Six participants each in the 2 treatment groups had concomitant giardiasis, although this probably did not introduce additional bias because of equal distribution between the 2 groups. It is not mentioned whether concomitant infection with pathogenic bacteria or helminth parasites was determined

Sitepu 1982

Methods	*Generation of allocation sequence:* random numbers table *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but the procedure for blinding participants, care providers, and outcome assessors was not described *Inclusion of all randomized participants:* 82% (41/50) included in analysis on third day or 2 days after treatment, 36% (18/50) 1 week after treatment
Participants	*Numbers:* 50 enrolled; 41/50 (82%) analysed on the third day or 2 days after treatment, 18/50 (36%) analysed 1 week after treatment *Losses to follow-up:* 9/51 (18%) were lost to follow-up by the third day or 2 days after treatment - 7 participants in the tinidazole group and 2 in the ornidazole group; 32/50 (64%) were lost to follow-up 1 week after treatment - 18 in the tinidazole group and 14 in the ornidazole group *Inclusion criteria:* children with amoebic dysentery presenting with bloody diarrhoea and motile haematophagous trophozoites of *E histolytica* in stools examined by direct smear method with eosin 1% stain *Exclusion criteria:* not stated *Concomitant intestinal infection:* trichuriasis (12 in tinidazole group and 15 in ornidazole group)
Interventions	• Tinidazole: 50 mg/kg body weight in a single oral dose • Ornidazole: 50 mg/kg body weight in a single oral dose
Outcomes	• Parasitological response: clearance of *E histolytica* from stools on subsequent follow-up visits on days 2 to 4 and 1 week after treatment • Clinical response: disappearance of diarrhoea, and faeces no longer contained mucus or red blood cells on days 2 to 4 and 1 week after treatment
Notes	*Location:* outpatient clinic of the Pediatric Gastroenterology Subdivision, Department of Child Health, School of Medicine, University of North Sumatra/Dr Pirngadi Hospital, Medan, Indonesia *Date:* August 1978 to May 1979

Sitepu 1982 *(Continued)*

Source of funding: PT. Pfizer Indonesia and PT. Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation to the tinidazole and ornidazole groups was done by random numbers" Comment: probably refers to table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported to be a double-blind trial, but it is unclear who was blinded Comment: insufficient information on how blinding of participants, study personnel, and clinical outcome assessors was ensured
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Reported to be a double-blind study, but blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	High risk	One day after treatment (day 2): 7/26 missing from the tinidazole group and 2/24 missing from the ornidazole group. Reason for non-inclusion in the analysis was inability to return for at least 2 follow-up visits. Imbalance in loss to follow-up between the 2 groups may induce clinically relevant bias in the intervention effect estimate
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	High risk	One week after treatment: 18/26 missing from the tinidazole group and 14/24 missing from the ornidazole group. Reason for non-inclusion in the analysis was inability to return for at least 2 follow-up visits. The high number of losses to follow-up in the 2 groups may induce clinically relevant bias in the intervention effect estimate
Selective reporting (reporting bias)	High risk	Only patients who returned for at least 2 follow-up visits were included in the final evaluation. Outcomes for those who had only 1 evaluation were not reported. Adverse effects were not reported
Other bias	Unclear risk	Trial enrolled only children with bloody stools who showed motile trophozoites of *E histolytica* containing red blood cells in diarrhoeal stools. However, only stool microscopy was used to diagnose amoebic dysentery, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is unclear how concomitant trichuriasis can affect evaluation of clinical response to antiamoebic drugs, but concomitant trichuriasis was found in similar numbers of children in the 2 groups (12 in the tinidazole group and 15 in the ornidazole group)

Soedin 1985

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open

Soedin 1985 *(Continued)*

	Inclusion of all randomized participants: 100%
Participants	*Number:* 80 enrolled and analysed *Inclusion criteria:* children with clinical symptoms of acute intestinal amoebiasis with stool specimens positive for trophozoites or haematophagous forms of *E histolytica* *Exclusion criteria:* not stated
Interventions	• Secnidazole: 2 g orally in a single dose • Tetracycline and clioquinol: tetracycline (750 mg) and clioquinol (1 g for 5 days) *Co-intervention:* 2 cases in secnidazole group were given spasmolytics (unspecified) for stomach cramps
Outcomes	• Parasitological response: eradication of *E histolytica* from stools examined on days 1 to 7, 7, 14, and 21 after start of treatment • Clinical response: disappearance of clinical symptoms on days 1 to 7, 14, 21, and 28 after start of treatment • Adverse events: clinical adverse events during follow-up
Notes	*Location:* outpatient in the Padang Bulan Health Centre, Medan, Indonesia *Date:* September 1982 to September 1983 *Source of funding:* not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: Patients were "randomly allocated to one or the other of two treatment groups" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (secnidazole 2 g single dose; combination of tetracycline 750 mg given as 2 capsules thrice daily plus clioquinol 1 g given as 4 tablets once daily for 5 days). Blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of treatment (day 5): No data were missing and no withdrawals or dropouts were reported
Incomplete outcome data (attrition bias)	Low risk	22 days after end of treatment (day 28): No data were missing and no withdrawals or dropouts were reported

Soedin 1985 *(Continued)*

For outcomes determined 15-60 days after end of treatment		
Selective reporting (reporting bias)	High risk	Participants were asked to return to the clinic on days 1 to 7, 14, 21, and 28 for assessment of clinical and parasitological efficacy, but clinical cure was reported only until day 5, while parasitological failure was reported until day 28. Clinical outcomes on day 28 were not reported
Other bias	Unclear risk	Trial enrolled only children with bloody stools who showed trophozoites or haematophagous forms of *E histolytica* in the stools. However, only stool microscopy was used to diagnose amoebic dysentery, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

Swami 1977

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear *Inclusion of all randomized participants:* 93.3% (56/60)
Participants	*Numbers:* 60 enrolled; 56/60 (93.3%) analysed; 3/60 (5%) lost to follow-up after day 4 (1 in tinidazole group, 2 in metronidazole group); 1 participant in the metronidazole group subsequently found to have amoebic liver abscess was excluded from the final analysis *Inclusion criteria:* adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica* *Exclusion criteria:* received antiamoebic treatment in previous 4 weeks; pregnant women; patients with marked dehydration; concomitant serious illness (not specified) *Type of amoebic colitis:* tinidazole group: amoebic dysentery 20/29, non-dysenteric amoebic colitis 9/29; metronidazole group: amoebic dysentery 22/27, non-dysenteric amoebic colitis 5/27
Interventions	• Tinidazole: 2 g single dose daily for 3 days • Metronidazole: 2 g single dose daily for 3 days Treatment was extended if *E histolytica* persisted in the stool on the day following the last treatment period
Outcomes	• Parasitological response: eradication of *E histolytica* on follow-up stool examinations on day 30 after start of treatment • Clinical response: relief of presenting clinical signs and symptoms on day 30 after start of treatment • Adverse events: voluntary reporting of adverse events by participants; laboratory tests monitored before and after treatment including blood counts, urinalysis, serum bilirubin, alkaline phosphatase, transaminases (SGOT, SGPT), and blood urea *Not included in this review:* number of participants who required extension of treatment beyond 3 days
Notes	*Geographic location:* Visakhapatnam, India *Date:* 1977 (date of publication only; actual study period not reported)

Swami 1977 *(Continued)*

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients received either tinidazole or to metronidazole according to a randomization schedule" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Blinding of participants, study personnel, and clinical outcome assessors was not mentioned. Both tinidazole and metronidazole were administered in a single daily dose of 2 grams on 3 consecutive days. It is reported that "treatment period was extended if *Entamoeba histolytica* persisted in the stools following the last treatment day" Comment: Blinding of participants, study personnel, and clinical outcome assessors was unclear, and the appearance of the 2 drugs was not described
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Unclear risk	Not reported
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	15 to 25 days after end of treatment (day 30): 1/30 missing data in the tinidazole group (owing to failure to return for follow-up after day 4); 3/30 in the metronidazole group (2 did not return for follow-up after day 4, 1 had concomitant amoebic liver abscess). Overall, 56/60 (93.3%) were included in the analysis
Selective reporting (reporting bias)	Low risk	Published report included pre-specified outcomes
Other bias	High risk	Diagnosis of intestinal amoebiasis was based only on stool microscopy demonstrating trophozoites or cysts of *E histolytica,* but differentiation of *E histolytica* from non-pathogenic species was not done by more specific tests such as stool antigen ELISA or PCR It is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined Duration of treatment varied and was determined by persistence of *E histolytica* in the stools 1 day after treatment. Treatment was extended beyond the planned 3 days of treatment for 3 participants in the tinidazole group (4 days in 1 case and 5 days in 2 cases) and for 10 participants in the metronidazole group (5 days in 4 cases, 6 days in 4 cases, 8 days in 1 case). All cases were analysed together in the group, regardless of duration of treatment

Toppare 1994

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* open *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 102 enrolled and analysed *Inclusion criteria:* children with gastrointestinal symptoms and stool specimens positive for haematophagous trophozoites of *E histolytica* *Exclusion criteria:* not stated *Concomitant intestinal infection:* All cases in both groups had negative stool cultures for pathogenic bacteria
Interventions	• Secnidazole: 30 mg/kg body weight as a single oral dose daily for 3 days • Ornidazole 15 mg/kg body weight given twice daily orally for 10 days
Outcomes	• Parasitological cure: clearance of *E histolytica* cyst or trophozoite from stools 10 days after completion of treatment • Clinical response: resolution of diarrhoea and abdominal discomfort • Time (median and range in days) from start of treatment to resolution of clinical symptoms • Adverse events: side effects; method for obtaining information and specific adverse events not reported
Notes	*Location:* Medical Center Hospital, Ankara, Turkey *Date:* 1994 (date of publication only; actual study period not reported) *Source of funding:* not stated Attempts to contact study authors were unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Sixty children were randomly allocated to receive secnidazole in a daily dose of 30 mg/kg for 3 days while the rest were given ornidazole in a dose of 15 mg/kg twice daily..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	High risk	Different dosages and regimens were used (secnidazole 30 mg/kg for 3 days; ornidazole 15 mg/kg twice daily for 10 days). Blinding of participants, study personnel, and clinical outcome assessors was not mentioned Comment: Blinding of participants, study personnel, and clinical outcome assessors probably was not done
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of the microscopist examining the stools was not mentioned

Toppare 1994 *(Continued)*

Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	10 days after end of treatment: No data were missing from both treatment groups; all randomized participants were included in the analysis
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Unclear risk	Not determined
Selective reporting (reporting bias)	High risk	Outcomes and analysis methods were not pre-specified
Other bias	Unclear risk	Trial enrolled only children with gastrointestinal symptoms who were found to have haematophagous trophozoites of *E histolytica* in stool samples. However, only stool microscopy was used to diagnose amoebic dysentery, and differentiation of *E histolytica* from non-pathogenic species by more specific tests such as stool antigen ELISA or PCR was not done Trial reported that all cases had negative stool cultures for pathogenic bacteria, but concomitant infection with other protozoa or helminth parasites was not determined

Tripathi 1986

Methods	*Generation of allocation sequence:* unclear *Allocation concealment:* unclear *Blinding:* unclear; reported as "double-blind", but procedure for blinding participants, care providers, and outcome assessors not described *Inclusion of all randomized participants:* 100%
Participants	*Numbers:* 40 enrolled and analysed *Inclusion criteria:* adults with symptoms of intestinal amoebiasis and stool specimens positive for *E histolytica* by direct smear and formol-ether concentration methods, sigmoidoscopy, colonic ulcer scrapings, and positive stool culture on NIH media *Exclusion criteria:* received amoebicidal drugs during previous 4 weeks; pregnant women; dehydrated patients; liver abscess and any evidence of hepatic, renal, haematological, and ECG abnormalities *Concomitant intestinal infection:* 4 in each group had concomitant *Giardia lamblia* in the stools
Interventions	• GO 10213 (satranidazole): 150 mg thrice daily for 10 days • Metronidazole: 400 mg thrice daily for 10 days
Outcomes	• Parasitological response: eradication of *E histolytica* on stool examinations on follow-up 28 days after start of treatment • Clinical response: relief of presenting clinical signs and symptoms and healing of ulcers on sigmoidoscopy on follow-up 28 days after start of treatment • Adverse events: volunteered by participants; laboratory tests monitored before and after treatment including complete blood count, liver transaminases (SGOT, SGPT), serum bilirubin, blood urea, urinalysis, and electrocardiogram

Tripathi 1986 *(Continued)*

	Not included in this review: frequency of loose stools/d from start of treatment
Notes	*Geographic location:* hospital in Bhopal, India *Date:* 1986 (date of publication only; actual study period not reported) *Source of funding:* Ciba-Geigy India Limited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Forty hospitalized patients with intestinal amoebiasis...were administered either GO 10213 or metronidazole in dose of 150 mg and 400 mg thrice daily for 10 days at random" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding (performance bias and detection bias) Clinical outcomes	Unclear risk	Reported as "double-blind", but it is unclear who was blinded. Different doses were used (GO 10213 150 mg and metronidazole 400 mg, both given thrice daily for 10 days), and the appearance of the drugs is not mentioned Comment: It is not specifically mentioned who among participants, study personnel, and clinical outcome assessors was blinded
Blinding (performance bias and detection bias) Parasitological outcomes	Unclear risk	Blinding of microscopist examining the stools was not specifically mentioned
Incomplete outcome data (attrition bias) For outcomes determined 1-14 days after end of treatment	Low risk	At end of therapy (day 12): no dropouts
Incomplete outcome data (attrition bias) For outcomes determined 15-60 days after end of treatment	Low risk	18 days after end of treatment (day 28): 1/20 from the metronidazole group dropped out of the study because of increased severity of symptoms by the seventh day; no dropouts or withdrawals from the GO 10213 group
Selective reporting (reporting bias)	Unclear risk	The published report mentions that at the end of 28 days, "patients were assessed as per W.H.O. criterion". The frequency of loose stools per day and the rate of disappearance of parasites from the stools were also reported but were not pre-specified
Other bias	Unclear risk	Diagnosis of intestinal amoebiasis was based only on stool microscopy (using direct smear and concentration techniques), sigmoidoscopy, and colonic ulcer scrapings demonstrating *E histolytica,* but differentiation from non-pathogenic species was not specifically mentioned Four patients in each group had *Giardia lamblia,* but it is not mentioned whether concomitant infection with pathogenic bacteria, other protozoa, or helminth parasites was determined

E histolytica: Entamoeba histolytica; ECG: electrocardiogram; ELISA: enzyme-linked immunosorbent assay; NIH: National Institute of Health culture media; PCR: polymerase chain reaction; *S boulardii: Saccharomyces boulardii*; SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase.

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

Study	Reason for exclusion
Abd-Rabbo 1969	Not an RCT
Abdallah 1969	Not an RCT
Achar 1967	Not an RCT
Ali Ata 1967	Not an RCT
Alterio 1968	Not an RCT
Amato Neto 1968	Not an RCT
Apt 1976	Not an RCT
Apt 1983	Not an RCT. The English translation says that a sample of adult patients infected with *E histolytica* was divided into 2 groups but does not mention randomization
Arredondo 1993	Ineligible study population: RCT that compared medical treatment with medical treatment plus liver puncture in patients with amoebic liver abscess
Atias 1972	Not an RCT
Bakshi 1978	Review of 17 RCTs conducted in India and comparing tinidazole with metronidazole over a 2-year period
Banerjee 1976	Not an RCT
Baranski 1966	Not an RCT
Barroso 1969	Not an RCT
Bassily 1987	Not an RCT
Belkind 2004	Ineligible study population: asymptomatic children positive for intestinal helminths or protozoa
Bezjak 1964	Not an RCT
Bhatia 1998	Ineligible study population: RCT comparing metronidazole with secnidazole in treating patients with amoebic liver abscess
Biagi 1966	Wrong intervention: RCT comparing clefamide with placebo given not as treatment but as chemoprophylaxis for intestinal amoebiasis among asymptomatic carriers of *E histolytica.* Both the primary trial and the subsidiary trial by Biagi are probably duplicate publications of the same study because the 2 trials are similar in all aspects
Biagi 1978	Not an RCT
Blanc 1965	Not an RCT. Reports (1965 and 1966) by Blanc are probably duplicate publications of the same study because the 2 trials are similar in all aspects

Study	Reason for exclusion
Blessman 2002	Ineligible study population: RCT comparing paromomycin with diloxanide furoate for treatment of asymptomatic carriers of *E histolytica*
Blessman 2003a	Wrong intervention and ineligible study population: RCT comparing metronidazole alone with ultrasound-guided needle aspiration of the abscess in addition to metronidazole in patients with amoebic liver abscess
Botero 1967	Not an RCT
Campos 1969	Not an RCT
Capparelli 2016	Not an RCT: a phase 1, open-label study with 15 healthy adult participants to determine the pharmacokinetics of gold, given as auranofin, during and after 7 days of once-daily oral dose administration
Cardoso Salles 1970	Not an RCT: alternate allocation of patients with intestinal amoebiasis to receive 2 different doses of ethylchlordiphene
Cariry 1969	Not an RCT
Chari 1970	Not an RCT
Chaudhuri 1966	Not an RCT
Cho 1972	Not reported to be randomized but described as a double-blind trial comparing Ro 7-0207 vs metronidazole in treating participants with intestinal amoebiasis or *E histolytica* asymptomatic carriers; repeated attempts to gather more details from study authors were unsuccessful because the primary study author is deceased and the other study authors cannot be contacted
Cohen 1975	Ineligible study population: RCT comparing chloroquine and metronidazole for treatment of amoebic liver abscess
da Cunha 1977	Not an RCT
Datta 1974	Ineligible study population: amoebic liver abscess
de Carvalho 1965	Not an RCT
de la Rey 1989	Wrong intervention and ineligible study population: RCT that randomized participants with amoebic liver abscess to either metronidazole alone or ultrasound-guided aspiration of the abscess in addition to metronidazole
de Oliveira 1969	Not an RCT
Delgado 1971	Not an RCT
Devic 1974	Not an RCT
Dhariwal 1963	Not an RCT
Dinleyici 2009	Quasi-randomized clinical trial in which randomization was performed by alternating patient inclusion to 1 of 2 treatment groups: 1 group treated with metronidazole alone for 7 days, and the second group treated with metronidazole and lyophilized *S boulardii*, also given for 7 days
Donckaster 1957	Not an RCT

Study	Reason for exclusion
dos Santos 1969	Not an RCT
Doshi 1968	Not an RCT
el Mofti 1965	Not an RCT
Esquivel 1979	Ineligible study population: RCT that compared metronidazole, emetine, or both for treating patients with amoebic liver abscess
Ey 1977	Not an RCT
Felix 1966	Not an RCT. Reports by Felix are probably duplicate publications of the same study because the 2 trials are similar in all aspects
Freeman 1990	Wrong intervention and ineligible study population: compared efficacy of antiamoebic drug therapy plus needle aspiration vs antiamoebic drug therapy alone for patients with amoebic liver abscess
Gilman 1980	Not an RCT: diagnostic validity study comparing conventional and immunofluorescent techniques for detection of *E histolytica* in rectal biopsy
Gorbea 1989	Not an RCT
Hatchuel 1975	Ineligible study population: double-blind trial that compared tinidazole and metronidazole for treating patients with amoebic liver abscess
Hoekenga 1951	Not an RCT
Holz 1965	Not an RCT
Huggins 1965	Not an RCT
Huggins 1969	Not an RCT
Huggins 1974	Not an RCT. Reports by Huggins are probably duplicate publications of the same study because the 2 trials are similar in all aspects
Huggins 1977	Not an RCT
Huggins 1980	Not an RCT
Huggins 1981	Not an RCT
Irusen 1992	Ineligible study population: amoebic liver abscess
Islam 1975	Not an RCT
Islam 1978a	Ineligible study population: RCT that compared metronidazole and tinidazole for treating patients with amoebic liver abscess
Islam 1978b	Ineligible study population: amoebic liver abscess
Jain 1990	Ineligible study population: open clinical trial that compared efficacy of various treatment regimens containing dehydroemetine and/or metronidazole for treating patients with hepatopulmonary amoebiasis

Study	Reason for exclusion
Jayawickrema 1975	Ineligible study population: RCT that compared metronidazole with emetine and chloroquine for treatment of patients with hepatic amoebiasis
Kahbazi 2016	Ineligible population: bacillary dysentery
Kaur 1972	Not an RCT
Khalil 1987	Not an RCT
Khokhani 1977	Ineligible study population: RCT that compared metronidazole with emetine and chloroquine for treatment of patients with hepatic amoebiasis
Khokhani 1978	Ineligible study population: RCT that compared metronidazole with tinidazole for treatment of patients with amoebic liver abscess
Konar 1963	Not an RCT
Krishnaiah 2003	Not an RCT: pharmacokinetic trial comparing 2 formulations of tinidazole given to healthy human volunteers
Kurt 2008	Ineligible study population: RCT comparing metronidazole with single-dose ornidazole for treatment of patients with dientamoebiasis
Laham 1951	Not an RCT
Levy 1967	Not an RCT
Martinez 1969	Not an RCT
Masters 1979	Not an RCT
Mathur 1974	Not an RCT
McAuley 1992	Not an RCT
McLeod 2014	Not an RCT
Mendis 1984	Ineligible study population: RCT that compared metronidazole with tinidazole for treatment of patients with hepatic amoebiasis
Misra 1976a	Not an RCT
Misra 1976b	Combination of an RCT involving 60 participants randomly assigned to either tinidazole or metronidazole and a non-randomized trial involving 30 participants given tinidazole 600 mg twice daily for 5 to 10 days and another 20 patients given tinidazole at 2 g once daily for 3 days. No separate analysis was performed for randomized participants only. Several attempts to contact study authors were unsuccessful
Montovani 2009	Not an RCT. Bioequivalence study comparing 2 oral formulations of secnidazole
Morales 1975	Ineligible study population: RCT that compared intravenous metronidazole vs intramuscular emetine for treating patients with amoebic liver abscess
Murray 1980	Wrong intervention: did not study effect of any antiamoebic drug for treating patients with amoebic colitis

Study	Reason for exclusion
Muzzafar 2006	Ineligible study population: amoebic liver abscess
Nahrevanian 2008	Ineligible study population and not an RCT: study to determine prevalence of *Cryptosporidium* in immunocompromised patients
Naik 1968	Not an RCT
Nanavati 1965	Not an RCT
O'Holohan 1972	Not an RCT
Ohnishi 2014	Not an RCT
Okeniyi 2007	Ineligible study population: no mention of amoebic colitis
Olaeta 1996	Not an RCT: quasi -randomized trial with alternate allocation of participants with intestinal amoebiasis to receive either quinfamide or etofamide
Omrani 1995	Not an RCT
Orozco 1975	Ineligible study population: amoebic liver abscess
Padilla 1995	Ineligible study population: asymptomatic amoebic infection
Padilla 1998	Unclear whether an RCT
Padilla 2002	Wrong intervention and ineligible study population: RCT in which children whose stools became negative for *E histolytica* cysts and who were asymptomatic after 1 or 2 doses of quinfamide were randomized to 3 groups to determine whether administering quinfamide every 3 to 6 months resulted in reduced frequency of amoebic infection to below 27%
Pang 2014	Not an RCT
Pimparkar 1966	Not an RCT
Populaire 1980	Not an RCT; pharmacokinetic study of secnidazole given to healthy human volunteers
Powell 1965a	Not an RCT
Powell 1965b	Ineligible study population: clinical trial of dehydroemetine, emetine, and chloroquine for treating patients with amoebic liver abscess
Powell 1965c	Ineligible study population: amoebic liver abscess
Powell 1965d	Not an RCT
Powell 1966a	Not an RCT
Powell 1966b	Not an RCT
Powell 1966c	Not an RCT
Powell 1967	Ineligible study population: asymptomatic amoebic colitis

Study	Reason for exclusion
Powell 1968	Report of 5 trials using metronidazole at different dosages and durations for treatment of patients with amoebic dysentery
Powell 1969a	Not an RCT
Powell 1969b	Review of several clinical trials using several amoebicides including niridazole, alone or in combination, for treatment of patients with amoebic dysentery or amoebic liver abscess
Powell 1969c	Guidelines on how to conduct drug trials in amoebiasis
Powell 1971a	Not an RCT
Powell 1971b	Letter relaying observations of study authors that no cases of liver abscess developed among patients with amoebic dysentery given chloroquine in addition to broad-spectrum antibiotics or luminal amoebicides compared with those not given chloroquine
Powell 1972a	Report of clinical trials of new nitroimidazole derivatives for treating patients with amoebic liver abscess
Powell 1972b	Review on the evolution of drug therapy for amoebiasis that also presents the latest developments on niridazole, metronidazole, and other nitroimidazole drugs undergoing clinical trials at that time
Powell 1973	Not an RCT
Prakash 1974	Not an RCT: quasi-randomized trial with alternate allocation of participants with intestinal amoebiasis to receive either tinidazole or metronidazole
Qureshi 1994	Not an RCT
Qureshi 1997	Not an RCT
Rodrigues 1968	Not an RCT
Ruas 1973	Ineligible study population: amoebic liver abscess
Ruchko 1978	Not an RCT
Saha 1966	Not an RCT
Saha 1970	Not an RCT
Salem 1964	Not an RCT
Salem 1967	Not an RCT
Sandia 1977	Not an RCT
Sangiuolo 1969	Ineligible study population: patients had "acute gastroenteritis, food-borne gastroenteritis, chronic enterocolitis, or ulcerative colitis". No mention of amoebic colitis or laboratory diagnosis of amoebic colitis among included patients
Sankale 1966	Not an RCT
Sankale 1969	Not an RCT

Study	Reason for exclusion
Sankale 1974	Not an RCT
Satpathy 1988	Ineligible study population: amoebic liver abscess
Schapiro 1967	Not an RCT
Scragg 1968	Ineligible study population: amoebic liver abscess
Scragg 1970	Study population: amoebic liver abscess
Segal 1967	Not an RCT
Sharif 2017	Ineligible study population: bacillary dysentery
Sharma 1989	Intervention and study populations: RCT that compared metronidazole alone vs needle aspiration of the abscess in addition to metronidazole in patients with amoebic liver abscess
Shrotriya 1985	Not an RCT
Simjee 1985	Ineligible study population: amoebic liver abscess
Simon 1967	Not an RCT
Sinuhaji 1986	Preliminary report of a trial on children with acute amoebic dysentery randomized to receive a single dose of metronidazole 50 mg/kg body weight/d or secnidazole 30 mg/kg body weight/d. Results were incomplete, and no final report of this trial was published. Attempts to contact study authors or the institution where the study was conducted were unsuccessful
Sladden 1964	Not an RCT
Soh 1980	Ineligible study population: amoebic liver abscess
Speich 2013	Ineligible study population: asymptomatic school children
Spellberg 1969	Study population: amoebic liver abscess
Spillman 1976	Ineligible study population: RCT that compared metronidazole vs tinidazole for treating those with asymptomatic *E histolytica* infection and/or *E hartmanni* infection
Sutrisno 1978	Not an RCT
Tandon 1997	Wrong Intervention and ineligible study population: RCT that compared metronidazole alone vs needle aspiration of the abscess in addition to metronidazole in patients with amoebic liver abscess
Thompson 2015	Not an RCT
Thoren 1990a	Ineligible study population: RCT that compared metronidazole, tinidazole, and diloxanide furoate for treating asymptomatic homosexual carriers of *E histolytica*
Thoren 1990b	Ineligible study population: asymptomatic *E histolytica* homosexual carriers
Tjaij 1969	Not an RCT
Tjaij 1970	Not an RCT

Study	Reason for exclusion
Vaidya 1983	Not an RCT: pharmacokinetic study of Go.10213 that does not compare the drug vs placebo or another antiamoebic drug
Vakil 1967	Not an RCT: alternate allocation of children and adults with amoebic dysentery, non-dysenteric intestinal amoebiasis, or hepatic amoebiasis to receive intramuscular dehydroemetine or emetine
Vakil 1971	Not an RCT
Vakil 1974	Summary report of several clinical trials of various amoebicidal drugs conducted at 1 medical centre in Bombay, India, over the past 12 years
Valencia 1973	Review on use of erythromycin stearate over the previous 3 years for 500 patients with intestinal amoebiasis, amoebic cysts, and other diseases of the colon
Vanijanonta 1985	Ineligible study population: patients with amoebic liver abscess treated with low-dose tinidazole and needle aspiration
Viswanathan 1968	Not an RCT
Waddington 2018	Protocol of an RCT but with wrong population: Study participants are Australian Aboriginal children aged greater than 3 months and less than 5 years with a primary diagnosis of acute gastroenteritis; no mention that those with intestinal amebiasis will be included
Wang 1971a	Not an RCT
Wang 1971b	Not an RCT: report of 2 cases of oxytetracycline-resistant amoebic dysentery
Watson 1975	Ineligible study population: amoebic infection of the eye
Welch 1978	Not an RCT
Widjaya 1991	Wrong Intervention and ineligible study population: RCT that compared various antiamoebic drug combinations vs percutaneous drainage in addition to combination drug therapy for treating patients with amoebic liver abscess
Wilmot 1962	Not an RCT
Wolfe 1973	Not an RCT
Wolfensberger 1968	Not an RCT
Zuberi 1973	Not an RCT

E histolytica:*Entamoeba histolytica*; *E hartmanii: Entamoeba hartmanii;* RCT: randomized controlled trial; *S boulardii: Saccharomyces boulardii*.

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

NIAID 2016

Trial name or title	Phase IIa Randomized, Single-blinded, Placebo-controlled Clinical Trial of the Reprofiled Drug Auranofin for GI Protozoa
Methods	Randomized single-blinded placebo-controlled

NIAID 2016 *(Continued)*

Participants	68 adults 18 to 65 years of age (34 per arm) with amebiasis identified by rapid EIA and positive antigen detection EIA of stool and with diarrhoea (defined as ≥ 3 loose stools) in the past 24 hours and assessed to be clinically stable and in otherwise good health *Note: This study will also enrol 68 participants with stools positive by rapid EIA and positive antigen detection EIA for* Giardia,*but results will not be included in this review. Participants infected with both* E histolytica*and* Giardia*will be enrolled in the* E histolytica*study arm. Once the* Entamoeba *study arm is fully enrolled, any subsequent dual-infected participants will be enrolled in the* Giardia*arm*
Interventions	• Auranofin 6 mg daily × 7 days • Placebo 6 mg daily × 7 days *Note that auranofin is a gold-containing chemical salt available as 3-mg capsules*
Outcomes	Primary outcome measure for *E histolytica* infection: • Proportion of participants with positive rapid EIA and positive antigen detection EIA for *E histolytica* and resolution of diarrhoea (< 3 loose stools/24 hours) by day 7 Secondary outcomes for *E histolytica* infection: • Proportion of participants with stools positive by rapid EIA and positive antigen detection EIA for *E histolytica* and trophozoites on smear at enrolment with parasitological response (no detection of trophozoites of *E histolytica* on microscopic exam by day 7 • Proportion of participants with stool positive rapid EIA and positive antigen detection EIA for *E histolytica* and trophozoites on smear at enrolment with parasitological response (no detection of trophozoites on microscopic exam or negative antigen detection) by days 3 and 5 • Rate of decrease of trophozoites/cyst load by qPCR in stools by days 3, 5, and 7 • Proportion of participants with negative stool antigen tests by days 3, 5, 7, and 14 • Proportion of participants with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days • Proportion of participants with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping initial versus subsequent strains
Starting date	19 August 2016
Contact information	Contact person: Sharon Reed; 18588222808; slreed@ucsd.edu Responsible party: National Institute of Allergy and Infectious Diseases (NIAID)
Notes	Location: International Center for Diarrheal Disease Research Bangladesh - Parasitology, Dhaka, Bangladesh Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) Estimated study completion date: 31 May 2019

Pfizer 2016

Trial name or title	Drug use investigation of paromomycin
Methods	Prospective cohort study

Pfizer 2016 *(Continued)*

Participants	200 participants 15 to 99 years old with intestinal amoebiasis
Interventions	Ameparomo (paromomycin) capsules 250 mg
Outcomes	Primary outcome: • Number of participants with adverse events (AEs) by seriousness and relationship to treatment [Time frame: maximum 10 days] Secondary outcome: • Number of participants with clinical response of cure [time frame: maximum 3 months]
Starting date	October 2015
Contact information	Study director: Pfizer CT.gov Call Center
Notes	Location: not specified Sponsor: Pfizer Estmated completion date: February 2019

AE: adverse event; *E histolytica: Entamoeba histolytica;* EIA: enzyme immunoassay; qPCR: quantitative polymerase chain reaction.

DATA AND ANALYSES

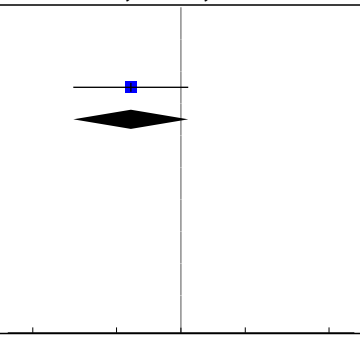
Comparison 1. Alternative drug versus metronidazole

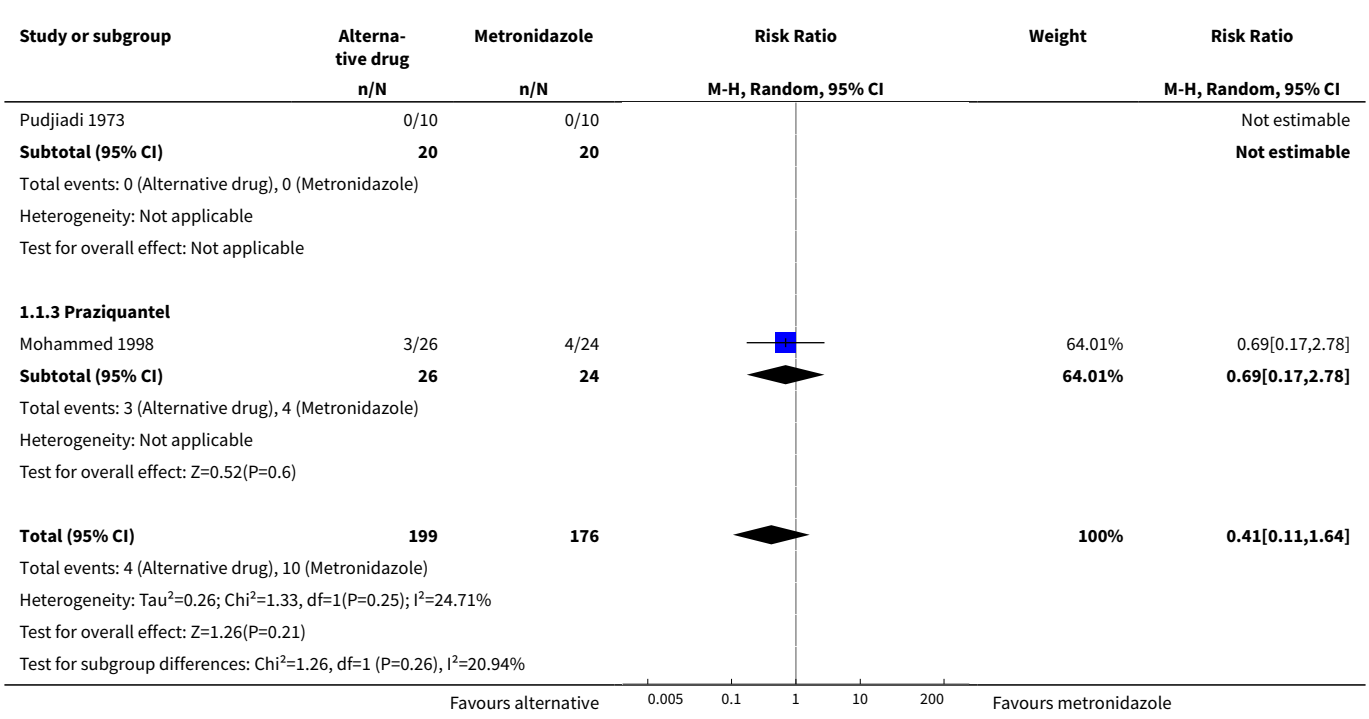
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	5	375	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.11, 1.64]
1.1 Tinidazole	2	285	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.30]
1.2 Ornidazole	2	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Praziquantel	1	50	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.17, 2.78]
2 Clinical failure: 15 to 60 days after end of treatment	12	679	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.21, 0.73]
2.1 Tinidazole	8	477	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.15, 0.51]
2.2 Ornidazole	2	118	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.89]
2.3 Panidazole	1	44	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Satranidazole (GO 10213)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.40, 1.60]
3 Parasitological failure: 1 to 14 days after end of treatment	6	419	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.85, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Tinidazole	2	285	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.58, 1.74]
3.2 Ornidazole	2	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Praziquantel	1	50	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.17, 2.78]
3.4 Secnidazole	1	44	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.12]
4 Parasitological failure: 15 to 60 days after end of treatment	13	768	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.37, 1.43]
4.1 Tinidazole	9	507	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.25, 1.64]
4.2 Ornidazole	2	135	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.41]
4.3 Panidazole	1	86	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.81, 3.60]
4.4 Satranidazole (GO 10213)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.72]
5 Relapse (ornidazole)	2	135	Risk Ratio (M-H, Random, 95% CI)	4.74 [1.07, 20.99]
6 Adverse events	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Tinidazole	8	477	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.92]
6.2 Ornidazole	3	155	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.73]
6.3 Satranidazole (GO 10213)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.27, 1.88]
6.4 Panidazole	1	100	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.87, 1.45]

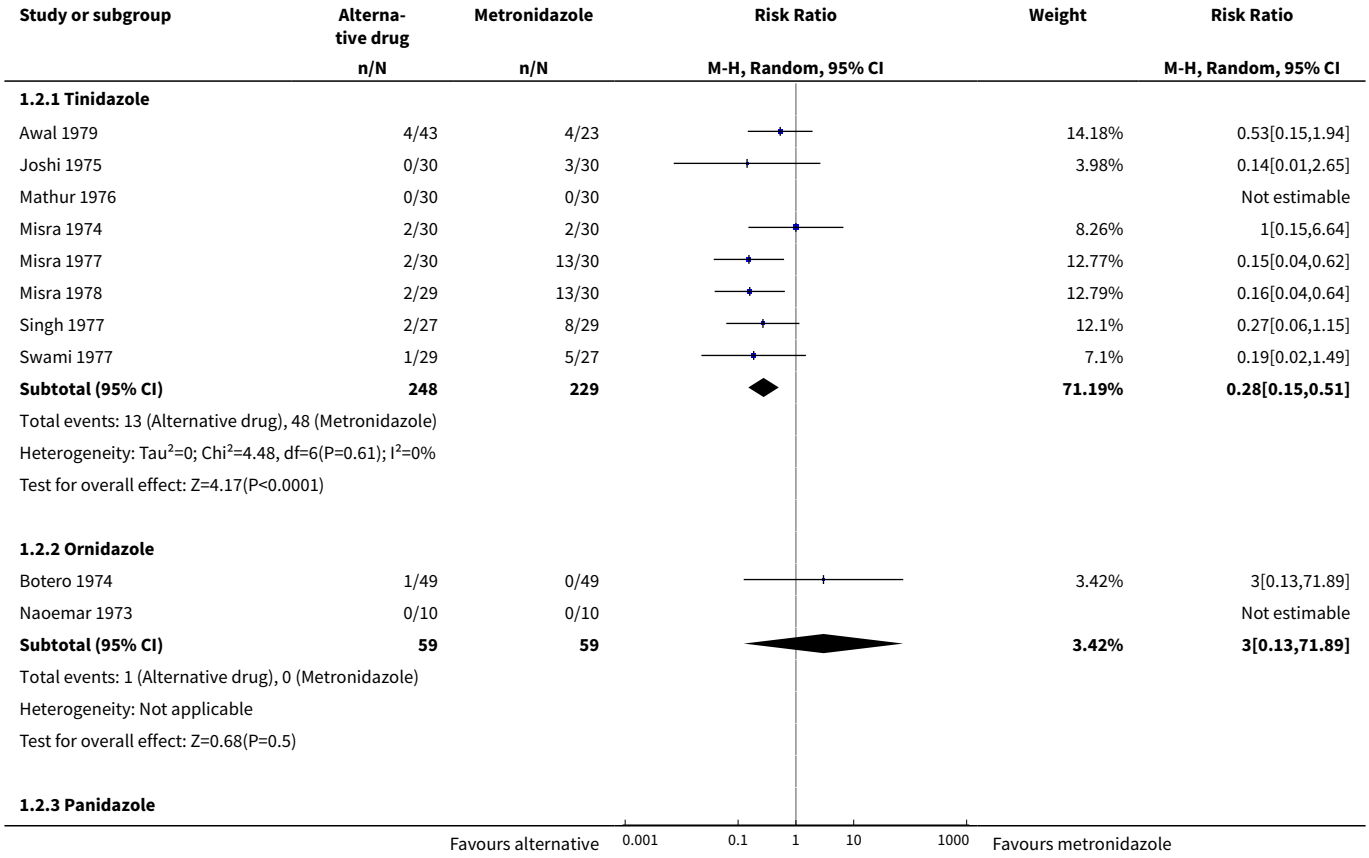
Analysis 1.1. Comparison 1 Alternative drug versus metronidazole, Outcome 1 Clinical failure: 1 to 14 days after end of treatment.

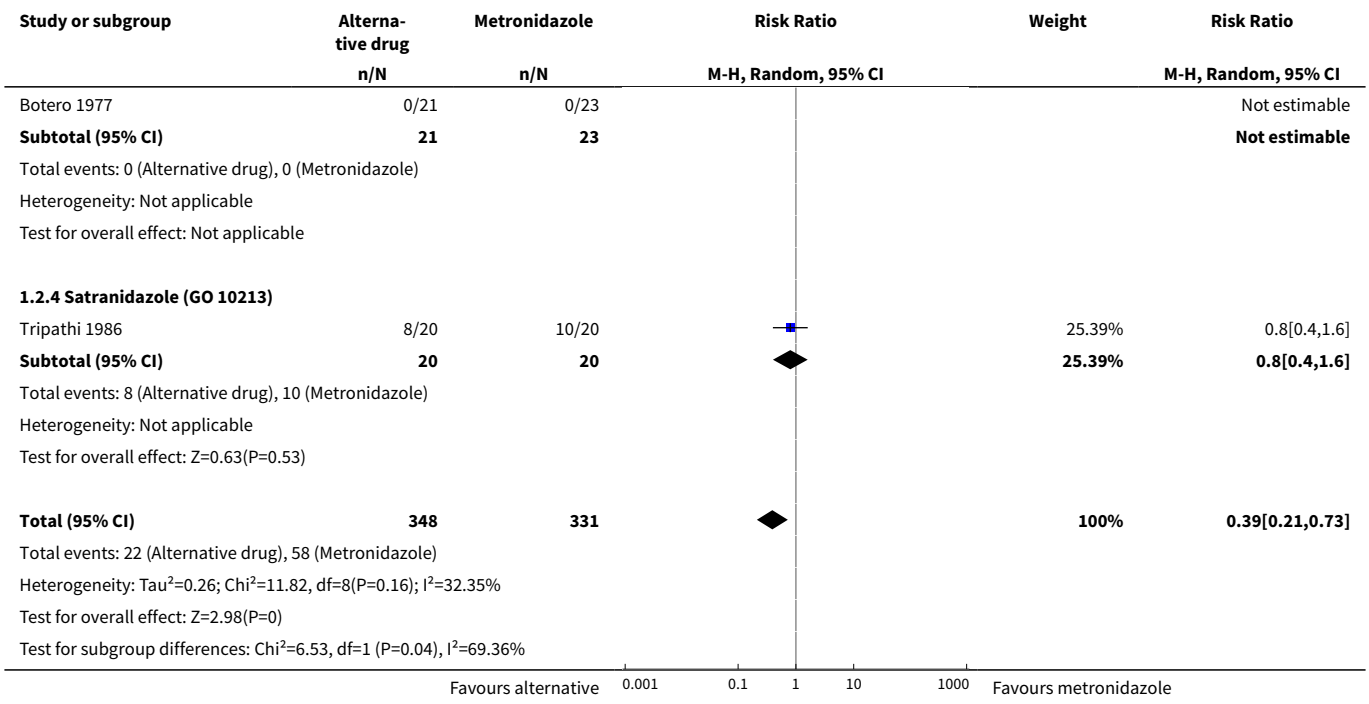
Study or subgroup	Alternative drug n/N	Metronidazole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Tinidazole					
Chunge 1989	0/123	0/102			Not estimable
Joshi 1975	1/30	6/30		35.99%	0.17[0.02,1.3]
Subtotal (95% CI)	**153**	**132**		**35.99%**	**0.17[0.02,1.3]**
Total events: 1 (Alternative drug), 6 (Metronidazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
1.1.2 Ornidazole					
Naoemar 1973	0/10	0/10			Not estimable



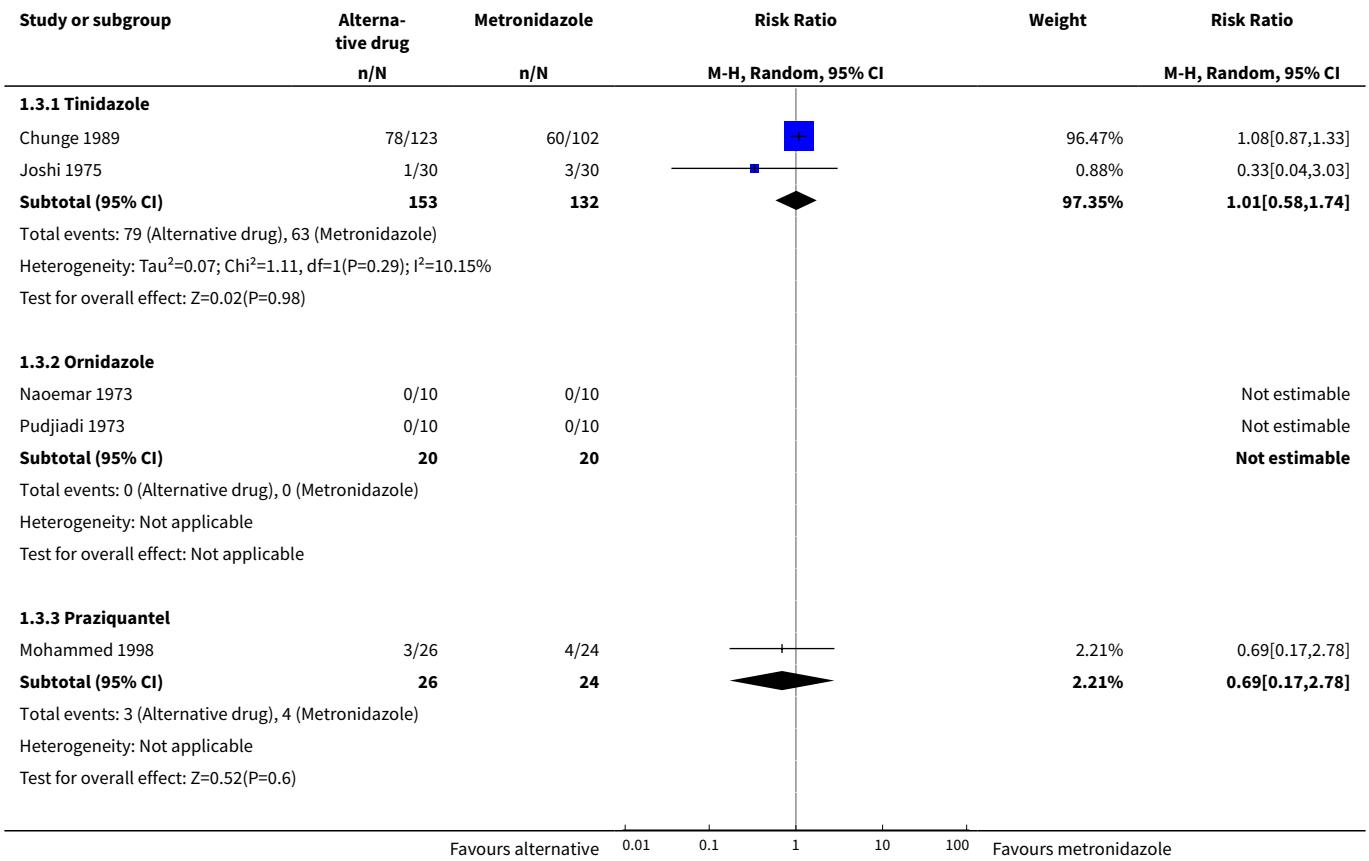


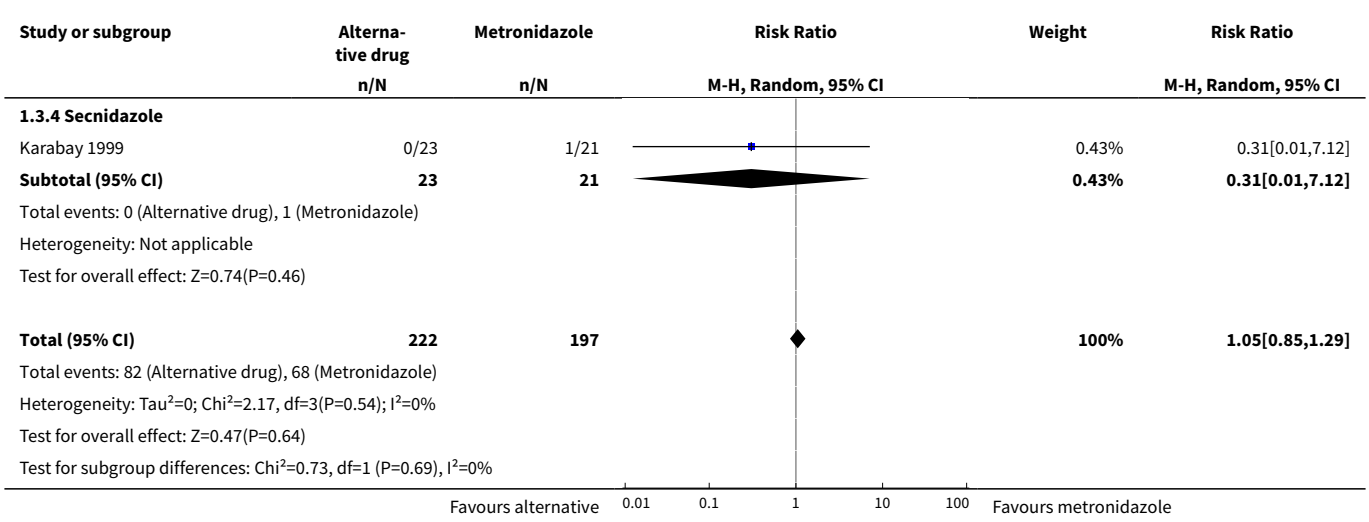
Analysis 1.2. Comparison 1 Alternative drug versus metronidazole, Outcome 2 Clinical failure: 15 to 60 days after end of treatment.



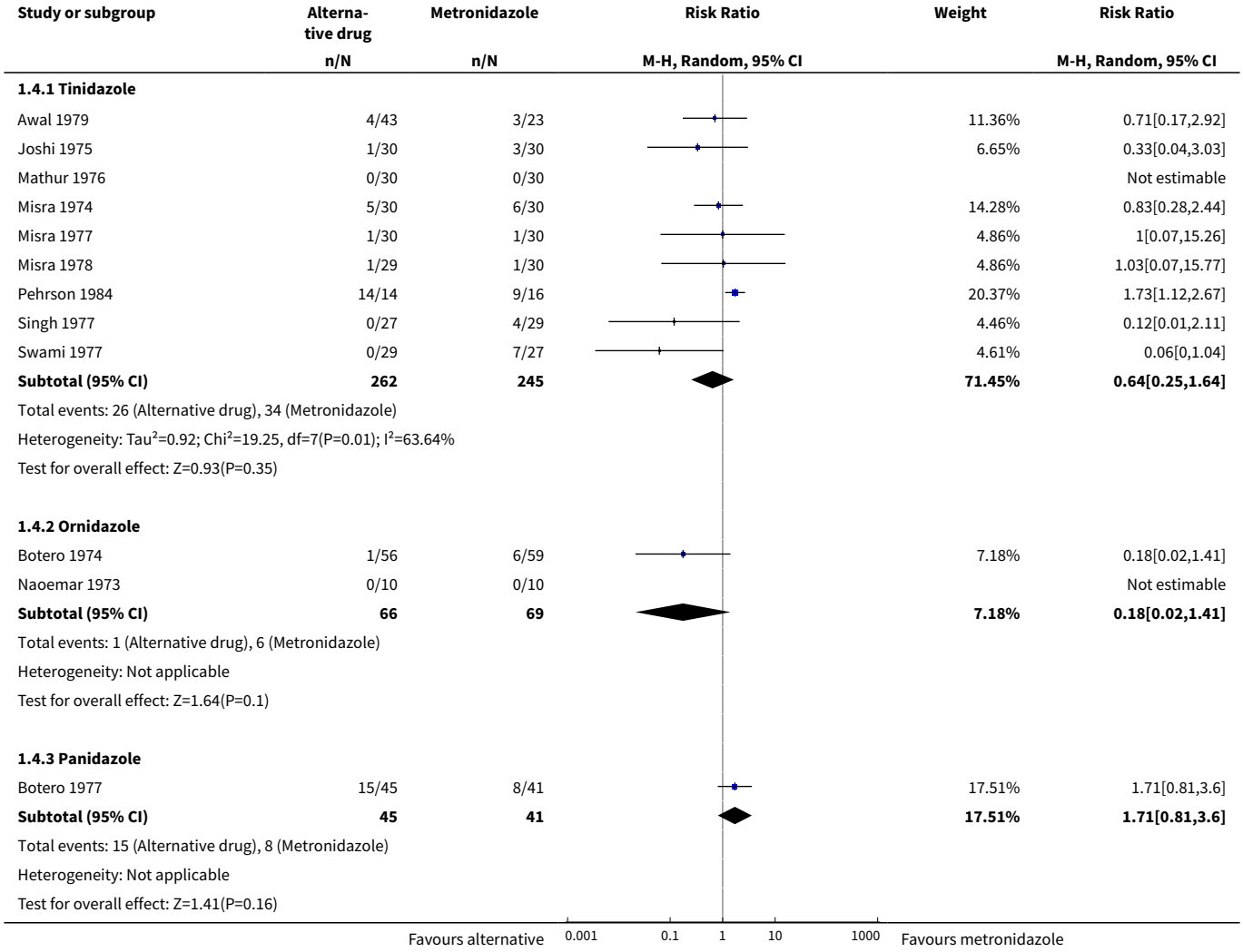


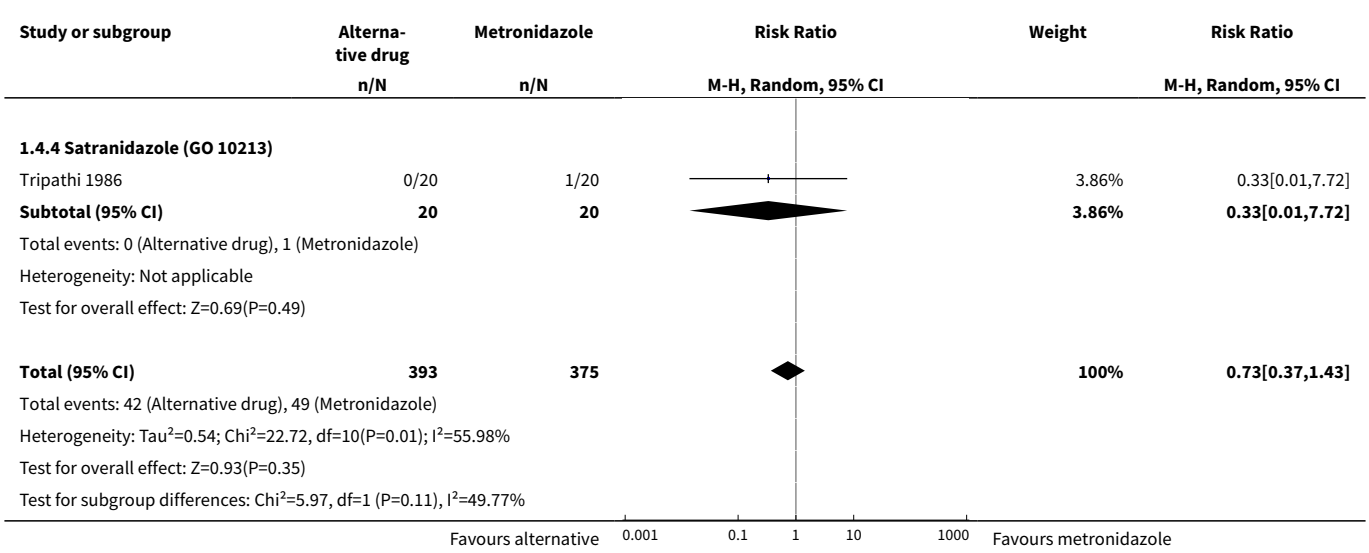
Analysis 1.3. Comparison 1 Alternative drug versus metronidazole, Outcome 3 Parasitological failure: 1 to 14 days after end of treatment.



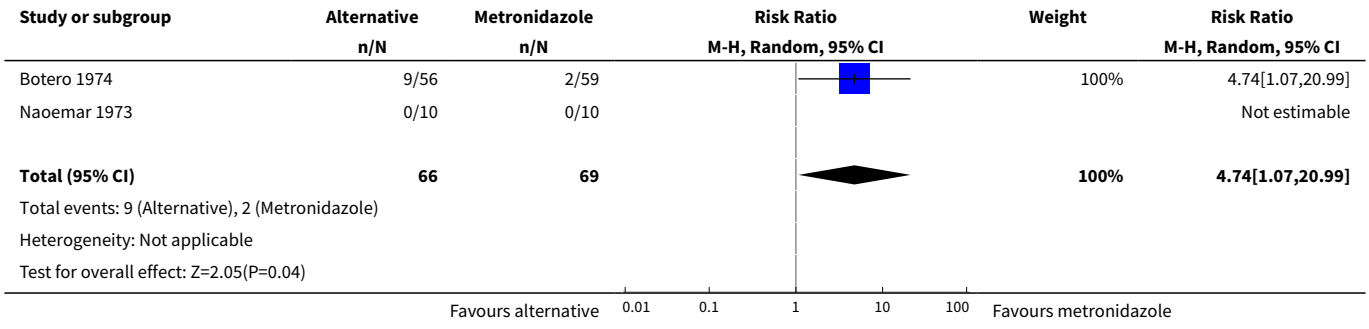


Analysis 1.4. Comparison 1 Alternative drug versus metronidazole, Outcome 4 Parasitological failure: 15 to 60 days after end of treatment.

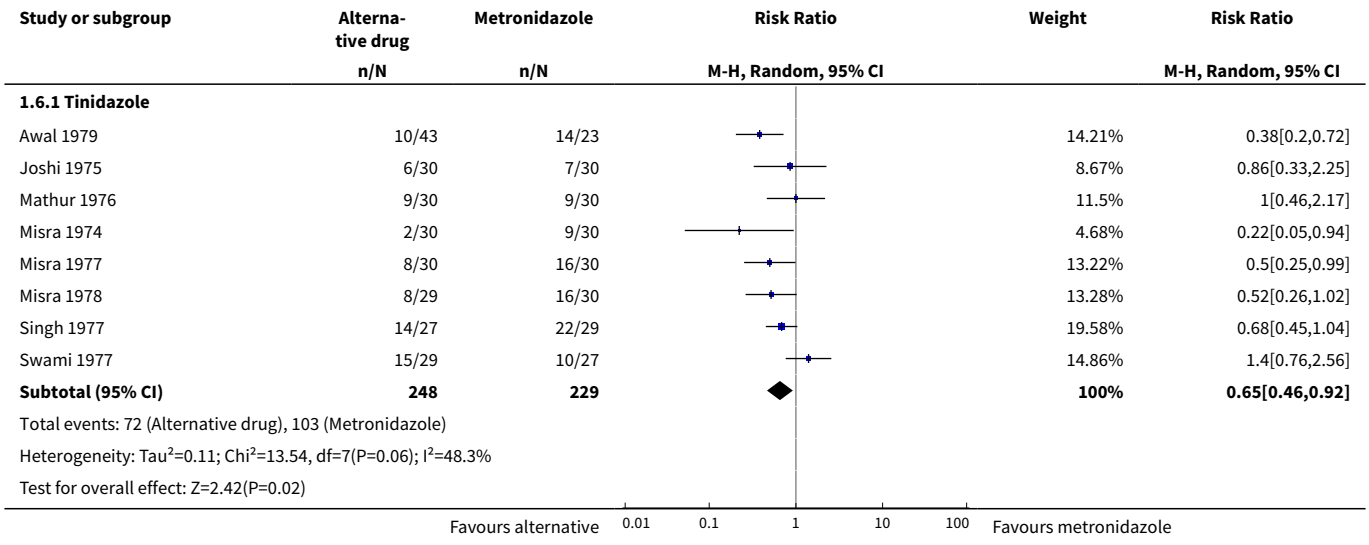


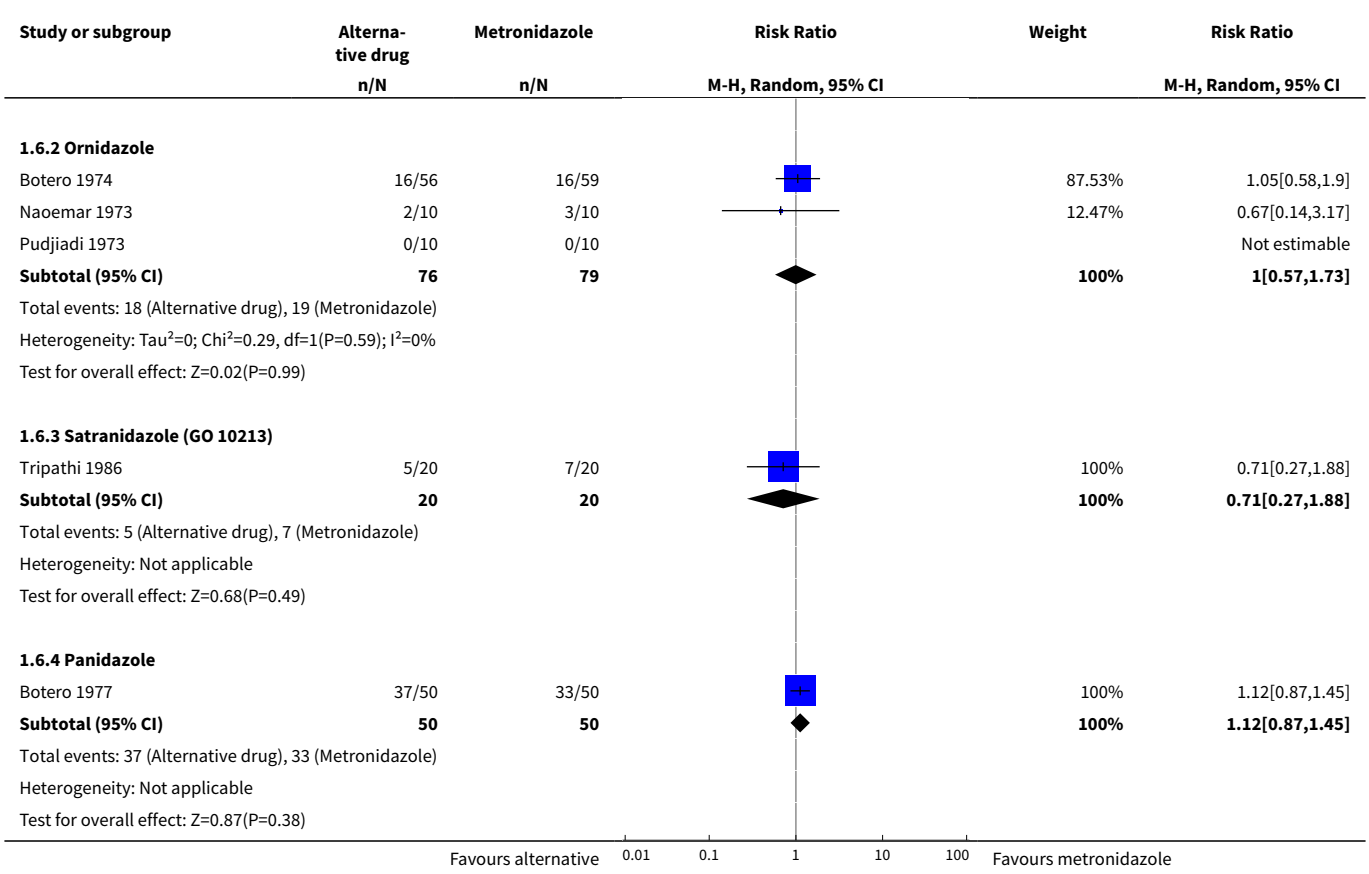


Analysis 1.5. Comparison 1 Alternative drug versus metronidazole, Outcome 5 Relapse (ornidazole).



Analysis 1.6. Comparison 1 Alternative drug versus metronidazole, Outcome 6 Adverse events.





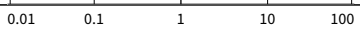
Comparison 2. Any antiamoebic drug versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	3	193	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.57]
1.1 Quinfamide	1	40	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.21, 0.60]
1.2 Nitazoxanide	2	153	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.06, 0.81]
2 Parasitological failure: 1 to 14 days after end of treatment	4	630	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.22, 0.50]
2.1 Quinfamide	1	96	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.19, 0.47]
2.2 Nitazoxanide	2	167	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.05, 1.27]
2.3 10 different drugs belonging to 6 drug classes	1	367	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.53]
3 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Quinfamide	1	96	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.22, 4.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Nitazoxanide	1	89	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.41, 4.43]
3.3 10 different drugs belonging to 6 drug classes	1	367	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.97, 4.88]

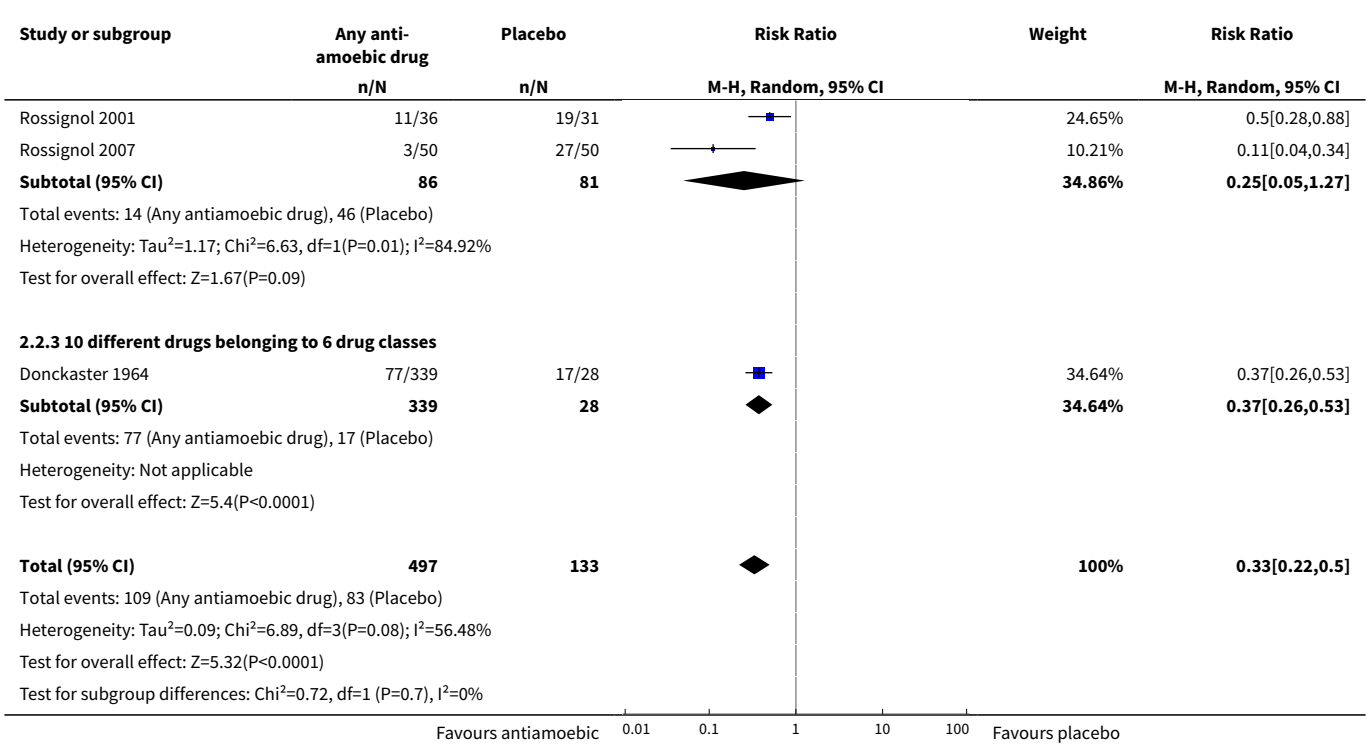
Analysis 2.1. Comparison 2 Any antiamoebic drug versus placebo, Outcome 1 Clinical failure: 1 to 14 days after end of treatment.

Study or subgroup	Any antiamoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Quinfamide					
Huggins 1982	9/27	13/13		43.12%	0.35[0.21,0.6]
Subtotal (95% CI)	**27**	**13**		**43.12%**	**0.35[0.21,0.6]**
Total events: 9 (Any antiamoebic drug), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.89(P=0)					
2.1.2 Nitazoxanide					
Rossignol 2001	6/30	12/23		32.85%	0.38[0.17,0.87]
Rossignol 2007	3/50	28/50		24.02%	0.11[0.03,0.33]
Subtotal (95% CI)	**80**	**73**		**56.88%**	**0.21[0.06,0.81]**
Total events: 9 (Any antiamoebic drug), 40 (Placebo)					
Heterogeneity: Tau^2=0.67; Chi^2=3.68, df=1(P=0.06); I^2=72.82%					
Test for overall effect: Z=2.28(P=0.02)					
Total (95% CI)	**107**	**86**		**100%**	**0.27[0.13,0.57]**
Total events: 18 (Any antiamoebic drug), 53 (Placebo)					
Heterogeneity: Tau^2=0.25; Chi^2=5.09, df=2(P=0.08); I^2=60.72%					
Test for overall effect: Z=3.49(P=0)					
Test for subgroup differences: Chi^2=0.47, df=1 (P=0.49), I^2=0%					

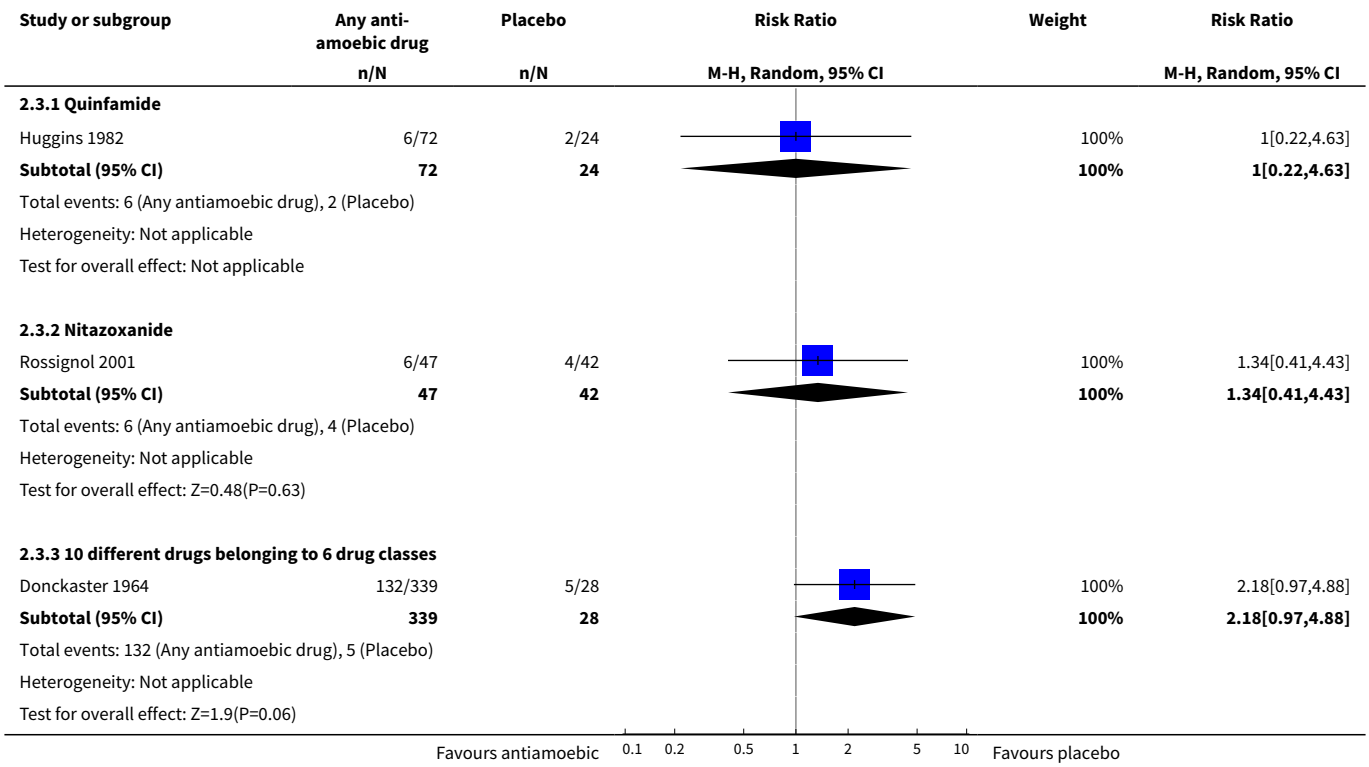


Analysis 2.2. Comparison 2 Any antiamoebic drug versus placebo, Outcome 2 Parasitological failure: 1 to 14 days after end of treatment.

Study or subgroup	Any antiamoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Quinfamide					
Huggins 1982	18/72	20/24		30.5%	0.3[0.19,0.47]
Subtotal (95% CI)	**72**	**24**		**30.5%**	**0.3[0.19,0.47]**
Total events: 18 (Any antiamoebic drug), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.38(P<0.0001)					
2.2.2 Nitazoxanide					



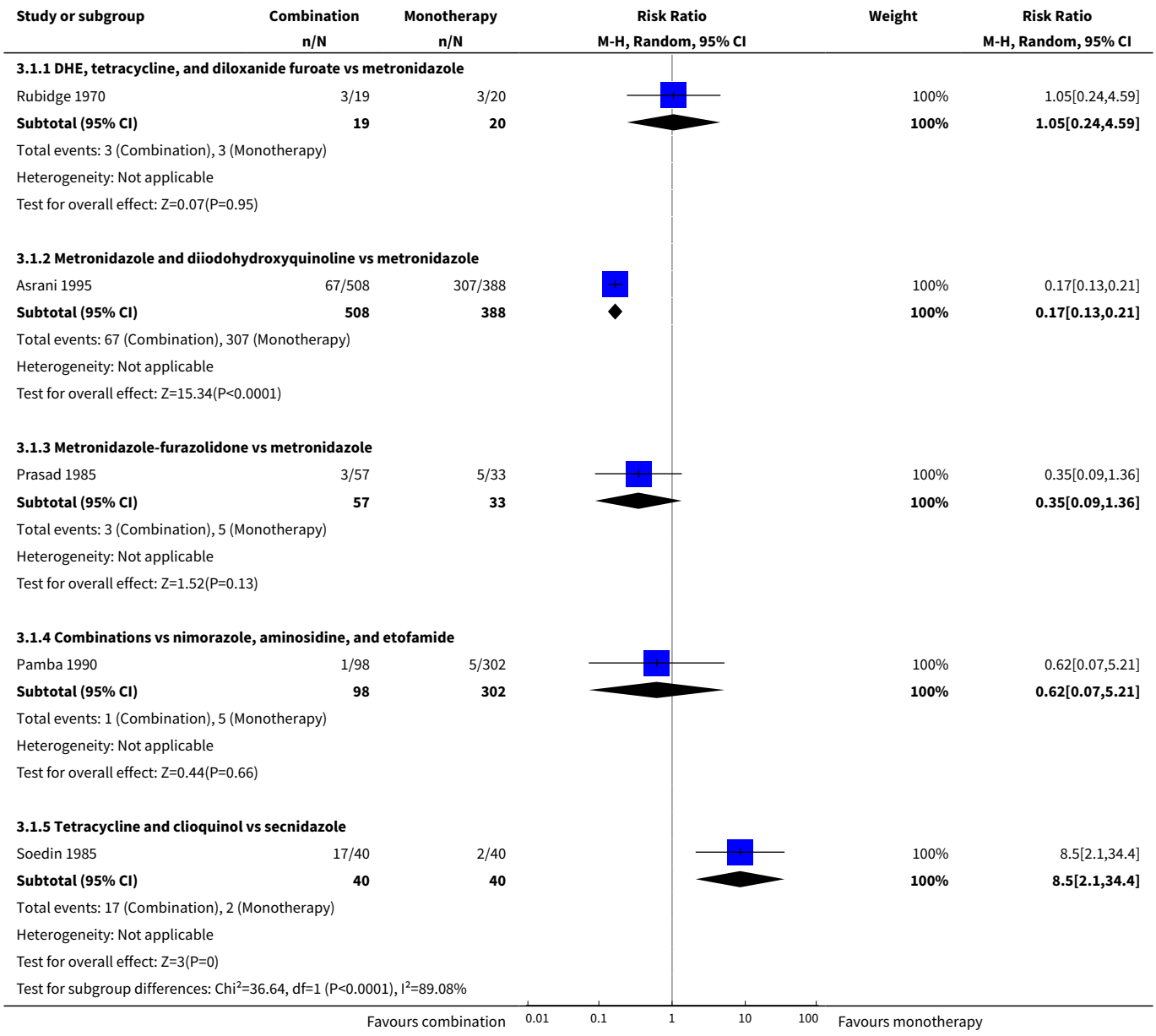
Analysis 2.3. Comparison 2 Any antiamoebic drug versus placebo, Outcome 3 Adverse events.



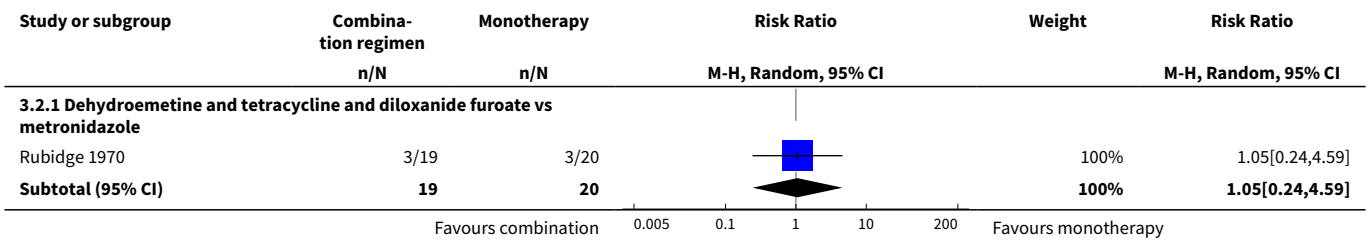
Comparison 3. Combination regimen versus monotherapy

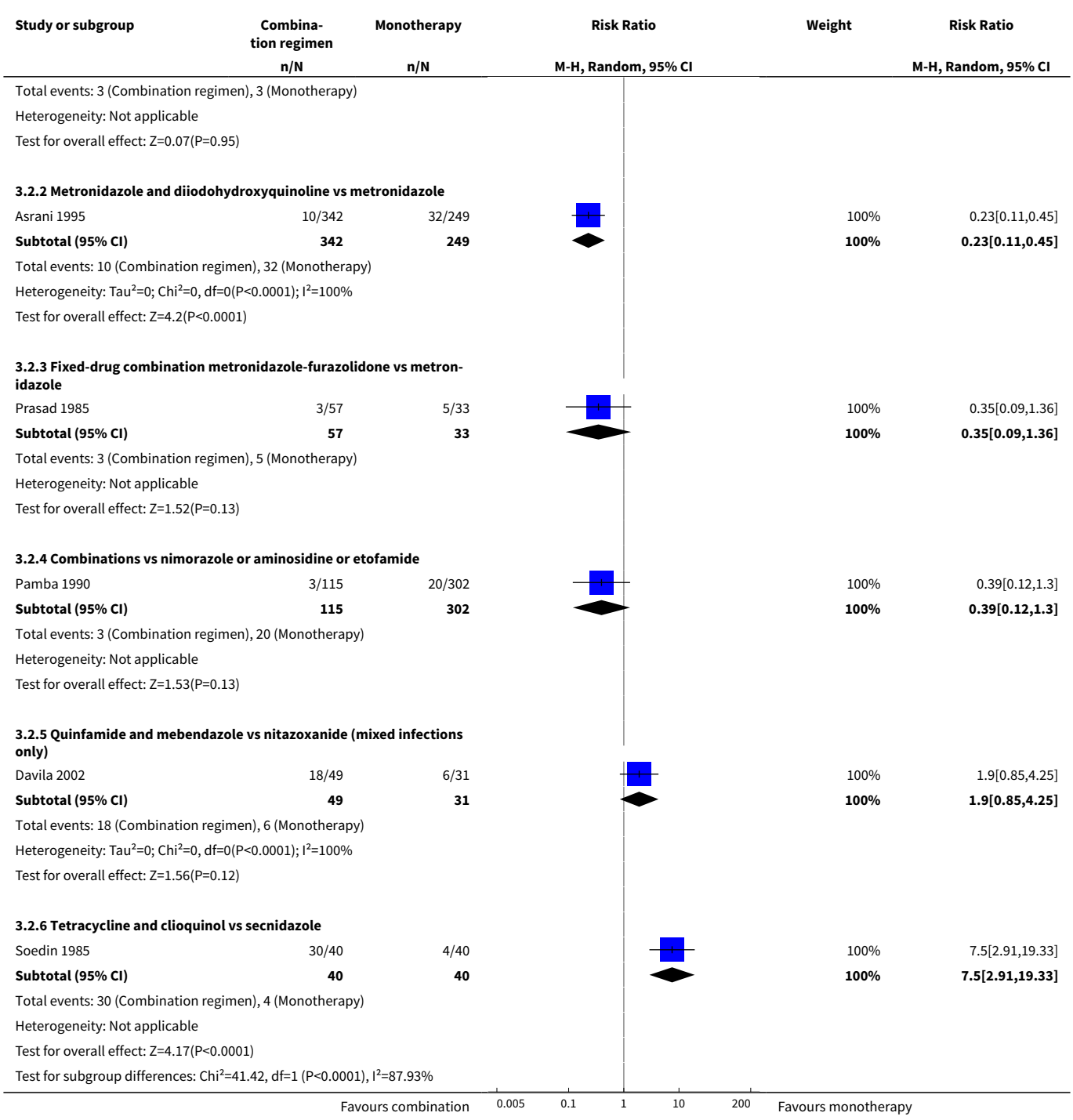
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 DHE, tetracycline, and diloxanide furoate vs metronidazole	1	39	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.24, 4.59]
1.2 Metronidazole and diiodohydroxyquinoline vs metronidazole	1	896	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.13, 0.21]
1.3 Metronidazole-furazolidone vs metronidazole	1	90	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.09, 1.36]
1.4 Combinations vs nimorazole, aminosidine, and etofamide	1	400	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.07, 5.21]
1.5 Tetracycline and clioquinol vs secnidazole	1	80	Risk Ratio (M-H, Random, 95% CI)	8.5 [2.10, 34.40]
2 Parasitological failure: 1 to 14 days after end of treatment	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Dehydroemetine and tetracycline and diloxanide furoate vs metronidazole	1	39	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.24, 4.59]
2.2 Metronidazole and diiodohydroxyquinoline vs metronidazole	1	591	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.11, 0.45]
2.3 Fixed-drug combination metronidazole-furazolidone vs metronidazole	1	90	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.09, 1.36]
2.4 Combinations vs nimorazole or aminosidine or etofamide	1	417	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.30]
2.5 Quinfamide and mebendazole vs nitazoxanide (mixed infections only)	1	80	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.85, 4.25]
2.6 Tetracycline and clioquinol vs secnidazole	1	80	Risk Ratio (M-H, Random, 95% CI)	7.50 [2.91, 19.33]
3 Parasitological failure: 15 to 60 days after end of treatment	1	41	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.63]
4 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 DHE, tetracycline, and diloxanide furoate vs metronidazole	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Combination regimen versus monotherapy, Outcome 1 Clinical failure: 1 to 14 days after end of treatment.

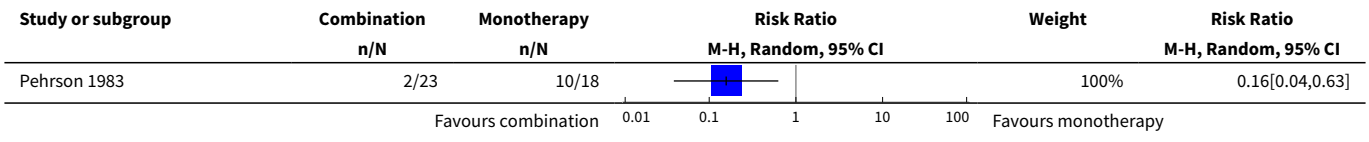


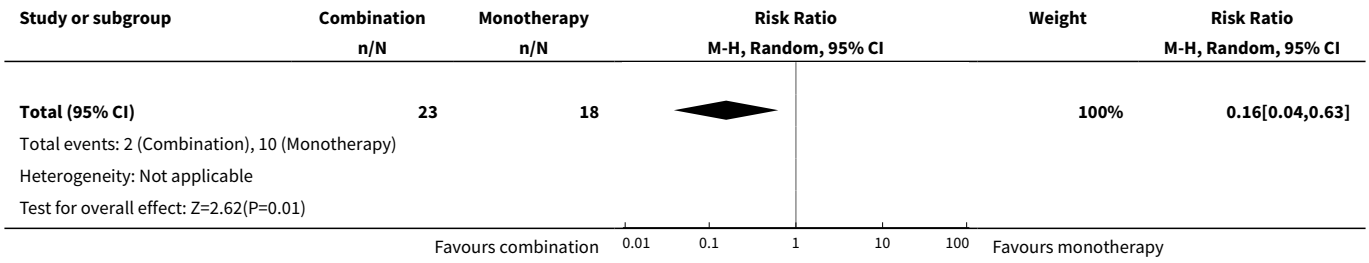
Analysis 3.2. Comparison 3 Combination regimen versus monotherapy, Outcome 2 Parasitological failure: 1 to 14 days after end of treatment.



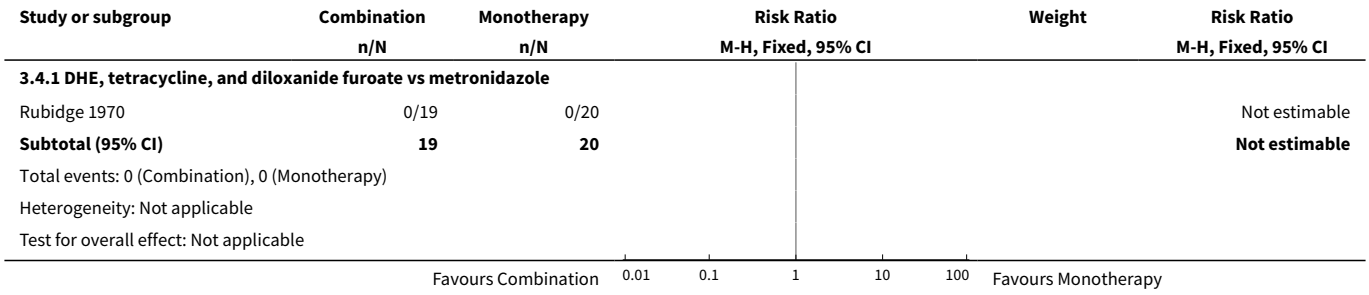


Analysis 3.3. Comparison 3 Combination regimen versus monotherapy, Outcome 3 Parasitological failure: 15 to 60 days after end of treatment.





Analysis 3.4. Comparison 3 Combination regimen versus monotherapy, Outcome 4 Adverse events.

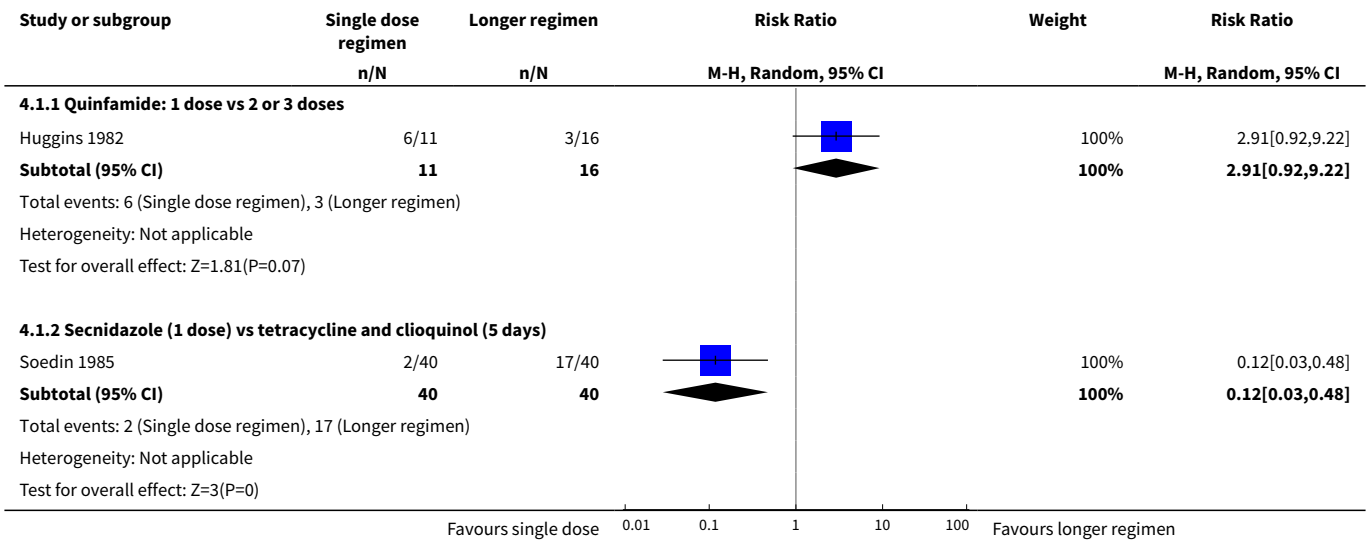


Comparison 4. Single-dose regimen versus longer regimen

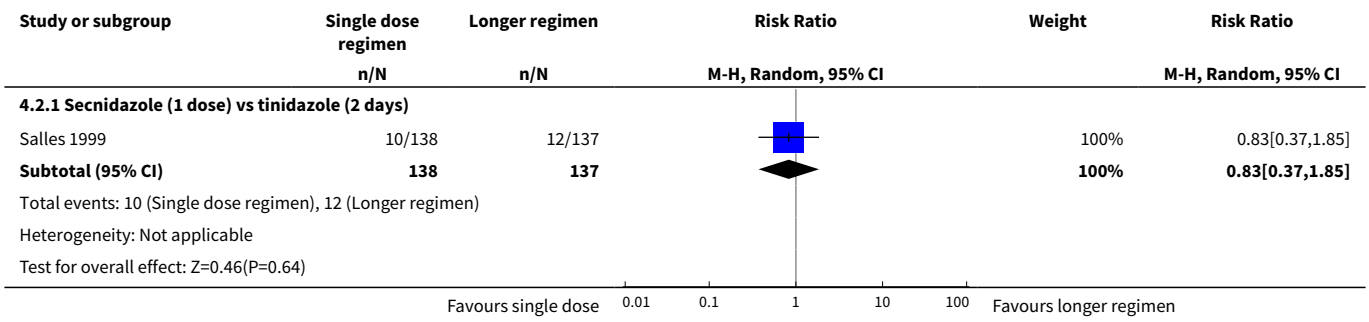
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Quinfamide: 1 dose vs 2 or 3 doses	1	27	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.92, 9.22]
1.2 Secnidazole (1 dose) vs tetracycline and clioquinol (5 days)	1	80	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.03, 0.48]
2 Clinical failure: 15 to 60 days after end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Secnidazole (1 dose) vs tinidazole (2 days)	1	275	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.37, 1.85]
3 Parasitological failure: 1 to 14 days after end of treatment	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Quinfamide (1 dose) vs nitazoxanide (3 days)	1	25	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.37, 33.98]
3.2 Quinfamide: 1 dose vs 2 or 3 doses	1	72	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.91, 4.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Secnidazole (1 dose) vs metronidazole (10 days)	1	44	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.12]
3.4 Secnidazole (1 dose) vs tetracycline and clioquinol (5 days)	1	80	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.05, 0.34]
4 Parasitological failure: 15 to 60 days after end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Secnidazole (1 dose) vs tinidazole (2 days)	1	300	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.43, 0.88]
5 Adverse events	2	375	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.87]
5.1 Quinfamide: 1 dose vs 2 or 3 doses	1	72	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.57]
5.2 Secnidazole (1 dose) vs tinidazole (2 days)	1	303	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.37, 1.56]

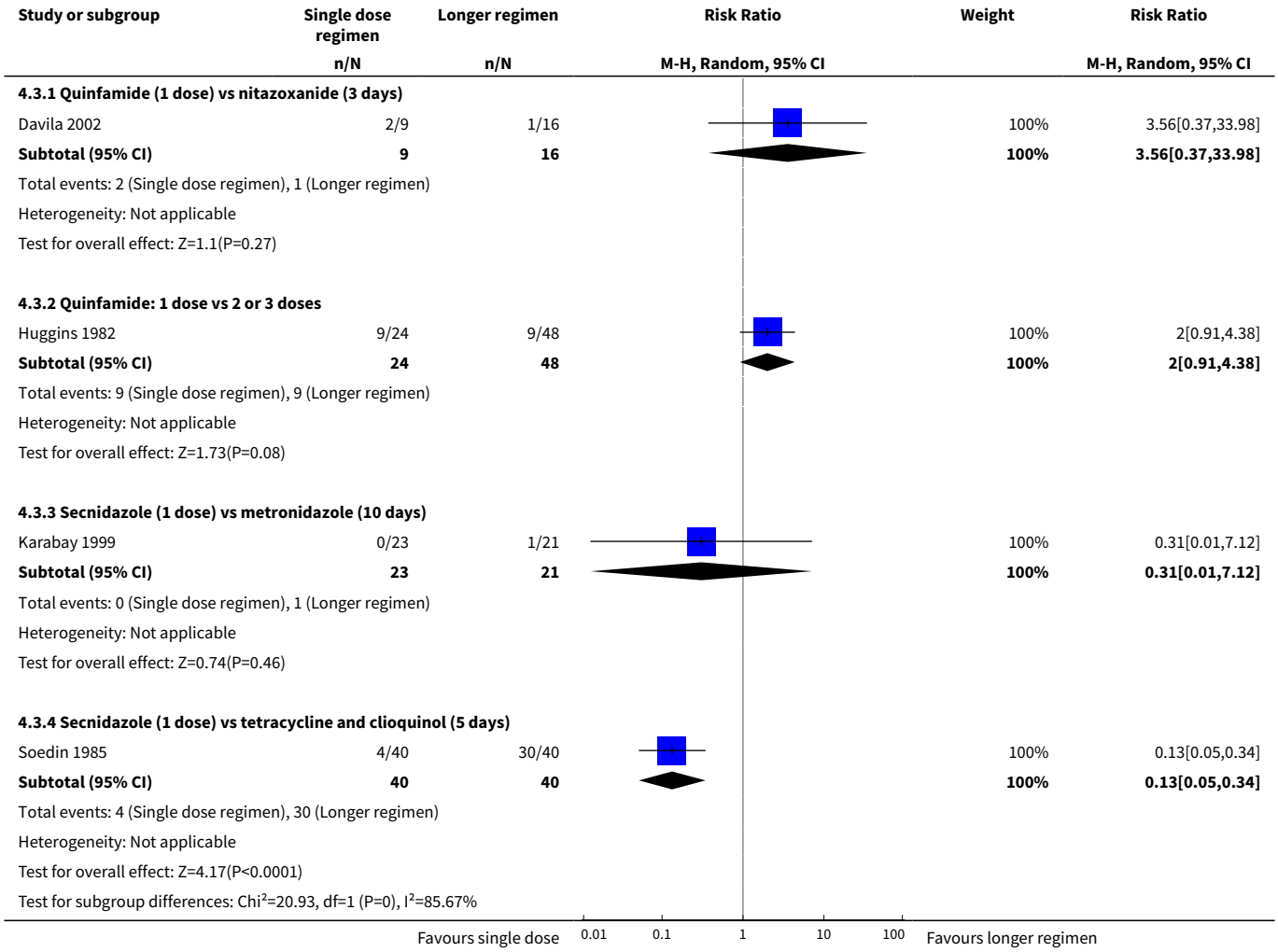
Analysis 4.1. Comparison 4 Single-dose regimen versus longer regimen, Outcome 1 Clinical failure: 1 to 14 days after end of treatment.



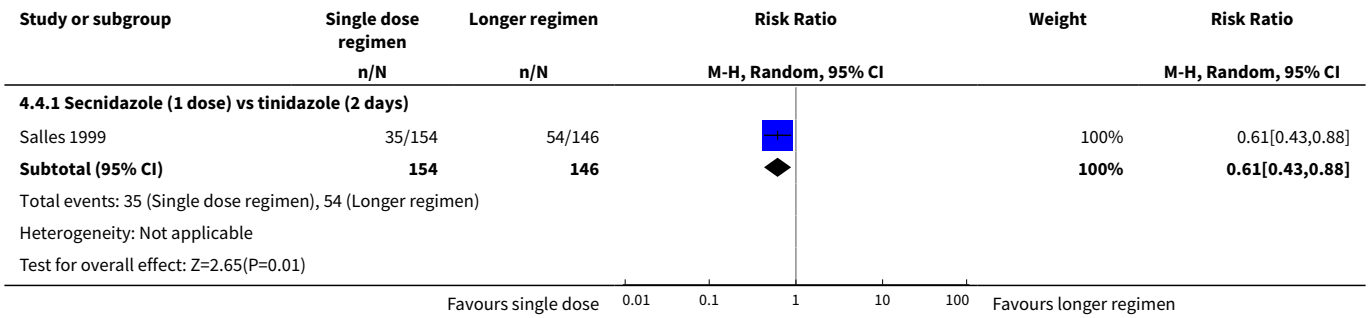
Analysis 4.2. Comparison 4 Single-dose regimen versus longer regimen, Outcome 2 Clinical failure: 15 to 60 days after end of treatment.



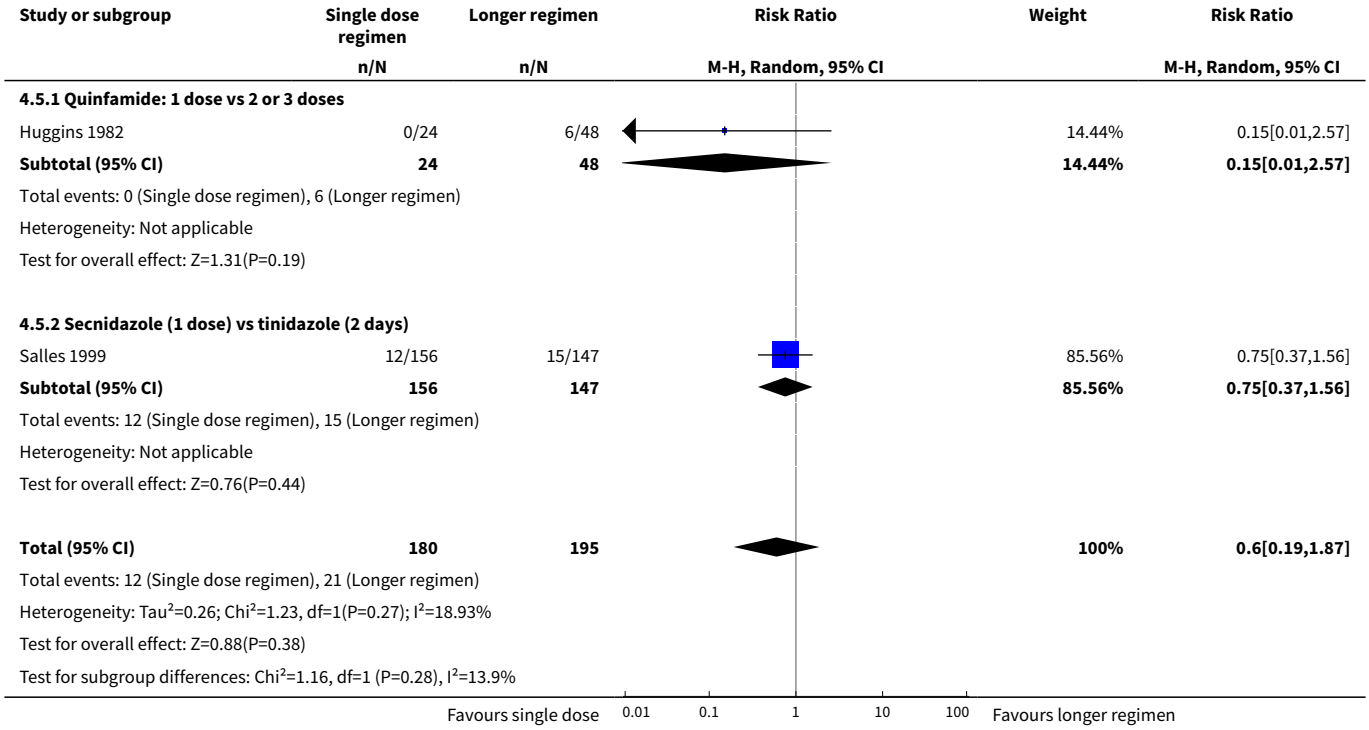
Analysis 4.3. Comparison 4 Single-dose regimen versus longer regimen, Outcome 3 Parasitological failure: 1 to 14 days after end of treatment.



Analysis 4.4. Comparison 4 Single-dose regimen versus longer regimen, Outcome 4 Parasitological failure: 15 to 60 days after end of treatment.



Analysis 4.5. Comparison 4 Single-dose regimen versus longer regimen, Outcome 5 Adverse events.



Comparison 5. Other antiamoebic drug comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Ornidazole vs tinidazole	2	74	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.07, 4.41]

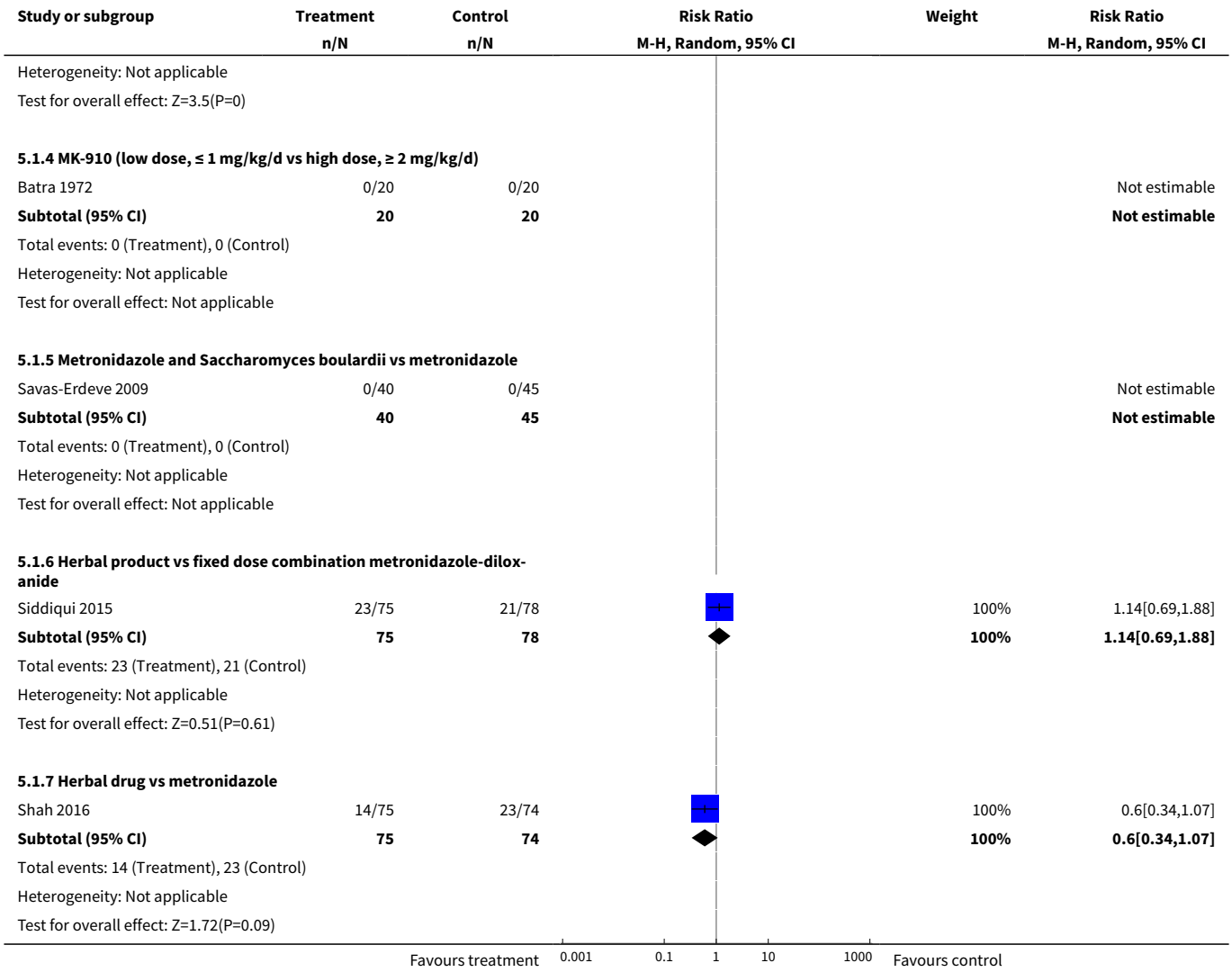
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Ornidazole vs secnidazole	1	102	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.17, 5.45]
1.3 Chlorhydroxyquinoline vs diiodohydroxyquinoline	1	100	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.53]
1.4 MK-910 (low dose, ≤ 1 mg/kg/d vs high dose, ≥ 2 mg/kg/d)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Metronidazole and *Saccharomyces boulardii* vs metronidazole	1	85	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Herbal product vs fixed dose combination metronidazole-diloxanide	1	153	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.69, 1.88]
1.7 Herbal drug vs metronidazole	1	149	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.07]
2 Parasitological failure: 1 to 14 days after end of treatment	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ornidazole vs tinidazole	2	74	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.11, 60.51]
2.2 Ornidazole vs secnidazole	1	102	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.45]
2.3 Chlorhydroxyquinoline vs diiodohydroxyquinoline	1	100	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.80]
2.4 MK-910 (low dose, ≤ 1 mg/kg/d vs high dose, ≥ 2 mg/kg/d)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.39, 2.58]
2.5 Quinfamide vs secnidazole	1	239	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.34, 0.96]
2.6 Quinfamide vs nitazoxanide (*Entamoeba* infection only)	1	25	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.37, 33.98]
2.7 Metronidazole and *Saccharomyces boulardii* vs metronidazole	1	85	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.20, 3.54]
2.8 Two fixed-drug combinations of diloxanide furoate and tetracycline with or without chloroquine	1	60	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.31, 1.12]
2.9 Herbal product vs fixed-dose combination metronidazole-diloxanide	1	153	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.67, 2.01]
2.10 Herbal drug vs metronidazole	1	184	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]
3 Parasitological failure: 15 to 60 days after end of treatment	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Quinfamide vs teclozan	1	37	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.08, 1.32]
3.2 Metronidazole and iodoquinol plus *Saccharomyces boulardii* vs metronidazole and iodoquinol	1	54	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.57]
3.3 Two fixed-drug combinations of diloxanide furoate and tetracycline with or without chloroquine	1	58	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.20, 0.96]
4 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Ornidazole vs tinidazole	1	35	Risk Ratio (M-H, Random, 95% CI)	2.84 [0.12, 65.34]
4.2 Quinfamide vs teclozan	1	40	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.41, 1.82]
4.3 MK-910 low dose vs high dose	1	40	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.26, 98.00]
4.4 Herbal vs fixed-drug combination metronidazole-diloxanide	1	153	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.09, 0.41]

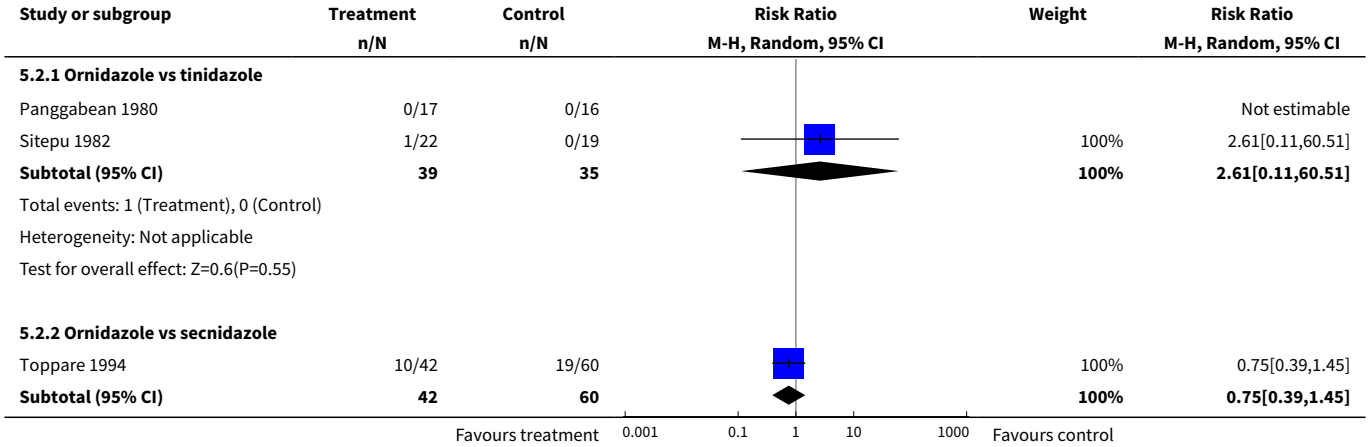
Analysis 5.1. Comparison 5 Other antiamoebic drug comparisons, Outcome 1 Clinical failure: 1 to 14 days after end of treatment.

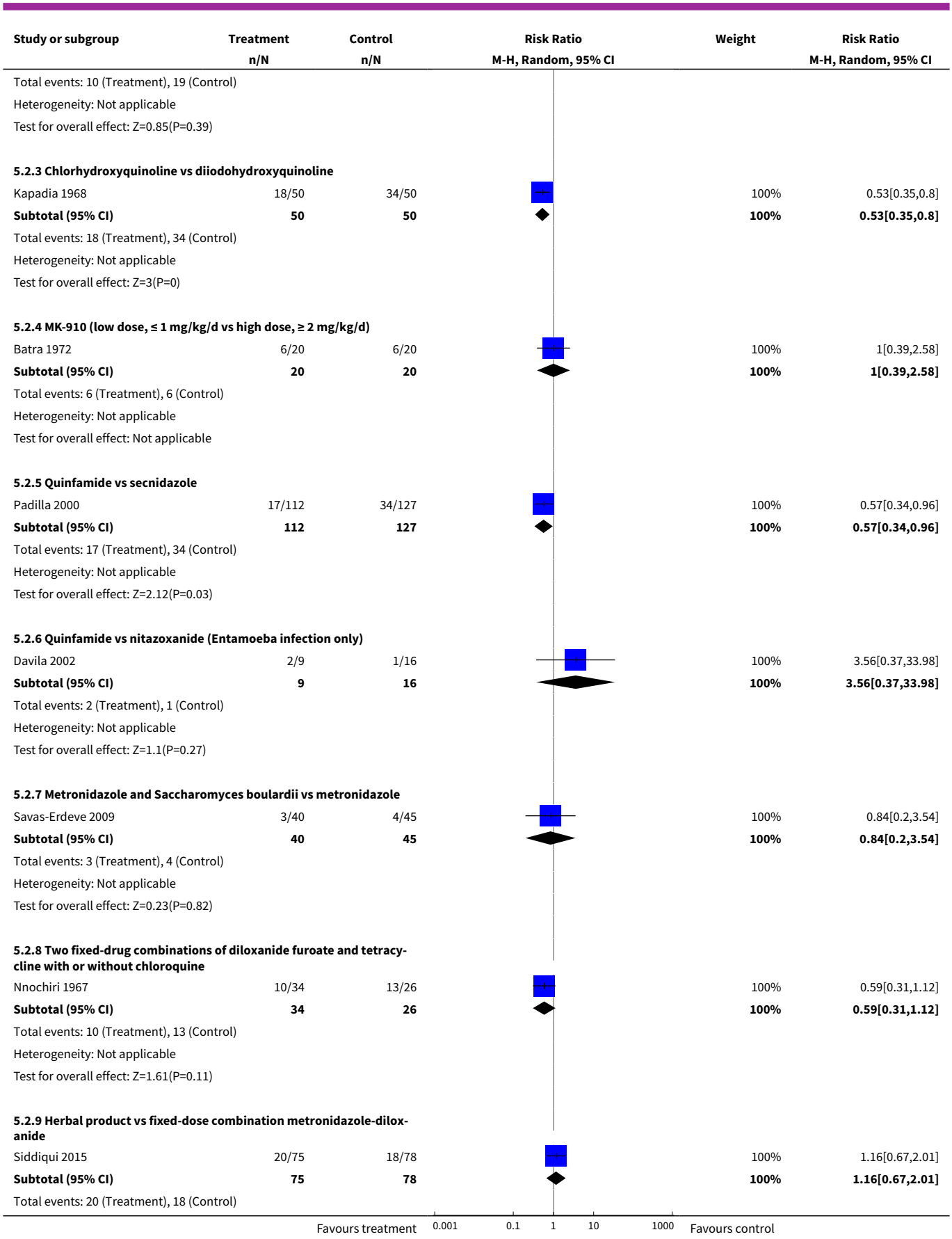
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Ornidazole vs tinidazole					
Panggabean 1980	1/17	1/16		57.8%	0.94[0.06,13.82]
Sitepu 1982	0/22	1/19		42.2%	0.29[0.01,6.72]
Subtotal (95% CI)	**39**	**35**		**100%**	**0.57[0.07,4.41]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
5.1.2 Ornidazole vs secnidazole					
Toppare 1994	2/42	3/60		100%	0.95[0.17,5.45]
Subtotal (95% CI)	**42**	**60**		**100%**	**0.95[0.17,5.45]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
5.1.3 Chlorhydroxyquinoline vs diiodohydroxyquinoline					
Kapadia 1968	6/50	25/50		100%	0.24[0.11,0.53]
Subtotal (95% CI)	**50**	**50**		**100%**	**0.24[0.11,0.53]**
Total events: 6 (Treatment), 25 (Control)					

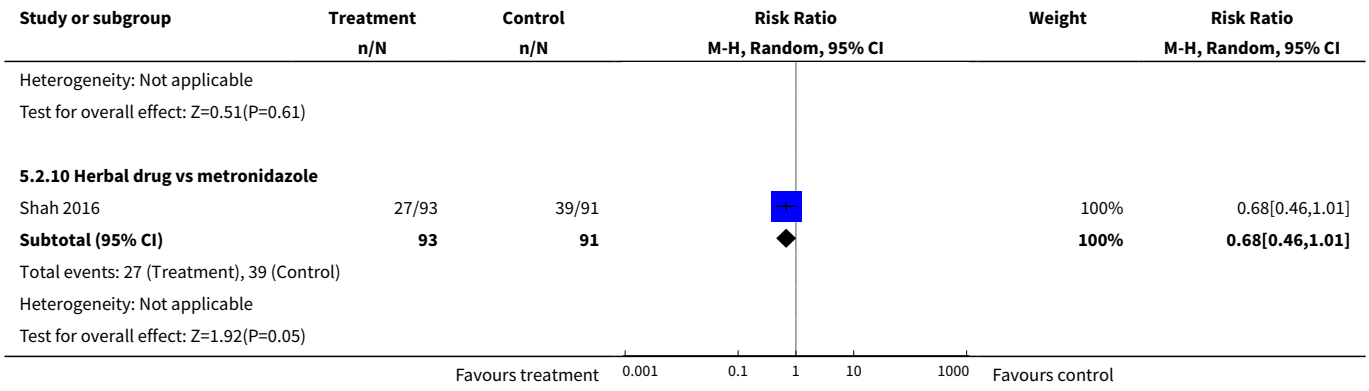
Favours treatment Favours control



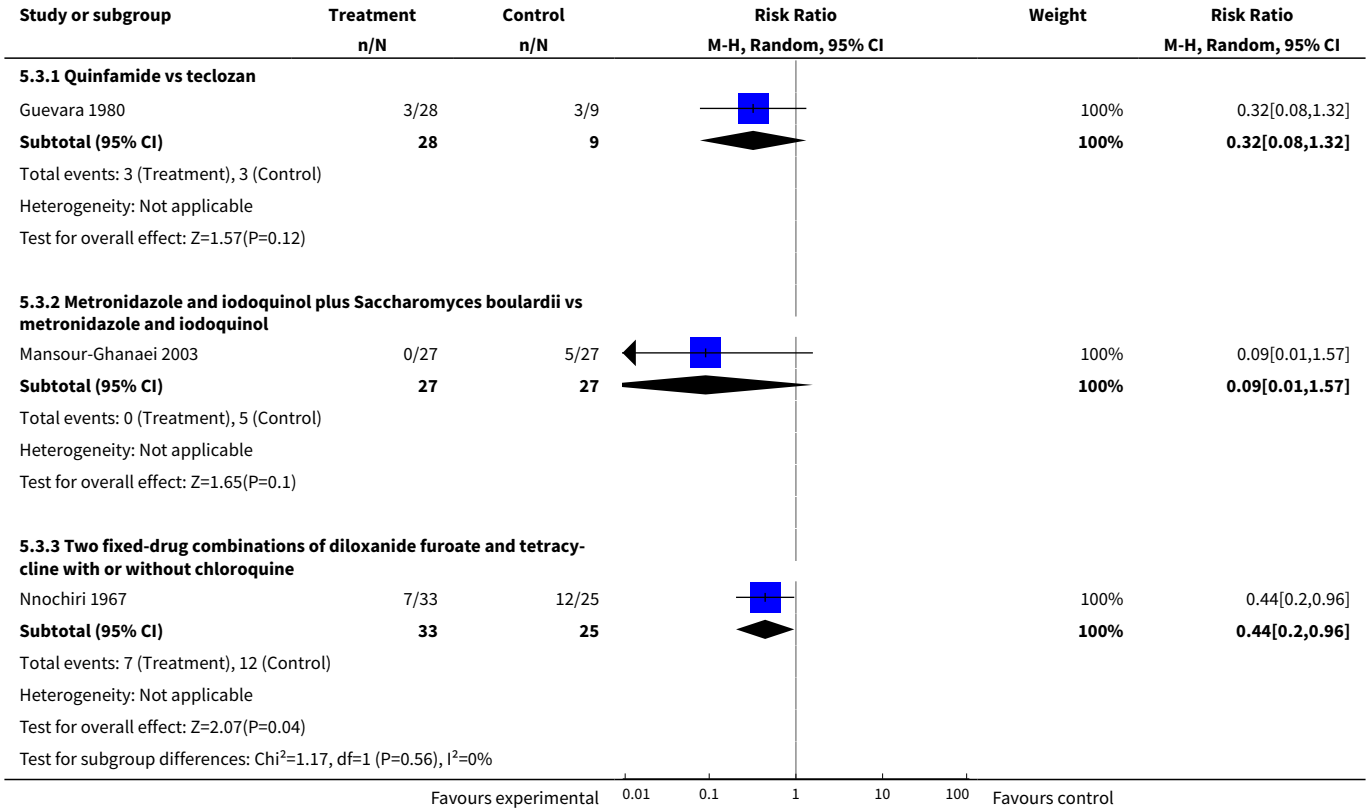
Analysis 5.2. Comparison 5 Other antiamoebic drug comparisons, Outcome 2 Parasitological failure: 1 to 14 days after end of treatment.



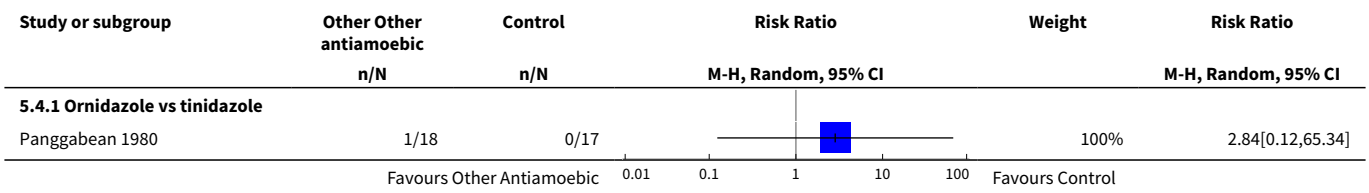


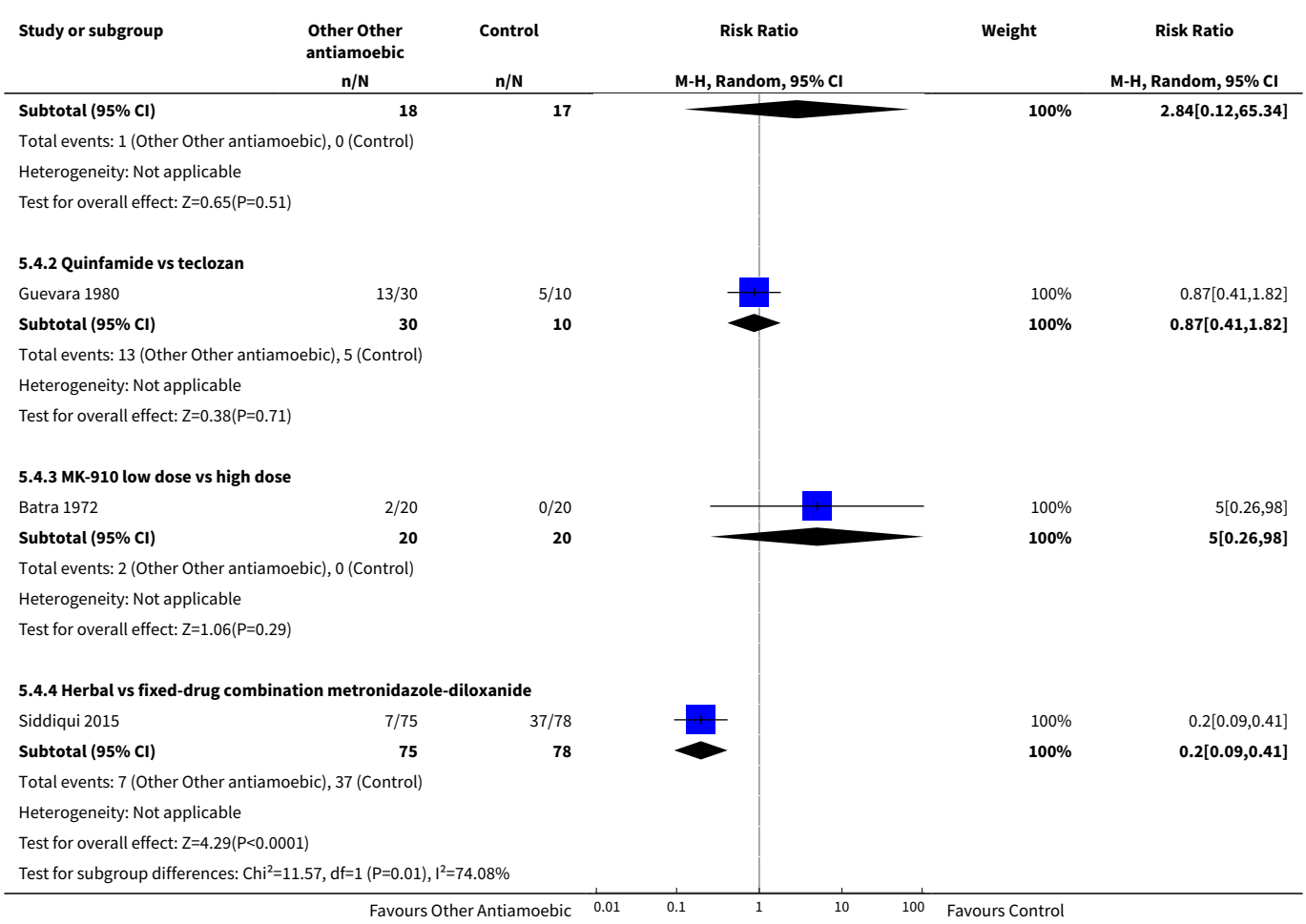


Analysis 5.3. Comparison 5 Other antiamoebic drug comparisons, Outcome 3 Parasitological failure: 15 to 60 days after end of treatment.



Analysis 5.4. Comparison 5 Other antiamoebic drug comparisons, Outcome 4 Adverse events.



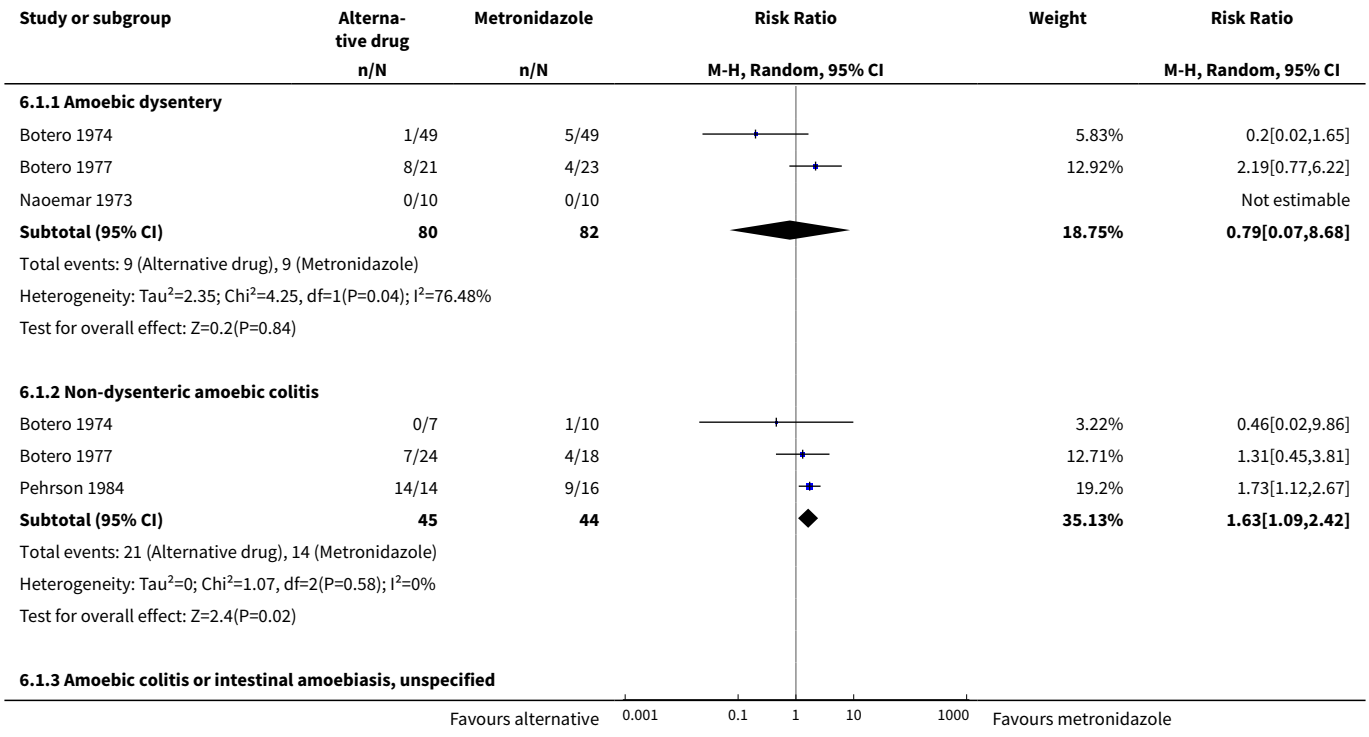


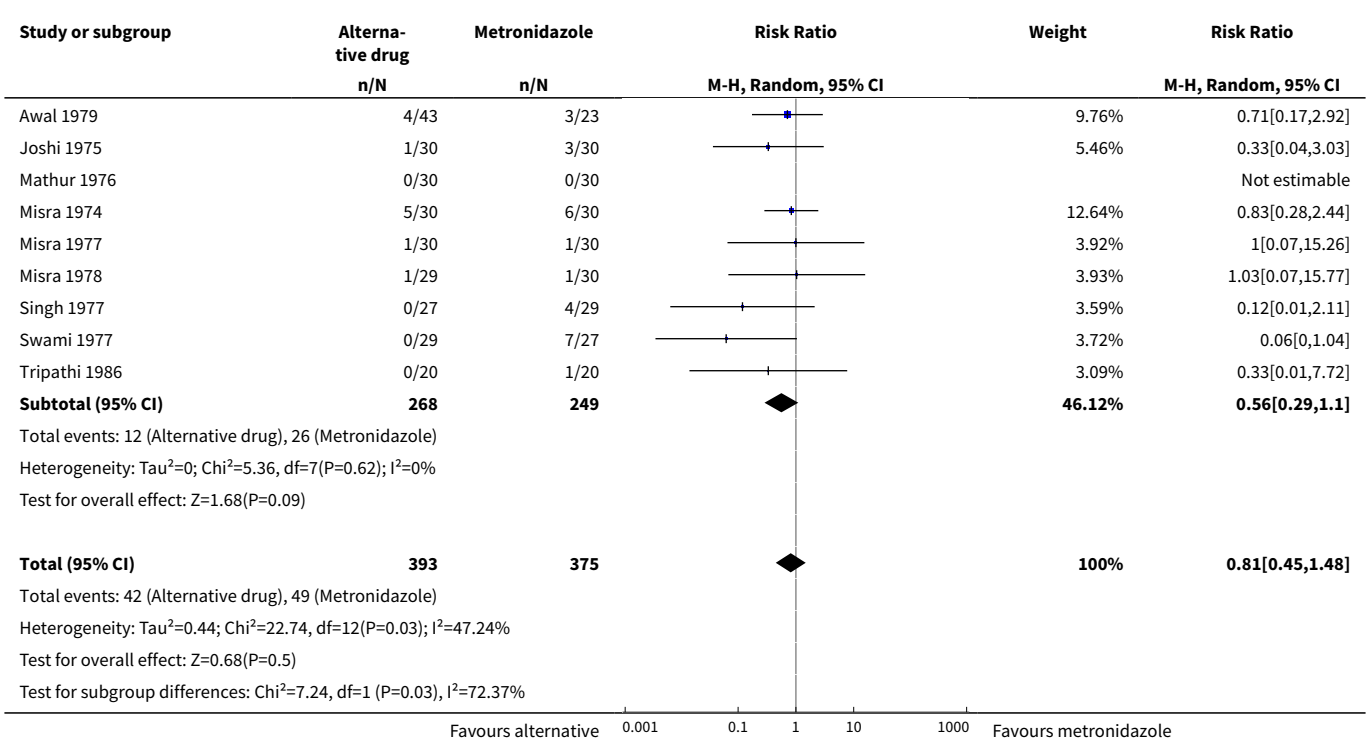
Comparison 6. Subgroup analyses: alternative drug versus metronidazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure 15 to 60 days after end of treatment, by clinical category	13	768	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.45, 1.48]
1.1 Amoebic dysentery	3	162	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.07, 8.68]
1.2 Non-dysenteric amoebic colitis	3	89	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.09, 2.42]
1.3 Amoebic colitis or intestinal amoebiasis, unspecified	9	517	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.29, 1.10]
2 Parasitological failure 15 to 60 days after end of treatment, by age group	13	768	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.37, 1.43]
2.1 Adults (age ≥ 15 years)	10	622	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.25, 1.54]

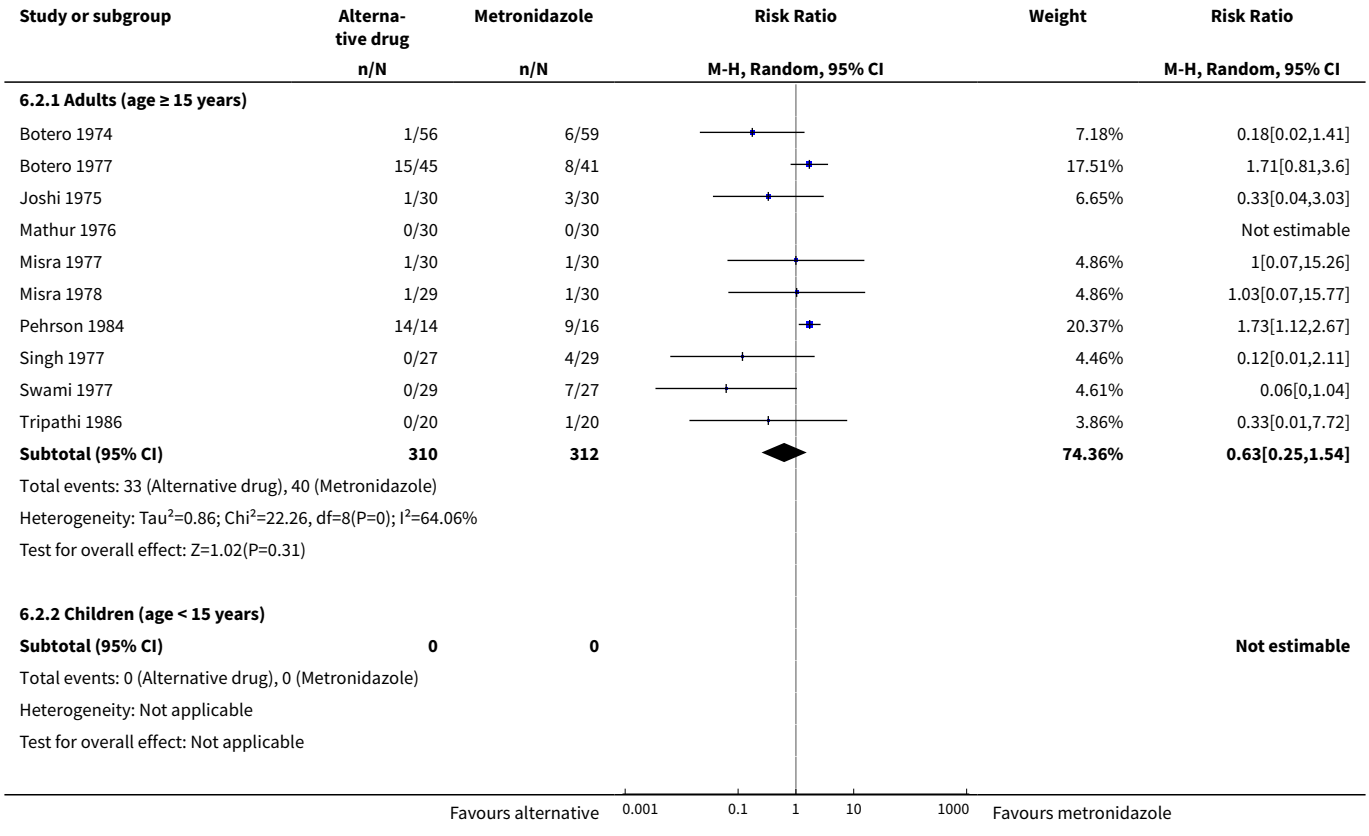
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Children (age < 15 years)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Both adults and children	3	146	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.85]
3 Parasitological failure 15 to 60 days after end of treatment, single or mixed intestinal infection	13	768	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.37, 1.43]
3.1 Amoebic infection only	10	586	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.25, 1.59]
3.2 Mixed intestinal infection	3	182	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.10, 3.91]
4 Parasitological failure 15 to 60 days after end of treatment, by criteria	13	768	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.37, 1.43]
4.1 WHO criteria	9	517	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.29, 1.10]
4.2 Other criteria	4	251	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.58, 2.94]

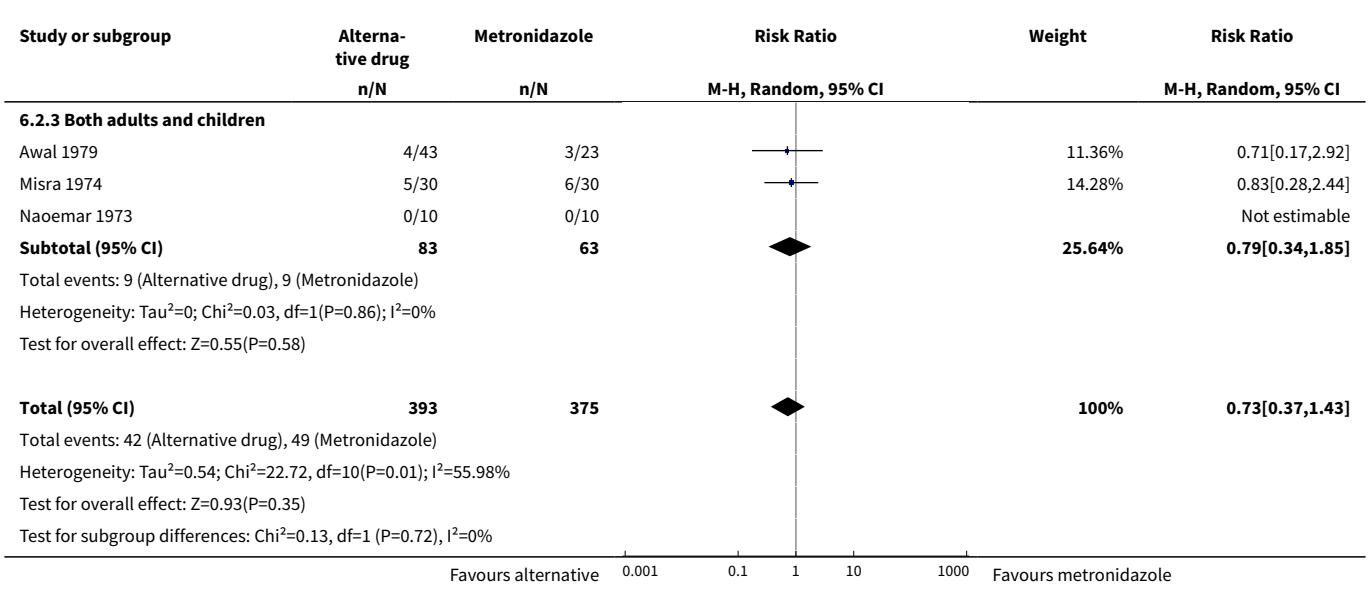
Analysis 6.1. Comparison 6 Subgroup analyses: alternative drug versus metronidazole, Outcome 1 Parasitological failure 15 to 60 days after end of treatment, by clinical category.



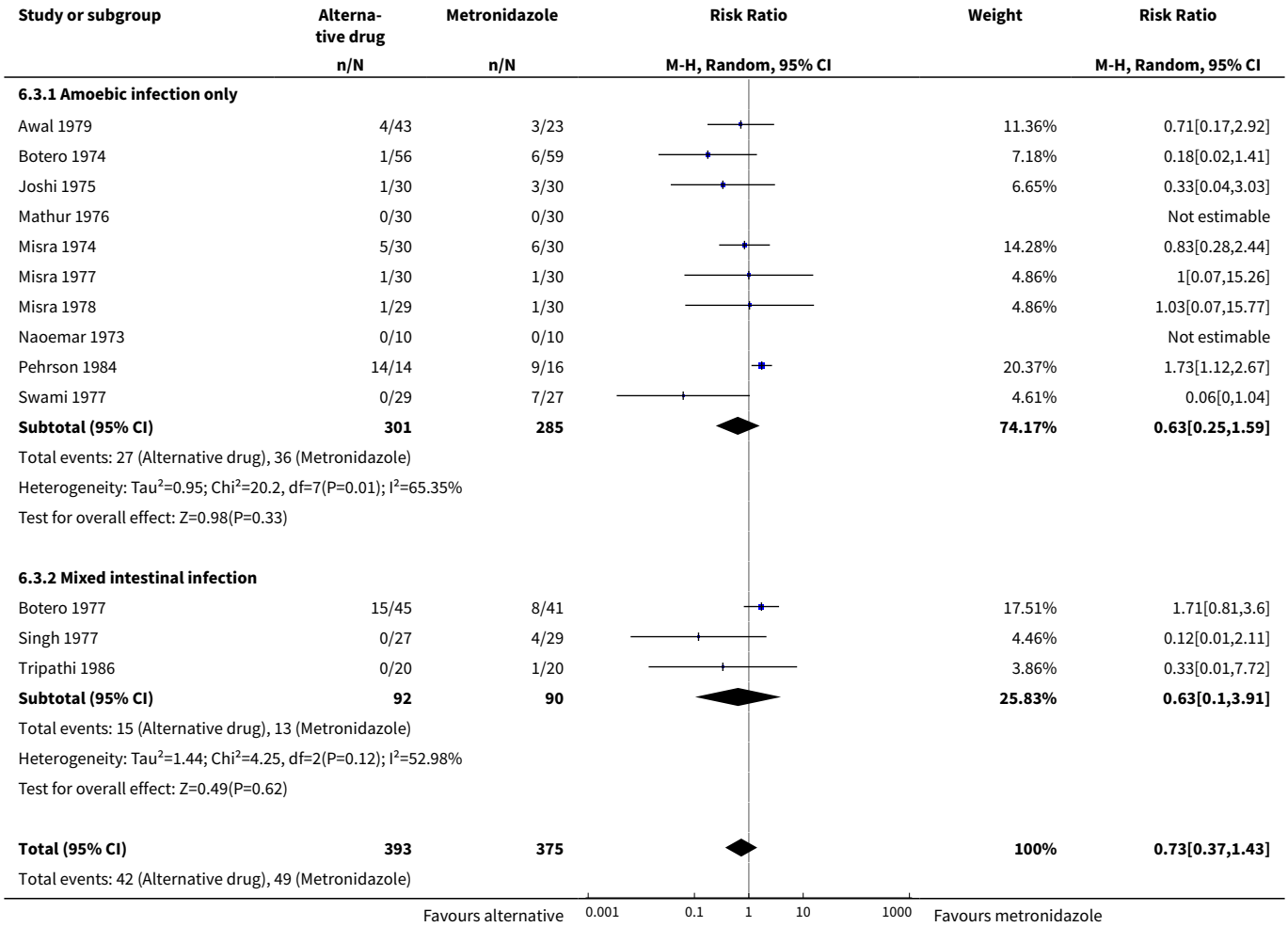


Analysis 6.2. Comparison 6 Subgroup analyses: alternative drug versus metronidazole, Outcome 2 Parasitological failure 15 to 60 days after end of treatment, by age group.





Analysis 6.3. Comparison 6 Subgroup analyses: alternative drug versus metronidazole, Outcome 3 Parasitological failure 15 to 60 days after end of treatment, single or mixed intestinal infection.



Study or subgroup	Alternative drug n/N	Metronidazole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.54; Chi²=22.72, df=10(P=0.01); I²=55.98%					
Test for overall effect: Z=0.93(P=0.35)					
Test for subgroup differences: Chi²=0, df=1 (P=0.99), I²=0%					

Favours alternative | Favours metronidazole

Analysis 6.4. Comparison 6 Subgroup analyses: alternative drug versus metronidazole, Outcome 4 Parasitological failure 15 to 60 days after end of treatment, by criteria.

Study or subgroup	Alternative drug n/N	Metronidazole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 WHO criteria					
Awal 1979	4/43	3/23		11.36%	0.71[0.17,2.92]
Joshi 1975	1/30	3/30		6.65%	0.33[0.04,3.03]
Mathur 1976	0/30	0/30			Not estimable
Misra 1974	5/30	6/30		14.28%	0.83[0.28,2.44]
Misra 1977	1/30	1/30		4.86%	1[0.07,15.26]
Misra 1978	1/29	1/30		4.86%	1.03[0.07,15.77]
Singh 1977	0/27	4/29		4.46%	0.12[0.01,2.11]
Swami 1977	0/29	7/27		4.61%	0.06[0,1.04]
Tripathi 1986	0/20	1/20		3.86%	0.33[0.01,7.72]
Subtotal (95% CI)	**268**	**249**		**54.94%**	**0.56[0.29,1.1]**
Total events: 12 (Alternative drug), 26 (Metronidazole)					
Heterogeneity: Tau²=0; Chi²=5.36, df=7(P=0.62); I²=0%					
Test for overall effect: Z=1.68(P=0.09)					
6.4.2 Other criteria					
Botero 1974	1/56	6/59		7.18%	0.18[0.02,1.41]
Botero 1977	15/45	8/41		17.51%	1.71[0.81,3.6]
Naoemar 1973	0/10	0/10			Not estimable
Pehrson 1984	14/14	9/16		20.37%	1.73[1.12,2.67]
Subtotal (95% CI)	**125**	**126**		**45.06%**	**1.31[0.58,2.94]**
Total events: 30 (Alternative drug), 23 (Metronidazole)					
Heterogeneity: Tau²=0.3; Chi²=5.48, df=2(P=0.06); I²=63.49%					
Test for overall effect: Z=0.65(P=0.51)					
Total (95% CI)	**393**	**375**		**100%**	**0.73[0.37,1.43]**
Total events: 42 (Alternative drug), 49 (Metronidazole)					
Heterogeneity: Tau²=0.54; Chi²=22.72, df=10(P=0.01); I²=55.98%					
Test for overall effect: Z=0.93(P=0.35)					
Test for subgroup differences: Chi²=2.48, df=1 (P=0.12), I²=59.72%					

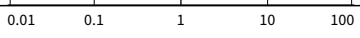
Favours alternative | Favours metronidazole

Comparison 7. Subgroup analyses: any antiamoebic drug versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure 1 to 14 days after end of treatment, by clinical category	4	630	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.22, 0.50]
1.1 Non-dysenteric amoebic colitis	1	96	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.19, 0.47]
1.2 Amoebic colitis or intestinal amoebiasis, unspecified	3	534	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.17, 0.62]
2 Clinical failure 1 to 14 days after end of treatment, by age group	3	193	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.51]
2.1 Adults (age ≥ 15 years)	3	143	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.16, 0.60]
2.2 Children (age < 15 years)	1	50	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.04, 0.56]
3 Parasitological failure 1 to 14 days after end of treatment, by age group	4	630	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.23, 0.48]
3.1 Adults (age ≥ 15 years)	3	213	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.56]
3.2 Children (age < 15 years)	1	50	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.54]
3.3 Both adults and children	1	367	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.53]
4 Clinical failure 1 to 14 days after end of treatment, by diagnostic method	3	193	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.57]
4.1 Stool microscopy with staining or concentration technique	2	93	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.23, 0.56]
4.2 Antigen-based ELISA test	1	100	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.03, 0.33]
5 Parasitological failure 1 to 14 days after end of treatment, by diagnostic method	4	630	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.22, 0.50]
5.1 Stool microscopy with staining or concentration technique	3	530	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.29, 0.47]
5.2 Antigen-based ELISA test	1	100	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.34]

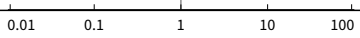
Analysis 7.1. Comparison 7 Subgroup analyses: any antiamoebic drug versus placebo, Outcome 1 Parasitological failure 1 to 14 days after end of treatment, by clinical category.

Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Non-dysenteric amoebic colitis					
Huggins 1982	18/72	20/24		30.5%	0.3[0.19,0.47]
Subtotal (95% CI)	**72**	**24**		**30.5%**	**0.3[0.19,0.47]**
Total events: 18 (Any antiamoebic drug), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.38(P<0.0001)					
7.1.2 Amoebic colitis or intestinal amoebiasis, unspecified					
Donckaster 1964	77/339	17/28		34.64%	0.37[0.26,0.53]
Rossignol 2001	11/36	19/31		24.65%	0.5[0.28,0.88]
Rossignol 2007	3/50	27/50		10.21%	0.11[0.04,0.34]
Subtotal (95% CI)	**425**	**109**		**69.5%**	**0.33[0.17,0.62]**
Total events: 91 (Any antiamoebic drug), 63 (Placebo)					
Heterogeneity: Tau^2=0.21; Chi^2=6.64, df=2(P=0.04); I^2=69.9%					
Test for overall effect: Z=3.4(P=0)					
Total (95% CI)	**497**	**133**		**100%**	**0.33[0.22,0.5]**
Total events: 109 (Any antiamoebic drug), 83 (Placebo)					
Heterogeneity: Tau^2=0.09; Chi^2=6.89, df=3(P=0.08); I^2=56.48%					
Test for overall effect: Z=5.32(P<0.0001)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.83), I^2=0%					



Analysis 7.2. Comparison 7 Subgroup analyses: any antiamoebic drug versus placebo, Outcome 2 Clinical failure 1 to 14 days after end of treatment, by age group.

Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Adults (age ≥ 15 years)					
Huggins 1982	9/27	13/13		43.81%	0.35[0.21,0.6]
Rossignol 2001	6/30	12/23		30.95%	0.38[0.17,0.87]
Rossignol 2007	1/25	14/25		9.16%	0.07[0.01,0.5]
Subtotal (95% CI)	**82**	**61**		**83.92%**	**0.31[0.16,0.6]**
Total events: 16 (Any antiamoebic drug), 39 (Placebo)					
Heterogeneity: Tau^2=0.14; Chi^2=3.31, df=2(P=0.19); I^2=39.54%					
Test for overall effect: Z=3.51(P=0)					
7.2.2 Children (age < 15 years)					
Rossignol 2007	2/25	14/25		16.08%	0.14[0.04,0.56]
Subtotal (95% CI)	**25**	**25**		**16.08%**	**0.14[0.04,0.56]**
Total events: 2 (Any antiamoebic drug), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.78(P=0.01)					
Total (95% CI)	**107**	**86**		**100%**	**0.27[0.14,0.51]**



Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 18 (Any antiamoebic drug), 53 (Placebo)					
Heterogeneity: Tau²=0.17; Chi²=5.14, df=3(P=0.16); I²=41.61%					
Test for overall effect: Z=4.01(P<0.0001)					
Test for subgroup differences: Chi²=0.99, df=1 (P=0.32), I²=0%					

Favours antiamoebic 0.01 0.1 1 10 100 Favours placebo

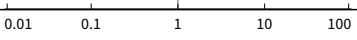
Analysis 7.3. Comparison 7 Subgroup analyses: any antiamoebic drug versus placebo, Outcome 3 Parasitological failure 1 to 14 days after end of treatment, by age group.

Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 Adults (age ≥ 15 years)					
Huggins 1982	18/72	20/24		30.62%	0.3[0.19,0.47]
Rossignol 2001	11/36	19/31		23.81%	0.5[0.28,0.88]
Rossignol 2007	2/25	14/25		6.42%	0.14[0.04,0.56]
Subtotal (95% CI)	**133**	**80**		**60.86%**	**0.34[0.2,0.56]**
Total events: 31 (Any antiamoebic drug), 53 (Placebo)					
Heterogeneity: Tau²=0.09; Chi²=3.66, df=2(P=0.16); I²=45.31%					
Test for overall effect: Z=4.15(P<0.0001)					
7.3.2 Children (age < 15 years)					
Rossignol 2007	1/25	13/25		3.37%	0.08[0.01,0.54]
Subtotal (95% CI)	**25**	**25**		**3.37%**	**0.08[0.01,0.54]**
Total events: 1 (Any antiamoebic drug), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.57(P=0.01)					
7.3.3 Both adults and children					
Donckaster 1964	77/339	17/28		35.77%	0.37[0.26,0.53]
Subtotal (95% CI)	**339**	**28**		**35.77%**	**0.37[0.26,0.53]**
Total events: 77 (Any antiamoebic drug), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.4(P<0.0001)					
Total (95% CI)	**497**	**133**		**100%**	**0.33[0.23,0.48]**
Total events: 109 (Any antiamoebic drug), 83 (Placebo)					
Heterogeneity: Tau²=0.07; Chi²=6.87, df=4(P=0.14); I²=41.81%					
Test for overall effect: Z=5.79(P<0.0001)					
Test for subgroup differences: Chi²=2.46, df=1 (P=0.29), I²=18.76%					

Favours antiamoebic 0.01 0.1 1 10 100 Favours placebo

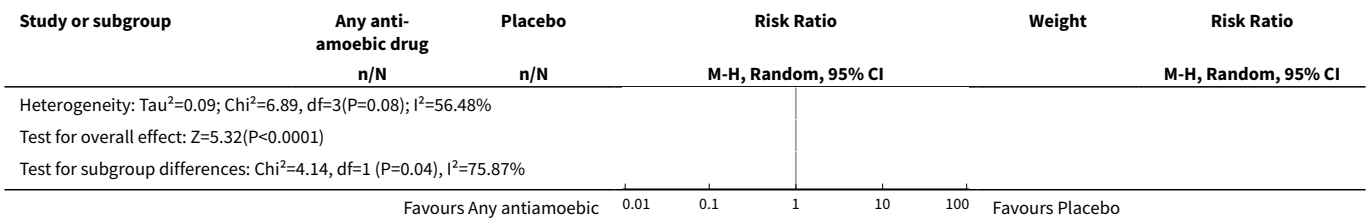
Analysis 7.4. Comparison 7 Subgroup analyses: any antiamoebic drug versus placebo, Outcome 4 Clinical failure 1 to 14 days after end of treatment, by diagnostic method.

Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.4.1 Stool microscopy with staining or concentration technique					
Huggins 1982	9/27	13/13		43.12%	0.35[0.21,0.6]
Rossignol 2001	6/30	12/23		32.85%	0.38[0.17,0.87]
Subtotal (95% CI)	**57**	**36**		**75.98%**	**0.36[0.23,0.56]**
Total events: 15 (Any antiamoebic drug), 25 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=4.52(P<0.0001)					
7.4.2 Antigen-based ELISA test					
Rossignol 2007	3/50	28/50		24.02%	0.11[0.03,0.33]
Subtotal (95% CI)	**50**	**50**		**24.02%**	**0.11[0.03,0.33]**
Total events: 3 (Any antiamoebic drug), 28 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.89(P<0.0001)					
Total (95% CI)	**107**	**86**		**100%**	**0.27[0.13,0.57]**
Total events: 18 (Any antiamoebic drug), 53 (Placebo)					
Heterogeneity: Tau^2=0.25; Chi^2=5.09, df=2(P=0.08); I^2=60.72%					
Test for overall effect: Z=3.49(P=0)					
Test for subgroup differences: Chi^2=3.88, df=1 (P=0.05), I^2=74.23%					



Analysis 7.5. Comparison 7 Subgroup analyses: any antiamoebic drug versus placebo, Outcome 5 Parasitological failure 1 to 14 days after end of treatment, by diagnostic method.

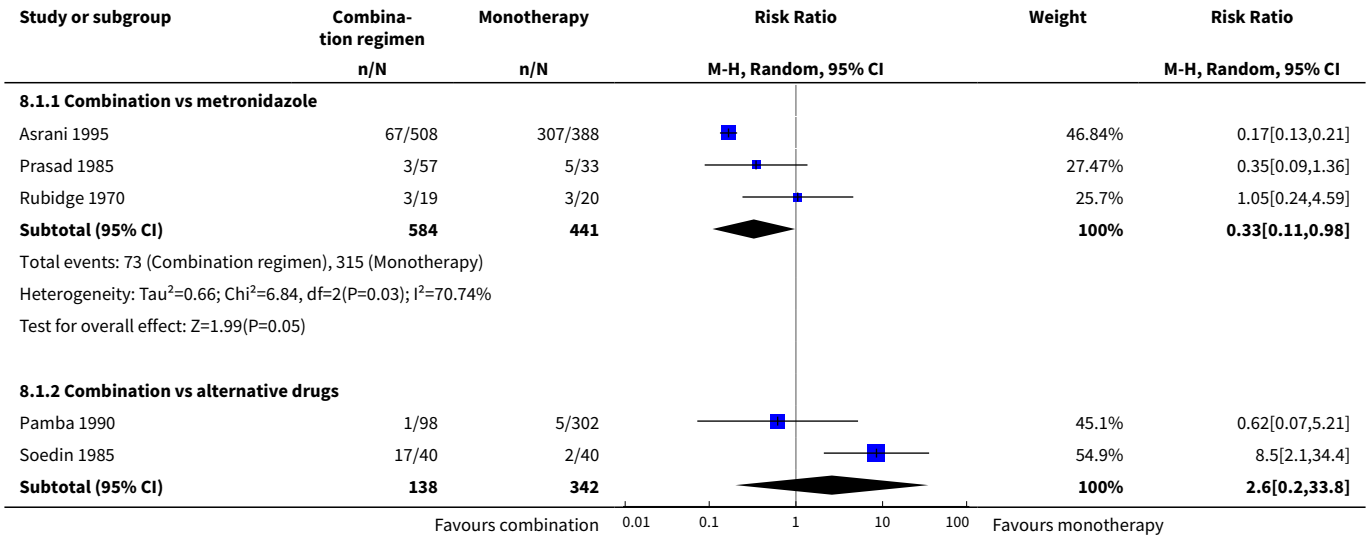
Study or subgroup	Any anti-amoebic drug n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.5.1 Stool microscopy with staining or concentration technique					
Donckaster 1964	77/339	17/28		34.64%	0.37[0.26,0.53]
Huggins 1982	18/72	20/24		30.5%	0.3[0.19,0.47]
Rossignol 2001	11/36	19/31		24.65%	0.5[0.28,0.88]
Subtotal (95% CI)	**447**	**83**		**89.79%**	**0.37[0.29,0.47]**
Total events: 106 (Any antiamoebic drug), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.99, df=2(P=0.37); I^2=0%					
Test for overall effect: Z=7.87(P<0.0001)					
7.5.2 Antigen-based ELISA test					
Rossignol 2007	3/50	27/50		10.21%	0.11[0.04,0.34]
Subtotal (95% CI)	**50**	**50**		**10.21%**	**0.11[0.04,0.34]**
Total events: 3 (Any antiamoebic drug), 27 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.82(P=0)					
Total (95% CI)	**497**	**133**		**100%**	**0.33[0.22,0.5]**
Total events: 109 (Any antiamoebic drug), 83 (Placebo)					

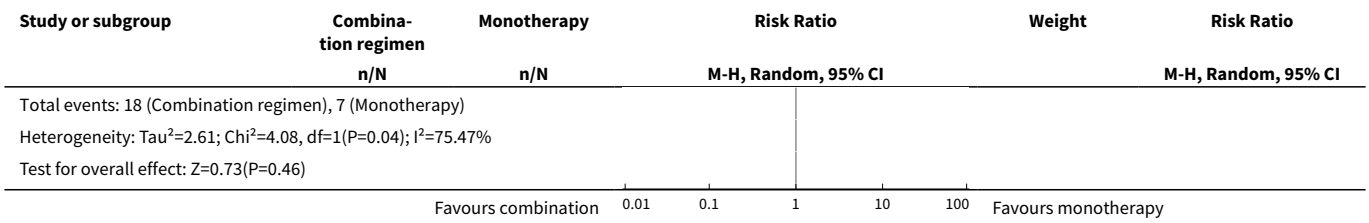


Comparison 8. Subgroup analyses: combination regimen versus monotherapy

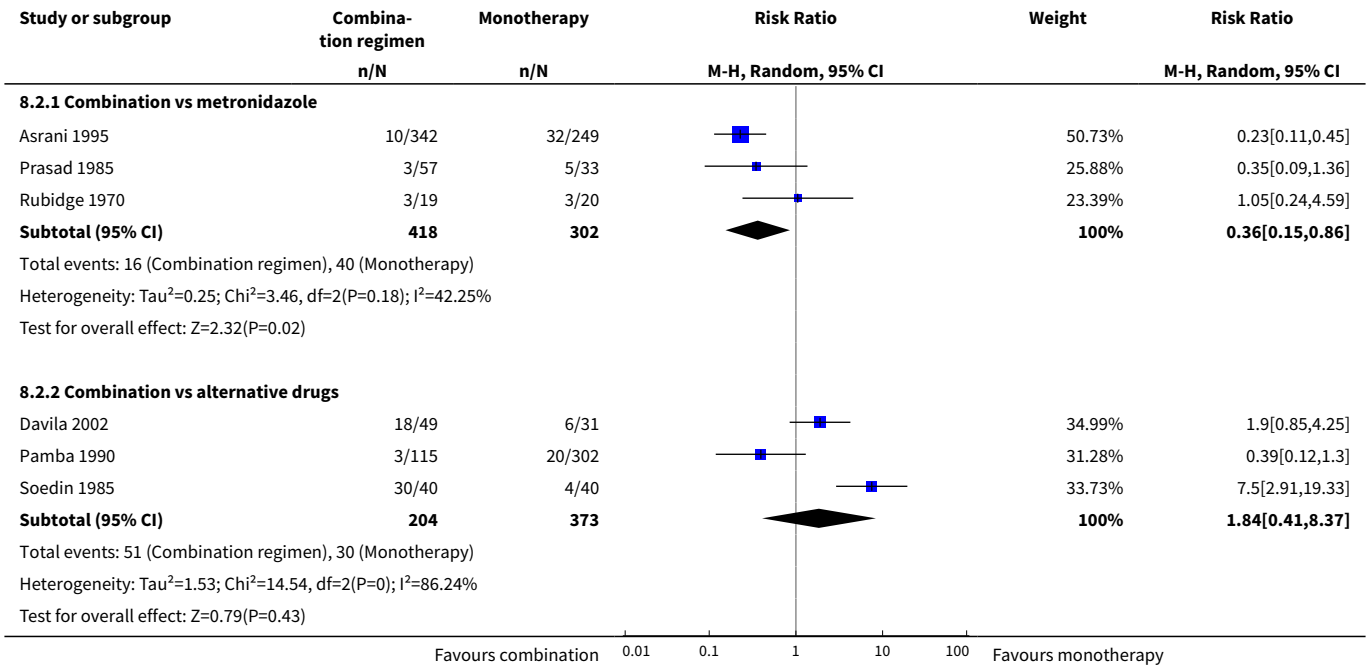
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment, by intervention	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Combination vs metronidazole	3	1025	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 0.98]
1.2 Combination vs alternative drugs	2	480	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.20, 33.80]
2 Parasitological failure: 1 to 14 days after end of treatment, by intervention	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Combination vs metronidazole	3	720	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.86]
2.2 Combination vs alternative drugs	3	577	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.41, 8.37]

Analysis 8.1. Comparison 8 Subgroup analyses: combination regimen versus monotherapy, Outcome 1 Clinical failure: 1 to 14 days after end of treatment, by intervention.





Analysis 8.2. Comparison 8 Subgroup analyses: combination regimen versus monotherapy, Outcome 2 Parasitological failure: 1 to 14 days after end of treatment, by intervention.

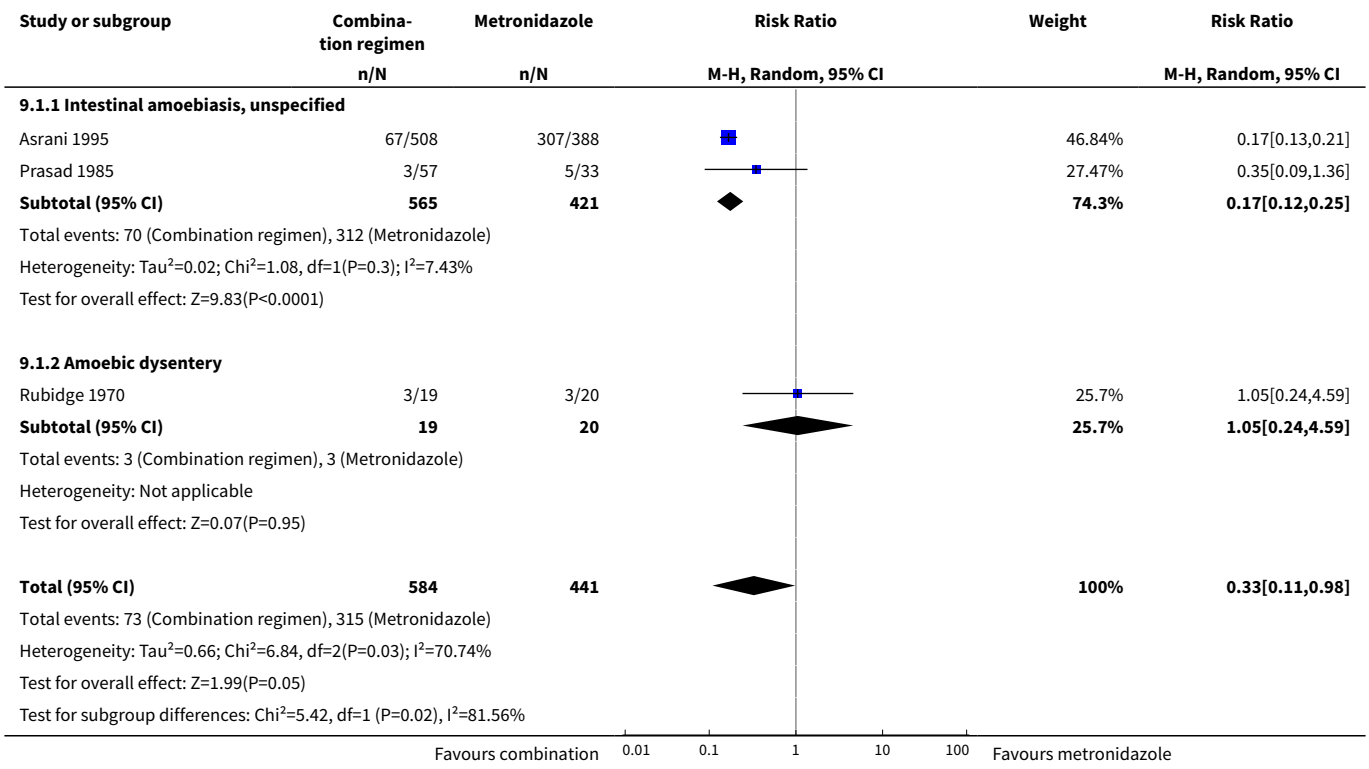


Comparison 9. Subgroup analyses: combination regimen versus metronidazole

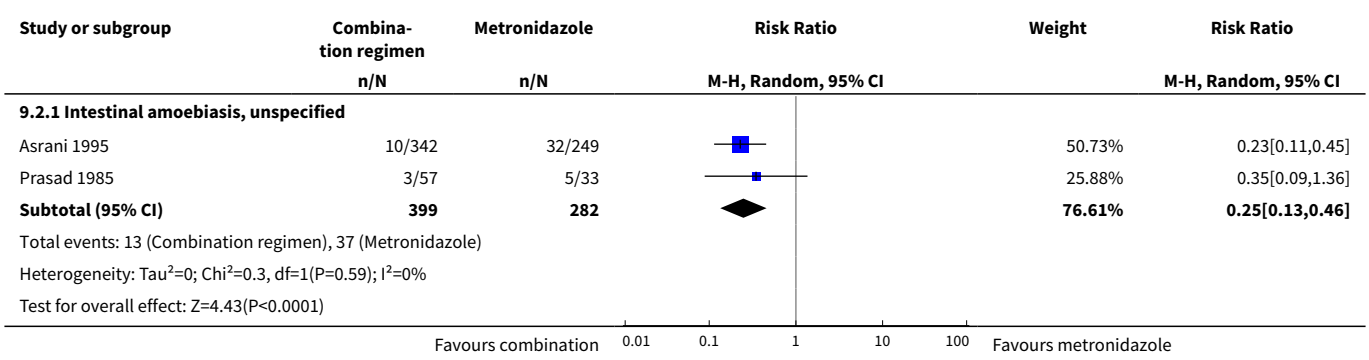
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment, by clinical diagnosis	3	1025	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 0.98]
1.1 Intestinal amoebiasis, unspecified	2	986	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.12, 0.25]
1.2 Amoebic dysentery	1	39	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.24, 4.59]
2 Parasitological failure: 1 to 14 days after end of treatment, by clinical diagnosis	3	720	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.86]

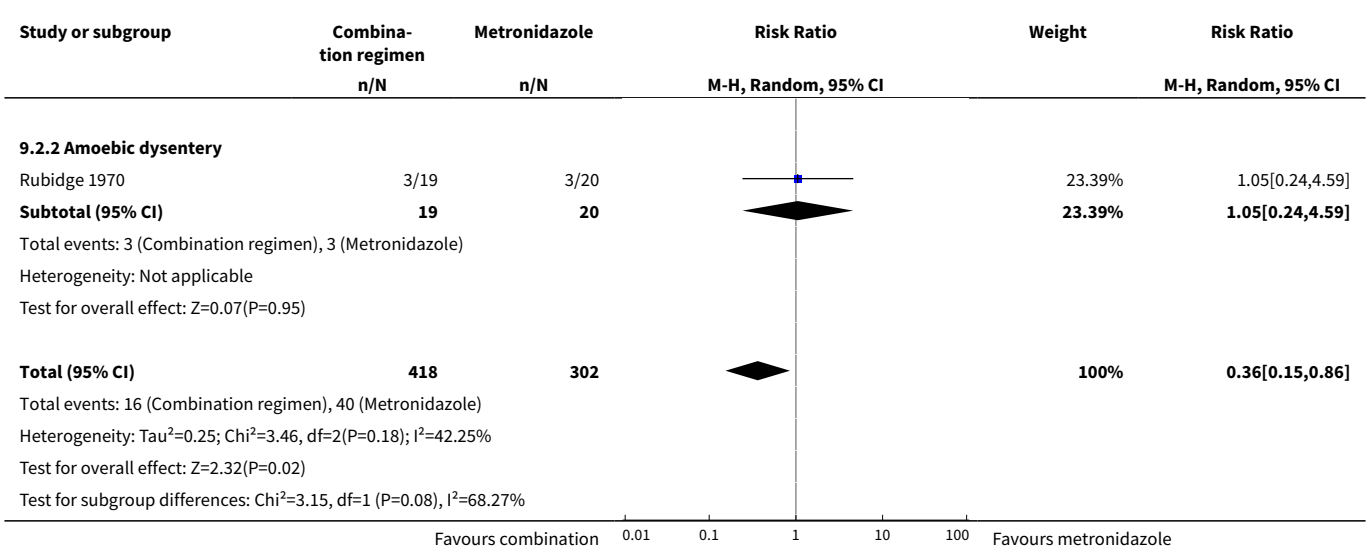
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Intestinal amoebiasis, unspecified	2	681	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.13, 0.46]
2.2 Amoebic dysentery	1	39	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.24, 4.59]

Analysis 9.1. Comparison 9 Subgroup analyses: combination regimen versus metronidazole, Outcome 1 Clinical failure: 1 to 14 days after end of treatment, by clinical diagnosis.



Analysis 9.2. Comparison 9 Subgroup analyses: combination regimen versus metronidazole, Outcome 2 Parasitological failure: 1 to 14 days after end of treatment, by clinical diagnosis.

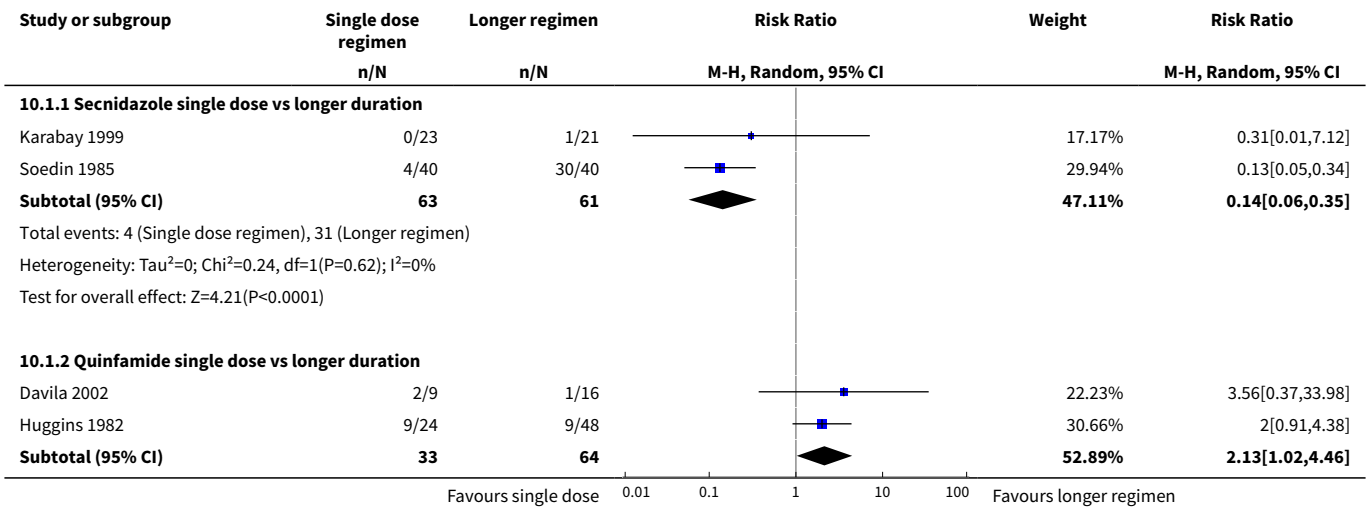


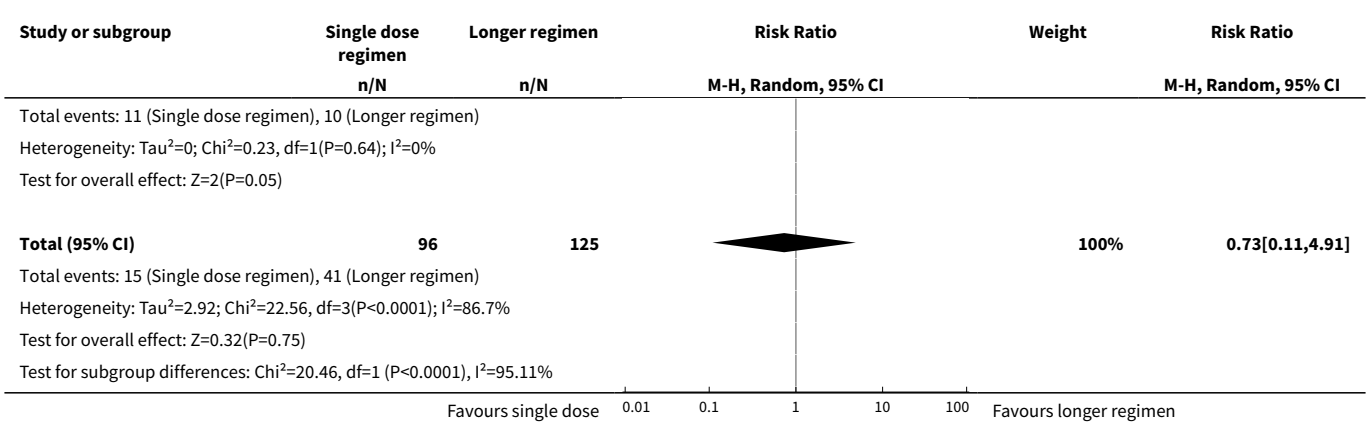


Comparison 10. Subgroup analyses: any single-dose regimen versus longer regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure: 1 to 14 days after end of treatment, by intervention	4	221	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.11, 4.91]
1.1 Secnidazole single dose vs longer duration	2	124	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.06, 0.35]
1.2 Quinfamide single dose vs longer duration	2	97	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.02, 4.46]

Analysis 10.1. Comparison 10 Subgroup analyses: any single-dose regimen versus longer regimen, Outcome 1 Parasitological failure: 1 to 14 days after end of treatment, by intervention.

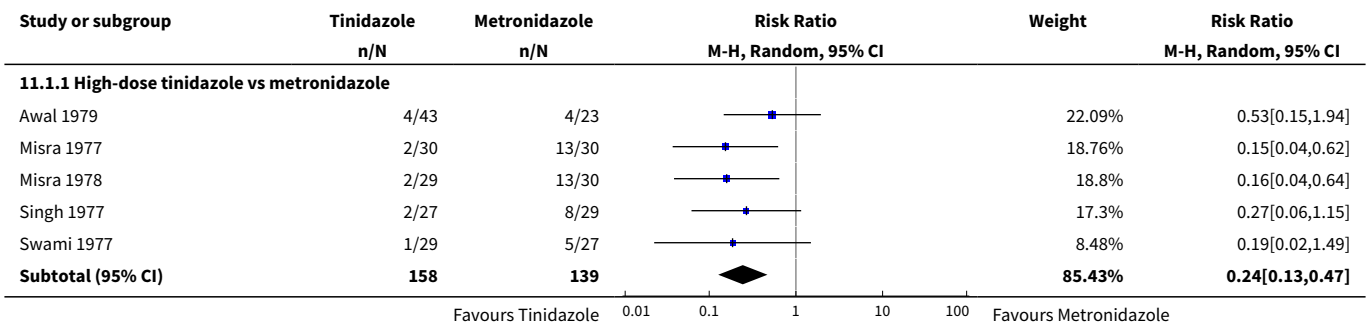


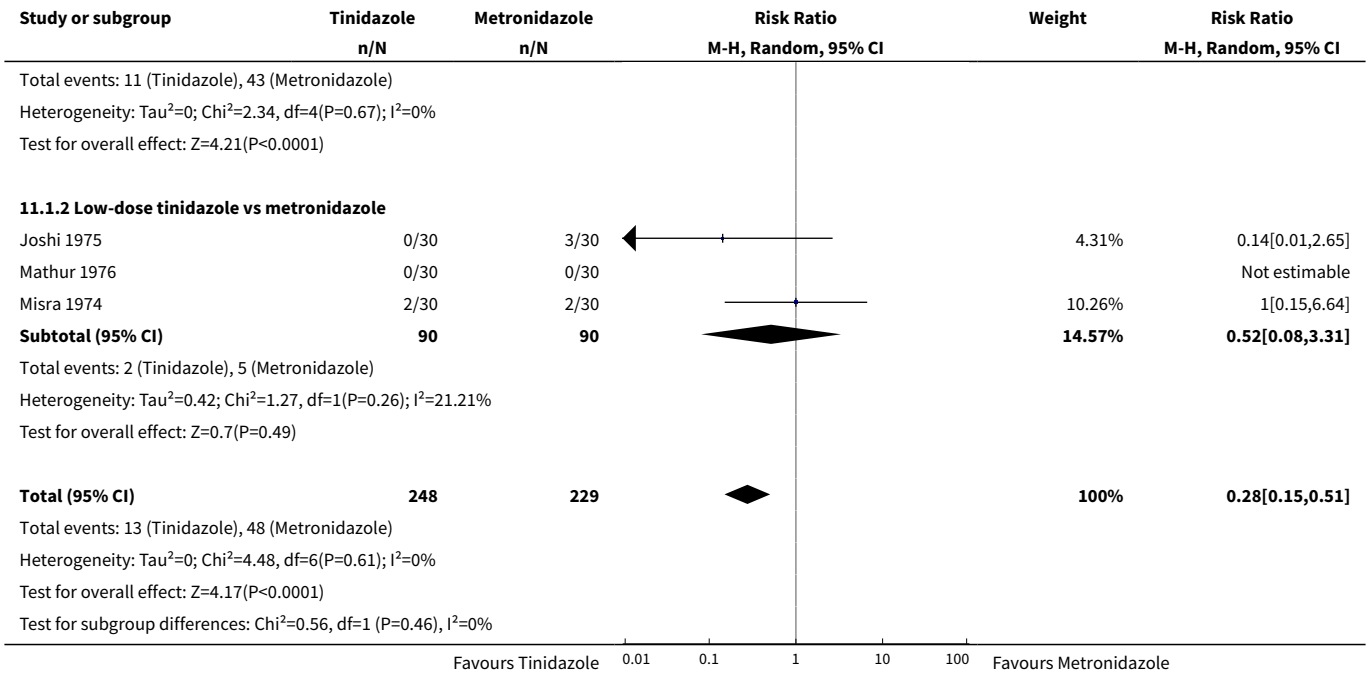


Comparison 11. Subgroup analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment, based on tinidazole dose

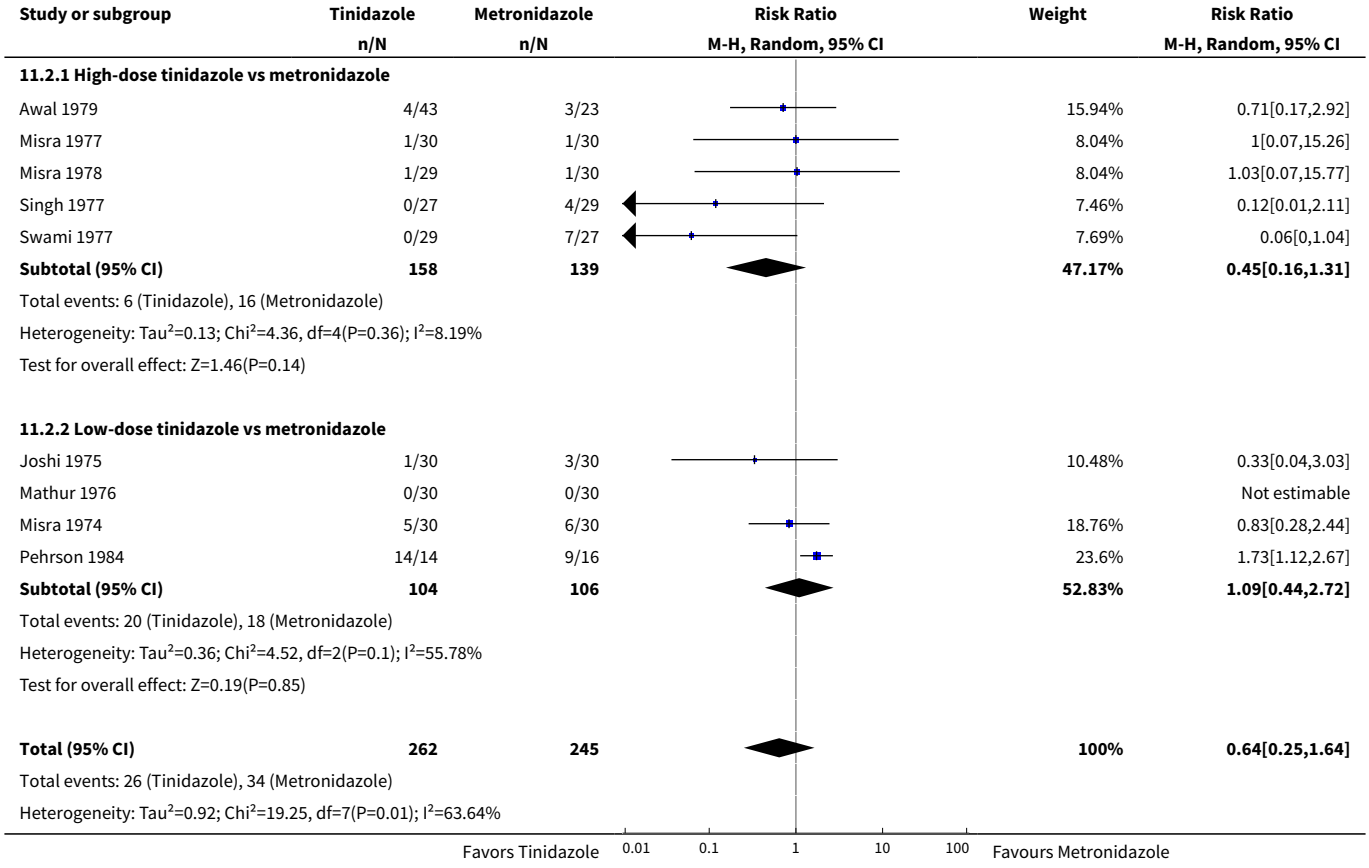
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 15 to 60 days after end of treatment	8	477	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.15, 0.51]
1.1 High-dose tinidazole vs metronidazole	5	297	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.13, 0.47]
1.2 Low-dose tinidazole vs metronidazole	3	180	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.08, 3.31]
2 Parasitological failure: 15 to 60 days after end of treatment	9	507	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.25, 1.64]
2.1 High-dose tinidazole vs metronidazole	5	297	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.31]
2.2 Low-dose tinidazole vs metronidazole	4	210	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.44, 2.72]

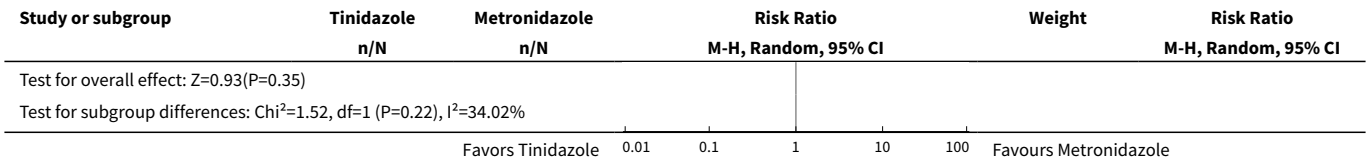
Analysis 11.1. Comparison 11 Subgroup analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment, based on tinidazole dose, Outcome 1 Clinical failure: 15 to 60 days after end of treatment.





Analysis 11.2. Comparison 11 Subgroup analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment, based on tinidazole dose, Outcome 2 Parasitological failure: 15 to 60 days after end of treatment.

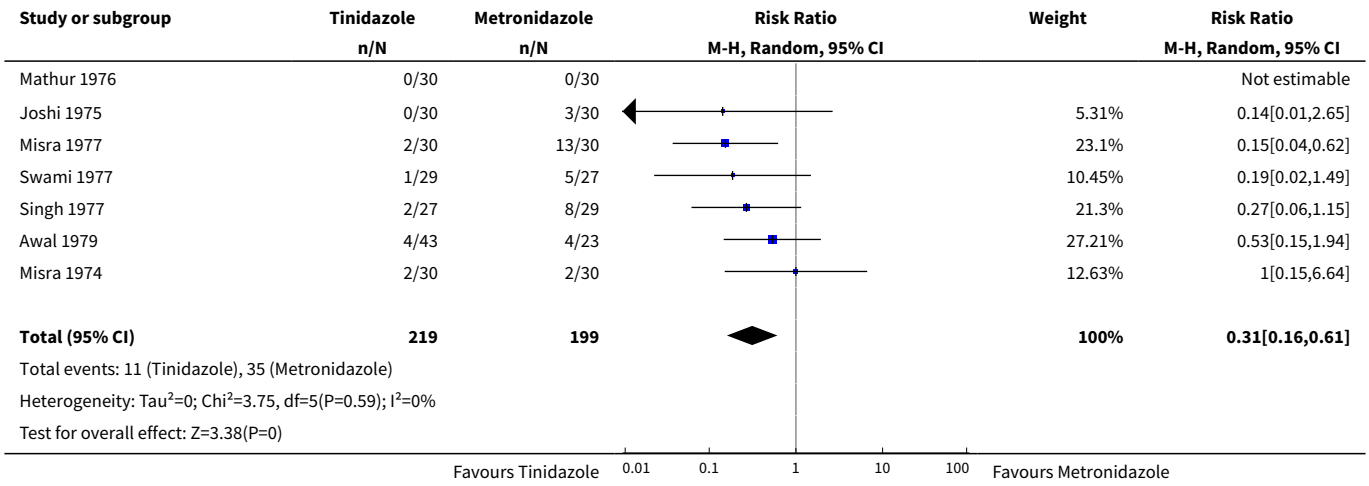




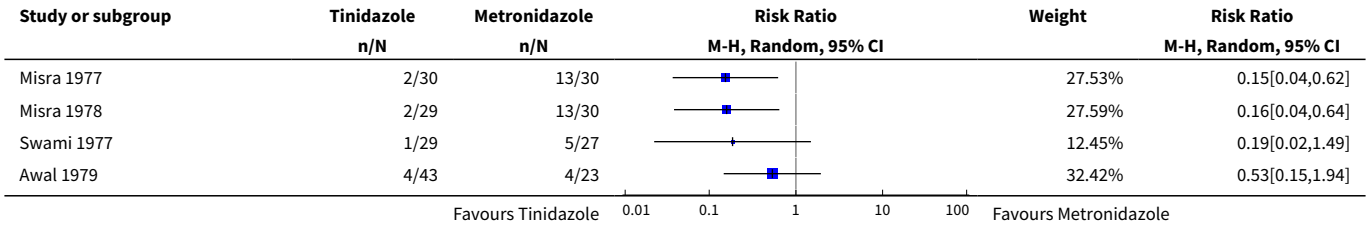
Comparison 12. Sensitivity analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment

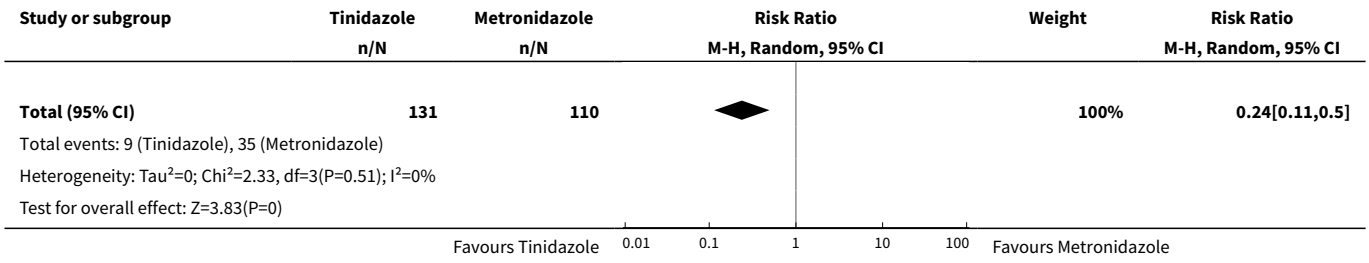
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 15 to 60 days after end of treatment, excluding Misra 1978	7	418	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.16, 0.61]
2 Clinical failure: 15 to 60 days after end of treatment, excluding trials sponsored by pharmaceutical companies	4	241	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.50]

Analysis 12.1. Comparison 12 Sensitivity analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment, Outcome 1 Clinical failure: 15 to 60 days after end of treatment, excluding Misra 1978.



Analysis 12.2. Comparison 12 Sensitivity analysis: tinidazole versus metronidazole 15 to 60 days after end of treatment, Outcome 2 Clinical failure: 15 to 60 days after end of treatment, excluding trials sponsored by pharmaceutical companies.

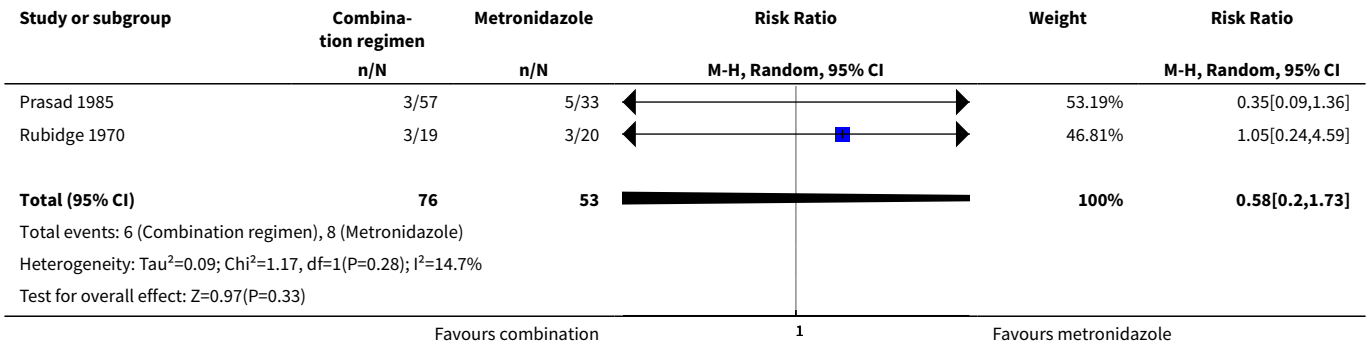




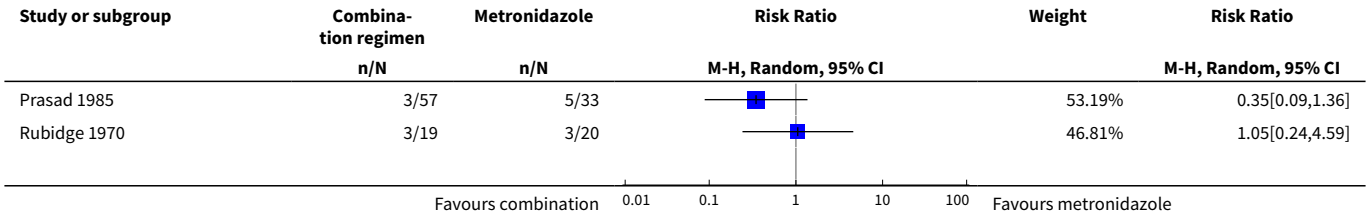
Comparison 13. Sensitivity analyses: combination regimen versus metronidazole alone, excluding pharmaceutical company-sponsored study (Asrani 1995)

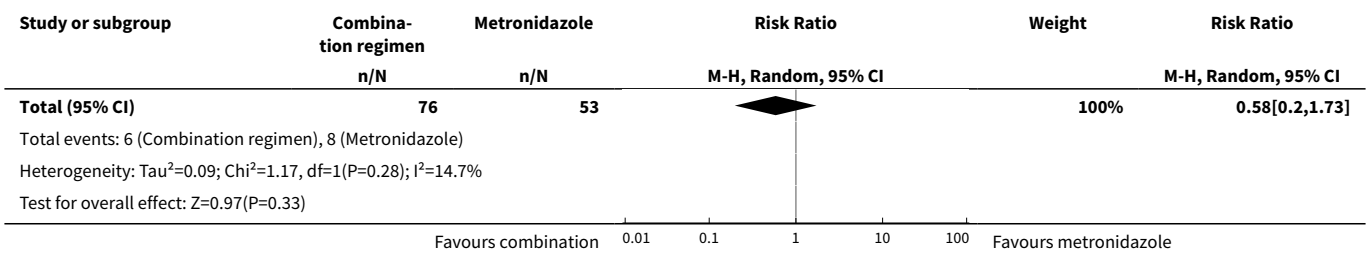
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure: 1 to 14 days after end of treatment	2	129	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.73]
2 Parasitological failure: 1 to 14 days after end of treatment, by intervention	2	129	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.73]

Analysis 13.1. Comparison 13 Sensitivity analyses: combination regimen versus metronidazole alone, excluding pharmaceutical company-sponsored study (Asrani 1995), Outcome 1 Clinical failure: 1 to 14 days after end of treatment.



Analysis 13.2. Comparison 13 Sensitivity analyses: combination regimen versus metronidazole alone, excluding pharmaceutical company-sponsored study (Asrani 1995), Outcome 2 Parasitological failure: 1 to 14 days after end of treatment, by intervention.





ADDITIONAL TABLES

Table 1. Amoebicide classes and examples

Amoebicide	Class	Examples
Luminal	Arsenical compounds	Carbarsone, acetarsone or acetarsol, treparsol, diphetarsone, glycobiarsol or bismuth glycolylarsanilate, stovarsol, thioarsenite, thiocarbarsone, and arsthinol
	Hydroxyquinoline derivatives	Chiniofon or quinoxyl, clioquinol or iodochlorhydroxyquin, and iodoquinol or diiodohydroxyquin
	Dichloroacetamide derivatives	Diloxanide furoate or entamide furoate, clefamide, eticlordifene or ethylchlordiphene, etofamide or etophamide, and quinfamide
	Benzylamine derivatives	Teclozan, chlorbetamide or mantomide, and chlorphenoxamide or mebinol
	Antibiotic amoebicides	Tetracycline, oxytetracycline, chlortetracycline, erythromycin, paromomycin, and fumagillin
Tissue	Emetine and its derivatives	Emetine hydrochloride, emetine bismuth iodide, dehydroemetine dihydrochloride, and dehydroemetine resinate
	Aminoquinoline	Chloroquine
	Thiazole derivative	Niridazole
	Nitroimidazoles	Metronidazole, tinidazole, ornidazole, secnidazole, and nimorazole
	Nithrothiazole salicylamide	Nitazoxanide

Table 2. Summary of included studies

Study ID	Year completed	Setting	Participants	Intervention	Control	Outcome measures	Test used to measure parasitological outcome
Various antiamoebic drugs versus placebo							
Donckaster 1964	1964	Outpatient clinic of the University of Chile in Santiago, Chile	346 adults and children with clinical symptoms of intestinal amoebiasis and stool specimens positive for cysts and/or trophozoites of *E histolytica*	• Dimethychlortetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 15 mg/kg and adults 900 mg • Oxytetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 25 mg/kg and adults 1500 mg • Tetracycline: once daily on an empty stomach for 10 days at the following oral daily doses – children 25 mg/kg and adults 1500 mg • Chlorphenoxamide: once daily after meals for 10 days at the following oral	Placebo (starch): once daily after meals for 10 days at the following oral daily doses – children 250 mg for every 2 years of age and adults 1500 mg	• Parasitological failure: presence of cysts and/or trophozoites in stool examinations done 10 and 40 days after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants every 3 days during treatment and every 10 to 15 days after treatment	Stool microscopy using modified Telemann concentration technique (centrifugation with saline formol and ether) for cysts; polyvinyl alcohol with fixative of Schaudinn for the trophozoites

Table 2. Summary of included studies *(Continued)*

					daily doses – children 125 mg for every 2 years of age and adults 1500 mg • Chlorbetamide: once daily after meals for 10 days at the following oral daily doses – children 100 mg/kg and adults 4000 mg • Racemic dehydroemetine: once daily after meals for 10 days at the following oral daily doses – children 5 mg for every 2 years of age and adults 40 mg • Diiodohydroxyquinoline: once daily after meals for 21 days at the following oral daily doses – children 200 mg for every 2 years of age and adults 1800 mg • Phenanthridinone: once daily after meals for 10 days at the

Table 2. Summary of included studies *(Continued)*

				following oral daily doses – children 25 mg for every 2 years of age and adults 300 mg • Bismuth glycoarsanilate: once daily after meals for 10 days at the following oral daily doses – children 250 mg for every 2 years of age and adults 2000 mg • Iodochlorhydroxyquinoline: once daily after meals for 21 days at the following oral daily doses – children 125 mg for every 2 years of age and adults 1000 mg			
Huggins 1982	1982	Clinical Hospital of the Federal University of Pernambuco, Brazil	96 adults with chronic intestinal amoebiasis and stool specimens positive for *E histolytica*	• Win 40.014 (quinfamide): 100 mg single oral dose • Win 40.014 (quinfamide): 100 mg twice a day orally at 12-hourly intervals for 1 day • Win 40.014 (quinfamide):	Placebo: 300 mg daily dose orally, no information given on the frequency of administration	• Parasitological cure: clearance of amoebae from stools on days 2 and 7 after treatment • Clinical cure: disappearance of the 4 symptoms recorded at baseline (pain, colic, diarrhoea, and constipation) evaluated on days 2 and 7 after treatment • Adverse events: only 2 symptoms (nausea and headache) solicited from participants; laboratory tests done before and after treatment but results not presented	Stool microscopy using Lugol's stain (Telemann-Richter or Hoffman, Pons, and Janer methods)

Table 2. Summary of included studies *(Continued)*

				100 mg thrice a day orally at 8-hourly intervals for 1 day			
Rossignol 2001	2001	Outpatient clinic of the Department of Hepatology, Gastroenterology, and Infectious Diseases of the Benha University Hospital, Governorate of Kalubia, Nile Delta, Egypt	67 adults and children with diarrhoea and stool specimens positive for cysts or trophozoites of *E histolytica* and/or *E dispar* alone or with concomitant *G intestinalis*	Nitazoxanide: 500 mg twice daily orally for 3 days	Placebo tablet (identical): twice daily orally for 3 days	• Parasitological response: clearance of *E histolytica* from 2 stool specimens collected between days 7 and 10 after start of treatment • Clinical response: disappearance of symptoms, resolution of diarrhoea and haematochezia on day 7 after start of treatment • Median duration of diarrhoea (days) • Adverse events: clinical adverse events monitored by study personnel	Stool microscopy using direct saline smear, concentration technique, Ziehl-Neelsen stain, and immunofluorescent assay (MeriFluor Meridian Diagnostics)
Rossignol 2007	2005	Outpatient clinic of the Benha University Hospital, Benha, Egypt	100 adults and children with diarrhoea; ≥ 1 enteric symptoms; *E histolytica*/*E dispar* trophozoites identified in stool and stool-positive for *E histolytica* by antigen-based ELISA	Nitazoxanide: for 3 days; adults aged ≥ 12 years, 500-mg tablet twice daily; children 100 mg/5 mL suspension – 1 to 3 years received 5 mL twice daily, 4 to 11 years received 10 mL twice daily	Placebo: matching placebo tablet or suspension twice daily for 3 days	• Parasitological response: clearance of *E histolytica* from 2 stool specimens collected between days 7 and 10 after start of treatment • Clinical response: disappearance of symptoms, resolution of diarrhoea and haematochezia on day 7 after start of treatment • Adverse events: monitored by patient diary *Not included in this review:* time from first dose to passage of last unformed stool (survival graph)	Stool microscopy using direct saline smear and concentration technique; *E histolytica* by antigen-based ELISA
Tinidazole versus metronidazole							
Awal 1979	1979	Hospital in Bangladesh	66 adults and children with clinical signs and symptoms of intestinal amoebiasis and motile haematophagous trophozoites of	• Tinidazole: 2 g single oral dose daily for 3 days • Tinidazole: 2 g single oral dose daily for 2 days	Metronidazole: 2 g single dose for 2 days	• Parasitological cure: eradication of *E histolytica* from stools on day 30 from start of therapy • Clinical cure: resolution of baseline symptoms of intestinal amoebiasis on day 30 from start of therapy • Adverse events: voluntary reporting of side effects by participants; laboratory	Stool microscopy using direct saline smear

Table 2. Summary of included studies *(Continued)*

			E histolytica in fresh stool specimens and on sigmoidoscopy			tests monitored before and after treatment including complete blood count, serum bilirubin, alkaline phosphatase, and liver transaminase (SGOT)	
Chunge 1989	1989	Outpatient departments of 3 district hospitals in Kiambo, Kilifi, and Machakos in Kenya	225 adults and children presenting with at least any 4 of the following symptoms of intestinal amoebiasis: abdominal pain, diarrhoea, constipation, mucoid stools, malaise, flatulence, nausea, fever, tenesmus, and stool specimens positive for trophozoites or cysts of *E histolytica*	• Tinidazole (Fasigyn): 2 g single oral dose daily for 3 days • Tinidazole (Tynazole): 2 g single oral dose daily for 3 days	• Metronidazole (Flagyl): 400 mg thrice daily orally for 5 days • Metronidazole (Metrozol): 400 mg thrice daily orally for 5 days	• Parasitological cure: absence of trophozoites or cysts from stool specimens on day 6 after start of treatment • Clinical cure: absence of any 4 of the symptoms initially present at day 6 after start of treatment	Stool microscopy using direct smear or formol-ether concentration technique
Joshi 1975	1975	Ahmedabad, India (location not stated)	60 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 600 mg twice daily orally for 5 days Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*	Metronidazole: 400 or 800 mg thrice daily orally for 5 days	• Parasitological response: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical response: complete or partial relief of symptoms and healing of ulcers on sigmoidoscopy, when carried out • Adverse events: voluntary reporting by participants; laboratory tests monitored before and after treatment including haemogram, urinalysis, serum bilirubin, serum transaminases (SGOT, SGPT), alkaline phosphatase, and blood urea	Stool microscopy using direct saline smear
Mathur 1976	1976	India (location not stated)	60 adults and adolescents with clinical symptoms of intestinal amoebiasis and stool speci-	Tinidazole: 600 mg twice daily orally for 5 days Treatment period was extended to 10 days in both	Metronidazole: 400 mg thrice daily orally for 5 days (for acute amoe-	• Parasitological cure: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical cure: relief of presenting clinical signs and symptoms and healing of	Stool microscopy using direct saline smear

Table 2. Summary of included studies *(Continued)*

			mens positive for trophozoites or cysts of *E histolytica*	groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*	bic dysentery) or 800 mg thrice daily for 5 days (for other cases)	ulcers on sigmoidoscopy, when carried out • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including haemogram, urinalysis, serum bilirubin, transaminases (SGOT, SGPT), alkaline phosphatase, and blood urea	
Misra 1974	1974	Medical College Hospital in Bhopal, India	60 adults and children with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E. histolytica*	Tinidazole: 600 mg twice daily orally for 5 days Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to relieve symptoms or clear the stools of *E histolytica*	Metronidazole: 400 mg thrice daily orally for 5 days (for acute amoebic dysentery) or 800 mg thrice daily orally for 5 days (for chronic intestinal amoebiases if symptoms were of more than 15 days' duration)	• Parasitological cure: eradication of *E histolytica* on follow-up stool examinations or ulcer scrapings on day 30 after start of treatment • Clinical cure: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before and after treatment including complete blood count and platelet count, urinalysis, electrocardiogram, blood urea, serum bilirubin, alkaline phosphatase, and liver transaminases (SGOT, SGPT)	Stool microscopy using direct saline smear or concentration method
Misra 1977	1977	Hospital in Bhopal, India	60 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 2 g single oral dose daily for 3 days	Metronidazole: 2 g single oral dose daily for 3 days	• Parasitological response: eradication of *E histolytica* from stools or ulcer scrapings on day 30 after start of treatment • Clinical response: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including urinalysis, complete blood count, serum bilirubin, alkaline phosphatase, liver transaminases (SGOT, SGPT), blood urea, and electrocardiogram	Stool microscopy using direct saline smear or formol-ether concentration technique

Table 2. Summary of included studies *(Continued)*

Misra 1978	1978	Hospital in Bhopal, India	60 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 2 g single oral dose daily for 3 days	Metronidazole: 2 g single oral dose daily for 3 days	• Parasitological cure: eradication of *E histolytica* from stools on day 30 after start of treatment • Clinical cure: disappearance of presenting clinical symptoms and healing of ulcers on sigmoidoscopy on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory monitoring done before and after treatment including complete blood count, urinalysis, and blood chemistry	Stool microscopy using direct smear or formol-ether concentration technique, sigmoidoscopy for colonic pathology
Pehrson 1984	1984	Outpatient clinic in Stockholm, Sweden	30 adults with clinical symptoms of intestinal amoebiasis but no signs of invasion (e.g. no fever or acute dysentery) and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 600 mg twice daily orally for 5 days	Metronidazole: 800 mg thrice daily orally for 5 days	• Parasitological cure: clearance of *E histolytica* trophozoites or cysts in any of the 3 stool specimens taken 1 month after end of treatment • Adverse events: only adverse events severe enough to result in cessation of therapy	Stool microscopy using direct saline smear or formol-ether concentration technique
Singh 1977	1977	Medical outpatient department of the Government Medical College and Hospital, Patiala, India	60 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 500 mg tablets × 4 (2 g) single dose daily for 3 days	Metronidazole: 400-mg tablets × 5 (2 g) single dose daily for 3 days	• Parasitological response: eradication of *E histolytica* on follow-up stool examinations on day 30 after start of treatment • Clinical response: disappearance of presenting clinical signs and symptoms on day 30 after start of treatment • Adverse events: voluntary reporting of clinical adverse events by participants; laboratory tests monitored before and after treatment including complete blood count, urinalysis, serum bilirubin, alkaline phosphatase, transaminases, and blood urea	Stool microscopy using direct saline smear or formol-ether concentration technique

Table 2. Summary of included studies *(Continued)*

Swami 1977	1977	Visakhapatnam, India (location not stated)	60 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites or cysts of *E histolytica*	Tinidazole: 2 g single dose daily for 3 days Treatment was extended if *E histolytica* persisted in the stool on the day following the last treatment period	Metronidazole: 2 g single dose daily for 3 days	• Parasitological response: eradication of *E histolytica* on follow-up stool examinations on day 30 after start of treatment • Clinical response: relief of presenting clinical signs and symptoms on day 30 after start of treatment • Adverse events: voluntary reporting of adverse events by participants; laboratory tests monitored before and after treatment including blood counts, urinalysis, serum bilirubin, alkaline phosphatase, transaminases (SGOT, SGPT), and blood urea *Not included in this review:* number of participants who required extension of treatment beyond 3 days	Stool microscopy using direct saline smear
Ornidazole versus metronidazole							
Botero 1974	1974	Hospital in Medellin, Colombia	120 adult males with clinical symptoms of intestinal amoebiasis confirmed by the presence of *E histolytica* in the stools	Ro 7-0207 (ornidazole): 2 × 250-mg capsules twice daily for 10 days	Metronidazole: 2 × 250-mg capsules twice daily for 10 days	• Parasitological response: clearance of *E histolytica* from stools at end of treatment and at weekly intervals on follow-up for at least 1 month • Relapse: reappearance of *E histolytica* in the stools within 1 month after becoming negative at end of treatment • Clinical response: disappearance of or improvement in clinical signs and symptoms on day 5, at end of treatment, and at weekly intervals during follow-up for at least 1 month • Adverse events: clinical adverse events monitored for all participants, but cardiovascular, neurological, and laboratory monitoring only for the first 20 participants (laboratory tests not specified)	Stool microscopy using direct saline smear and Ritchie formalin-ether concentration methods
Naoemar 1973	1973	Outpatient clinics in Jakarta, Indonesia	20 adults and children with bloody diarrhoea and stools positive for motile	Ro 7-0207 (ornidazole) given as follows: 2 to 6 years of age – 125 mg daily in	Metronidazole given as follows: 2 to 6 years of age – 125 mg dai-	• Parasitological response: clearance of *E histolytica* from stools at end of treatment and 1 month after end of treatment	Stool microscopy using direct saline smear and stained

Table 2. Summary of included studies *(Continued)*

			haematophagous trophozoites of *E histolytica*	3 divided doses for 7 days; 7 to 12 years of age – 250 mg daily in 3 divided doses for 7 days; adults – 1500 mg daily in 3 divided doses for 5 days	ly in 3 divided doses for 7 days; 7 to 12 years of age – 250 mg daily in 3 divided doses for 7 days; adults – 1500 mg daily in 3 divided doses for 5 days	• Clinical cure: disappearance of symptoms at end of treatment and at 1 month after end of treatment • Relapse: reappearance of *E histolytica* in stools 1 month after end of treatment • Time (range in days) from start of treatment to clearance of *E histolytica* in stool specimens • Time (range in days) from start of treatment to disappearance of bloody diarrhoea • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before and after end of treatment including complete blood counts, liver transaminase (SGPT), alkaline phosphatase, urinalysis, blood urea, and electrocardiogram	smears using eosin and iodine
Pudjiadi 1973	1973	Hospital Department of Child Health, Medical School University of Indonesia, Jakarta, Indonesia	20 children with bloody diarrhoea and stools positive for *E histolytica*	Ro 7-0207 (ornidazole): 125-mg capsule given as follows: up to 2 years of age – 62.5 mg, 2 to 6 years of age – 125 mg, and 6 to 12 years of age 250 mg daily, divided into 3 daily doses for 7 days	Metronidazole: 125-mg capsule given as follows: up to 2 years of age – 62.5 mg, 2 to 6 years of age – 125 mg, and 6 to 12 years of age 250 mg daily, divided into 3 daily doses for 7 days	• Parasitological response: clearance of *E histolytica* from stools after 7 days of treatment • Clinical response: disappearance of clinical symptoms after 7 days of treatment • Time (range in days) from start of treatment to disappearance of *E histolytica* from the stools • Time (range in days) from start of treatment to disappearance of bloody diarrhoea • Adverse events: clinical adverse events monitored during treatment; laboratory tests monitored before, during, and after treatment including complete blood count, urinalysis, electrocardiogram, liver transaminases (SGPT), and alkaline phosphatase	Stool microscopy using direct saline smear and eosin and Lugol's solution
Secnidazole versus metronidazole							
Karabay 1999	1999	Military hospital in Erzurum, Turkey	44 adults with acute amoebic dysentery and	Secnidazole: 2 g single oral dose	Metronidazole: 750 mg thrice daily	• Parasitological response: clearance of *E histolytica* from stools on days 14 and 21	Stool microscopy using 0.85%

Table 2. Summary of included studies *(Continued)*

			stool specimens positive for *E histolytica* cysts and/or trophozoites		orally for 10 days	• Time (mean number of days) from start of treatment to resolution of clinical symptoms (abdominal pain, diarrhoea, bloody diarrhoea, abdominal distension, tenesmus, fever)	saline water, Lugol's solution, and trichrome stain
Panidazole versus metronidazole							
Botero 1977	1977	Colombia (location not stated)	100 adult males with clinical symptoms of intestinal amoebiasis and stools positive for *E histolytica*	Panidazole: 2 × 250-mg tablets (500 mg), 4 times daily for 6 days	Metronidazole: 2 × 250-mg tablets (500 mg), 4 times daily for 6 days	• Parasitological cure: eradication of parasites in any of the post-treatment laboratory examinations • Clinical response: improvement in or disappearance of symptoms during weekly follow-up until 4 weeks after treatment • Adverse events: clinical adverse events monitored during treatment and on follow-up; laboratory tests monitored before and after treatment including complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, liver transaminases, urinalysis, and electrocardiogram *Not included in this review:* number of stools passed in 24 hours on day 3 and day 6 of treatment, and on days 7 and 21 after treatment; clearance of *E histolytica* in 14 asymptomatic carriers	Stool microscopy using direct saline smear and Ritchie formalin-ether concentration methods
Satranidazole versus metronidazole							
Tripathi 1986	1986	Hospital in Bhopal, India	40 adults with symptoms of intestinal amoebiasis and stool specimens positive for *E histolytica*	GO 10213 (satranidazole): 150 mg thrice daily for 10 days	Metronidazole: 400 mg thrice daily for 10 days	• Parasitological response: eradication of *E histolytica* on stool examinations on follow-up 28 days after start of treatment • Clinical response: relief of presenting clinical signs and symptoms and healing of ulcers on sigmoidoscopy on follow-up 28 days after start of treatment • Adverse events: volunteered by participants; laboratory tests monitored before and after treatment including complete blood count, liver transaminas-	Stool microscopy using formol-ether concentration methods, sigmoidoscopy, colonic ulcer scrapings, and positive stool culture on NIH media

Table 2. Summary of included studies *(Continued)*

						es (SGOT, SGPT), serum bilirubin, blood urea, urinalysis, and electrocardiogram *Not included in this review:* frequency of loose stools/d from start of treatment	
Praziquantel versus metronidazole							
Mohammed 1998	1995	Outpatients in Iraq	69 adults with clinical symptoms of intestinal amoebiasis and stool specimens positive for vegetative trophozoite forms (acute amoebic dysentery) or cysts of *E histolytica*	Praziquantel: 40 mg/kg body weight divided into 2 doses orally and taken 4 to 6 hours apart	Metronidazole: 800 mg thrice daily orally for 5 days	• Parasitological response: disappearance of *E histolytica* from stools 1 week after treatment • Clinical response: disappearance of baseline clinical signs and symptoms at end of treatment • Adverse events: voluntary reporting of clinical adverse events by participants only for praziquantel	Stool microscopy using direct saline smear
Combination versus metronidazole							
Rubidge 1970	1970	Hospital in Durban, South Africa	39 children with amoebic dysentery presenting with acute onset of diarrhoea with blood, mucus, and actively motile haematophagous trophozoites of *E histolytica* in stool specimens	Dehydroemetine, tetracycline, and diloxanide furoate: dehydroemetine (2 mg/kg body weight daily by subcutaneous injection for 10 days), tetracycline (50 mg/kg body weight daily orally for 7 days), and diloxanide furoate (25 mg/kg body weight daily orally for 10 days)	Metronidazole: 50 mg per kg body weight orally for 7 days	• Parasitological response: clearance of *E histolytica* at end of treatment and on subsequent stool specimens during follow-up until 28 days after start of treatment • Clinical response: disappearance of symptoms at end of treatment and during follow-up until 28 days after start of treatment • Adverse events: only tolerance to drugs reported	Stool microscopy using direct saline smear and zinc sulphate flotation technique
Asrani 1995	1995	Various cities in India (not specified)	961 male and non-pregnant female patients > 12 years of	Metronidazole and diiodohydroxyquinoline: fixed-drug combi-	Metronidazole: 400 mg thrice daily	• Parasitological cure: clearance of *E histolytica* from stool specimens at end of treatment	Stool microscopy using direct smear

Table 2. Summary of included studies *(Continued)*

			age with clinical symptoms of intestinal amoebiasis and/or presence of trophozoites or cysts of*E histolytica* in stool specimens	nation of metronidazole (200 mg) plus diiodohydroxyquinoline (325 mg) (Qugyl by Sil Pharma, Bombay, India) given as 2 tablets thrice daily for 5 days	orally for 5 days Treatment period was extended to 10 days in both groups when 5 days' treatment was inadequate to clear the stools of *E histolytica*	• Clinical cure: remission of clinical symptoms on days 5 and 10 after start of treatment • Adverse events: clinical adverse events monitored by study personnel during treatment *Not included in this review:* average daily frequency of stools on admission and on day 5 and day 10 of treatment; overall clinical response (rated as "poor" if < 25% relief and not tolerated, "fair" if 25% to 49% relief and not well tolerated, "poor" if 50% to 74% relief and well tolerated, or "excellent" if 75% to 100% relief and well tolerated)	
Prasad 1985	1985	Paediatric outpatient department of S.N. Medical College, Agra, India	180 children with clinical symptoms of intestinal amoebiasis or giardiasis (diarrhoea, abdominal pain, dysentery, gastrocolic urgency, etc.) and whose stools were positive for amoebae or *Giardia*	Metronidazole plus furazolidone: fixed-drug combination suspension of (per 5 mL) metronidazole 75 mg plus furazolidone 25 mg, given as 5 mL thrice daily for those 1 to 5 years of age and as 10 mL thrice daily for those 6 to 15 years of age for 5 or 10 days depending on severity of disease	Metronidazole: 100 mg/5 mL suspension, given as 5 mL thrice daily for those 1 to 5 years of age and as 10 mL thrice daily for those 6 to 15 years of age for 5 or 10 days depending on severity of disease	• Parasitological and clinical response: evaluated jointly on day 7 after start of therapy; overall outcome was reported as complete cure, partial cure, and no cure, but these terms were not defined • Adverse events: clinical adverse events reported by participants during treatment *Not included in this review:* clinical and parasitological response in those with mixed amoebiasis and giardiasis infection; 12/63 from the metronidazole group and 15/101 from the fixed-drug combination metronidazole plus furazolidone had mixed amoebiasis and giardiasis and were not included in this review	Stool microscopy using direct saline smear
Combination versus aminosidine or etophamide or nimorazole							
Pamba 1990	1990	3 district hospitals of Kiambo, Machakos, and Kilifi in Kenya, Africa	417 adults and children with clinical symptoms of intestinal amoebiasis with stool specimens	• Combination of nimorazole and aminosidine (NA): same doses as	• Aminosidine (A): 500 mg twice daily orally for adults,	• Parasitological cure: disappearance of any form of *E histolytica* from stools or ulcer scrapings at end of treatment • Recurrence (relapse): reappearance of *E histolytica* during follow-up on days 15, 30, and 60 after initial disappear-	Stool microscopy using direct smear and a concentration

Table 2. Summary of included studies *(Continued)*

			positive for *E histolytica*	above for 5 days • Combination of nimorazole and etophamide (NE): same doses as above for 5 days • Combination of etophamide and aminosidine (EA): same doses as above for 5 days	15 mg/kg body weight twice daily orally for children for 5 days • Etophamide (E): 600 mg twice daily orally for adults, 15 mg/kg body weight twice daily orally for children for 5 days • Nimorazole (N): 1 g twice daily orally for adults, 20 mg/kg body weight twice daily orally for children for 5 days	ance; owing to incomplete data on follow-up, results could not be included in the meta-analysis • Clinical cure: disappearance of all baseline symptoms at end of treatment • Adverse events: clinical adverse events monitored during treatment *Not included in this review:* cumulative daily clearance of *E histolytica* from stools during treatment, at end of treatment, and on days 15, 30, and 60 after start of treatment; evolution of mild and severe amoebic ulcers seen on rectosigmoidoscopy; and anatomical cure (healing of previous ulceration)	method (not specified)
Quinfamide and mebendazole versus nitazoxanide							
Davila 2002	2002	3 communities in Colima, Mexico	275 children enrolled with various helminthic and protozoal intestinal infections; 105/275 (38%) had *E histolytica* or *E dispar* infection (25 single infection and 80 mixed in-	Quinfamide: 100 mg/5 mL single oral dose; mebendazole 100 mg/5 mL twice daily orally for 3 days was added to quinfamide when another parasite other than *E histolyti-*	Nitazoxanide: 100 mg/5 mL twice daily orally for 3 days	• Parasitological cure: eradication of *E histolytica/E dispar* in stool examination 14 days after treatment • Adverse events: only tolerance to drugs reported Data for parasitological cure were presented separately for nitazoxanide versus quinfamide for single infections and for nitazoxanide versus quinfamide plus	Stool microscopy with direct smear or Kato-Katz technique

Table 2. Summary of included studies *(Continued)*

			fection with other intestinal parasites) and were included in the review	*ca*/*E dispar* was observed		mebendazole for mixed infections, and were included in a separate meta-analysis	
Combination tetracycline and clioquinol versus secnidazole							
Soedin 1985	1983	Outpatient in the Padang Bulan Health Centre, Medan, Indonesia	80 children with clinical symptoms of acute intestinal amoebiasis with stool specimens positive for trophozoites or haematophagous forms of *E histolytica*	Tetracycline and clioquinol: tetracycline (750 mg) and clioquinol (1 g for 5 days)	Secnidazole: 2 g orally in a single dose *Co-intervention:* 2 patients in secnidazole group were given spasmolytics (unspecified) for stomach cramps	• Parasitological response: eradication of *E histolytica* from stools examined on days 1 to 7, and on days 7, 14, and 21 after start of treatment • Clinical response: disappearance of clinical symptoms on days 1 to 7, and on days 14, 21, and 28 after start of treatment • Adverse events: clinical adverse events during follow-up	Stool microscopy using direct saline smear
Combination tinidazole and diloxanide versus tinidazole							
Pehrson 1983	1983	Hospital in Stockholm, Sweden	41 adults and children with clinical symptoms of intestinal amoebiasis but no signs of invasion (e.g. no fever or acute dysentery) and stool specimens positive for trophozoites or cysts of *E histolytic*	Tinidazole plus diloxanide furoate: tinidazole 40 mg/kg body weight in a single oral dose daily for 5 days plus diloxanide furoate 20 mg/kg body weight divided into 3 daily doses for 10 days	Tinidazole: 40 mg/kg body weight in a single oral dose daily for 5 days	• Parasitological response: clearance of *E histolytica* from any of the 3 stool specimens evaluated 1 month after end of treatment • Adverse events: only adverse events severe enough to result in cessation of therapy	Stool microscopy using direct smear or formol-ether concentration technique by Ridley and Hawgood
Secnidazole single dose versus tinidazole for 2 days							
Salles 1999	1999	5 different centres in Brazil	303 children with clinical symptoms of intestinal amoebiasis with	Secnidazole: 1 mL/kg body weight orally in a single dose	Tinidazole: 0.5 mL/kg body weight once daily	• Parasitological response: clearance of *E histolytica* from stool specimens collected on days 7, 14, and 21 following treatment	Stool microscopy using direct smear and

Table 2. Summary of included studies *(Continued)*

			stool specimens positive for *E histolytica* enrolled; 275/303 (90.7%) included in evaluation for clinical efficacy; 300/303 (99%) included in evaluation for parasitological efficacy		orally for 2 days	• Clinical response: disappearance of all symptoms at end of the study (day 21) • Adverse events: solicited from participants or their guardians during follow-up visits	the Faust and Katz method and no history of intolerance to imidazole drugs
Ornidazole versus tinidazole							
Panggabean 1980	1978	Outpatient clinic of the sub-department of Gastroenterology, Department of Child Health Medical School, General Hospital, Medan, Indonesia	40 children with amoebic dysentery presenting with bloody stools and motile haematophagous trophozoites of *E histolytica* in stools: 25/40 (62.5%) analysed 1 week after treatment, 17/40 (42.5%) analysed 2 weeks after treatment, 11/40 (27.5%) analysed 3 weeks after treatment, and 6/40 (15%) analysed 4 weeks after treatment	Ornidazole: 50 mg/kg body weight in a single oral dose daily for 3 days *Other interventions:* Children with concomitant intestinal helminthic infection were given single-dose pyrantel pamoate 10 mg/kg; those with trichuriasis were given mebendazole 1 tablet twice daily for 3 consecutive days	Tinidazole: 50 mg/kg body weight in a single oral dose daily for 3 days	• Parasitological cure: disappearance of all forms of *E histolytica* on stool examinations done weekly until 4 weeks after completion of treatment • Re-infection: reappearance of *E histolytica* after the second month • Clinical cure: disappearance of blood and mucus from stools at follow-up examinations done weekly until 4 weeks after completion of treatment • Adverse events: clinical adverse effects reported by participants during treatment	Stool microscopy using direct smear and eosin 2% stain
Sitepu 1982	1979	Outpatient clinic of the Pediatric Gastroenterology Subdivision, Department of Child Health, School of	50 children with amoebic dysentery presenting with bloody diarrhoea and motile haematophagous trophozoites of *E histolytica* in stools: 41/50	Ornidazole: 50 mg/kg body weight in a single oral dose	Tinidazole: 50 mg/kg body weight in a single oral dose	• Parasitological response: clearance of *E histolytica* from stools on subsequent follow-up visits on days 2 to 4 and 1 week after treatment • Clinical response: disappearance of diarrhoea, and faeces no longer contained mucus or red blood cells on days 2 to 4 and 1 week after treatment	Stool microscopy using direct smear and eosin 1% stain

Table 2. Summary of included studies *(Continued)*

		Medicine, University of North Sumatra/Dr Pirngadi Hospital, Medan, Indonesia	(82%) analysed on the third day or 2 days after treatment, 18/50 (36%) were analysed 1 week after treatment *Losses to follow-up:* 9/51 (18%) were lost to follow-up by the third day or 2 days after treatment - 7 participants in the tinidazole group and 2 in the ornidazole group; 32/50 (64%) were lost to follow-up 1 week after treatment - 18 in the tinidazole group and 14 in the ornidazole group				
Secnidazole versus quinfamide							
Padilla 2000	2000	2 urban federal elementary schools in Celaya, Guanajuato, Mexico (Urban Federal Elementary schools 'Carmen Serdan' and 'Juan Jesus de los Reyes')	239 children with clinical symptoms of non-dysenteric amoebic colitis with at least 1 of 3 stool specimens positive for *E histolytica* cysts	Secnidazole: 30 mg/kg body weight orally in a single dose	Quinfamide: 4.3 mg/kg body weight orally in a single dose	• Parasitological response: clearance of *E histolytica* cysts on days 5, 6, and 7 after administration of drugs • Adverse events: Clinical adverse events were solicited by investigators through direct questioning for the presence of abdominal pain, nausea, vomiting, headache, diarrhoea, and unpleasant taste in the mouth *Not included in this review:* acceptability of the test	Stool microscopy using direct smear and the Faust concentration method
Ornidazole versus secnidazole							

Table 2. Summary of included studies *(Continued)*

Toppare 1994	1994	Medical Center Hospital, Ankara, Turkey	102 children with gastrointestinal symptoms and stool specimens positive for haematophagous trophozoites of *E histolytica*	Ornidazole 15 mg/kg body weight given twice daily orally for 10 days	Secnidazole: 30 mg/kg body weight given as a single oral dose daily for 3 days	• Parasitological cure: clearance of *E histolytica* cysts or trophozoites from stools 10 days after completion of treatment • Clinical response: resolution of diarrhoea and abdominal discomfort • Time (median and range in days) from start of treatment to resolution of clinical symptoms • Adverse events: side effects; method for obtaining information and specific adverse events not reported	Stool microscopy using direct saline smear
Quinfamide versus teclozan							
Guevara 1980	1980	Patients were hospitalized for 1 day, then were followed up as outpatients	40 adults with non-dysenteric amoebiasis with trophozoites of *E histolytica* in recently emitted faecal material and/or in recto-colonic mucosal exudate; recto-colonic lesions suggestive of amoebiasis present or not; and not presenting clinical manifestations of acute amoebic recto-colitis	Quinfamide given at 3 doses in 1 day: 100 mg for 3 doses (300 mg), 200 mg for 3 doses (600 mg), 400 mg for 3 doses (1200 mg)	Teclozan at 3 doses in 1 day: 500 mg for 3 doses (1500 mg)	• Parasitological failure: persistence of trophozoites in rectal exudates by rectosigmoidoscopy 15 and 30 days after end of treatment and in fresh faecal material 8, 15, and 30 days after treatment • Adverse events: Clinical and laboratory tests were monitored on the day after drug administration, then 8, 15, and 30 days after treatment	Stool microscopy using direct saline smear
Chlorhexidine versus diiodohydroxyquinoline							
Kapadia 1968	1968	Bombay, India (location not stated)	100 patients with clinical symptoms of intestinal amoebiasis and stool specimens positive for trophozoites	Chlorhydroxquinoline: 500 mg thrice daily orally for 10 days	Di-diiodohydroxyquinoline: 500 mg thrice daily orally for 10 days	• Parasitological cure: eradication of *E histolytica* from stools at the end of the 10-day treatment period • Clinical cure: improvement in or disappearance of symptoms at the end of the 10-day treatment period	Stool microscopy using direct saline smear

Table 2. Summary of included studies *(Continued)*

			and/or cysts of *E histolytica*			• Adverse events: clinical adverse events and liver function test monitored before and after treatment including total bilirubin, serum albumin and globulin, and zinc sulphate	
MK-910 low dose versus high dose							
Batra 1972	1972	Hospital in New Delhi, India	40 patients (age unspecified) with acute amoebic dysentery and stool specimens positive for trophozoites of *E histolytica*	1-Methyl-2-(4'fluorophenyl)-5-nitroimidazole (MK-910) at low doses: 0.5 mg/kg body weight or 1.0 mg/kg body weight, given in 3 divided doses orally for 10 days	1-Methyl-2-(4'fluorophenyl)-5-nitroimidazole (MK-910) at high doses: 2.0 mg/kg body weight or 3.0 mg/kg body weight, given in 3 divided doses orally for 10 days	• Parasitological response: disappearance of *E histolytica* from stools on day 5 and day 10 of treatment, on both saline and iodine smear examination and on stool culture using NIH medium • Clinical response: reduction in clinical signs and symptoms (tenesmus, diarrhoea, bloody stools) • Time (range in hours) until disappearance of *E histolytica* cysts and trophozoites in stools • Adverse events: monitored by study personnel during treatment; laboratory tests monitored before and on day 5 and day 11 of treatment including complete blood count, platelet count, urinalysis, blood urea, blood sugar, serum bilirubin, alkaline phosphatase, liver transaminases (SGOT, SGPT), thymol turbidity tests, and 12-lead electrocardiogram *Not included in this review:* disappearance of colonic ulcers on sigmoidoscopic examination on day 5 and at end of treatment on day 10	Stool microscopy using direct saline and iodine smears
Fixed drug combination diloxanide-tetracycline-chloroquine versus fixed-drug combination diloxanide-tetracycline							
Nnochiri 1967	1966	Yaba Military Hospital in Lagos, Nigeria	60 military personnel and their families given diagnosis of acute amoebic dysentery and stool specimens positive for *E histolyti-*	Diloxanide furoate, tetracycline hydrochloride, and chloroquine phosphate (per capsule): diloxanide furoate (187.5	Diloxanide furoate and tetracycline hydrochloride (per capsule): diloxanide furoate (187.5 mg) and tetra-	• Parasitological response: clearance of *E histolytica* cysts and trophozoites at end of treatment, then on follow-up 7 weeks from completion of treatment; patients whose stools remained negative 7 weeks after treatment were followed up 3 and 6 months from completion of treatment	Stool microscopy using direct saline and iodine-stained smears

Table 2. Summary of included studies *(Continued)*

			ca: 60 analysed at end of treatment, and 58 (96.8%) analysed 7 weeks after end of treatment	mg), tetracycline hydrochloride (125 mg), and chloroquine phosphate (50 mg) given in 3 dosage regimens of 2 capsules 4 times a day for 5 days, 2 capsules 4 times a day for 7 days, or 2 capsules 4 times a day for 10 days	cycline hydrochloride (125 mg) given in 3 dosage regimens of 2 capsules 4 times a day for 5 days, 2 capsules 4 times a day for 7 days, or 2 capsules 4 times a day for 10 days	• Clinical response: recurrence of symptoms (reported only for those given 10 days' treatment: 16/34 in the diloxanide furoate-tetracycline hydrochloride-chloroquine phosphate group and 10/26 in the diloxanide furoate-tetracycline hydrochloride group) • Adverse events: clinical adverse events monitored during treatment and on follow-up; laboratory tests monitored before and after treatment including urine cytology and presence of protein, blood examination for haemoglobin, total erythrocyte and leucocyte counts, and differential count *Not included in this review:* results of stool examination 3, 6, and 12 months after treatment; clearance of *E histolytica* from stools of 36 asymptomatic cyst carriers	
Metronidazole and *S boulardii* versus metronidazole							
Savas-Erdeve 2009	2007	Outpatient in Turkey	90 children from 1 to 15 years of age who presented with *E histolytica*-associated diarrhoea defined as presence of compatible clinical presentations (acute diarrhoea, fever, and abdominal pain) and presence of *E histolytica* trophozoite engulfing red blood cells in diarrhoeal stool	Metronidazole: 30 to 50 mg/kg/d orally for 10 days (maximum: 500 to 750 mg)	Metronidazole plus *S boulardii* (Reflor, Sanofi-Synthelabo, France): metronidazole 30 to 50 mg/kg/d orally (maximum: 500 to 750 mg) plus lyophilized *S boulardii* 250 mg (includes 5,000,000 living microorganisms) orally once a day for 10 days	• Parasitological response: clearance of *E histolytica* from stool specimens collected 14 days after end of treatment • Clinical response: disappearance of all symptoms (diarrhoea, bloody diarrhoea, vomiting, fever, abdominal pain) at the end of the study (day 10) • Time (median and range in days) to resolution of diarrhoea, bloody diarrhoea, vomiting, fever, abdominal pain • Adverse events: recorded during the active treatment period *Not included in this review:* survival analysis graph of the number of stools per day during the 10-day treatment period	Stool microscopy using direct saline and trichrome stain
Metro-iodoquinol versus metro-iodoquinol + *Saccharomyces*							

Table 2. Summary of included studies *(Continued)*

Mansour-Ghanaei 2003	1996	Shahid Beheshti Educational and Therapeutic Center in Shiraz, Iran	57 adults with amoebic dysentery presenting with mucous bloody diarrhoea, fever, and abdominal pain; stool specimens positive for haematophagous trophozoites of *E histolytica* in the laboratory	Metronidazole, iodoquinol, and placebo: metronidazole 750 mg and iodoquinol 650 mg given thrice daily orally with placebo tablets for 10 days	Metronidazole, iodoquinol, and *S boulardii*: 750 mg and iodoquinol 650 mg thrice daily given orally for 10 days plus lyophilized *S boulardii* 250 mg orally thrice daily given for 10 days	• Parasitological failure: persistence of amoebic cysts at stool examination at 4 weeks after treatment • Mean duration of diarrhoea, abdominal pain, fever, and headache from start of treatment to resolution of symptoms	Stool microscopy using direct faecal smear and flotation technique
Herbal versus fixed-drug combination metronidazole-diloxanide							
Siddiqui 2015	2009	Outpatient department of 2 centres in Pakistan (Shifa-Ul-Maluk Hospital, Gadap and Zahida Medical Centre, North Karachi)	171 patients between the ages of 5 and 60 years with symptoms of amoebiasis (abdominal pain, blood in stool, or diarrhoea) and positive for *E histolytica* cyst or trophozoite: 153 analysed; 18/171 were not included in the analysis	Herbal product (Endemali, Pakistan) available in 4-g sachet containing *Boswellia glabra* 270.9 mg, *Kaolinum ponderosum* 255 mg, *Ocimum pilosum* 580 mg, *Pistacia terebinthus* 116.1 mg, *Plantago ispagula* 812.7 mg, and *Vateria indica* 232.2 mg sweetening agent q.s. Endemali was given 4 times a day for 10 days	Combination of metronidazole 400 mg + diloxanide furoate 500 mg (Entamizole DS, Pakistan) in tablet form given 3 times a day for 5 days	• Parasitological response: no *E histolytica* cyst found in the stool 5 days after treatment was stopped • Clinical response: absence (partial or complete) of symptoms after treatment was stopped • Adverse events: Clinical adverse events were reported by participants after they received study drugs, but the method of reporting was not specified; no biochemical tests were monitored	Stool microscopy using direct smear, Lugol's iodine smear, zinc sulphate flotation preparation, or formalin-ether sedimentation method
Herbal product versus metronidazole							
Shah 2016	2012	Hospital, multi-centre (Shifa-ul-	184 adult patients suffering	Herbal drug Amoebex 400-mg tablet 2 tablets	Metronidazole 400 mg 2 tablets thrice	• Parasitological response: eradication of *E histolytica* from stool specimens at end of treatment	Stool microscopy us-

Table 2. Summary of included studies *(Continued)*

	mulk Memorial Hospital, Hamdard University Karachi, Hakeem, Pakistan)	from amoebiasis infection	after meal thrice daily, duration not reported	daily for 5 days	• Clinical response: disappearance of signs and symptoms of amoebiasis at the end of the study *Not included in this review:* improvement in intensity of symptoms	ing direct saline smear

E dispar: *Entamoeba dispar*; *E histolytica*:*Entamoeba histolytica*; ELISA: enzyme-linked immunosorbent assay; *G intestinalis*: *Giardia intestinalis*; SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase.

Table 3. Time-to-event in trials using various antiamoebic drugs

Outcome	Trial	Intervention	Control	Comments
Time to resolution of diarrhoea	Batra 1972	**MK-910 low dose (≤ 1 mg/kg/d)** Range (h) = 24 to 72, n = 20	**MK-910 high dose (≥ 2 mg/kg/d)** Range (h) = 24 to 48, n = 20	Mean (SD) and median not reported
	Karabay 1999	**Secnidazole** Mean (d) = 1; n = 23	**Metronidazole** Mean (d) = 2, n = 21	SD not reported P > 0.05
	Mansour-Ghanaei 2003	**Metronidazole, iodoquinol and *S boulardii*** Mean (h) = 12 ± 3.7 (SD), n = 28	**Metronidazole, iodoquinol and placebo** Mean (h) = 48 ± 18.5 (SD), n = 29	P < 0.0001
	Rossignol 2001	**Nitazoxanide** Median (d) = 3, n = 36	**Placebo** No median presented because 60% still had diarrhoea at end of follow-up period, n = 31	Mean (SD) and range not reported
	Rossignol 2007	**Nitazoxanide** Mean or median and range not presented, n = 50	**Placebo** Mean or median and range not presented, n = 50	Results presented as survival analysis graph of time from first dose to passage of last unformed stools
	Savas-Erdeve 2009	**Metronidazole and *S boulardii*** Median (range, days) = 4.5 (1 to 10), n = 40	**Metronidazole** Median (range, days) = 5 (1 to 10), n = 45	Mean (SD) not reported
	Toppare 1994	**Ornidazole** Mean (d) = 2 to 3, range (d) = 1 to 5, n = 42	**Secnidazole** Mean (d) = 5, range (d) = 1 to 29, n = 60	SD of mean and median not reported
Time to resolution of bloody stools	Batra 1972	**MK-910 low dose, ≤ 1 mg/kg/d** Range = 48 to 72 hours, n = 20	**MK-910 high dose, ≥ 2 mg/kg/d** Range = 48 to 72, n = 20	Mean (SD) and median not reported
	Karabay 1999	**Secnidazole** Mean (d) = 1, n = 23	**Metronidazole** Mean (d) = 1, n = 21	SD not reported P > 0.05
	Naoemar 1973	**Ornidazole** Range (h) = 48 to 72, n = 10	**Metronidazole** Range (h) = 48 to 72, n = 10	Mean (SD) and median not reported
	Pudjiadi 1973	**Ornidazole** Range (d) = 3 to 7, n = 10	**Metronidazole** Range (d) = 3 to 7, n = 10	Mean (SD) and median not reported
	Savas-Erdeve 2009	**Metronidazole and *S boulardii*** Mean (SD) not reported	**Metronidazole**	

Table 3. Time-to-event in trials using various antiamoebic drugs *(Continued)*

		Median (range, days) = 2 (1 to 5), n = 40	Median (range, days) = 2 (1 to 3), n = 45	
Time to resolution of abdominal pain	Karabay 1999	**Secnidazole** Mean (d) = 2, n = 23	**Metronidazole** Mean (d) = 3, n = 21	SD not reported P > 0.05
	Mansour-Ghanaei 2003	**Metronidazole, iodoquinol, and** ***S boulardii*** Mean (h) = 12 ± 3.2 (SD), n = 28	**Metronidazole, iodoquinol, and placebo** Mean (h) = 24 ± 7.3 (SD), n = 29	P < 0.0001
	Savas-Erdeve 2009	**Metronidazole and *S boulardii*** Median (range, days) = 3 (1 to 10), n = 40	**Metronidazole** Median (range, days) = 2 (1 to 10), n = 45	Mean (SD) not reported
Time to disappearance of *E. histolytica* in stools	Naoemar 1973	**Ornidazole** Range (d) = 2 to 3, n = 8	**Metronidazole** Range (d) = 2 to 3, n = 7	Mean (SD) and median not reported
	Pudjiadi 1973	**Ornidazole** Range (d) = 2 to 4, n = 10	**Metronidazole** Range (d) = 2 to 4, n = 10	Mean (SD) and median not reported

E histolytica: *Entamoeba histolytica*; *S boulardii*:*Saccharomyces boulardii*; SD: standard deviation.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	amoeb*	amoeb*	amoebiasis	amoebiasis	amoeb*
2	Entamoeba	Entamoeba histolytica	DYSENTERY, AMEBIC/DRUG THERAPY	NITROIMIDAZOLE-DERIVATIVE	Entamoeba
3	1 or 2	1 or 2	1 OR 2	EMETINE	1 or 2
4	nitroimidazoles	amoebicides	AMEBICIDES/THERAPEUTIC USE	DILOXANIDE FUROATE	nitroimidazoles
5	emetine	NITROIMIDAZOLES	NITROIMIDAZOLES	carbarsone	emetine
6	diloxanide furoate	emetine	EMETINE	acetarsone	diloxanide furoate
7	quinfamide	diloxanide furoate	carbarsone	acetarsol	quinfamide
8	etofamide	quinfamide	acetarsone	diphetarsone	etofamide

(Continued)

9	etophamide	etofamide	acetarsol	glycobiarsol	etophamide
10	HYDROX-YQUINOLINES	etophamide	diphetarsone	stovarsol	HYDROX-YQUINOLINES
11	chloroquine	HYDROX-YQUINOLINES	glycobiarsol	thioarsenite	chloroquine
12	tetracycline	ARSENICALS	stovarsol	diloxanide furoate	tetracycline
13	erythromycin	chloroquine	thioarsenite	quinfamide	erythromycin
14	niridazole	tetracycline	diloxanide furoate	etofamide	niridazole
15	nitazoxanide	oxytetracycline	quinfamide	etophamide	nitazoxanide
16	4-15/OR	chlortetracycline	etofamide	chiniofon	4-15/OR
17	3 AND 16	erythromycin	etophamide	clioquinol	3 AND 16
18	—	niridazole	HYDROXYQUINOLINES	dichloroacetamide	—
19	—	nitazoxanide	chiniofon	chlorbetamide	—
20	—	4-19/OR	clioquinol	chlorphenoxamide	—
21	—	3 AND 20	dichloroacetamide	chloroquine	—
22	—	—	chlorbetamide	tetracycline	—
23	—	—	chlorphenoxamide	erythromycin	—
24	—	—	chloroquine	oxytetracycline	—
25	—	—	tetracycline	chlortetracycline	—
26	—	—	erythromycin	niridazole	—
27	—	—	oxytetracycline	nitazoxanide	—
28	—	—	chlortetracycline	nimorazole	—
29	—	—	niridazole	nitrimidazine	—
30	—	—	nitazoxanide	2-29/OR	—
31	—	—	nimorazole	1 AND 30	—
32	—	—	nitrimidazine	Limit 31 to human	—
33	—	—	4-32/OR	—	—
34	—	—	3 AND 33	—	—
35	—	—	Limit 34 to human	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Search methods: conference proceedings searched

Conference proceedings	Date and location of conference
Annual Meeting of the American Society of Tropical Medicine and Hygiene	52nd: 3-7 December 2003, Philadelphia, PA, USA 53rd: 7-11 November 2004, Florida, USA 54th: 11-15 December 2005, Washington, DC, USA 55th: 12-16 November 2006, Atlanta, GA, USA 57th: 7-11 December 2008, New Orleans, LA, USA 58th: 18-22 November 2009, Washington, DC, USA 59th: 3-7 November 2010, Atlanta, GA, USA 60th: 4-8 December 2011, Philadelphia, PA, USA 62nd: 13-17 November 2013, Washington, DC, USA 63rd: 2-6 November 2014, New Orleans, LA, USA 64th: 25-29 October 2015, Philadelphia, PA, USA 65th: 13-17 November 2016, Atlanta, GA, USA 66th: 5-9 November 2017, Baltimore, MD, USA
Annual Scientific Conference (ASCON) of the ICCDRB	11th: 4-6 March 2007, ICDDRB, Dhaka, Bangladesh 12th: 9-12 February 2009, ICDDRB, Dhaka,Bangladesh 13th: 14-17 March 2011, ICDDRB, Dhaka, Bangladesh
Asian Conference on Diarrheal Disease and Nutrition	13th: 10 to 12 January 2012, Tagaytay City, Philippines
Asian Congress of Pediatric Infectious Diseases	4th (in conjunction with 14th Indonesian Congress of Pediatrics, Konika): 5-9 July 2008, Surabaya, Indonesia 5th: 23-26 September 2010, Taipei, Taiwan 6th: 28 November-01 December 2012, Colombo, Sri Lanka 7th: 12-15 October 2014, Beijing, China 8th: 8-10 November 2016, Bangkok, Thailand
ASM Microbe (starting in 2016, American Society for Microbiology General Meeting and ICAAC were combined into one meeting - "ASM Microbe")	ASM 2017/ICAAC 2017: 1-5 June 2017, New Orleans, LA, USA
Commonwealth Association of Paediatric Gastroenterology & Nutrition (CAPGAN) Common-	7th (part of 2nd World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition): 3-7 July 2004, Paris, France 8th: 6-8 February 2006, International Centre for Diarrhoeal Diseases Research in Bangladesh (ICCDRB), Dhaka, Bangladesh

(Continued)

wealth Congress on Diarrhoea and Malnutrition	10th: 12-16 August 2009, Blantyre, Malawi 11th: 21-23 July 2011, London, United Kingdom 14th: 2-4 October 2015, New Delhi, India
European Congress of Clinical Microbiology and Infectious Diseases	15th: 2-5 April 2005, Copenhagen, Denmark 16th: 1-4 April 2006, Nice, France 17th (joint conference with 25th International Congress of Chemotherapy): 31 March-3 April 2007, Munich, Germany 18th: 19–22 April 2008, Barcelona, Spain 19th: 17-19 May 2009, Helsinki, Finland 20th: 10-13 April 2010, Vienna, Austria 21st: 7-10 May 2011, Milan, Italy 22nd: 31 March-03 April 2012; London, United Kingdom 23rd: 27-30 April 2013, Berlin, Germany 24th: 10-13 May 2014, Barcelona, Spain 25th: 25-28 April 2015, Copenhagen, Denmark 26th: 9-12 April 2016, Amsterdam, Netherlands 27th: 22-25 April 2017, Vienna, Austria
European Congress on Tropical Medicine and International Health	5th: 24-28 May 2007, Amsterdam, the Netherlands (Workshop on Amoebiasis, Side Meeting, 24 to 25 May 2007) 6th: 6-10 September 2009, Verona, Italy 7th: 3-6 October 2011, Barcelona, Spain 8th: 10-13 September 2013, Copenhagen, Denmark 9th: 6-10 September 2015, Basel, Switzerland 10th: 16-20 October 2017, Antwerp, Belgium
European Society for Paediatric Infectious Diseases Annual Meeting	25th: 2-4 May 2007, Porto, Portugal 26th: 13-17 May 2008. Graz, Austria 27th: 9-13 June 2009, Brussels, Belgium 28th: 4-8 May 2010, Nice, France 29th: 7-11 June 2011, The Hague, The Netherlands 30th: 8-12 May 2012, Thessaloniki, Greece 32nd: 12-15 May 2014, Dublin, Ireland 33rd: 12-16 May 2015, Leipzig, Germany 34th: 10-14 April 2016, Brighton, United Kingdom 35th: 23-27 May 2017, Madrid, Spain

(Continued)

ID Week Meeting (Joint Conference of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society)	1st: 17-20 October 2012, San Diego, CA, USA 2nd: 2-6 October 2013, San Francisco, CA, USA 3rd: 8-12 October 2014, Philadelphia, PA, USA 4th: 7-11 October 2015, San Diego, CA, USA 5th: 26-30 October 2016, New Orleans, LA, USA 6th: 4-8 October 2015, San Diego, CA, USA
Infectious Disease Society of America Annual Meeting	47th: 29 October-1 November 2009, Philadelphia, PA, USA 48th: 21-24 October 2010, Vancouver, BC, Canada 49th: 20-23 October 2011, Boston, MA, USA (last meeting as IDSA Annual Meeting, changed to ID week from 2012 onwards)
International Congress of Chemotherapy	24th: 4-6 June 2005, Manila, Philippines 25th (Joint Conference With 17th European Congress of Clinical Microbiology and Infectious Diseases): 31 March to 3 April 2007, Munich, Germany 26th: 18-21 June 2009, Toronto, ON, Canada 27th (held in conjunction with the 21st European Congress of Clinical Microbiology and Infectious Diseases): 7-10 May 2011, Milan, Italy 28th: 5-8 June 2013, Yokohama, Japan 29th (Joint With the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy), 17 to 21 September 2015, San Diego, CA, USA 30th:4-7 November 2017, Taipei, Taiwan
International Congress on Infectious Diseases	11th: 4-7 March 2004, Cancun, Mexico 12th: 15-18 June 2006, Lisbon, Portugal 13th: 19-22 June 2008, Kuala Lumpur, Malaysia 14th: 9-12 March 2010 Miami, FL, USA 15th: 13-16 June 2012, Bangkok, Thailand 16th: 2-5 April 2014, Capetown, South Africa 17th: 2-5 March 2016, Hyderabad, India
International Society for Infectious Diseases-Neglected Tropical Diseases Meeting	1st: 8-10 July 2011, Boston, MA, USA
Interscience Conference on Antimicrobial Agents and Chemotherapy	44th: 30 October-2 November 2004, Washington, DC, USA 45th: 16-19 December 2005, Washington, DC, USA 46th: 27-30 September 2006, San Francisco, CA, USA 48th (Joint Conference With 46th Annual Meeting of the Infectious Diseases Society of America): 25-28 October 2008, Washington, DC, USA 49th: 12-15 September 2009, San Francisco, CA, USA 50th: 12-15 September 2010, Boston. MA, USA 51st: 17-20 September 2011, Chicago, IL, California, USA

(Continued)

	52nd: 9-12 September 2012, San Francisco, CA, USA 53rd: 10-13 September 2013, Denver, CO, USA 55th (Joint With the 28th International Congress of Chemotherapy Meeting): 17-21 September 2015, San Diego, CA, USA 56th (starting in 2016, General Meeting and ICAAC were combined into 1 meeting - "ASM Microbe": 16-20 June 2016, Boston, MA, USA
Seminars in Amebiasis	14th: 27-30 November 2000, Mexico City, Mexico EMBO Global Lecture Course and Symposium on Amebiasis: 4-7 March, 2012, Khajuraho, India

Appendix 3. Search methods: organizations or institutions contacted for trials on amoebic colitis

Organization	Date contacted
Department of Parasitology, College of Public Health, University of the Philippines, Manila, Philippines	5 July 2005; 3 September 2012; 01 February 2018
Tropical Medicine, Mahidol University, Bangkok, Thailand	7 July 2005; 4 September 2012; 01 February 2018
National Institute of Health, Manila, Philippines	22 July 2005; 3 September 2012; 01 February 2018
South East Asian Ministers Education Organization (SEAMEO) TROPMED Network	27 July 2005; 4 September 2012; 01 February 2018
Research Institute for Tropical Medicine, Alabang, Muntinglupa, Philippines	5 September 2006; 10 August 2012; 01 February 2018
Waterborne and Parasitic Diseases, World Health Organization Regional Office for the Western Pacific, Manila, Philippines (now Malaria, Vector-borne and Parasitic Diseases, World Health Organization Regional Office for the Western Pacific, Manila, Philippines)	5 September 2006; 6 September 2012
Communicable Disease Research, Eastern Mediterranean Regional Office, World Health Organization	23 August 2012
National Institute of Cholera and Enteric Diseases, Calcutta, India	24 September 2006; 14 August 2012; 01 February 2018
South African Medical Research Council, South Africa	17 October 2006; 14 August 2012; 01 February 2018
Department of Medicine, University of Minnesota, Minneapolis,MN, USA	5 June 2006; 16 January 2008
International Centre for Diarrhoeal Diseases Research in Bangladesh (ICCDRB), Dhaka, Bangladesh	7 July 2005; 3 February 2008; 21 August 2012
Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, England	1 February 2008; 10 August 2012; 01 February 2018

(Continued)

University of Guanajuato, Celaya, Mexico	3 February 2008; 01 February 2018
Laboratory of Parasitic Diseases, NIAID, National Institutes of Health, Bethesda, MD, USA	3 February 2008; 01 February 2018
Department of Medicine, Washington University School of Medicine, St. Louis, MN, USA	3 February 2008; 01 February 2018
Department of Infectious Diseases, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, Japan	3 February 2008; 01 February 2018
Division of Infectious Diseases and International Health, University of Virginia Health System, VA, USA	10 August 2012; 01 February 2018
Department of Biotechnology, Indian Institute of Technology, Roorkee, India	5 February 2008; 01 February 2018
Department of Pathology, Center for Discovery and Innovation in Parasitic Diseases, University of California, San Francisco, CA, USA	11 August 2012; 01 February 2018
Infectious Diseases, Departments of Medicine Microbiology and Immunology, Stanford University, Stanford, CA, USA	6 February 2008; 01 February 2018
Department of Molecular Biology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany	11 February 2008; 10 August 2012; 01 February 2018
Microbiology Laboratory, University of California San Diego Medical Center, San Diego, CA, USA	17 August 2012; 01 February 2018
Department of Experimental Medicine, National Autonomous University of Mexico, Mexico City, Mexico	15 August 2012; 01 February 2018

Appendix 4. Search methods: pharmaceutical companies

Company	Relevant drug(s)[a]	Date(s) contacted/database searched
Abbott India Ltd, Mumbai, India	Diloxanide furoate (Furamide); Ornidazole (ZIL) DIloxanide plus metronidazole (Entamizole)	4 September 2012; 30 December 2014; 01 February 2018 (no results found for diloxanide furoate (Furamide); Ornidazole (ZIL); dIloxanide plus metronidazole (Entamizole))
Abbott Laboratories (Pakistan) Limited	Diloxanide plus metronidazole (Entamizole)	30 December 2014; 01 February 2018 (no results found for diloxanide plus metronidazole (Entamizole))
AHPL (Astamed Healthcare Pvt Ltd)	Secnidazole (Secnil, Secnil Forte)	4 September 2012; 30 December 2014; 01 February 2018 (no results found for secnidazole)
Boots Company Pharmaceuticals	Diloxanide furoate (Furamide)	22 September 2006; 01 February 2018 (no results found for diloxanide furoate (Furamide))
CIBA Pharmaceutical Company (merged with Sandoz to form Novartis)	Niridazole (Ambilhar)	22 September 2006; 3 February 2008
Glenmark Pharmaceuticals Ltd (Majesta)	Nitazoxanide (Nitazet)	4 September 2012; 31 December 2014; 01 February 2018

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Glenwood LLC	Iodoquinol (Yodoxin)	22 September 2006; 3 February 2008; 4 September 2012; 31 December 2014
Hoffmann-La Roche & Co Ltd	Oral and injectable dehydroemetine	22 September 2006; Yodoxin discontinued 1 December 2014
International Federation of Pharmaceutical Manufacturers and Association[b]	—	3 June 2006; 22 September 2006; 3 February 2008; 4 September 2012; 01 February 2018[h]
King Pharmaceuticals, Inc (now part of Pfizer)	Paromomycin (Humatin)	31 May 2006; 3 February 2008; 4 September 2012
Lupin Laboratories Ltd (Pinnacle)	Nitazoxanide (Nizonide)	4 September 2012; 31 December 2014; 01 February 2018
Medopharm	Ornidazole (Orizole)	4 September 2012; 31 December 2014; 01 February 2018
Mission Pharmacal Company	Tinidazole (Tindamax)	4 September 2012; 01 February 2018
Nicholas Piramal India Ltd	Ornidazole (Zil); Secnidazole (Secnil, Secnil Forte)	30 December 2014; 01 February 2018
Novartis: Clinical Trial Results Databases[c]	—	3 June 2006; 22 September 2006; 3 February 2008; 04 September 2012; 30 December 2014; 01 February 2018[h]
Presutti Laboratories	Tinidazole (Tindamax) - recently divested to Mission Pharmaceutical	3 June 2006
Pfizer[d]	Metronidazole (Flagyl) Tinidazole (Fasigyn) Etofamide (Kitnos) Paromomycin (Humatin) Quinfamide (Finalam; Amefin)	22 September 2006; 3 February 2008; 4 September 2012; 30 December 2014; 01 Febuary 2018
Roche	Ornidazole (Tiberal) – transferred to Laboratoires SERB	22 September 2006; 01 February 2018
Laboratoires SERB	Ornidazole (Tiberal)	4 September 2012; 01 February 2018
Roche: Clinical Trial Registry and Results Database[e]	—	3 June 2006; 22 September 2006; 3 February 2008; 4 September 2012; 30 December 2014; 01 February 2018[h]
Romark Laboratories, LC[f]	Nitazoxanide (Alinia)	22 September 2006; 3 February 2008; 4 September 2012; 30 December 2014; 01 February 2018
Sandoz (merged with Ciba Geigy to form Novartis)	Metronidazole (Servizol)	22 September 2006; 3 February 2008
Sanofi Aventis[g]	Secnidazole (Flagentyl, Secnidal); metronidazole, (Flagyl); quinfamide (Amenox)	22 September 2006; 3 February 2008; 4 September 2012; 30 December 2014; 01 February 2018

(Continued)

Sanvin Laboratories Pvt Ltd	Quinfamide	22 September 2006; 4 September 2012; 30 December 2014; 01 February 2018

[a]Trade name in brackets.
[b]www.ifpma.org/tag/clinical-trials/ .
[c]www.novartisclinicaltrials.com.
[d]www.pfizer.com/science/clinical-trials
[e]www.roche-trials.com (now provided through independent registries such as ClinicalTrials.gov
[f]www.romark.com/research
[g]www.sanofi.com/en/science-and-innovation/clinical-trials-and-results/
[h]Search terms: 'amoebiasis or amebiasis', 'amoebic dysentery or amebic dysentery', and 'amoebic colitis or amebic colitis'.

Appendix 5. Region and country of trial

Region	Country	Trial(s)
Asia	Bangladesh	Awal 1979
	India	Kapadia 1968; Batra 1972; Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Prasad 1985; Tripathi 1986; Asrani 1995
	Indonesia	Naoemar 1973; Pudjiadi 1973; Panggabean 1980; Sitepu 1982; Soedin 1985
	Pakistan	Siddiqui 2015; Shah 2016
Africa	Egypt	Rossignol 2001; Rossignol 2007
	Kenya	Chunge 1989; Pamba 1990
	Nigeria	Nnochiri 1967
	South Africa	Rubidge 1970
South and Central America	Brazil	Huggins 1982; Salles 1999
	Chile	Donckaster 1964
	Colombia	Botero 1974; Botero 1977
	Mexico	Guevara 1980; Padilla 2000; Davila 2002
Middle East	Iran	Mansour-Ghanaei 2003
	Iraq	Mohammed 1998
Europe and Euroasia	Sweden	Pehrson 1983; Pehrson 1984
	Turkey	Toppare 1994; Karabay 1999: Savas-Erdeve 2009

Appendix 6. Trial setting

Setting	Trial(s)
Hospital	Rubidge 1970; Batra 1972; Pudjiadi 1973; Botero 1974; Misra 1974; Misra 1977; Misra 1978; Awal 1979; Huggins 1982; Pehrson 1983; Tripathi 1986; Pamba 1990; Karabay 1999; Shah 2016
Outpatient clinic	Donckaster 1964; Nnochiri 1967; Naoemar 1973; Singh 1977; Panggabean 1980; Sitepu 1982; Pehrson 1984; Prasad 1985; Soedin 1985; Chunge 1989; Mohammed 1998; Rossignol 2001; Rossignol 2007; Savas-Erdeve 2009; Siddiqui 2015
Community	Davila 2002
School	Padilla 2000
Not stated	Kapadia 1968; Joshi 1975; Mathur 1976; Botero 1977; Swami 1977; Asrani 1995; Salles 1999; Mansour-Ghanaei 2003
Other - most participants treated as outpatients, but a few with severe symptoms treated in hospital	Toppare 1994
Other - patients hospitalized for 1 day, then followed up as outpatients	Guevara 1980

Appendix 7. Participant age in included trials

Age	Number of trials	Trial ID
Adults only (≥ 15 years)	17	Nnochiri 1967; Botero 1974; Joshi 1975; Mathur 1976; Botero 1977; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Guevara 1980; Huggins 1982; Pehrson 1984; Tripathi 1986; Asrani 1995; Mohammed 1998; Karabay 1999; Mansour-Ghanaei 2003; Shah 2016
Children only (< 15 years)	11	Rubidge 1970; Pudjiadi 1973; Panggabean 1980; Sitepu 1982; Prasad 1985; Soedin 1985; Toppare 1994; Salles 1999; Padilla 2000; Davila 2002; Savas-Erdeve 2009
Adults and children	11	Donckaster 1964; Naoemar 1973; Misra 1974; Awal 1979; Pehrson 1983; Chunge 1989; Pamba 1990; Asrani 1995; Rossignol 2001; Rossignol 2007; Siddiqui 2015
Not stated	2	Kapadia 1968; Batra 1972

Appendix 8. Methods used to diagnose amoebic colitis

Method	Technique	Number of trials[a]	Trials
Stool microscopy only	Direct saline wet mount smear	13	Kapadia 1968; Joshi 1975[c]; Mathur 1976; Swami 1977[c]; Awal 1979[c]; Guevara 1980[c]; Prasad 1985;

(Continued)

			Soedin 1985; Toppare 1994; Asrani 1995; Mohammed 1998; Salles 1999; Davila 2002
Stool microscopy plus	Stained smears (Lugol's iodine, eosin, trichrome stain alone or in combination)	10	Nnochiri 1967[a]; Batra 1972[a,c]; Naoemar 1973; Pudjiadi 1973; Panggabean 1980; Huggins 1982; Sitepu 1982; Karabay 1999; Savas-Erdeve 2009; Siddiqui 2015
	Formalin or formol-ether concentration methods	12	Donckaster 1964[a]; Nnochiri 1967[a]; Botero 1974; Botero 1977; Misra 1977[c]; Singh 1977[c]; Misra 1978[c]; Pehrson 1983; Pehrson 1984; Tripathi 1986[a,c]; Chunge 1989; Siddiqui 2015[a]
	Zinc sulphate centrifugal flotation technique	4	Rubidge 1970; Padilla 2000; Mansour-Ghanaei 2003; Siddiqui 2015[a]
	Other concentration method (not specified)	4	Misra 1974[c]; Pamba 1990[c]; Rossignol 2001; Rossignol 2007
	Polvinyl alcohol fixative for detection of trophozoites	1	Donckaster 1964
Stool microscopy plus stool amoebic culture	NIH culture media for xenic cultivation of *E histolytica*[b]	2	Batra 1972; Tripathi 1986
Stool microscopy plus antibody detection test	—	1	Shah 2016
Stool microscopy plus stool antigen-based ELISA test	—	1	Rossignol 2007

[a]Combination of methods in addition to direct stool microscopy: Nnochiri 1967 used iodine-stained smears and formalin-ether concentration technique; Donckaster 1964 used the formalin-ether concentration method for cysts and polvinyl alcohol for trophozoites; Siddiqui 2015 used the zinc sulphate flotation method primarily but also used the formalin-ether sedimentation method when fatty substances in stools interfered with the zinc sulphate flotation method; Batra 1972 used stool microscopy with saline and iodine smears with stool culture for *E histolytica* on NIH media.
[b]Batra 1972 and Tripathi 1986 used NIH media to culture for *E histolytica* in addition to stool microscopy to evaluate parasitological response, but one trial did not use this as an inclusion criterion to enrol participants with amoebic dysentery (Batra 1972).
[c]In addition to stool examination, rectosigmoidoscopy was performed whenever possible in 11 trials to determine the appearance of the bowel mucosa and the presence of ulcers, but it was not used as a sole criterion for enroling participants or evaluating outcome (Batra 1972; Misra 1974; Joshi 1975; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979; Guevara 1980; Tripathi 1986; Pamba 1990).

Appendix 9. Interventions and comparisons included in the trials

Comparison	A	B	Trial(s)
Alternative drug (A) versus metronidazole (B)	Ornidazole (a nitroimidazole)	Metronidazole	Naoemar 1973; Pudjiadi 1973; Botero 1974
	Praziquantel	Metronidazole	Mohammed 1998

(Continued)

	Tinidazole (a nitroimidazole)	Metronidazole	Misra 1974; Joshi 1975; Mathur 1976; Misra 1977; Singh 1977; Swami 1977; Misra 1978; Awal 1979; Pehrson 1984; Chunge 1989
	Secnidazole (a nitroimidazole)	Metronidazole	Karabay 1999
	Panidazole (a nitroimidazole)	Metronidazole	Botero 1977
	Satranidazole (GO 10213) (a nitroimidazole)	Metronidazole	Tripathi 1986
Any antiamoebic drug (A) versus placebo (B)	Quinfamide (all 3 doses combined)	Placebo	Huggins 1982
	Nitazoxanide	Placebo	Rossignol 2001; Rossignol 2007
	10 different drugs belonging to 6 drug classes (dimethyl chlortetracycline, oxytetracycline, tetracycline, chlorphenoxamide, chlorbetamide, dehydroemetine, diiodohydroxyquinoline, iodohydroxyquinoline, phenanthridinone, bismuth glycoarsanilate)	Placebo	Donckaster 1964
Combination regimen (A) versus monotherapy (B)	Dehydroemetine and oral tetracycline and diloxanide furoate	Metronidazole	Rubidge 1970
	Metronidazole and diiodohydroxyquinolone	Metronidazole	Asrani 1995
	Metronidazole and furazolidone	Metronidazole	Prasad 1985
	Nimorazole and aminosidine, nimorazole and etofamide, etofamide and aminosidine	Nimorazole or aminosidine or etofamide	Pamba 1990
	Tetracycline and clioquinol	Secnidazole	Soedin 1985
	Quinfamide and mebendazole	Nitazoxanide	Davila 2002[a] (mixed infections only)
	Tinidazole and diloxanide furoate	Tinidazole	Pehrson 1983
Single-dose regimen versus longer regimen	Quinfamide (1 dose)	Quinfamide (2 or 3 doses)	Huggins 1982
	Secnidazole (1 dose)	Tetracycline and clioquinol (5 days)	Soedin 1985
	Secnidazole (1 dose)	Tinidazole (2 days)	Salles 1999
	Quinfamide (1 dose)	Nitazoxanide (3 days)	Davila 2002[a] (*Entamoeba* infection only)
	Secnidazole (1 dose)	Metronidazole (10 days)	Karabay 1999
Other antiamoebic drug comparisons	Ornidazole	Tinidazole	Panggabean 1980; Sitepu 1982

(Continued)

	Ornidazole	Secnidazole	Toppare 1994
	Chlorhydroxyquinoline	Diiodohydroxyquinoline	Kapadia 1968
	MK-910 low dose (0.5 mg/kg and 1 mg/kg)	MK-910 high dose (2 mg/kg and 3 mg/kg)	Batra 1972
	Quinfamide	Secnidazole	Padilla 2000
	Quinfamide	Teclozan	Guevara 1980
	Quinfamide	Nitazoxanide	Davila 2002[a] (*Entamoeba* infection only)
	Metronidazole and iodoquinol with *Saccharomyces boulardii*	Metronidazole and iodoquinol with placebo	Mansour-Ghanaei 2003
	Metronidazole and *Saccharomyces boulardii*	Metronidazole	Savas-Erdeve 2009
	Herbal drug	Metronidazole	Shah 2016
	Fixed-drug combination of metronidazole and diloxanide furoate	Herbal product	Siddiqui 2015
	Fixed-drug combination of diloxanide furoate and tetracycline with chloroquine	Fixed-drug combination of diloxanide furoate and tetracycline without chloroquine	Nnochiri 1967
Not used but mentioned in Description of studies	Quinfamide (3 doses)	Placebo	Huggins 1982[b]
	Tinidazole (2 durations)	Metronidazole	Awal 1979[c]
	Tinidazole (2 brands)	Metronidazole (2 brands)	Chunge 1989[d]

[a]Different interventions for single and mixed infections.
[b]Trial included in comparison ‘single dose regimen versus longer regimen'.
[c]Trial included in comparison ‘alternative drug versus metronidazole'.
[d]Two brands of tinidazole compared with two brands of metronidazole and included in comparison ‘alternative drug versus metronidazole'.

Appendix 10. Adverse events: alternative drug versus metronidazole

Alternative drug	Trial	General/systemic	Gastrointestinal	Dermatological	Central nervous system	Other	Laboratory abnormal	Remarks
Tinidazole	Awal 1979	—	Anorexia, nausea, vomiting, metallic taste in the mouth reported in both groups, but exact numbers not stated	—	Vertigo: metronidazole - 2 participants	—	No abnormalities in complete blood count, serum bilirubin, alkaline phosphatase, and aspartate aminotransferase noted after treatment in both groups	More adverse effects reported in the metronidazole group (14/23, 61%) compared with the tinidazole group (10/43, 23%). All were mild and transient
	Joshi 1975	—	—	—	—	—	No abnormalities in complete blood count, urinalysis, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and blood urea noted during and after treatment in both groups	Mild adverse effects such as general malaise, nausea, and vertigo not requiring any treatment or change in drug treatment: metronidazole - 7 participants; tinidazole - 6 participants
	Mathur 1976	—	—	—	—	—	No abnormalities in complete blood count, urinalysis, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and blood urea noted during or after treatment in both groups	Mild adverse effects such as metallic taste, anorexia, nausea, and giddiness, which did not require treatment or discontinuation of drug treatment: 9 participants in each group
	Misra 1974	Malaise: tinidazole (1 participant); metronidazole (0 participants)	Loss of appetite, nausea, and vomiting: tinidazole - 1 participant);	No skin rashes noted in either group	Vertigo: metronidazole - 5 participants, tinidazole	Blurring of vision and dysuria: metronidazole - 1 participant	No abnormalities seen in complete blood count, urinalysis, serum bilirubin, alanine aminotransferase, aspartate	Tinidazole better tolerated than metronidazole; Tinidazole group: 2 participants developed a total of 8 adverse effects;

(Continued)

		Loss of appetite and nausea: tinidazole - 2 participants, metronidazole - 2 participants; Vomiting: metronidazole - 1 participant; Altered taste: tinidazole - 2 participants, metronidazole - 2 participants		- 2 participants Headache: metronidazole - 1 participant; Sleep disturbance: metronidazole - 2 participants		aminotransferase, alkaline phosphatase, blood urea, and electrocardiography after treatment in both groups	Metronidazole group: 9 participants developed a total of 17 adverse effects
Misra 1977	—	—	—	—	—	No abnormalities seen in complete blood count, urinalysis, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea, and electrocardiography after treatment in both groups	Significantly more adverse effects reported in participants on metronidazole (16/30, 53.3%) compared with those on tinidazole (8/30, 26.7%) (P < 0.05); 40% of adverse effects in the metronidazole group moderate in intensity, and all side effects in the tinidazole group mild; Most adverse effects were gastrointestinal complaints: nausea, anorexia, vomiting, abdominal discomfort
Misra 1978	—	Nausea: tinidazole - 3 participants, metronidazole - 15 participants; Bitter taste: tinidazole - 3 participants, metronidazole - 1 participant;	—	—	Dark urine: tinidazole - 2 participants, metronidazole - 2 participants	No abnormalities seen in complete blood count, urinalysis, and blood chemistry after treatment in both groups	Significantly more adverse effects reported in participants on metronidazole (16/30, 53.3%) versus tinidazole (8/29, 27.6.%) (P < 0.01); 40% of adverse effects in the metronidazole group moderate in intensity, and all side effects in the tinidazole group mild

(Continued)

		Vomiting: tinidazole - 1 participant; Anorexia: metronidazole - 8 participants; Abdominal pain: metronidazole - 1 participant; Furry tongue: metronidazole - 4 participants; Diarrhoea: metronidazole - 1 participant					
Pehrson 1984	—	—	—	—	—	Not monitored	No participant had any adverse effects severe enough to cause cessation of treatment; Specific adverse effects not reported
Singh 1977	—	—	—	—	—	No abnormalities seen in complete blood count, urinalysis, alkaline phosphatase, transaminases, and blood urea after treatment in both groups	Adverse effects reported in 14/27 (51.9%) participants in the tinidazole group and in 22/29 (75.9%) participants in the metronidazole group; Adverse effects referable to the gastrointestinal tract consisting of anorexia, nausea, bitter taste, and vomiting; Adverse effects mild in the tinidazole group and of mild to moderate intensity in the metronidazole group
Swami 1977	General malaise: metronida-	Metallic taste: tinidazole - 9 participants;	Pruritus: metronida-	Vertigo: tinidazole - 1 par-	Dark-coloured urine:	No abnormalities seen in complete blood count, urinal-	22 adverse effects reported in 15/29 (51.7%) participants in the tinidazole group, 33

(Continued)

		zole - 1 participant	Bitter taste: tinidazole - 4 participants; Anorexia: tinidazole - 2 participants, metronidazole - 3 participants; Abdominal pain: tinidazole - 2 participants, metronidazole - 4 participants; Nausea: tinidazole - 1 participant, metronidazole - 7 participants; Vomiting: tinidazole - 1 participant, metronidazole - 3 participants; Diarrhoea: metronidazole - 2 participants; Excessive salivation: metronidazole - 2 participants	zole -3 participants; Skin rash: metronidazole - 1 participant	ticipant, metronidazole - 2 participants	tinidazole - 2 participants, metronidazole - 4 participants	ysis, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and blood urea during or after treatment in both groups	adverse effects reported in 10/27 (37%) participants in the metronidazole group; Adverse effects moderate in intensity in 2 participants on tinidazole and in 8 participants on metronidazole
Ornidazole	Botero 1974	—	Nausea or vomiting with or without dizziness: ornidazole - 2 participants, metronidazole - 5 participants	—	Dizziness with or without headache: ornidazole - 8 participants, metronidazole - 4 participants;	Joint and muscle pains: ornidazole - 4 participants, metronidazole - 6 participants	Not reported	The first 20 participants were given complete cardiovascular, neurological, and laboratory workup, but these were not specified or reported in detail

(Continued)

				Numbness of the hands and tongue, difficulty in speaking, and headache on day 6 of treatment, which disappeared after treatment was terminated: ornidazole - 1 participant			
Naoemar 1973	—	Severe nausea: metronidazole - 1 participant; Nausea associated with hypersalivation, anorexia, and dizziness: metronidazole - 1 participant; Both improved with rest and reduction in metronidazole dosage from 1500 mg to 1000 mg	—	Dizziness, which disappeared after the dose was reduced from 1500 mg to 1000 mg daily: ornidazole - 2 participants; Slight dizziness, which disappeared with rest: metronidazole - 1 participant	—	No abnormalities seen in complete blood count, urinalysis, alanine aminotransferase, alkaline phosphatase, blood urea, and electrocardiography after treatment in both groups	No significant difference observed in adverse effects of the 2 drugs
Pudjiadi 1973	—	—	—	—	—	No abnormalities seen in the complete blood count, urinalysis, alanine aminotransferase, alkaline phosphatase, and electrocardiography during	No clinical adverse effects (e.g. nausea, loss of appetite, neurological signs) observed

(Continued)

							and after treatment in both groups	
Panidazole	Botero 1977	—	—	—	—	—	No significant changes from pre-treatment results seen after treatment in complete blood count, urinalysis, transaminases, blood urea, and electrocardiography in both groups	37/50 (74%) participants on panidazole presented with ≥ 1 of following adverse effects in order of frequency: dizziness, nausea, headache, vomiting, epigastric pain, cutaneous rash, numbness of mouth, and weakness; 33/50 (66%) participants on metronidazole presented with ≥ 1 of following adverse effects in order of frequency: nausea, dizziness, headache, epigastric pain, vomiting, poor appetite, and metallic taste in the mouth; All symptoms were of low to medium intensity and disappeared after treatment was terminated
Praziquantel	Mohammed 1998	—	—	—	—	—	Not monitored	Main adverse effects reported by participants on praziquantel were nausea and vomiting (5.3%) and dizziness (5.3%); Other adverse effects encountered occasionally included mild fever, joint pain, sore throat, dysuria, retention of urine, and severe apprehension; No adverse events were reported for metronidazole
Satranidazole (GO 10213)	Tripathi 1986	—	—	—	—	—	Complete blood count, urinalysis, serum bilirubin, alanine aminotransferase, aspartate aminotrans-	7 participants in the metronidazole group and 5 participants in the satranidazole group presented with ≥ 1 of following adverse effects:

	ferase, alkaline phosphatase, blood urea, and electrocardiography were done after treatment, but results were not presented	nausea, vomiting, burning in the epigastrium, headache, abdominal distension, and generalized itching;. None were serious or necessitated withdrawal from treatment

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Appendix 11. Adverse events: any antiamoebic versus placebo

Trial	General/systemic	Gastrointestinal	Dermatologic	Central nervous system	Others	Laboratory abnormal	Remarks
Donckaster 1964	General adverse effects (headache, asthenia, vertigo, anorexia): antiamoebic drugs (34/339 participants, 10%); placebo (0) Breakdown in general adverse effects in antiamoebic drugs: dimethylchlortetracycline - 7 participants; oxytetracycline - 1 participant; tetracycline - 4 participants; chlorphenoxamide - 6 participants; chlorbetamide - 2 participants; dehydroemetine - 9 participants; diiodohydroxyquinoline - 1 participant; phenanthridinone - 2 participants; bismuth glycoarsanilate - 2 participants	Gastrointestinal symptoms (nausea and vomiting, meteorism, hyperacidity, epigastric pain, intestinal colic, diarrhoea): antiamoebic drugs (114/339 participants, 34%); placebo (5/28 participants, 18%) Breakdown in antiamoebic drugs: dimethylchlortetracycline - 18 participants; oxytetracycline - 7 participants; tetracycline - 9 participants; chlorphenoxamide - 18 participants; chlorbetamide - 16 participants; dehydroemetine - 27 participants; diiodohydroxyquinoline - 5 participants; phenanthridinone - 4 participants; bismuth glycoarsanilate - 5 participants; iodochlorhydroxyquinoline - 5 participants	Cutaneous symptoms (anal pruritis, erythema): antiamoebic drugs (21/339, 6%); placebo (0) Breakdown in antiamoebic drugs: dimethylchlortetracycline - 5 participants; oxytetracycline - 1 participant; tetracycline - 2 participants; chlorphenoxamide - 2 participants; chlorbetamide - 2 participants; dehydroemetine - 5 participants; phenanthridinone - 3 participants; iodochlorhydroxyquinolone - 1 participant	—	Not monitored	Not monitored	Tolerance was classified as good, fair, or bad according to the number of symptoms presented and their intensity; Tolerance was rated as bad in 27% of participants given dehydroemetine, 23% of participants given dimethylchlortetracycline, and 0% of those given placebo; 1 participant given diiodochlorydroxyquinoline presented with intense and frequent intestinal colic
Huggins 1982	—	Nausea: quinfamide (6/72 participants, 8%); placebo (1/24 participants, 4%)	—	Headache: quinfamide (1/72 partic-	—	Complete blood count, urinalysis,	Adverse effects were based on participants' complaints, consisting

(Continued)

				ipants, 1%); placebo (2/24 participants, 8%)		total cholesterol, blood sugar, bilirubin, urea, creatinine, alkaline phophatase, transaminases, and serum calcium were examined, but results were not presented before or after treatment	of only 2 symptoms - nausea and headache
Rossignol 2001	—	Abdominal pain: nitazoxanide - 1 participant; placebo - 1 participant; Nausea: nitazoxanide - 1 participant; Dyspepsia: nitazoxanide - 2 participants; Worsening diarrhoea: placebo - 1 participant	—	Headache: nitazoxanide - 1 participant; Dizziness: nitazoxanide - 1 participant, placebo - 10 participants; Drowsiness: nitazoxanide - 2 participants, placebo - 1 participant	Dysuria: nitazoxanide - 1 participant	Not monitored	9 adverse effects were reported in 6 participants in the nitazoxanide group, and 4 adverse effects were reported in 4 participants in the placebo group; All adverse effects were mild and transient and none resulted in discontinuation of therapy
Rossignol 2007	Drowsiness: nitazoxanide - 4 participants; Fatigue: nitazoxanide - 1 participant; placebo - 1 participant	Abdominal pain: nitazoxanide - participants, placebo - 1 participant; Dyspepsia: nitazoxanide - 1 participant; Nausea: placebo - 1 participant; Vomiting: placebo - 1 participant	—	Headache: nitazoxanide - 2 participants, placebo - 1 participant	Yellowish urine: nitazoxanide - 1 participant, placebo - 1 participant	Not monitored	All adverse effects were mild and transient and none required discontinuation of treatment

Appendix 12. Adverse events: other comparisons

Comparison	Trial	General/systemic	Gastrointestinal	Dermatologic	Central nervous system	Others	Laboratory abnormal	Remarks
Ornidazole versus tinidazole	Panggabean 1980	—	Vomiting: ornidazole - 1 participant	—	—	—	Not monitored	Adverse effects with both drugs were minimal; no specific details were provided
Secnidazole versus tinidazole	Salles 1999	Fever: secnidazole - 1 participant	Bitter taste: secnidazole - 4 participants, tinidazole - 8 participants; Nausea: secnidazole - 4 participants, tinidazole - 7 participants; Vomiting: secnidazole - 4 participants, tinidazole - 1 participant; Abdominal pain: secnidazole - 1 participant, tinidazole - 1 participant; Flatulence: secnidazole - 1 participant; Soft stools: secnidazole - 1 participant; Diarrhoea: tinidazole - 1 participant	—	Headache: secnidazole - 2 participants, tinidazole - 1 participant; Dizziness: tinidazole - 1 participant	Pharyngeal erythema: secnidazole - 1 participant	Not monitored	Adverse effects were reported in 12/156 (7.7%) participants on secnidazole and in 15/147 (10.2%) participants on tinidazole; all were mild to moderate in intensity' No statistically significant difference in frequency of adverse effects was noted between the 2 groups
Secnidazole versus quinfamide	Padilla 2000	—	Abdominal pain: secnidazole - 18 participants, quinfamide - 4 participants ($P < 0.05$); Nausea: secnidazole - 20 participants, quinfamide - 1 participant ($P < 0.05$); Unpleasant taste in the mouth: secnidazole - 18 participants, quinfamide - 0 ($P < 0.0001$);	—	Headache: secnidazole - 2 participants, quinfamide - 0	—	Not monitored	Adverse effects were significantly higher in the secnidazole group than in the quinfamide group as determined by Chi^2 test ($P \leq 0.05$ considered statistically significant)

(Continued)

			Vomiting: secnidazole - 3 participants, quinfamide - 0; Diarrhoea: secnidazole - 3 participants, quinfamide - 0					
Ornidazole versus secnidazole	Toppare 1994	—	—	—	—	—	Not monitored	No adverse effects were seen; no further details were provided
Quinfamide versus nitazoxanide	Davila 2002	—	—	—	—	—	Not monitored	Both treatments were well tolerated by participants; no further details were given
Quinfamide versus teclozan	Guevara 1980	Mild malaise: quinfamide - none reported; teclozan - 1 participant; Serious adverse events and adverse events necessitating withdrawal: None were reported in both treatment groups	Nausea: quinfamide - 3 participants with moderate nausea, teclozan - 2 participants with mild nausea, 1 with moderate nausea; Vomiting: quinfamide - 3 participants with mild vomiting, 4 with moderate vomiting, teclozan - no vomiting reported; Abdominal pain: quinfamide - 3 participants with mild abdominal pain, 3 with moderate abdominal pain, teclozan - none with abdominal pain; Flatulence: quinfamide - 1 participant with mild flatulence, teclozan - none with flatulence; Burning sensation in the stomach: quinfamide - 1 participant, teclozan - none with burning sensation		Headache: teclozan - 1 participant, quinfamide - 0; Dizziness: quinfamide - 1 participant, teclozan - 0		Haemocytology, serum bilirubin, transaminases, alkaline phosphatase, and urinalysis were determined at baseline, then at 8 and 30 days after treatment, but results were not reported	Gastrointestinal adverse effects such as vomiting and abdominal pain were more common in those given the intermediate dose of quinfamide (200 mg 3 times a day) than in those given 100 mg 3 times a day and 400 mg 3 times a day
Etophamide versus quinfamide	Olaeta 1996	—	Meteorism (developed during treatment period): etophamide - 1 infant	—	—	—	Not monitored	No participant needed to stop treatment because of adverse events;

(Continued)

								no further details were given
Chlorhydroxyquinoline versus diiodohydroxyquinoline	Kapadia 1968	—	Nausea: chlorhydroxyquinoline - 1 participant; Epigastric discomfort with vomiting: chlorhydroxyquinoline - 6 participants, diiodohydroxyquinoline - 0	Mild rash: chlorhydroxyquinoline - 1 participant, diiodohydroxyquinoline - 1 participant	—	Coryza: diiodohydroxyquinoline - 2 participants; Conjunctivitis: diiodohydroxyquinoline - 1 participant	Liver function test before and after treatment remained within the normal range in both groups	—
Combination dehydroemetine, tetracycline, and diloxanide furoate versus metronidazole	Rubidge 1970	—	—	—	—	—	Not monitored	Tolerance of both regimens was reported to be "excellent", and no toxicity was encountered; tolerance was not defined, and no further details were given
Combination metronidazole and diiodohydroxyquinoline versus metronidazole	Asrani 1995	—	Metallic taste: metronidazole alone - 225 participants, metronidazole plus diiodohydroxyquinoline - 224 participants; Abdominal pain: metronidazole alone - 45 participants, metronidazole plus diiodohydroxyquinoline - 46 participants; Vomiting: metronidazole alone - 45 participants, metronidazole plus diiodohydroxyquinoline - 36 participants; Nausea: metronidazole alone - 121 participants, metronidazole plus diiodohydroxyquinoline - 125 participants;	—	Headache: metronidazole alone - 29 participants, metronidazole plus diiodohydroxyquinoline - 26 participants; Drowsiness: metronidazole alone - 3 participants, metronidazole plus diiodohydroxyquinoline	Unspecified allergic reaction (and had to be withdrawn from trial): metronidazole plus diiodohydroxyquinoline - 1 participant	Not monitored	Overall incidence of adverse effects was not statistically significantly different between the 2 groups

(Continued)

			Diarrhoea: metronidazole alone - 5 participants, metronidazole plus diiodohydroxyquinoline - 5 participants		- 11 participants			
Metronidazole and *S boulardii* versus metronidazole	Savas-Erdeve 2009	No adverse effects reported for all patients enrolled in the study	—	—	—	—	Not monitored	*S boulardii* was well tolerated
Fixed drug combination metronidazole and furazolidone versus metronidazole	Prasad 1985	—	—	—	—	—	Not monitored	Both regimens were well tolerated; adverse effects were usually mild in the form of distaste, flatulence, and nausea; Incidence of adverse effects was reported to be greater with metronidazole suspension than with the combination, but no specific details were reported
Combination tetracycline and clioquinol versus secnidazole	Soedin 1985	—	—	—	—	—	Not monitored	Both treatment regimens were reasonably well tolerated and few adverse effects were reported; no further details were given
Combination tinidazole and diloxanide furoate versus tinidazole	Pehrson 1983	—	—	—	—	—	Not monitored	No adverse effects were severe enough to cause cessation of treatment; no further details were given
Fixed drug combination diloxanide furoate, tetracycline with chloroquine	Nnochiri 1967	—	Flatulence and abdominal discomfort: 8 participants in both groups (unclear whether adverse effects were seen in 8 participants in each of the two	—	—	—	No abnormalities were noted in complete blood count and urinaly-	—

(Continued)

versus fixed drug combination diloxanide furoate and tetracycline without chloroquine			groups, or in a total of 8 participants in both groups)				sis during or after treatment	
Aminosidine, etophamide, nimorazole alone or in combination	Pamba 1990	—	—	—	—	—	Not monitored	Drug tolerance was rated as poor in 1.0% of patients given aminosidine, 2.0% of patients given combination nimorazole and aminosidine, and 76.5% of patients given etophamide and aminosidine; Recruitment of participants in the etophamide-aminosidine group was discontinued because of the high incidence of severe diarrhoea; no other details of adverse events were given
MK-910 low dose (0.5 mg/kg and 1 mg/kg) versus MK-910 high dose (2 mg/kg and 3 mg/kg)	Batra 1972	—	Vague abdominal pain: 1 participant each in the low dosage groups (total of 2 participants), 3 participants each in the higher dosage groups (total of 6 participants); Nausea and vomiting: 4 participants each in the higher dosage groups (total of 8 participants), 2 participants, 1 in each of the higher dosage groups had to be removed from the trial because of the severity of gastrointestinal symptoms	—	—	—	Not monitored	—

(Continued)

Herbal versus fixed drug combination metronidazole-diloxanide	Siddiqui 2015	Serious adverse events and adverse events necessitating withdrawal: none reported in both treatment groups; Headache: herbal - 1 participant, metrodiloxanide combination - 5 participants	Anorexia: herbal - 2 participants, metrodiloxanide combination - 14 participants; Metallic taste: herbal - 2 participants, metrodiloxanide combination - 7 participants; Flatulence: herbal - 0, metrodiloxanide combination - 5 participants; Abdominal pain: herbal - 1 participant, metrodiloxanide combination - 4 participants		Others (not specified) : herbal - 1 participant, metrodiloxanide combination - 2 participants	Not monitored	Significantly more side effects were reported in those given metronidazole-diloxanide than in those given herbal (P < 0.00)

Abbreviations:*S boulardii*:*Saccharomyces boulardii.*

WHAT'S NEW

Date	Event	Description
7 January 2019	New citation required but conclusions have not changed	Four new trials met the inclusion criteria. We assessed the certainty of the evidence using the GRADE approach.
7 January 2019	New search has been performed	This is an update of a review published in 2009. We included four new trials to the previously published review version

CONTRIBUTIONS OF AUTHORS

MLMG conceived and designed the review, co-ordinated its development, and prepared initial drafts of the Background and Methods, selected studies, extracted data, synthesized data in RevMan 5, and prepared the initial draft of the Results, Discussion, and 'Summary of findings' tables. LFD advised MLMG about design and co-ordination of the review and, together with MLMG, selected studies and extracted data, assessed risk of bias, and contributed to the Discussion and Authors' conclusions. JSA evaluated full-text articles, extracted data from the included trials, resolved differences between the other two review authors regarding assessment of papers, and contributed to the Discussion and Authors' conclusions.

DECLARATIONS OF INTEREST

MLMG has no known conflicts of interest.
LFD was an invited lecturer on a talk sponsored by Wyeth Nutrition. She has no other conflicts of interest to declare.
JSA has no known conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since many trials reported outcomes 28 days or one month after treatment, we decided to stratify outcomes from end of treatment to 14 days and 15 to 60 days after end of treatment, instead of reporting outcomes at end of treatment until seven days after treatment and eight to 21 days after end of treatment, as stated in the protocol (Gonzales 2006). We performed subgroup analysis, not mentioned in the protocol, based on clinical categories (amoebic dysentery, non-dysenteric amoebic colitis, or not specified) and participant age (adults or children). Additional sources of heterogeneity explored included types of intestinal infection (*Entamoeba histolytica* infection alone or mixed intestinal infection), and criteria for determining outcomes (based on WHO 1969 criteria or other criteria). We were unable to undertake sensitivity analysis based on type of diagnostic test because only one included trial used stool antigen-based ELISA to confirm *E histolytica*. However, we performed sensitivity analysis to determine the possible effect of pharmaceutical industry-sponsored trials on trial quality.

Differences between review and review update

MLMG, LFD, and EGM authored the protocol and the previous published review version (Gonzales 2006; Gonzales 2009). For this review update, EGM stepped down from the review author team, and JSA joined as a review author. We updated epidemiological data on amoebiasis and amoebic colitis. We re-classified nitazoxanide, initially classified as a luminal amoebicide in the earlier version of this review, as a tissue amoebicide in Table 1 since more recent studies reported effectiveness of this drug against invasive trophozoites. We added four specific objectives to Gonzales 2009 to provide a more focused direction for the review.

We created a study flow diagram based on the PRISMA template (Figure 1). We prepared a 'Risk of bias' table for each included trial, including the four new trials added to this review update. We summarized continuous data (duration of clinical symptoms) that were

measured in the included studies in a new table (Table 3). We assessed the certainty of the evidence for two important outcomes (tinidazole compared with metronidazole as treatment for amoebic colitis, and combination therapy compared with metronidazole alone as treatment for amoebic colitis) using the GRADE approach (GRADE 2004), and we presented this information in 'Summary of fIndings' tables (Summary of findings for the main comparison; Summary of findings 2).

INDEX TERMS

Medical Subject Headings (MeSH)

*Entamoeba histolytica; Amebicides [adverse effects] [*therapeutic use]; Drug Therapy, Combination; Dysentery, Amebic [*drug therapy] [parasitology]; Metronidazole [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Tinidazole [adverse effects] [therapeutic use]

MeSH check words

Animals; Humans