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Prevention and treatment of cryptosporidiosis in immunocompromised patients (Review)

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TABLE OF CONTENTS

Prevention and treatment of cryptosporidiosis in immunocompromised patients

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A B S T R A C T

Background

Cryptosporidiosis is a disease that causes diarrhoea lasting about one to two weeks, sometimes extending up to 2.5 months among the immunocompentent and becoming a more severe life-threatening illness among immunocompromised individuals. *Cryptosporidium* is a common cause of gastroenteritis. Cryptosporidiosis is common in HIV-infected individuals.

Objectives

The objective of the review was to assess the efficacy of interventions for the treatment and prevention of cryptosporidiosis among immunocompromised individuals.

Search methods

We searched the following databases for randomised controlled trials up to August 2005: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, AIDSLINE, AIDSearch, EMBASE, CINAHL, Current Contents, Geobase, and the Environmental Sciences and Pollution Management.

Selection criteria

Randomised controlled trials that compared the use of any intervention to treat or prevent cryptosporidiosis in immunocompromised persons were included. The outcome measures for treatment studies included symptomatic diarrhoea and oocyst clearance.

Data collection and analysis

Two reviewers independently assessed the trials for quality of randomisation, blinding, withdrawals, and adequacy of allocation concealment. The relative risk for each intervention was calculated using a random effects model.

Main results

Seven trials involving 169 participants were included. There were 130 adults with AIDS enrolled in five studies. Evidence of significant heterogeneity was present. There was no evidence for a reduction in the duration or frequency of diarrhoea by nitazoxanide (RR 0.83 (95% CI 0.36-1.94)) and paramomycin (RR 0.74 (95% CI 0.42-1.31)) compared with placebo. Nitazoxanide led to a significant evidence of oocyst clearance compared with placebo among all children with a relative risk of 0.52 (95% CI 0.30-0.91). The effect was not significant for HIV-seropositive participants (RR 0.71 (95% CI 0.36-1.37)). HIV-seronegative participants on nitazoxanide had a significantly higher relative risk of achieving parasitological clearance of 0.26 (95% CI 0.09-0.80) based on a single study. The single study comparing spiramycin with placebo found no significant difference in reduction of the duration of hospitalisation (mean difference -0.40 days (95% CI -6.62-5.82)) or in mortality between the two arms of the trial (RR 0.43 (95% CI 0.04-4.35)). One study assessed the role of bovine dialyzable leukocyte extract, reporting a relative risk for decreased stool frequency of 0.19 (95% CI 0.03-1.19), while another compared bovine hyperimmune colostrum with placebo and found no evidence for improvement of stool volume (RR 3.00 (95% CI 0.61-14.86)) or in oocyst concentration per ml of stool (RR 0.27 (95% CI 0.02-3.74)). No studies were found that assessed prevention.

Authors' conclusions

This review confirms the absence of evidence for effective agents in the management of cryptosporidiosis. The results indicate that nitaxozanide reduces the load of parasites and may be useful in immunocompetent individuals. Due to the seriousness of the potential outcomes of cryptosporidiosis, the use of nitaxozanide should be considered in immunocompromised patients. The absence of effective therapy highlights the need to ensure that infection is avoided. Unfortunately, evidence for the effectiveness and cost-effectiveness of preventive interventions is also lacking.

PLAIN LANGUAGE SUMMARY

Not enough evidence on effectiveness of drugs or preventive measures on disease caused by *Cryptosporidium*.

Cryptosporidiosis is a disease that causes diarrhoea, and can be life-threatening in individuals whose bodies are not able to resist infections. It causes disease in the both the developed and the developing world. This review of trials found insufficient evidence to say whether any drug is able to reduce or cure the symptoms of *Cryptosporidium* infection or to effectively kill the organism among individuals who cannot resist infections. A limited amount of evidence was found indicating that the drug nitaxozanide can kill the organism in individuals with a normal immunity.

BACKGROUND

Cryptosporidiosis is a disease caused by a coccidial parasite of the genus Cryptosporidium. *Cryptosporidium hominis*, formally *Cryptosporidium parvum* genotype 1(Morgan-Ryan 2002) and *C. parvum*, are the most frequent cause of human infection. Cryptosporidiosis affects immunocompetent (particularly children under the age of five years) and immunocompromised individuals worldwide, especially HIV-infected individuals. It causes diarrhoea lasting about one to two weeks, sometimes extending up to 2.5 months among the immunocompetent and resulting in a more severe life-threatening illness among immunocompromised individuals (Hunter 2002). The World Health Organisation's guideline for drinking water classifies *Cryptosporidium* as a pathogen of significant public health importance, aided in part by

the organisms low infective dose and its resistance to conventional water treatment, such as chlorination (Havelaar 2003).

Cryptosporidium has been responsible for major outbreaks, (MacKenzie 1994; Cicirello 1997) as well as sporadic cases of gastroenteritis in the developed world (McLauchlin 2000). *Cryptosporidium* is also widespread in the developing world, with 10-30% of individuals being asymptomatic cyst excretors (Current 1991). Cryptosporidiosis is common in HIV-infected individuals.

Treatment of underlying immunosuppression with antiretrovirals has been found to reduce the severity of cryptosporidiosis in HIV-positive persons (Carr 1998; Maggi 2000), but does not result in a parasitological cure. Immunocompromised persons who are not HIV-infected do not have the option of using antiretrovirals. Ef-

fective treatment for cryptosporidiosis will be useful as an adjunct to antiretroviral therapy, as well as in settings where antiretrovirals are either too expensive or not availableSYMBOL 190 \f "Symbol" \s 9for example, for malnourished children in the developing world. Also, if effective treatments were available, cancer and post-transplant patients would not be required to interrupt immunosuppression in order to control cryptosporidiosis.

Several antimicrobials have been proposed for the treatment of cryptosporidiosis among the immunocompromised. Evidence from clinical trials has shown that some of the antimicrobials ameliorate the disease. Several drugs have been tested in clinical trials, including nitazoxanide, paromomycin, rifabutin, and several macrolides (azithromycin, clarithromycin, and spiramycin). In a review of current and potential therapeutic agents available for the treatment of cryptosporidiosis among immunocompromised persons, Mead suggested the need to explore newer agents, because effective drugs to eradicate *Cryptosporidium* are lacking (Mead 2002). The evidence summarised showed limited effectiveness in clinical trials with macrolides (azithromycin and clarithromycin), paromomycin, and nitazoxamide. The reviewed trials showed that statistically there were no significant effects for other agents, such as spiramycin, diclazuril, and letrazuril, and only mixed results with immunotherapy using agents such as hyperimmune bovine colostrums. A variety of approaches to using passive antibody immunotherapy were found to have some degree of efficacy, though the responses have been, for the most part, partial rather than complete resolution of disease (Crabb 1998). There is very little evidence for preventive measures for cryptosporidiosis among immunocompromised individuals. Most guidelines are based on expert opinion and observational studies (CDC 1995; Juranek 1995; Okhuysen 1997; Hunter 2000). A variety of measures can be used to either reduce exposure to *Cryptosporidium* or to increase the individuals' resistance to infection. Possible measures include boiling drinking water for over a minute, point of use filter, and the use of hyperimmune bovine colostrums as a prophylactic agent (Greenberg 1996). Bovine antibodies and hyperimmune bovine colostrums have also shown encouraging results (McMeeking 1990; Nord 1990).

The management of *Cryptosporidium* infection is likely to vary between the developed world and the developing world, as drug interventions may not be readily available, especially in developing countries, within the first few years of marketing. It is unlikely that the effectiveness of the drugs will vary in the two different settings for individuals with similar nutritional and immunity status. Prevention will be more relevant to a developing country situation, but effective measures identified in one setting may apply to both.

AIMS OF TREATMENT

Cryptosporidiosis is self-limiting in the immunocompetent but not in the immunocompromised patient, where it can be life threatening. The aim of treatment is to reduce the duration of diarrhoea, prevent complications, eliminate the organism from the host, and reduce mortality.

Aim of prevention

The primary aim of prevention is to reduce the number of new cases of cryptosporidiosis.

OBJECTIVES

Treatment:

·To assess the effect of antimicrobials or antibodies on the duration and frequency of diarrhoea as a result of cryptosporidiosis among immunocompromised persons.

·To assess the effect of antimicrobials or antibodies on parasite clearance among immunocompromised persons with cryptosporidiosis.

·To assess the effect of antimicrobials or antibodies on mortality among immunocompromised persons with cryptosporidiosis.

·To estimate the tolerability and adverse effects of antimicrobials used for the treatment of cryptosporidiosis.

Prevention:

·To assess the effect of boiling water or point of use filter in the prevention of *Cryptosporidium* infection among immunocompromised persons.

·To assess the effect of antimicrobials or antibodies in the prevention of cryptosporidiosis.

METHODS

Criteria for considering studies for this review

Types of studies

All published or unpublished randomised controlled trials (RCT) where a specified agent (antimicrobial or antibodies) was compared with placebo or no treatment in patients with cryptosporidiosis. RCTs of interventionsSYMBOL 190 \f "Symbol" \s 9use of filters, boiling water, other water treatment, or drugs for the prevention of infection were considered.

Types of participants

The types of participants included immunocompromised adults and children with proven cryptosporidiosis for treatment, and those without evidence of infection for prevention trials. Immunocompromised persons for the purpose of this review included

the following three categories: 1) HIV-infected individuals (with or without AIDS), 2) malnourished children, and 3) individuals on immunosuppressive therapy. Subgroup analysis was planned where appropriate to explore the effect of interventions in each group. We planned to split the data based on developing or developed country status.

Types of interventions

In the intervention group, we considered specific, identified trials that utilised antibiotics or antibodies to treat persons with diagnosed cryptosporidiosis. The antibiotics and antibodies included the following:

·Paromomycin
·Nitazoxanide
·Macrolides: azithromycin, clarithromycin, or spiramycin
·Rifabutin, rifaximin
·Bovine immunoglobulin.

In the control group, a placebo or no antibiotics were used.

We considered prevention trials evaluating the effect of bovine immunoglobulin, macrolides, water boiling, use of filters, and other water treatment measures.

Control group: people randomised to placebo in the case of prophylactic drug interventions, or ineffective or routine water treatment or filtration methods.

Types of outcome measures

PRIMARY OUTCOMES
Treatment
·Duration of diarrhoea (defined by time from onset of unformed stools to last unformed stool) and stool volume/number of bowel motions. Resolution of diarrhoea is defined as no further loose stools for 72 hours.
·Recurrence of diarrhoea
·Parasitological clearance/concentration of oocyst /oocyst shedding
·The number of deaths
Prevention
·Episodes of diarrhoea due to *Cryptosporidium* occurring in control compared to intervention group.
SECONDARY OUTCOMES
·The occurrence of side effects.

Search methods for identification of studies

Please refer to the HIV/AIDS Group search strategy.

We utilised a search strategy that combines a highly sensitive filter for randomized controlled trials and subject specific terms. Although the protocol included terms to limit the search to specific drugs/preventive interventions, this review has not used this limi-

tation to enhance the ability to detect all relevant studies. We did not have any language or publication status restrictions.

We used the following terms to search for eligible randomised controlled trials or review articles: subject terms (Cryptosporidiosis) OR (*Cryptosporidium*) OR (*Cryptosporidium parvum*) AND the revised optimised search strategy for trials (Robinson 2002) using the OVID interface.

Other search terms used for prevention trials include Prevention [MeSH] OR Water Purification [MeSH] OR Biofilter[MeSH] OR Water Quality [MeSH] OR Water Supply [MeSH] "OR" the following non MESH terms: boiling water OR water-treatment devices OR filters AND the subject terms outlined above.

The following databases were searched:
·The Cochrane Controlled Trials Register (CCTR)
·MEDLINE (1966 - August 2005)
·EMBASE (1980 - August 2005)
·AIDSLINE 1980 to 2000
·AIDSearch (MEDLINE AIDS/HIV Subset, AIDSTRIALS & AIDSDRUGS databases) 1980 to August 2005
·Biosis (1969 - August 2005)
·Current Contents (1993 to August 2005)
·Web of Science (1945 to August 2005)
·Database of Abstracts and Reviews of Effects (1994 to August 2005)
·CINAHL (1982 - August 2005)
·Conference proceedings of the World AIDS Conference and abstracts
·Geobase (1980 - August 2005)
·Environmental Sciences and Pollution Management (1981 to August)
·Environment Abstracts (1975 to August 2005)

Reference lists of review articles, included, and excluded studies were used to identify further studies for the review. Authors and other researchers working on were consulted to aid in the identification of unpublished studies or other studies missed by our search strategy.

Data collection and analysis

Study eligibility and application of inclusion and exclusion criteria

Using the above search strategy, two reviewers independently reviewed all identified titles and abstracts. If the title and/or abstract was felt to be relevant by either reviewer, the full text of the article was reviewed. From the full text, and using specific criteria, we independently selected trials for inclusion. We measured agreement using the kappa statistic and resolved disagreement by consensus. All randomised controlled trials of interventions (drug treatment or preventive measures) identified using the search strategy outlined above and meeting the set criteria were included.

Data extraction
Two reviewers independently extracted data in a standard form. Disagreements were resolved by consensus. Trials that satisfied the

inclusion criteria were reviewed and the following information recorded: study setting, year of study, participant characteristics (age and cause of immunosuppression), intervention and control given, co-intervention (such as use of antiretrovirals), duration of diarrhoea, location, outcome measures, whether the study was conducted in a developed or developing country, and the source of funding for the study. Other characteristics recorded included publication details, allocation concealment, blinding after allocation, generation of allocation sequence, the inclusion of all randomised participants, and loss to follow-up (intention to treat analysis).

Assessment of methodological quality

The quality of the included studies was independently assessed. The following quality criteria were assessed:

·Allocation concealment, in which trials were scored with the following grades: Grade A: adequate concealment; Grade B: unclear; Grade C: clearly inadequate concealment.

·The Jadad Scale (Jadad 1996) was used to assess the methodological quality of the included studies. This scale scores three dimensions of study quality: randomisation, blinding, and study withdrawals. The maximum possible score is five. See Table 1.

The scale is as follows:

·Was the study described as randomised (this includes words such as randomly, random, and randomisation)? 0/1

·Was the method used to generate the sequence of randomisation described and appropriate (table of random numbers, computer-generated, etc)? 0/1

·Was the study described as double blind? 0/1

·Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)? 0/1

·Was there a description of withdrawals and dropouts? 0/1

·Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate (e.g., participants were allocated alternately, or according to date of birth, hospital number, etc). 0/-1

·Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy). 0/-1

Conflicts in coding were resolved by discussion.

Statistical analysis

A meta-analysis was performed to generate summary point estimates and corresponding confidence intervals for the relevant outcomes. Evidence for statistical heterogeneity of results was assessed using Cochrane Q Chi square test and I squared statistic. A significance level of less than 0.10 and I squared greater than 50% was interpreted as evidence of heterogeneity. If significant heterogeneity was found, the results from the random effects model were emphasised and the relevant factors explored in subgroup analysis where data is available. Analyses were performed with Cochrane's Review Manager (Version 4.2.8).

We planned to conduct subgroup analysis of HIV status in developing or developed country studies, but there was insufficient data

to carry these out. We planned sensitivity analysis by removing lower-quality studies, but due to the absence significant results, this plan was not carried out. The potential for publication bias will be assessed by visually examining funnel plots for evidence of asymmetry.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The initial search identified 1503 potentially relevant titles. After reviewing the titles and abstracts, 21 papers in full text were obtained for consideration of inclusion into the review. Fourteen papers were excluded. Details are provided in the table "Characteristics of excluded studies." The main reasons for exclusion were the non-randomised nature of the studies (;Saez-Llorens 1989; Flanigan 1996; Dionisio 1998; Smith 1998; Sprinz 1998; Uip 1998; Amenta 1999; Fichtenbaum 2000), the use of healthy, immunocompetent adults or children (Woolf 1987; Okhuysen 1997; Hellard 2001; Rossignol 2001) single patient trial (Greenberg 1996), or the lack of adequate placebo or comparator (Kadappu 2002).

The review identified seven studies. All identified studies were "treatment" studies; there were no "prevention" studies. The details are provided in the table "Characteristics of included studies."

Participants

Studies that considered treatments for cryptosporidiosis were based on immunocompromised participants randomised to either antibiotics or antibodies. Of the seven treatment studies, two (Amadi 2002) and (Wittenberg 1989) involved children. Amadi's nitazoxanide study involved 100 malnourished children (age range 12-85 months), including 50 HIV-positive children and 50 children who were HIV negative. Wittenberg tested the effectiveness of spiramycin on 39 malnourished paediatric participants whose ages ranged from 5.8 +/- 3.9 months in the treatment group, and 6.3+/- 5.2 months in the placebo group. Although the children were described as being malnourished in both studies, only Amadi defined malnutrition status as being severely, moderate, or mildly underweight. The remaining five treatment studies (Nord 1990; McMeeking 1990; White 1994; Rossignol 1998; Hewitt 2000) involved immunocompromised adults with AIDS. The age range of subjects in four of these studies was 21-60 years. The ages of participants in the study by Nord was not given. The presence of *Cryptosporidium* oocysts in stools was a prerequisite in the treatment studies. However, the duration of infection was not made clear in all studies. In three studies, subjects were included in the trials if there were *Cryptosporidium* oocysts in stools at entry. In order to be eligible subjects in the studies by Amadi/Rossignol,

Hewitt and Nord, subjects had to have had *C. parvum* oocysts in their stools for at least 7, 14 or 30 days, respectively. The laboratory methods used to diagnose *Cryptosporidium* oocysts were clearly described in four studies (Wittenberg 1989; White 1994; Rossignol 1998; Amadi 2002).

Interventions

Of the seven treatment studies, two studies looked at the effectiveness of nitazoxanide (Rossignol 1998; Amadi 2002), two studies were on paramomycin (White 1994; Hewitt 2000), one study was on spiramycin (Wittenberg 1989), one study on bovine immunoglobulin (Nord 1990) and another on bovine dialyzable leukocyte extract (McMeeking 1990).

In the study by Amadi, children received 100mg nitazoxanide or matching placebo twice daily for three consecutive days, whilst Rossignol randomised adults to receive either 500mg or 1000mg of Nitazoxanide or placebo 12 hourly for fourteen days.

In one of the two paramomycin studies, Hewitt randomised participants to receive 500mg of paramomycin or placebo for 21 days, after which all were given paramomycin non-blinded. White randomised participants to receive 25-35 mg/kg/day paramomycin or placebo for 14 days. They were crossed over to the other treatment for an additional 14 days. In the only spiramycin study, Wittenberg randomised participants to receive 75 mg/kg/day of spiramycin for five days. In the two bovine immunoglobulin studies, McMeeking gave bovine dialyzable leukocyte extract, 5 IU or 5x108 lymphocyte equivalent, weekly for eight weeks. Nord used bovine hyperimmune colostrum or bovine colostrum with no anti-cryptosporidial activity at a dose of 30 mg total immunoglobulin / ml for 10 days.

Outcomes

This review's primary outcome measures include clinical response based on change in frequency or duration of diarrhoea and mortality and parasitological response as assessed by oocyst clearance. Recurrence of diarrhoea was not measured because there was insufficient data in the included studies. This review's secondary outcome measure is the occurrence of side effects.

Paramomycin

Hewitt defined clinical response as measured by an average number of bowel movements per day, in association with a concurrent need for anti-diarrhoeal agents that was lower than that required for entry to the study. Three categories of clinical response were investigated: complete, partial, and no change/increase in use of anti-diarrhoeal preparations. Other outcome measures included quantification of *Cryptosporidium* oocytes (defined as the number of parasites in the stool), drug tolerance (as defined by the occurrence of dose limiting toxicity), changes in weight and abdominal symptoms as reported by the participant, and adverse events. White defined a clinical response based on stool frequency (the number of stools in 24 hours at baseline and at the end of treatment) and stool weight in grams, comparing baseline measurement with end of treatment. The participant assessed stool firmness subjectively as watery, loose, or firm. Oocyst counts (defined

as mean concentration and as total 24-hour excretion) were compared at baseline and at the end of therapy.

Nitazoxanide

Amadi defined clinical response on day seven as either "well" (defined as no symptoms, no watery stools, no more than two soft stools per 24 hours, or no symptoms and no unformed stools within the past 48 hours) or "continuing illness" (not fulfilling the definition of "well"), while parasitological response was assessed by collection of two stool samples on day seven and eight and examination for the presence of oocyst of *C. parvum* by auramine phenol smear microscopy. Response was categorised as either eradication (no oocyst observed in either post-treatment stool sample) or persistence (oocyst observed in either or both post-treatment stool samples). Rossignol defined clinical cure as complete resolution of diarrhoea and other symptoms of cryptosporidiosis assessed on day 15 and 29, while parasitological cure was defined as three consecutive negative faecal examinations on days 15, 22 and 29 in the treatment group and days 7 and 15 for the placebo group.

Spiramycin

Wittenberg defined clinical response based on the stool frequency for both arms and parasitological response based on the number with a negative stool before discharge.

Bovine dialyzable leukocyte extract

McMeeking defined clinical response based on stool frequency (change in frequency defined as an increase or decrease from baseline over eight weeks), stool consistency (formed, semi-formed, or liquid) and stool volume. Parasitological response was defined, based on oocyst eradication, as either negative or positive.

Bovine hyperimmune colostrum

Outcomes considered by Nord include stool frequency (number of stools in 24 hours), stool consistency (firm, soft, thick liquid, watery, or rice-water as assessed by physician) and stool volume in mls. Parasitological response was defined based on the quantitative excretion of cryptosporidium oocyst (oocyst per ml)

Risk of bias in included studies

Jadad score (Jadad 1996) ranged from four to five (see table of Jadad scores). Three studies scored five (Wittenberg 1989; Hewitt 2000; Amadi 2002), whilst the remaining scored four (McMeeking 1990; Nord 1990; White 1994; Rossignol 1998). There was no disagreement in the allocation of quality scores between the two reviewers.

Randomisation

All studies were described as randomised. However, the method of randomisation was described and appropriate in only three studies (Wittenberg 1989; Hewitt 2000; Amadi 2002) who described the use of computer-generated lists or tables of random number lists. The remaining four studies (McMeeking 1990; Nord 1990; White 1994; Rossignol 1998) did not describe the method of randomisation.

Blinding
All seven studies were described as double blind. Within three of these studies (White 1994; Rossignol 1998; Amadi 2002) participant, clinician, laboratory personnel/investigators blinding was described.

Concealment of allocation
Concealment of allocation was clear in three of seven studies. (Nord 1990; Rossignol 1998; Hewitt 2000; White 1994) did not describe the method of allocation concealment.

Effects of interventions

Prevention
No studies were found that assessed prevention.

Treatment
Seven trials involving 169 participants were included. There were 130 adults with AIDS enrolled in five studies. The remaining two studies enrolled 139 children. Amadi enrolled 100 children over one year old, whilst Wittenberg's study was based on 39 infants, all less than one year old. All children were either malnourished or had AIDS. Due to the limited number of studies available, it was not possible to assess evidence of publication bias using funnel plots.

Duration of diarrhoea, mortality and parasitological clearance
Comparison one: Nitazoxanide versus placebo. The random effects summary estimate of the relative risk for resolution of diarrhoea for the two studies (Rossignol 1998; Amadi 2002) was 0.83 (95% CI 0.36 - 1.94), showing no evidence of effectiveness compared with placebo. There were data on deaths from Amadi et al that showed a relative risk of 0.61 (95% CI 0.22 - 1.63) among all 96 children, based on five and eight deaths in the intervention and control arms respectively. Nitazoxanide led to a significant parasitological response compared with placebo among all children with a relative risk of 0.52 (95% CI 0.30 - 0.91). The effect was not significant for HIV-seropositive participants (RR 0.71 (95% CI 0.36 - 1.37)). HIV-seronegative participants on nitazoxanide had a significantly higher relative risk of achieving parasitological clearance of 0.26 (95% CI 0.09 - 0.80) based on a single study.

Comparison two: Paramomycin versus placebo. The two studies (White 1994; Hewitt 2000) showed no evidence that paramomycin is more effective in reducing the frequency of diarrhoea than placebo with a summary relative risk of 0.74 (95% CI 0.42 - 1.31). The use of paramomycin does not significantly lead to a parasitological response with a relative risk of 0.73 (95% CI 0.38 - 1.39) for oocyst clearance.

Comparison three: Spiramycin versus placebo. Only one study (Wittenberg 1989) compared the effect of spiramycin with placebo. No outcome data was presented on diarrhoea duration or frequency. There was no difference in mortality between the two arms of the trial (RR 0.43 (95% CI 0.04 - 4.35)), with one and two deaths among 21 and 18 participants in the intervention and control arms respectively. Spiramycin did not significantly lower oocyst concentration compared with placebo (RR 0.88 (95% CI 0.37 - 2.05)). Although duration of hospitalisation was not a primary outcome, this study found no significant difference in reduction of the duration of hospitalisation (mean difference of -0.40 days (95% CI -6.62 to 5.82)).

Comparison four: Bovine dialyzable leukocyte extract. Only one study (McMeeking 1990) compared this intervention with placebo. The relative risk for decreased stool frequency was 0.19 (95% CI 0.03 - 1.19) and there was no evidence of a significant decrease in stool volume (mean difference of 4.74 (95% CI 0.75 - 8.73)). There was no evidence that bovine dialyzable leukocyte extract reduced oocyst concentration among participants with cryptosporidiosis compared to controls (RR 0.24 (95% CI 0.04 - 1.44).

Comparison five: Bovine hyperimmune colostrums. A pilot study (Nord 1990) of five participants showed no evidence in improvement, as assessed by volume of stool, following 10 days infusion of bovine colostrums (RR 3.00 (95% CI 0.61 - 14.86)). There was no evidence of a reduction in oocyst concentration per ml of stool (RR 0.27 (95% CI 0.02 - 3.74)).

The secondary outcomes measured in this review (adverse effects) occurred infrequently in all the studies. A variety of adverse effects were reported in the studies. None of the papers reported sufficiently similar results to allow a meta-analysis of adverse effects. Similarly, none of the individual trials reported data on tolerability to allow a comparison. In one study (Rossignol 1998), nitazoxanide use was stated as "probably related" to a case of viral myocarditis (none in placebo group) and two cases of vomiting (one in placebo group). In the second study (Amadi 2002), 58 adverse events were observed. None of them were considered related or possibly related to the blinded intervention, but rather to features of HIV infection and AIDS. One participant had vomiting after responding parasitologically, possibly related to nitazoxanide. Twelve adverse events were reported by 11 participants in the nitazoxanide treatment group, compared with 14 adverse events reported by 13 patients in the placebo group. The adverse events consisted of abdominal pain, dyspepsia, constipation, yellow discoloration of urine, dysuria dry mouth (1 nitazoxanide). Two adverse events, both episodes of dizziness in adult patients, resulted in discontinuation of therapy. No side effects of paramomycin were noted in one study (Hewitt 2000), while the second study (White 1994) did not report adverse events. The spiramycin study did not report adverse events. Patients on Bovine dialyzable leukocyte extract experienced no adverse signs, while bovine hyperimmune colostrum caused nausea and vomiting in two patients and mild abdominal cramps in one patient. One control patient on bovine colostrum also had nausea and vomiting.

Developed versus developing country
Subgroup analysis by developed versus developing country was not possible due to the limited number of eligible studies identified. Both nitazoxanide studies were conducted in developing countries.

DISCUSSION

The studies presented in this review are disparate in design, and several are small in size. Based upon the paucity of evidence, we were not able to demonstrate the effectiveness of any therapeutic agent in the treatment of immunocompromised persons with cryptosporidiosis. A significant effect on parasitological clearance was observed with nitazoxanide when all patient groups were included. A randomised, double-blind placebo-controlled trial was excluded from this analysis because the target population is not immunocompromised (Rossignol 2001). This study found nitazoxanide treatment reduced the duration of both diarrhoea (P<.0001) and oocyst shedding (P<.0001). The effect of nitazoxanide in immunocompromised persons needs investigating in a larger trial.

None of the prevention studies were of sufficiently adequate quality to be included in this study. There are several published studies of interventions for the prevention of diarrhoea (not specifically due to cryptosporidiosis), especially from developing countries, summarised in a recent systematic review and meta-analysis (Fewtrell 2005). The authors reported that multiple interventions, hygiene, and water quality improvement measures significantly reduce the levels of diarrhoeal illness. The impact of hygiene and household treatment interventions was the strongest. Some of these diarrhoeal illnesses may have been due to cryptosporidiosis.

Since the emergence of AIDS, medical interest in the diagnosis and management of cryptosporidiosis has increased dramatically. There are currently several published practice guidelines for the prevention and treatment of cryptosporidiosis (CDC 1995; Hunter 2000; Kaplan 2002). The paucity of evidence for an effective intervention has meant that most of these guidelines rely on studies that are of poor quality. For HIV-infected persons, highly active antiretroviral therapy (HAART) is the mainstay of preventing and managing cryptosporidiosis. HAART can lead to complete resolution of clinical symptoms and oocysts (Grube 1997; Maggi 2000; Miao 2000). This intervention is not available for HIV patients who are failing HAART or those unable to access HAART in developing countries. Among these immunocompromised persons without the option of an effective treatment for the underlying disease, supportive management, including rehydration therapy, electrolyte replacement, and anti-motility agents will remain the only alternatives for care until better drugs emerge.

Limitations

The studies were limited by variation in important indicators of quality, such as allocation concealment, description of randomisation, and power and dropout rates. The paramomycin study by White et al had a high dropout rate and was underpowered. The study by Nord et al was very small (5 participants). For three interventions, only a single study was identified; therefore, a meta-analysis was not possible. Due to the small number of studies, identified formal assessment of publication bias using funnel plots

and Eggers test was not possible. Also, we did not explore heterogeneity using statistical approaches.

The development of new therapies must rely on knowledge of *Cryptosporidium* biology. Progress in developing tissue culture systems capable of sustaining *C. parvum* infection for in vitro test of therapies has only been achieved to a limited degree (Theodos 1998). A large number of antimicrobial drugs have been tested in animals and humans infected with *Cryptosporidium* with no clear evidence of consistent effectiveness against this parasite (Mead 2002). The completion of the genome sequence of *C. parvum* (Abrahamsen 2004) provides an important opportunity to understand the mechanisms of resistance, identify targets, and produce candidate agents. Recent advances in our understanding of the mechanism of resistance have shed light on the reasons for treatment failure. Unlike other parasites, *Cryptosporidium* salvages pyrimidine and purine bases from its host (Striepen 2004). This is the key reason why *Cryptosporidium* has remained resistant to anti-folate drugs, which usually inhibit the de novo synthesis of these nucleotides. *C. parvum* relies on inosine 5'-monophosphate dehydrogenase (IMPDH) to produce guanine nucleotides, and is highly susceptible to IMPDH inhibition (Umejiego 2004). Both ribavirin and mycophenolic acid, which inhibit IMPDH, have been shown to have dose dependent effect on *C. parvum* development. It appears very likely that, based on these observations, more effective drugs for cryptosporidiosis will be designed and should be evaluated rapidly with randomised controlled trials in immunocompromised individuals.

This review concludes that there is no evidence to support the role of chemotherapeutic agents in the management of cryptosporidiosis among immunocompromised individuals. Some evidence of effectiveness for nitazoxanide in a combined population of immunocompetent and immunocompromised individuals was identified and is worth further study. There were no randomised controlled trials of preventive interventions primarily targeted at preventing cryptosporidiosis in immunocompromised individuals.

AUTHORS' CONCLUSIONS

Implications for practice

This review confirms the absence of evidence for effective agents in the management of cryptosporidiosis. The results indicate that nitazoxanide reduces the load of parasites and may be useful in immunocompetent individuals. Given the seriousness of the outcomes of this infection in immunocompromised individuals and the potential to improve compliance by decreasing nausea and vomiting, it is worth considering using nitazoxanide while clinicians await further evidence for its effectiveness in immunocompromised patients. The use of fluid and electrolyte replacement and anti-motility agents may be the only option for the majority of immunocompromised patients. The absence of effective ther-

apy highlights the need to ensure that infection is avoided. Unfortunately, evidence for the effectiveness and cost-effectiveness of preventive interventions is also lacking.

Implications for research

The consequences of cryptosporidiosis to immunocompromised individuals and the health services are of major importance. All interventions with the potential to decrease the risk of mortality and morbidity need appropriate evaluation so that any benefits may be maximised. A large-scale trial of nitazoxanide among immunocompromised individuals is needed. Due to the inability of most current interventions to reduce the severity of or provide a cure for cryptosporidiosis, there is an urgent need for high-quality randomised controlled trials of new agents such as ribavirin and mycophenolic acid for the treatment of cryptosporidiosis. Large-scale randomised controlled trials and cost-effectiveness studies of interventions to prevent cryptosporidiosis, especially among immunocompromised persons, are needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amadi 2002

Methods	Randomised controlled, double blind study 10 days duration (3 days drug treatment) blinding: yes 13 deaths during week after start of treatment: HIV negative: drug 0 deaths, placebo 4; HIV positive: drug 5 deaths, placebo 4. 5 deaths among HIV positive group 2 weeks after study
Participants	Malnourished children, 50 HIV infected, 50 HIV uninfected. 50 patients assigned to Nitoxozanide and 46 to placebo University hospital, Zambia. inclusion criteria: diarrhoea and C. parvum oocysts in stools within 7 days before enrolment. exclusion criteria: children< 1 yr and those given any drug with antiprotozoal activity within 2 weeks of enrolment. male=59% (57/96), female=41% (39/96) Mean age = 21.89 months, range = 12-85 months malnutrition status (severely/moderate underweight) = 79/96 CD4 count
Interventions	100mg nitazoxanide or matching palcebo twice daily for 3 consecutive days
Outcomes	clinical response (recorded on day 7 after the start of treatment) parasitogical response duration of diarrhoea mortality to study day 8
Notes	HIV negative children 3 cases of vomiting and 1 tetany

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hewitt 2000

Methods	Randomised Controlled Double Blind Cross Over Trial 21 days duration antiretroviral use - nucleoside monotherapy certain specified antidiarroeal agents dropouts: 10 deaths, 4 refused contact, 1 withdrawn from study

Participants	35 AIDS patients. 17 in intervention arm and 18 in placebo arm followed by all patients on Paramomycin.
	6 sites in USA and 1 site in Puerto Rico.
	incusion criteria: age greater than or equal to 13, documented HIV infection, absolute CD4 cell count < or equal to 150/mm3, presence of diarrhoea, documented Crypto. oocysts in 2 stool samples prior to study drug administration, Karnfsky score of at least 40,
	exclusion criteria: hypersensitivity to aminogycosides, treatment during the 14 day period immediately before study drug administration with any putative anticryptosporidial agent, receipt of paromomycin at dosage of > 1g/d for > or equal to 14 days before study enrolment, newly diagnosed infection due to other enteric pathogens, patient known to have chronic microsporidiosis.
	male = 32, female= 3
	White=15, Black=6, Hispanic=14
	disease stage: paromomycin group 25 cells/mm3, placebo 23 cells/mm3
Interventions	Paramomycin 500 mg qid for 21 days or placebo.
	Then non blinded all patients received paromomycin 500mg qid
Outcomes	Stool frequency in association with concurrent need for antidiarrhoeal agents
	Oocyst excretion
	Adverse effects
	drug tolerance
Notes	cross over design
	small study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

McMeeking 1990

Methods	Randomised Controlled Double Blind Trial
	Duration 8 weeks. Four patients on Zidovudine. No drop outs.
Participants	14 male AIDS patients with diarrhoeal longer than a month. 7 randomised to intervention and 7 to placebo
Interventions	Bovine immune dialyzable leukocyte extract or non immune DLE
Outcomes	Stool Volume
	Stool frequency
	Stool consistency
	Parasite clearance

McMeeking 1990   *(Continued)*

Notes	small study unclear what component of extract is the active agent

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nord 1990

Methods	Randomised Controlled Double Blind Trial 10 days duration no drop outs/losses to follow-up 1 patient taking zidovudine (control)
Participants	study setting USA 5 patients with AIDS, chronic diarrhoea associated with Cryptosporidium oocysts in the stool. No other pathogens present in stool culture. 3 patients on intervention and 2 on placebo. Age not given Sex not given disease stage not given
Interventions	Bovine hyperimmune colostrum or Bovine Colostrum with no anti cryptosporidial activity 30 mg total immunoglobulin /ml for 10 days.
Outcomes	Number and grade of stools Stool volume Quantitative excretion of oocysts
Notes	Small sample size No Measurement at baseline Nausea and vomitting in two interven and control patient Both control patients had higher volumes of diarrhoea and numbers of stools per day than intervention group. one patient (intervention) had significantly smaller parasite load than the others

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rossignol 1998

Methods	Randomised Controlled Double Blind Trial study duration - 28 days, 56/66 were receiving antiretroviral therapy for HIV infection (mainly Zidovudine, four were receiving treatment with protease inhibitors) 54/66 patients completed all four weeks of study of the 12 who did not completed, one patient died before day 7 with AIDS associated pancreatitis, four failed to return for follow up on day seven and two were removed from the study by the investigator and placed on compationate therapy due to disease severity. There was no evaluable data for the seven patients. Of the five remaining, three failed to return for follow up visits on day 15 or 22 and one died of pnuemonia before day 15 of treatment and one removed from the study by investigator due to severity of illness
Participants	66 patients, aged between 21 and 60 years, HIV positive population, 63 males and 3 females, all participants are AIDS patients with CD4 of 0 to 389 (mean 98.97 SD 94.56), all are hispanics Inclusion criteria: Oocyst of C parvum in a stool specimen within seven days before enrolment, seropositive for HIV and diarrhoea of more than two weeks duration. Exclusion criteria: patients treated with paramomycin, azithromycin and clarithromycin within one month before enrolment, Patients who have been treated with Zidovudine, Zalcitabine, didanoside or other antiviral drugs unless daily daily dosage stabilised before inclusion, terribly ill, seriously ill, history alcohol or IV drug abuse, patient requiring treatment with pentamidine, sulphamethoxazole-trimethoprim during study
Interventions	Nitazoxanide Group 1: 500mg (one tablet) plus one placebo every 12 hours for 14 days, then two placebos every 12 hours for 14 days Group 2 1000mg (two tablets) 12 hourly for 14 days and then 2 placebos 12 hourly for fourteen days Group 3 Two placebo tables 12 hourly for fourteen days and then subdivided into group 3a - 500mg (one tablet) plus one placebo 12 hourly for fourteen days and group 3b - 1000mg (two tablets) 12 hourly for 14 days
Outcomes	Clinical cure was defined as complete resolution of diarrhoea and other symptoms of cryptosporidiosis assessed on day 15 and 29. Parasitogical cure defined as three consecutive negative faecal examinations on days 15, 22 and 29 in the treatment group and days 7 and 15 for the placebo group. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

White 1994

Methods	Randomised Controlled Double Blind Cross Over Trial
	28 days duration
	patient and provider blinding
	co-intervention: 6 AZT (zidovudine), 2 none, 1 ddI (didanosine), 1 AZT/ddC (zidovudine/zalcitabine)
	some continued antimotility agents (number not given)
Participants	10 AIDS patients with cryptosporidiosis
	Specialist AIDS clinic, Houton, USA
	inclusion criteria: documented HIV infection, CD4 cell count < 100/mm3, chronic diarrhoea, positive for crypto. oocysts
	exclusion criteria: history of hearing difficulties, intolerance of aminoglycosides, initial creatinine of > or equal to 2.0 mg/dL, liver enzymes or bilirubin > or equal to 3 times normal, Hb < 10 g/dL, WCC < or equal to 500/mm3, Karnofsky score of < or equal to 60, other known active opportunistic infection.
	Mean age 33.3 range = 25-38
	ethnicity: 6 White, 2 African-American, 2 Hispanic
	Disease stage: 8 CD4 = < 50/ mm3, 2 CD4 = 50-100/mm3
Interventions	Paramomycin 25-35 mg/kg/day or Placebo for 2 weeks.
	Then switched to other treatment for additional 2 weeks
Outcomes	Stool frequency
	Stool weight
	Oocyst concentration
	Mortality
Notes	Small study
	Adverse events not recorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wittenberg 1989

Methods	Randomised Controlled Double Blind Trial
	5 days duration
	patient, provider, outcome assessor blinding - yes
	additional antibiotic use consisted of trimethoprim - sulfamethoxazole in majority of cases but also aminoglycosides
	dropouts: 2 deaths (1 placebo, 1 intervention)
Participants	39 of 376 paediatric patients admitted with diarrhoea
	setting: hospital, South Africa
	malnourished children
	inclusion criteria: diarrhoea with crpto. oocysts in stools

Wittenberg 1989   (*Continued*)

	exclusion criteria: if diarrhoea was improving at 48 hours, or if suffering from kwashiorkor or if had significant hepatomegaly. sex not given age (months): treatment group 5.8 +/- 3.9 months, placebo group 6.3 +/- 5.2 months
Interventions	Spiramycin 75 mg/kg/day for five days or equivalent placebo
Outcomes	Stool frequency Excretion of oocysts Duration of Hospital stay Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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

Study	Reason for exclusion
Amenta 1999	Comparison of different courses of rifaximin, no randomisation
Dionisio 1998	All trial arms received Azithromycin, no randomisation
Fichtenbaum 2000	A cross protocol retrospective analysis of data from two randomised controlled trials. Therefore, not an RCT. This was a study to assess the effectiveness of rifabutin and clarithromycin in doses used to treat Mycobacterium avium complex infection in the prevention of cryptosporidiosis in AIDS
Flanigan 1996	Single arm, no comparison group
Greenberg 1996	Patients randomised to receiving different formulations of Bovine Immunoglobulin concentrate. No control groups
Hellard 2001	Population studied not immunocompromised
Kadappu 2002	Randomised trial comparing varying duration of treatment with Azithromycin, No allocation concealment
Okhuysen 1997	Randomised trial of the prophylactic effect of Bovine anti-Cryptosporidium Hyperimmune Colostrum Immunoglobulin in healthy adults challenged with C. parvum

Rossignol 2001	Randomised, double blind comparison of Nitazoxanide with placebo among immunocompetent adults and children
Saez-Llorens 1989	Randomised double blind comparison of spiramycin with placebo among healthy children (with no Immuno-compromised groups)
Smith 1998	Single arm open label design with no allocation concealment or randomisation
Sprinz 1998	Single arm trial, no comparison group
Uip 1998	Single arm trial, no comparison group
Woolf 1987	Single patient study

DATA AND ANALYSES

Comparison 1.   Treatment with Nitazoxamide versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison of resolution of diarrhoea with Nitazoxanide versus Placebo	2	150	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.36, 1.94]
1.2 HIV seropositive participants	2	103	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.35, 5.15]
1.3 HIV seronegative participants	1	47	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.17, 0.95]
2 Comparison of number of individuals acheiving oocyst clearance with Nitazoxanide versus Placebo	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.91]
2.1 HIV seronegative patients	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.09, 0.80]
2.2 HIV seropositive participants	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.36, 1.37]
3 Comparison of mortality with Nitazoxanide versus Placebo	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.22, 1.63]
3.1 HIV seronegative children	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.73]
3.2 HIV seropositive children	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.37, 3.94]

Comparison 2.   Treatment with Paramomycin or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison of the number of individuals with decreased stool frequency - Paramomycin and placebo	2	51	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.31]
2 Comparison of the number of individuals with oocyst clearance - Paramomycin versus placebo	2	53	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.38, 1.39]

Comparison 3.   Treatment with Spiramycin and Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison of the number of individuals with oocyst clearance - Spiramycin versus placebo	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.37, 2.05]
2 Comparison of mortality - Spiramycin versus placebo	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.04, 4.35]
3 Comparison of duration of hospital stay in days - Spiramycin and placebo	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-6.62, 5.82]

Comparison 4.   Treatment with Bovine dialyzable leukocyte extract

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison of the number of individuals with decreased stool frequency	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.03, 1.19]
2 Comparison of the change in stool volume - Bovine DLE versus Non immune DLE	1	14	Mean Difference (IV, Fixed, 95% CI)	4.74 [0.75, 8.73]
3 Comparison of the number of individuals with oocyst clearance	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.04, 1.44]

Comparison 6.   Treatment using Bovine Hyperimmune Colostrum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison bovine hyperimmune colostrum with placebo on the number of subjects with a decreased stool volume	1	5	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.57, 8.68]
2 Comparison of the number of individuals with oocyst clearance - bovine hyperimmune colostrum versus placebo	1	5	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.02, 3.74]

Analysis 1.1. Comparison 1 Treatment with Nitazoxamide versus Placebo, Outcome 1 Comparison of resolution of diarrhoea with Nitazoxanide versus Placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 1 Treatment with Nitazoxamide versus Placebo

Outcome: 1 Comparison of resolution of diarrhoea with Nitazoxanide versus Placebo

Study or subgroup	Placebo	Nitazoxanide	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
2 HIV seropositive participants					
Amadi 2002	6/24	2/25		20.0 %	3.13 [0.70, 13.99]
Rossignol 1998	10/20	21/34		44.9 %	0.81 [0.49, 1.35]
Subtotal (95% CI)	**44**	**59**		**65.0 %**	**1.34 [0.35, 5.15]**
Total events: 16 (Placebo), 23 (Nitazoxanide)					
Heterogeneity: Tau² = 0.69; Chi² = 3.10, df = 1 (P = 0.08); I² =68%					
Test for overall effect: Z = 0.42 (P = 0.67)					
3 HIV seronegative participants					
Amadi 2002	5/22	14/25		35.0 %	0.41 [0.17, 0.95]
Subtotal (95% CI)	**22**	**25**		**35.0 %**	**0.41 [0.17, 0.95]**
Total events: 5 (Placebo), 14 (Nitazoxanide)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.037)					
Total (95% CI)	**66**	**84**		**100.0 %**	**0.83 [0.36, 1.94]**
Total events: 21 (Placebo), 37 (Nitazoxanide)					
Heterogeneity: Tau² = 0.35; Chi² = 5.62, df = 2 (P = 0.06); I² =64%					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Chi² = 2.16, df = 1 (P = 0.14), I² =54%					

```
            0.1  0.2   0.5   1    2    5   10

      Favours Nitazoxanide      Favours Placebo
```

Analysis 1.2. Comparison 1 Treatment with Nitazoxamide versus Placebo, Outcome 2 Comparison of number of individuals acheiving oocyst clearance with Nitazoxanide versus Placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 1 Treatment with Nitazoxamide versus Placebo

Outcome: 2 Comparison of number of individuals acheiving oocyst clearance with Nitazoxanide versus Placebo

Study or subgroup	Placebo n/N	Nitazoxanide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 HIV seronegative patients					
Amadi 2002	3/22	13/25		41.6 %	0.26 [0.09, 0.80]
Subtotal (95% CI)	**22**	**25**		**41.6 %**	**0.26 [0.09, 0.80]**
Total events: 3 (Placebo), 13 (Nitazoxanide)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 HIV seropositive participants					
Amadi 2002	5/24	4/25		13.4 %	1.30 [0.40, 4.28]
Rossignol 1998	5/21	22/49		45.1 %	0.53 [0.23, 1.21]
Subtotal (95% CI)	**45**	**74**		**58.4 %**	**0.71 [0.36, 1.37]**
Total events: 10 (Placebo), 26 (Nitazoxanide)					
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² =32%					
Test for overall effect: Z = 1.02 (P = 0.31)					
Total (95% CI)	**67**	**99**		**100.0 %**	**0.52 [0.30, 0.91]**
Total events: 13 (Placebo), 39 (Nitazoxanide)					
Heterogeneity: Chi² = 3.73, df = 2 (P = 0.16); I² =46%					
Test for overall effect: Z = 2.28 (P = 0.023)					
Test for subgroup differences: Chi² = 2.24, df = 1 (P = 0.13), I² =55%					

0.1 0.2 0.5 1 2 5 10

Favours Nitazoxanide   Favours Placebo

Analysis 1.3.   Comparison 1 Treatment with Nitazoxamide versus Placebo, Outcome 3 Comparison of mortality with Nitazoxanide versus Placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 1 Treatment with Nitazoxamide versus Placebo

Outcome: 3 Comparison of mortality with Nitazoxanide versus Placebo

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 HIV seronegative children					
Amadi 2002	0/25	4/22		53.9 %	0.10 [0.01, 1.73]
Subtotal (95% CI)	**25**	**22**		**53.9 %**	**0.10 [0.01, 1.73]**
Total events: 0 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
2 HIV seropositive children					
Amadi 2002	5/25	4/24		46.1 %	1.20 [0.37, 3.94]
Subtotal (95% CI)	**25**	**24**		**46.1 %**	**1.20 [0.37, 3.94]**
Total events: 5 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Total (95% CI)	**50**	**46**		**100.0 %**	**0.61 [0.22, 1.63]**
Total events: 5 (Treatment), 8 (Control)					
Heterogeneity: Chi² = 2.81, df = 1 (P = 0.09); I² =64%					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Chi² = 2.50, df = 1 (P = 0.11), I² =60%					

```
        0.001 0.01  0.1   1   10  100 1000
      Favours Nitazoxanide    Favours Placebo
```

Analysis 2.1. Comparison 2 Treatment with Paramomycin or placebo, Outcome 1 Comparison of the number of individuals with decreased stool frequency - Paramomycin and placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 2 Treatment with Paramomycin or placebo

Outcome: 1 Comparison of the number of individuals with decreased stool frequency - Paramomycin and placebo

Study or subgroup	Placebo n/N	Paramomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hewitt 2000	5/14	8/17		50.8 %	0.76 [0.32, 1.80]
White 1994	5/10	7/10		49.2 %	0.71 [0.34, 1.50]
Total (95% CI)	**24**	**27**		**100.0 %**	**0.74 [0.42, 1.31]**

Total events: 10 (Placebo), 15 (Paramomycin)

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² =0.0%

Test for overall effect: Z = 1.05 (P = 0.30)

Test for subgroup differences: Not applicable

```
       0.1  0.2  0.5  1  2  5  10
    Favours Paramomycin    Favours Placebo
```
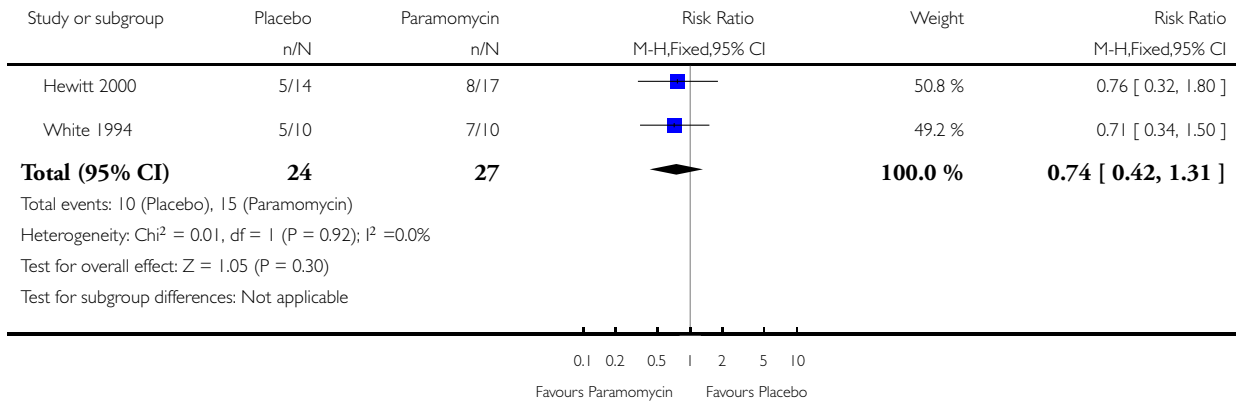
Analysis 2.2. Comparison 2 Treatment with Paramomycin or placebo, Outcome 2 Comparison of the number of individuals with oocyst clearance - Paramomycin versus placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 2 Treatment with Paramomycin or placebo

Outcome: 2 Comparison of the number of individuals with oocyst clearance - Paramomycin versus placebo

Study or subgroup	Placebo n/N	Paramomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hewitt 2000	4/18	6/17		50.7 %	0.63 [0.21, 1.85]
White 1994	5/9	6/9		49.3 %	0.83 [0.40, 1.76]
Total (95% CI)	**27**	**26**		**100.0 %**	**0.73 [0.38, 1.39]**

Total events: 9 (Placebo), 12 (Paramomycin)

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² =0.0%

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

```
       0.1  0.2  0.5  1  2  5  10
    Favours Paramomycin    Favours Placebo
```
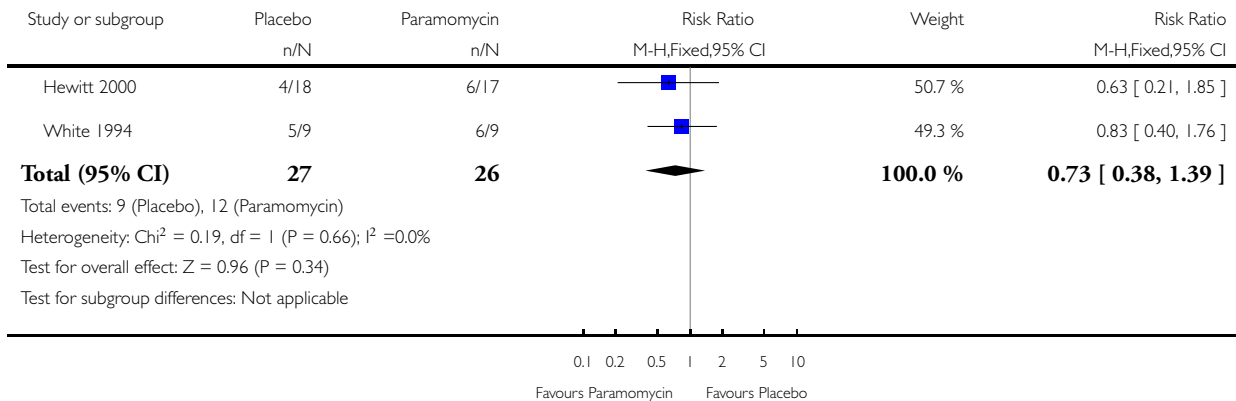
Analysis 3.1.   Comparison 3 Treatment with Spiramycin and Placebo, Outcome 1 Comparison of the number of individuals with oocyst clearance - Spiramycin versus placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 3 Treatment with Spiramycin and Placebo

Outcome: 1 Comparison of the number of individuals with oocyst clearance - Spiramycin versus placebo

Study or subgroup	Placebo	Spiramycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Wittenberg 1989	6/18	8/21		100.0 %	0.88 [0.37, 2.05]
Total (95% CI)	**18**	**21**		**100.0 %**	**0.88 [0.37, 2.05]**
Total events: 6 (Placebo), 8 (Spiramycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
Test for subgroup differences: Not applicable					

0.1 0.2   0.5   1   2   5   10

Favours Spiramycin   Favours Placebo
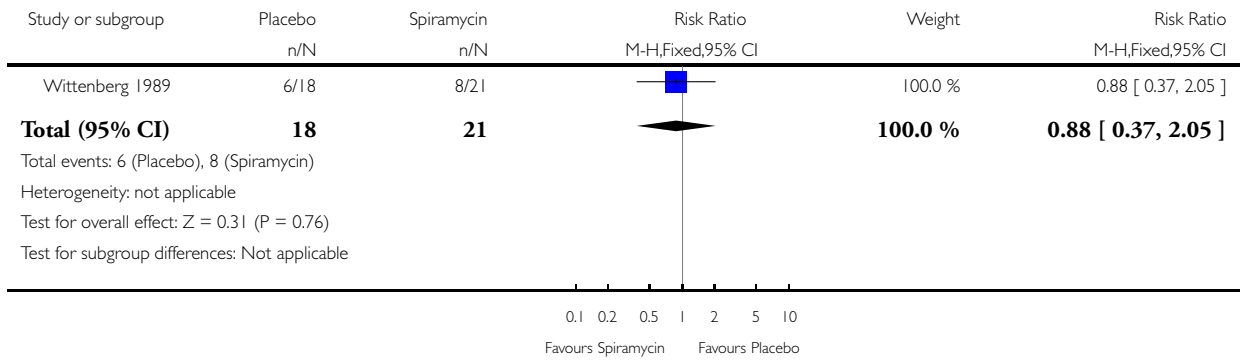
Analysis 3.2. Comparison 3 Treatment with Spiramycin and Placebo, Outcome 2 Comparison of mortality - Spiramycin versus placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 3 Treatment with Spiramycin and Placebo

Outcome: 2 Comparison of mortality - Spiramycin versus placebo

Study or subgroup	Spiramycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wittenberg 1989	1/21	2/18		100.0 %	0.43 [0.04, 4.35]
Total (95% CI)	**21**	**18**		**100.0 %**	**0.43 [0.04, 4.35]**

Total events: 1 (Spiramycin), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable

```
        0.1  0.2   0.5   1   2    5   10
    Favours Spiramycin      Favours Placebo
```
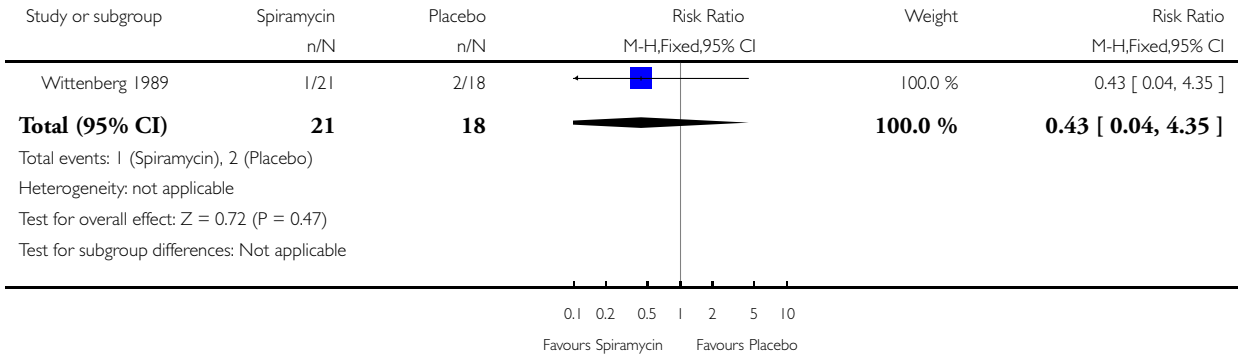
Analysis 3.3. Comparison 3 Treatment with Spiramycin and Placebo, Outcome 3 Comparison of duration of hospital stay in days - Spiramycin and placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 3 Treatment with Spiramycin and Placebo

Outcome: 3 Comparison of duration of hospital stay in days - Spiramycin and placebo

Study or subgroup	Spiramycin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wittenberg 1989	18	18.2 (10.1)	21	18.6 (9.6)		100.0 %	-0.40 [-6.62, 5.82]
Total (95% CI)	**18**		**21**			**100.0 %**	**-0.40 [-6.62, 5.82]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable

```
        -10    -5    0    5    10
    Favours Spiramycin      Favours Placebo
```
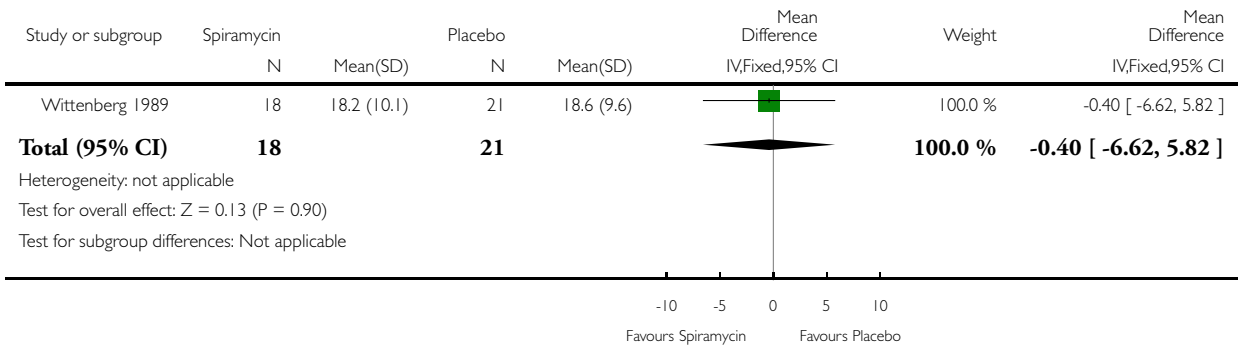
Analysis 4.1.   Comparison 4 Treatment with Bovine dialyzable leukocyte extract, Outcome 1 Comparison of the number of individuals with decreased stool frequency.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 4 Treatment with Bovine dialyzable leukocyte extract

Outcome: 1 Comparison of the number of individuals with decreased stool frequency

Study or subgroup	Control n/N	Treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McMeeking 1990	1/6	6/7		100.0 %	0.19 [0.03, 1.19]
Total (95% CI)	**6**	**7**		**100.0 %**	**0.19 [0.03, 1.19]**

Total events: 1 (Control), 6 (Treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 1.77 (P = 0.077)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours Treatment   Favours Control

Analysis 4.2.   Comparison 4 Treatment with Bovine dialyzable leukocyte extract, Outcome 2 Comparison of the change in stool volume - Bovine DLE versus Non immune DLE.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 4 Treatment with Bovine dialyzable leukocyte extract

Outcome: 2 Comparison of the change in stool volume - Bovine DLE versus Non immune DLE

Study or subgroup	Bovine DLE N	Mean(SD)	Nonimm. DLE N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McMeeking 1990	7	2.74 (3.5)	7	-2 (4.1)		100.0 %	4.74 [0.75, 8.73]
Total (95% CI)	**7**		**7**			**100.0 %**	**4.74 [0.75, 8.73]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.33 (P = 0.020)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours Treatment   Favours Control

Analysis 4.3.   Comparison 4 Treatment with Bovine dialyzable leukocyte extract, Outcome 3 Comparison of the number of individuals with oocyst clearance.
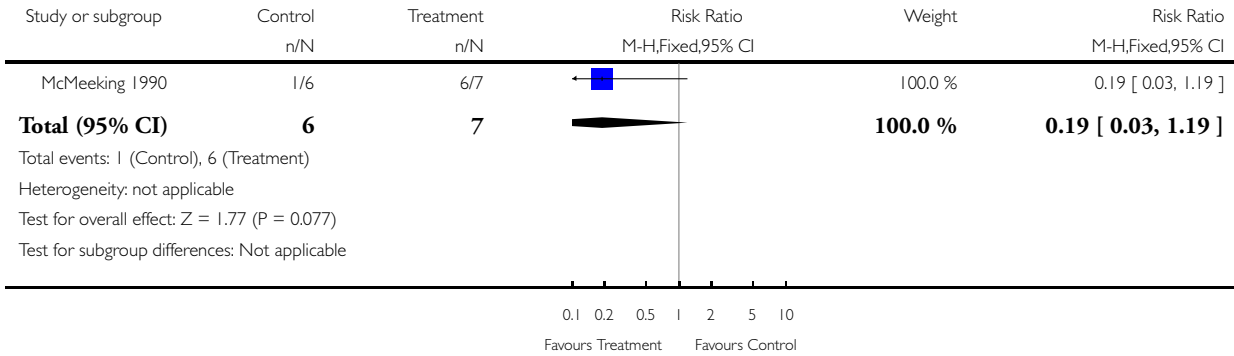
Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 4 Treatment with Bovine dialyzable leukocyte extract

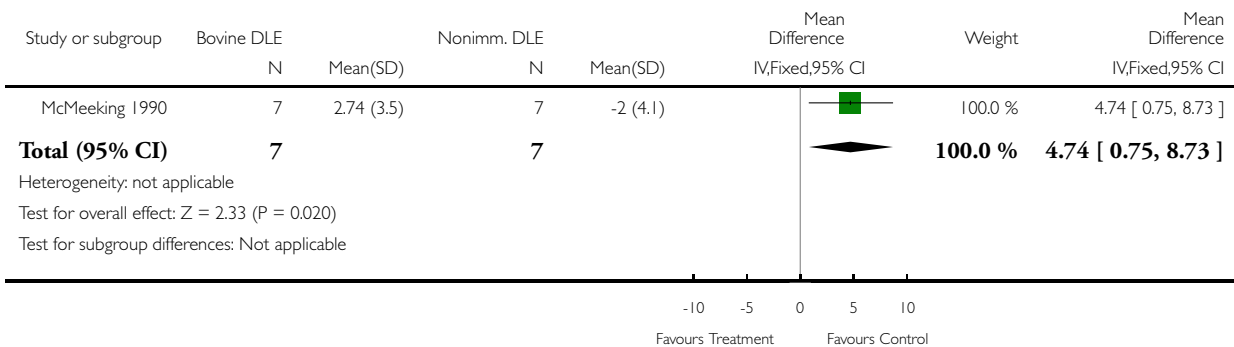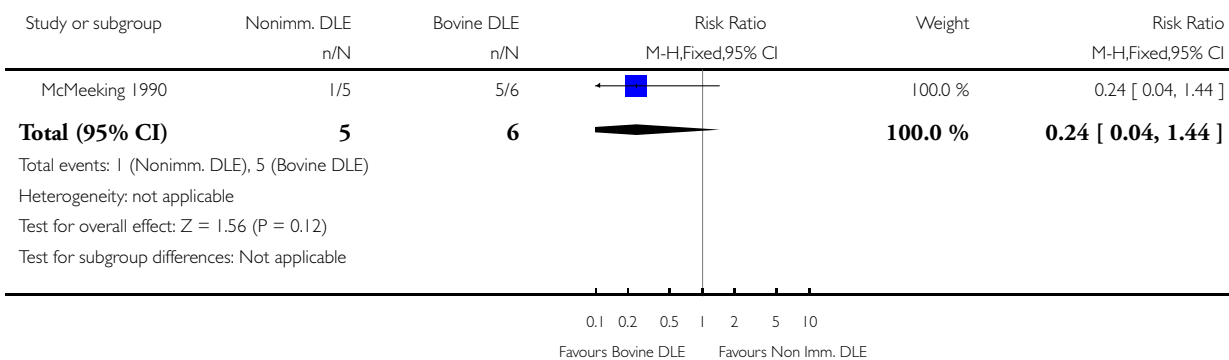Outcome: 3 Comparison of the number of individuals with oocyst clearance

Study or subgroup	Nonimm. DLE n/N	Bovine DLE n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McMeeking 1990	1/5	5/6		100.0 %	0.24 [0.04, 1.44]
Total (95% CI)	**5**	**6**		**100.0 %**	**0.24 [0.04, 1.44]**

Total events: 1 (Nonimm. DLE), 5 (Bovine DLE)

Heterogeneity: not applicable

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10

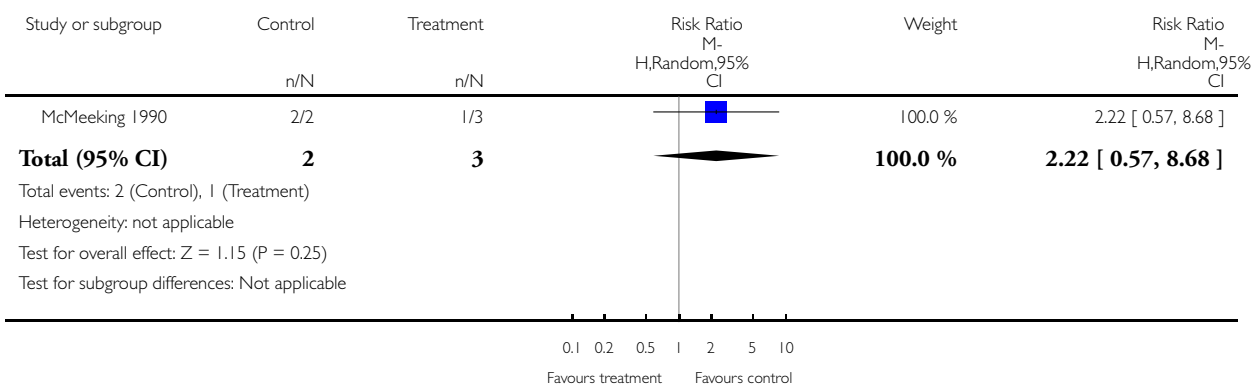Favours Bovine DLE   Favours Non Imm. DLE

Analysis 6.1.   Comparison 6 Treatment using Bovine Hyperimmune Colostrum, Outcome 1 Comparison bovine hyperimmune colostrum with placebo on the number of subjects with a decreased stool volume.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 6 Treatment using Bovine Hyperimmune Colostrum

Outcome: 1 Comparison bovine hyperimmune colostrum with placebo on the number of subjects with a decreased stool volume

Study or subgroup	Control n/N	Treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
McMeeking 1990	2/2	1/3		100.0 %	2.22 [0.57, 8.68]
Total (95% CI)	**2**	**3**		**100.0 %**	**2.22 [0.57, 8.68]**

Total events: 2 (Control), 1 (Treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10

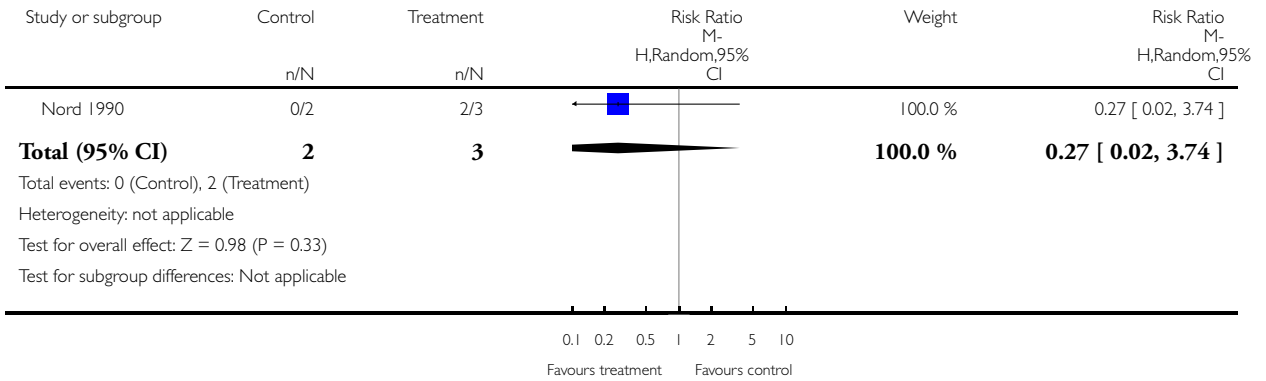Favours treatment   Favours control

Analysis 6.2. Comparison 6 Treatment using Bovine Hyperimmune Colostrum, Outcome 2 Comparison of the number of individuals with oocyst clearance - bovine hyperimmune colostrum versus placebo.

Review: Prevention and treatment of cryptosporidiosis in immunocompromised patients

Comparison: 6 Treatment using Bovine Hyperimmune Colostrum

Outcome: 2 Comparison of the number of individuals with oocyst clearance - bovine hyperimmune colostrum versus placebo

Study or subgroup	Control n/N	Treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Nord 1990	0/2	2/3		100.0 %	0.27 [0.02, 3.74]
Total (95% CI)	**2**	**3**		**100.0 %**	**0.27 [0.02, 3.74]**

Total events: 0 (Control), 2 (Treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable

```
0.1  0.2  0.5  1  2  5  10
```
Favours treatment   Favours control

ADDITIONAL TABLES

Table 1. Jadad Score for included studies (see text for questions)

Study	1	2	3	4	5	6	7	Total
Amadi	1	1	1	1	1	0	0	5
Rossignol	1	0	1	1	1	0	0	4
McMeeking	1	1	1	1	1	0	0	5
Wittenberg	1	1	1	1	1	0	0	5
Hewitt	1	0	1	1	1	0	0	4
Nord	1	0	1	1	1	0	0	4
White	1	0	1	1	1	0	0	4

WHAT'S NEW

Last assessed as up-to-date: 15 November 2006.

Date	Event	Description
12 April 2012	Amended	Fixed table-linking.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2007

Date	Event	Description
30 October 2008	Amended	Converted to new review format.
15 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ibrahim Abubakar wrote the protocol and the first draft of the review, Usman Nuhu and Chitra Arumugam extracted the data from studies and contributed to the writing of the review, Paul Hunter and Sani Aliyu contributed to the development of the protocol and writing the review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- School of Medicine, Health Policy and Practice, University of East Anglia, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Immunocompromised Host; Antiprotozoal Agents [*therapeutic use]; Cryptosporidiosis [*drug therapy; prevention & control]; Diarrhea [*drug therapy; parasitology; prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans