Drugs for treating urinary schistosomiasis (Review)

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[Intervention Review]

Drugs for treating urinary schistosomiasis

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ABSTRACT

Background

Urinary schistosomiasis causes long-term ill-health. This review examines the various treatment options and newer drugs.

Objectives

To evaluate antischistosomal drugs, used alone or in combination, for treating urinary schistosomiasis.

Search methods

In August 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, LILACS, *m*RCT, and reference lists of articles. We also contacted experts in schistosomiasis research.

Selection criteria

Randomized and quasi-randomized controlled trials of praziquantel, metrifonate, artemisinin derivatives, or albendazole, alone or in combination, versus placebo, different doses, or other antischistosomal drugs for treating urinary schistosomiasis.

Data collection and analysis

One author extracted data, and assessed eligibility and methodological quality, which were cross-checked by a second person. Dichotomous outcomes were combined using risk ratio (RR), and continuous data were combined using weighted mean difference (WMD); both presented with 95% confidence intervals (CI).

Main results

Twenty-four trials (6315 participants) met the inclusion criteria. Compared with placebo, participants receiving metrifonate had fewer parasitological failures at follow up at one to three months (1 trial) and three to 12 months (3 trials). Egg reduction rate was over 90%, and no adverse events were reported (1 trial). One metrifonate dose was inferior to three doses given fortnightly (both used 10 mg/kg). Praziquantel (standard single 40 mg/kg oral dose) was more effective than placebo at reducing parasitological failure at one to three months' follow up and three to 12 months. Egg reduction rates were improved with praziquantel (over 95% versus 5.3% to 64% with placebo). Mild to moderate adverse events were recorded in two trials. A comparison of metrifonate (10 mg/kg x 3, once every 4 months for one year) with praziquantel (standard dose) showed little difference in parasitological failure. For praziquantel, there was

no significant difference in effect between 20 mg/kg x 2, 30 mg/kg x 1, and 20 mg/kg x 1, and the standard dose for all outcomes. One small trial of artesunate showed no obvious benefit compared with placebo, and the artesunate-praziquantel combination was similar to praziquantel alone.

Authors' conclusions

Praziquantel and metrifonate are effective treatments for urinary schistosomiasis and have few adverse events. Metrifonate requires multiple administrations and is therefore operationally less convenient in community-based control programmes. Evidence on the artemisinin derivatives is currently inconclusive, and further research is warranted on combination therapies. We suggest metrifonate be reconsidered for the WHO Model List of Essential Medicines.

PLAIN LANGUAGE SUMMARY

Drug treatments for worms in the bladder (urinary schistosomiasis)

Worms residing in blood vessels of the bladder cause a chronic disease known as urinary schistosomiasis. The disease is commonly found in African and Eastern Mediterranean countries, especially in poor, rural areas. Humans become infected when they come into contact with contaminated water. The infection occurs when small larvae shed from snails in infected waters get into the individual through the skin and develop into adult worms that travel to the blood vessels of the bladder. There they can produce a large number of eggs, and the worm can live for three to five years. It is mainly the eggs that cause the disease. The main symptoms are blood in the urine and pain when passing urine. The eggs also cause tissue damage, and the severity of disease depends upon the intensity of the infection. Sometimes the infection can lead to bladder cancer or other kidney problems, including kidney failure. There are a number of measures that have been introduced to try to reduce the risk of infection. These include health education, improving clean water supplies and sanitation, environmental control measures to reduce numbers of intermediate host snails, and drug treatments. The review looked at the efficacy of drugs to reduce the ill-health associated with these infections. The review identified 24 trials involving 6315 people. Praziquantel and metrifonate were both found to be efficacious with few adverse events, although adverse outcomes were poorly assessed. Evidence on the artemisinins was inconclusive, and further research is warranted on combination therapies.

BACKGROUND

Urinary schistosomiasis is caused by the blood fluke, *Schistosoma haematobium*. The disease, which causes chronic ill-health, is endemic in most African and Eastern Mediterranean countries (Chitsulo 2000; Engels 2002; Steinmann 2006). It is especially important in poor, rural areas where attempts to alleviate poverty also promote water resources development that may increase transmission and hence exacerbate the disease burden (Danso-Appiah 2004; Fenwick 2006b; Steinmann 2006). In some areas of sub-Saharan Africa there is an overlap in distribution with *S. mansoni* resulting in mixed infections (WHO 2002). The two parasites infect about 131 million people (Davis 2003) and are associated with considerable morbidity and even mortality (van der Werf 2003). A recent meta-analysis suggested that the burden due to schistosomiasis has been significantly underestimated, since disability weights might be two to 15 times higher than previously estimated (King 2005). The social and economic burden of schistosomiasis is thought to be even greater (WHO 2002).

Mode of infection

The infection is acquired through contact with freshwater infested with the infective cercariae shed from the intermediate host snail (*Bulinus* spp.). Once cercariae have penetrated the human skin, the parasites develop into the adult worm within, on average, 63 to 65 days (Smith 1976; Ghandour 1978), and the worms usually migrate to the blood vessels draining the bladder where they reside and produce large numbers of eggs. On average, adult worm pairs live for three to five years, but some can live up to 30 years with the reproduction potential of one schistosome pair estimated to be up to 600 billion schistosomes (Gryseels 2006). The eggs of *S. haematobium* have a terminal spine and must traverse the bladder tissues towards the lumen of the bladder and urinary tract for elimination via urine. In the process, a considerable number become trapped in the bladder walls and surrounding tissues to initiate immune-induced inflammatory reactions, which subsequently lead to morbidity. It is important to note that eggs trapped in the tissues cause disease rather than the worms themselves.

Symptoms and effects

The disease can present as chronic, which is most common, or acute. Haematuria (blood in urine) and dysuria (painful urination) are the main early symptoms of the disease. For most people who are regularly exposed, the severity of disease depends upon the intensity of infection. Mostly individuals with few schistosome worms, and especially adults, remain asymptomatic, although about 80% of infected children show early symptoms and signs of disease (Mott 1983; Olds 2000). Late-stage complications are insidious and include calcification of the bladder wall, bladder stones, and secondary bacterial infection (Jordan 1993). Tissue damage caused by trapped eggs can lead to diffuse or localized wall thickening of the bladder and the distal ureter hydronephrosis or hydroureter, which may eventually lead to kidney failure (Kardorff 2001; WHO 2002; van der Werf 2003).

Elevated urine albumin levels and reported pain upon micturition by children have a strong correlation with *S. haematobium* infection (Rollinson 2005). An important long-term consequence of infection is squamous cell carcinoma of the bladder (Jordan 1993; King 2005; Shiff 2006). A recent review points out that bladder carcinoma is the seventh most common cancer worldwide in men and that the highest incidence rate among men is found in Egypt (37.1 per 100,000 person-years) (Murta-Nascimento 2007), which might be related to *S. haematobium* infection and morbidity (Jordan 2000). Eggs produced in venous blood vessels elsewhere such as the vertebral column, and resulting in granuloma formation, may cause spinal cord compression and neurological complications. Severe chronic disease occurs later in life following the infection, and many deaths are rarely acknowledged to be due to schistosomiasis because there is hardly any recognition of the link between infection in early life and later development of severe disease.

Sustained heavy infection leads to iron deficiency anaemia and other nutritional deficiencies, especially in children (Awasthi 2003; King 2005). The disease often results in retarded growth, reduced physical activity, and impaired cognitive function in children (Stephenson 1993; Nokes 1999; PCD 1999; Jukes 2002; WHO 2002).

Diagnosis

Parasitological diagnosis by microscopy of urine for parasite eggs is the most practical and widely used method for identifying infected individuals (Hassan 1994). Egg output in urinary schistosomiasis can be influenced by several factors, such as time of collection of urine (peak egg excretion occurs around noon), day-to-day variations, seasonal variations, and environmental conditions (Braun-Munzinger 1992). Therefore negative results following microscopic examination of a single urine specimen, as with a single stool for intestinal schistosomiasis, are not reliable, particularly in areas characterized by low intensities of infection (de Vlas 1992). Indeed, measurement of prevalence and intensities of infection by egg count has shortcomings (Gryseels 1996; de Vlas 1997; Utzinger 2001b). Egg count is quantified using a nucleopore membrane by urine filtration of a standard 10 mL volume of urine. Reagent strips for detecting blood in the urine (haematuria), and recently, monoclonal antibody-based dipstick tests for detecting schistosome-specific by-products are used to diagnose the disease (Bosompem 1997; Bosompem 2004). Clinically, the disease is diagnosed by reported terminal blood after urination or by inspecting urine for haematuria. Diagnosis on the basis of presence of blood in urine is less reliable in adults (RUSG 1995; Ansell 1997). This is because blood in the urine of an adult may be due to causes other than urinary schistosomiasis. Ultrasound was introduced in the 1970s to detect schistosomal pathology first in the hospital and then in field studies (Hatz 2001). It is a safe, rapid, non-invasive, and relatively inexpensive technique for assessing bladder or urinary tract pathology both in the hospital and in community surveys (Hatz 1990).

Disease control strategies

There is no effective antischistosomal vaccine (Gryseels 2000; Fenwick 2006a), although significant progress has been made in recent years (McManus 2008). Therefore, schistosomiasis control programmes have the primary objective of reducing the burden of disease. Four main control strategies have been employed with varying success.

- **Health education** to promote good hygiene and sanitation, especially among school-aged children and caregivers. It discourages practices such as bathing in streams and indiscriminate disposal of refuse that tend to increase risk of the infection. The ultimate goal is to decrease the number of eggs reaching and contaminating the environment, particularly freshwater bodies. However, the long-term impact of health education on the transmission of schistosomiasis in rural traditional communities is questionable (Kloos 1995; Sow 2003).

- **Water supply and sanitation** to reduce frequency of water contact for most domestic activities such as fetching water for drinking, washing clothing, or bathing in streams and ponds; and access to adequate sanitation to avoid environmental contamination with parasite eggs.

- **Control of the intermediate host snail** by environmental management such as removal of vegetation around banks of streams and lining irrigation canals with concrete slabs (Steinmann 2006); and treating infested water bodies with molluscicide to destroy the intermediate host snail. The important role environmental management as part of an integrated control approach has played in conquering *S. japonicum* in China has been emphasized (Utzinger 2005).

- **Morbidity control** by chemotherapy of the human population aims to reduce disease burden and thereby transmission. Past control measures focused largely on reducing

or interrupting transmission, but such measures have not been sustainable due to high cost and operational difficulties (WHO 2002). The advent of safe, efficacious, and inexpensive drugs shifted the emphasis to morbidity control in areas of high disease burden, endorsed by the World Health Organization (WHO) in the mid-1980s (WHO 1993; WHO 2002), while in low-burden areas the emphasis is to interrupt transmission of the infection. Although chemotherapy has emerged as the most cost-effective control strategy because of availability of inexpensive drugs, it has been suggested that in most endemic areas addition of preventive measures focusing on clean water, adequate sanitation, and health education to complement chemotherapy is necessary to achieve long-term sustainable schistosomiasis control (Utzinger 2001a; Singer 2007).

Chemotherapy

Chemotherapy is targeted especially at school-aged children (Magnussen 2001; WHO 2002; Savioli 2004). The assumption is that reducing the worm burden in childhood, when infection intensity is highest, will prevent most long-term complications occurring later in adulthood.

Several drugs have been used or tried for the treatment of urinary schistosomiasis and later abandoned because of poor effect or adverse events: antimonials, niridazole, lucanthone, hycanthone, oltipraz, cyclosporin A, levamisole, and oxamniquine; see Cioli 1995 for a comprehensive review.

Current treatment options are limited to praziquantel and metrifonate.

- **Praziquantel**. Praziquantel is the only drug on the WHO Model List of Essential Medicines for treating *S. haematobium*. This broad-spectrum antischistosomal drug is effective against all *Schistosoma* species, although it is refractory against immature parasites (Sabah 1986). Praziquantel is administered orally at a standard dose of 40 mg/kg body weight. The most common adverse effects are gastrointestinal, including abdominal pain, nausea, vomiting and diarrhoea, and are usually mild and last less than 24 hours.

- **Metrifonate**. Metrifonate was introduced as a drug for humans in the 1960s (Snellen 1981) and has been used extensively to treat urinary schistosomiasis. The standard dose of 7.5 to 10 mg/kg given three times at 14-day intervals has been used extensively and is mostly well tolerated (Forsyth 1967; Davis 1969; Rugemalila 1981; Feldmeier 1987). Adverse effects are mainly as a result of cholinergic stimulation and include fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhoea, nausea, vomiting, and bronchospasm. Its use has been limited after a suggestion that it was inferior clinically, economically, and operationally to praziquantel (Feldmeier 1999). Subsequently, metrifonate was withdrawn from the WHO Model List of Essential Medicines (Cioli 2000; Utzinger 2004).

Other drugs have potential as treatment options for urinary schistosomiasis, such as artemisinin derivatives, albendazole, and amoscanate. Albendazole is often administered together with praziquantel for simultaneous control of schistosomiasis and soil-transmitted helminthiasis.

- **Artemisinins**. The antischistosomal activity of the artemisinins, such as artesunate and artemether, was discovered in the early 1980s (Le 1982; Le 1983). The artemisinins are active against the liver stages (immature) worms, while the invasive stages and adult worms are less susceptible to the drugs. Adverse effects are minor and last for less than 24 hours. Artemisinin monotherapy may not be beneficial due to stage-specific activity, but combination with existing drugs effective against other stages (eg praziquantel) may improve therapeutic efficacy.

- **Albendazole**. Albendazole is indicated for the treatment of a variety of worm infestations. In recent years it has often been co-administered with praziquantel with the goal of simultaneously controlling schistosomiasis and soil-transmitted helminthiasis (Friis 2003; Zhang 2007). Albendazole is administered orally (usually as single 400 mg dose), and reported adverse effects include gastrointestinal upsets, headaches, and dizziness, while rash, fever, elevated liver enzymes, and hair loss occur less frequently. There have been reports of elevated liver enzymes, headaches, loss of hair, low levels of white blood cells (neutropenia), fever, and itching if taken at higher doses and/or for a long period of time.

- **Amoscanate**. Amoscanate is a broad-spectrum anthelminthic drug that exhibits activity against all major human schistosome parasites (Striebel 1976), other systemic parasites (eg filariae), and gastrointestinal nematodes (eg hookworms). It has been tested extensively in China using the locally produced equivalent called 'nithiocyaminum' (Bueding 1976; Striebel 1976). Toxicity in experimental animals was quite low, and mutagenicity tests in bacteria gave negative results; however, mutagenic metabolites were detected in urine of mammals given amoscanate (Batzinger 1977). It was abandoned because of concerns over liver toxicity and availability of better drugs, such as praziquantel (Cioli 1995). It is possible that amoscanate may represent a unique, broad-spectrum schistosomicide with the appropriate structural modifications to decrease liver toxicity (Cioli 1995).

Combinations of antischistosomal drugs have also been tested with the aim of improving therapeutic efficacy.

- **Artemisinin derivatives (artesunate or artemether) plus praziquantel**. This combination is suggested because artesunate and artemether are effective against immature worms, and artemether has shown in mouse models to prevent infection. Combining artesunate or artemether with praziquantel, which is effective against adult worms, may improve therapeutic efficacy.

- **Metrifonate plus praziquantel.** The rationale for this combination is that both drugs are independently effective against *S. haematobium* and that their targets of action in the parasite are not linked. Combination may improve therapeutic efficacy by offering mutual protection to each drug, and it may also slow or prevent the development of resistance.
- **Albendazole plus praziquantel**. Albendazole has broad activity, and it has been suggested that combining with praziquantel may help improve therapeutic efficacy. This combination has not been tested widely.

Praziquantel is virtually the only drug currently available for clinical management and control of urinary schistosomiasis. The sharp reduction in price of praziquantel has stalled advancement of other potential control options, such as vaccines, new drugs, and diagnostics (Utzinger 2007). It is noteworthy that pressure on praziquantel is growing, following the policy adopted at the 54^{th} World Health Assembly to increase distribution of the drug and treat at least 75% of school-aged children and other high-risk groups living in areas with high burden of the disease by 2010 (Colley 2001; WHO 2002; Hagan 2004), and new efforts made by the Schistosomiasis Control Initiative to treat millions of school-aged children in selected African countries (Fenwick 2006a). It is therefore timely to assess other antischistosomal compounds as potential alternatives should resistance to praziquantel develop, compare metrifonate with praziquantel as a potentially useful second-line drug, and assess the potential of combination treatments.

OBJECTIVES

To evaluate antischistosomal drugs, used alone or in combination, for treating urinary schistosomiasis. Specifically:

- Praziquantel, metrifonate, and artemisinin derivatives versus placebo; and to assess the appropriate dose for each from randomized comparisons by dose.
- Praziquantel versus metrifonate.
- Praziquantel plus other drugs (eg metrifonate, albendazole, or artemisinins) versus praziquantel alone.

Other relevant drugs or comparisons will be included in the future if they help address relevant safety, efficacy, or policy questions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Individuals infected with *S. haematobium* diagnosed either microscopically for the presence of *S. haematobium* eggs in a standard filtrate of 10 mL of urine or by haematuria in endemic areas.

Types of interventions

Praziquantel, metrifonate, artemisinin derivatives, or albendazole alone or in combination versus placebo or different doses of same drug; or other relevant antischistosomal drugs.

Types of outcome measures

Primary

Parasitological failure, defined as treated individuals who remained positive for eggs in the urine at follow up (distinguishing between one to three and three to 12 months post-treatment). Egg reduction rate (one to three or three to 12 months post-treatment).

Secondary

Laboratory indices

- Reduction in the percentage of people with a heavy infection (currently defined as $\geq$ 50 eggs/10 mL urine (WHO 2002).
- Clearance of haematuria.
- Measures of anaemia (mean haemoglobin; proportion of participants anaemic).

Functional indices (measured by standardized replicable techniques)

Resolution of bladder or urinary tract pathology, as measured by ultrasound, by standard international classification (CWG 1992; Richter 1996), or other standardized methods. Physical growth, including weight-for-age, height-for-age, weight-for-height, upper mid-arm circumference, and triceps skinfold thickness. Physical fitness. Cognitive function and educational achievement.

Adverse events

- Serious (fatal, life-threatening, requiring hospitalization, or discontinuation of treatment).
- Other.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (August 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 3); MEDLINE (1966 to August 2007); EMBASE (1974 to August 2007); and LILACS (1982 to August 2007). We also searched the *meta*Register of Controlled Trials (*m*RCT) using '*Schistosoma haematobium*' as the search term (August 2007).

Researchers and organizations

We contacted individual researchers working in the field and experts from the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) for unpublished data and information on ongoing trials.

Reference lists

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

Data collection and analysis

Selection of studies

Anthony Danso-Appiah (ADA), with assistance from Vittoria Lutje, the Cochrane Infectious Diseases Group (CIDG) Information Retrieval Specialist, searched the literature and retrieved studies. ADA screened the results to identify potentially relevant trials and assessed the eligibility of trials for inclusion in the review using an eligibility form based on the inclusion criteria; Paul Garner (PG) verified these procedures. ADA scrutinized each trial to ensure it has been included only once. If different parts of the same data were reported in different publications, ADA identified them and linked the data to the parent study. ADA attempted to contact the authors of potentially relevant trials for clarification if eligibility was unclear and listed all potential studies excluded along with the reason for exclusion in the Characteristics of excluded studies.

Data extraction and management

ADA extracted data of trial characteristics such as methods, participants, interventions, and outcomes. ADA recorded the data on standard forms, which PG cross-checked. ADA and PG resolved discrepancies through discussion and contacted Jianping Liu (JPL), Piero Olliaro (PO), and Jürg Utzinger (JU) on technical issues. Data were double-entered and cross-checked to make sure there were no errors. ADA scrutinized each trial to identify multiple publications from a single data set and attempted to contact trial authors for clarification, or insufficient or missing data. ADA extracted the number of participants randomized and number analysed in each treatment group, which allowed us assess the most appropriate type of analysis to carry out and to calculate the percentage loss to follow up. For dichotomous outcomes, ADA recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes summarized using geometric mean, ADA extracted means and their standard deviations on the log scale when provided. If the data were provided as arithmetic mean, ADA extracted the means for each group and their standard deviations (SD), standard error (SE), or confidence interval (CI), where possible.

Stratified data were extracted according to the stratifications and follow-up times. Most included trials defined intensity of infection by egg count as light, moderate, and heavy (instead of according to WHO 2002), and we based the treatment failure rate on these categories. We extracted information such as brand of drug used, dose, participant age, diagnostic criteria, endemicity, whether the trial was hospital- or community-based, and whether there had been simultaneous application of other control measures during the trial (eg health education or use of molluscides). To allow assessment of the interdependence between observations in a trial, we extracted data on repeated follow ups and number of communities involved in each trial. Data on haematuria from King 2002 were extracted from graphs.

Assessment of risk of bias in included studies

ADA examined design issues relating to internal validity, and PG checked the assessment. Generation of allocation sequence was described as adequate if the method used indicated that the resulting sequences were unpredictable, unclear if trial was randomized but method not described, inadequate if sequences could be predicted, or not described (Jüni 2001). Allocation concealment was described as adequate if methods used prevented prior knowledge of investigators enrolling participants and participants of treatment assignment, inadequate if participants and investigators enrolling participants could foresee upcoming assignment, or not described (Jüni 2001). ADA noted who was blinded to the interventions, such as the participants, care providers, or outcome assessors. The inclusion of all randomized participants in the main analysis was assessed as adequate if more than 90% were included in the analysis, inadequate if 90% or less, or unclear. Given that these cutoffs are arbitrary and subject to sample size for a given study, ADA also reported actual percentages. ADA reported the overall number randomized and the number included in the review for trials

not using all the trial arms in the analysis.

Data synthesis

Review Manager 4.2 was used for the statistical analyses and dichotomous outcomes (failure rates) were presented as risk ratios (RR) with 95% confidence intervals (CI). To minimize selection bias and the effect of participant attrition, we calculated the proportion of parasitological failure from the total number of participants at follow up and conducted per protocol analysis. We considered RR to be more appropriate because event rates were high. We intended to analyse by intention-to-treat, but this was not possible due to the lack of information in some trial reports. Continuous data were presented as weighted mean differences (WMD) with their standard deviation (SD) or standard error (SE). Egg counts were reported mostly as percentage reduction in geometric mean with rates of reduction over 90% across trials irrespective of background drug or dose. Because treatment effects were obvious in terms of egg excretion, we decided to report them in a table instead of combining in a meta-analysis.

The effects were obvious in comparisons against placebo; therefore we restricted the analysis to the two primary outcomes, three secondary outcomes, and adverse events. We expressed them by number-needed-to-treat (NNT), where possible, and related this to background endemicity.

The impact of follow-up time on cure rate has been elucidated and interpreted from the analysis of available research data; short follow-up times give better treatment effect in terms of parasitological cure than long follow-up times of same background drug and endemicity (Danso-Appiah 2002). To account for this, we analysed treatment failure based on two follow-up categories as short (one to three months) and long (three to 12 months), and also according to dose.

Where data were sufficient we conducted sensitivity analyses to assess the robustness of the results to the quality components. We tested for heterogeneity using the chi-squared and I^2 tests, and overall effect with Z score at 95% CI. We attempted to explore potential publication bias using funnel plots, but this was not possible because of the limited number of trials in comparisons.

RESULTS

Description of studies

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

Twenty-four trials (6315 participants), reported in 35 published articles, met the inclusion criteria (see Characteristics of included studies); none were cluster-randomized. Four articles were published from the same trial data (King 1988), and another three from the same study (Stephenson 1989). Wilkins 1987a reported two trials, but we included one (Nyamari trial named Wilkins 1987a) and excluded the other (Simote trial named Wilkins 1987b) because the latter did not randomize the participants. Nineteen trials were excluded from the review (see Characteristics of excluded studies).

Of the 24 trials included in the analysis, 20 evaluated praziquantel (eight specified Biltricide (Bayer)). Nine trials assessed metrifonate (three specified Bilarcil (Bayer)). Three trials assessed the combination of praziquantel with albendazole, and one trial assessed praziquantel plus artesunate. For the two primary outcomes, 21 trials reported cure rate or failure rate, and 20 reported egg reduction rate. Nine trials reported adverse events. There was lack of uniformity in diagnostic criteria (Table 2) and classification of intensity of infection across trials (Table 3). The WHO classifies the intensity of infection as light (1 to 49 eggs/10 mL urine) or heavy ($\geq$ 50 eggs/10 mL urine) (WHO 2002). However, the trials used different classifications for light infection (eg 1 to 5, 1 to 29, 60 to 249, and 250 to 500 eggs/10 mL urine). Moderate and heavy infections were classified the same way with often considerable overlaps between intensity categories.

Trial setting and participants

The trials were conducted in Africa: nine in East Africa (six in Kenya and three in Tanzania); five in Southern Africa; four in the Horn of Africa (three in Sudan and one in Somalia); four in West Africa; and two in Central Africa. Nineteen trials were conducted in the 1980s, shortly after praziquantel was introduced in the market, one in the early 1990s, and three in the new millennium. Twenty-two trials involved children aged up to 15 years; the other two trials recruited only boys (Doehring 1985; Befidi-Mengue 1992). Four trials recruited children with mixed infection of *S. haematobium* and *S. mansoni* (Jewsbury 1977; Doehring 1985; Kardaman 1985; Taylor 1988). Participants were identified in community surveys in all except two trials that recruited patients attending hospital (Davis 1981) or a combination of patients attending hospital and participants detected during a field survey (Omer 1981).

Risk of bias in included studies

See the Characteristics of included studies *and summary of the risk of bias* (Table 4).

The methods used to generate the allocation sequence were adequate in the 11 trials that used computer-generated numbers, random-number tables, randomized cards, permutation table, or randomized block design. One trial used sequential allocation (inadequate; Pugh 1983), and the methods used to generate the allocation sequence were unclear in 12 trials. Only three trials used adequate methods to conceal allocation (Aden Abdi 1989; Olds

1999; Borrmann 2001); the methods were unclear in the remaining 21 trials. Eight trials employed blinding and described who was blinded (six were double-blind and two single-blind); the remaining were unclear. For follow up at one to three months, 17 trials included 90% or more participants in the analysis (adequate), and two trials were unclear. For follow up at three to 12 months, 12 trials included 90% or more participants in the analysis (adequate) and five trials were unclear.

Effects of interventions

1. Metrifonate versus placebo

Four trials made this comparison (Jewsbury 1977; Doehring 1985; Stephenson 1985; Stephenson 1989).

Parasitological failure

Jewsbury 1977 measured parasitological failure at one to three months and showed a marked effect in favour of metrifonate (RR 0.42, 95% CI 0.27 to 0.64; 64 participants, Analysis 1.1), but loss to follow up was high (44%). The effect also favoured metrifonate when failure was measured at three to 12 months in Jewsbury 1977, Stephenson 1985, and Stephenson 1989 (RR 0.53, 95% CI 0.29 to 0.95; 680 participants, Analysis 1.1), although there was significant heterogeneity.

Loss to follow up was still high in Jewsbury 1977, but less marked in the other two trials (Stephenson 1985; Stephenson 1989). In terms of differences in failure rates, there seemed to be an association with the level of endemicity: Jewsbury 1977 and Stephenson 1989 (high endemicity) led to higher rates of failure at three to 12 months than Stephenson 1985 (low endemicity), but the lower dose used in Stephenson 1989 may confound the observed higher failure rate. There was no obvious association of failure with age (all trials included children of up to 15 years) or follow up (all three trials measured failure at eight months).

Egg reduction rate

All four trials measured this at three to 12 months and demonstrated that metrifonate reduced egg excretion by over 90%. The placebo groups ranged from a 5.5% decrease to a 66.2% increase (Table 5).

Mean haemoglobin

Two trials, Stephenson 1985 and Stephenson 1989, showed that participants in the metrifonate group had higher levels of mean haemoglobin than those in the placebo group (RR 0.30, 95% CI 0.28 to 0.32; 607 participants, Analysis 1.2).

Adverse events

Jewsbury 1977 assessed adverse events and recorded none.

2. Praziquantel versus placebo

Eight trials made this comparison (McMahon 1979; Oyediran 1981; Doehring 1985; Taylor 1988; Stephenson 1989; Befidi-Mengue 1992; Olds 1999; Borrmann 2001).

Parasitological failure

Praziquantel (40 mg/kg x 1 oral) was superior to placebo at one to three months' follow up (RR 0.39, 95% CI 0.27 to 0.55; 534 participants, 4 trials, Analysis 2.1) and at three to 12 months (RR 0.23, 95% CI 0.14 to 0.39; 433 participants, 3 trials, Analysis 2.1). There was significant heterogeneity in the meta-analysis, possibly due to loss to follow up, which was high in McMahon 1979 (31.6% and 36.9% for short and long follow-up times, respectively), less than 10% for Stephenson 1989, Olds 1999, and Borrmann 2001, and unreported in Taylor 1988.

Egg reduction rate

Praziquantel had egg reduction rates of over 98% (geometric mean) in four trials and a 95% rate in Befidi-Mengue 1992, and these were greater than those achieved with the placebo (5.3% to 64%). Doehring 1985 reported a median reduction rate of 98.7% in the praziquantel group and 48.6% in the placebo group. The trials used different dosing schedules, but there was no clear relationship between the egg reduction rates and dosing schedules (Table 5).

Mean haemoglobin

Stephenson 1989 reported a significant increase in mean haemoglobin with praziquantel (WMD 0.11, 95% CI 0.09 to 0.13; 209 participants, Analysis 2.2).

Adverse events

Olds 1999 recorded 15% excess of mild to moderate adverse events with praziquantel compared with placebo, and Borrmann 2001 reported combined events across comparison groups (127 mild and 6 moderate events); see Table 6. Neither trial recorded serious adverse events.

3. Artesunate versus placebo

One trial, Borrmann 2001, which had two months' follow up, made this comparison.

Parasitological failure

There was no obvious benefit with artesunate (118 participants, Analysis 3.1).

Egg reduction rate

There was no significant difference in the egg reduction rate at two months' follow up (ERR_{log} 0.7 versus 0.4).

Haematuria

There was no clear difference between artesunate and placebo at two months (65% versus 53%).

Adverse events

Adverse events were reported as combined events (127 mild and six moderate events, Table 6) and not by comparison group. No serious adverse events were reported.

4. Praziquantel plus artesunate versus placebo

One trial with two months' follow up made this comparison (Borrmann 2001).

Parasitological failure

There was a clear difference between the combination and placebo for failure rates at two months (RR 0.24, 95% CI 0.15 to 0.38; 118 participants, Analysis 4.1).

Egg reduction rate

The egg reduction rate was high for the combination compared with placebo (ERR_{log} 1.9 versus 0.4).

Haematuria

The urine erythrocyte counts were similar for the combination and placebo (65% versus 53%).

Adverse events

There were 127 mild and six moderate adverse events reported, but they were not separated by intervention group (Table 6).

5. Praziquantel plus albendazole versus placebo

Three trials made this comparison (Beasley 1999; Olds 1999; Jinabhai 2001).

Parasitological failure

Praziquantel plus albendazole significantly reduced parasitological failures compared to placebo (RR 0.45, 95% CI 0.35 to 0.59; 471 participants, 3 trials, Analysis 5.1). Jinabhai 2001, which was conducted in a low-endemic area, showed a better effect compared with Beasley 1999 (moderate and high endemicities) or Olds 1999 (very high endemicity).

Egg reduction rate

Beasley 1999 reported a geometric mean reduction rate of over 99% with the combination compared to a 12% increase with the placebo (Table 5).

Mean haemoglobin

Beasley 1999 showed marked improvement in mean haemoglobin with the combination (WMD 0.24, 95% CI 0.22 to 0.26; 250 participants, Analysis 5.2).

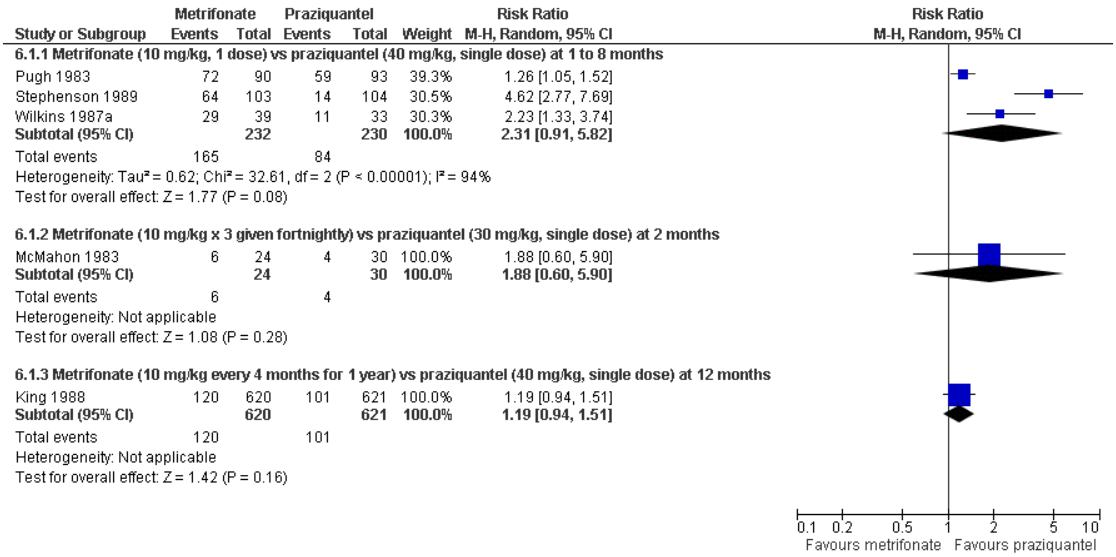
6. Metrifonate versus praziquantel

Five trials made this comparison (McMahon 1983; Pugh 1983; Wilkins 1987a; King 1988; Stephenson 1989).

Parasitological failure

Some early studies investigated a single dose of 10 mg/kg metrifonate (the standard dose is 7.5 to 10 mg/kg three times at 14-day intervals) with the standard single dose of 40 mg/kg praziquantel. Although the single metrifonate dose was inferior in three trials measuring failure at one to 12 months, the 95% CI were too wide for statistical significance (RR 2.31, 95% CI 0.91 to 5.82; 462 participants, Figure 1), due to significant heterogeneity between the trials (I^2 93.9%). A possible association with follow-up time was found: Pugh 1983 (RR 1.26 at one month), Wilkins 1987a (RR 2.23 at three months), and Stephenson 1989 (RR 4.62 at eight months).

Figure 1. Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose): Parasitological failure.



There was no significant difference in failure when metrifonate (10 mg/kg three times at 14-day intervals) was compared with praziquantel (30 mg/kg) in a small trial involving 54 participants (McMahon 1983, Analysis 6.1). The metrifonate regimen was then changed to three doses of 10 mg/kg every four months for one year), and this resulted in effects similar to the standard 40 mg/kg of praziquantel (Figure 1).

Effect on light and heavy infections

One trial reported a subgroup analysis that showed that there was no significant difference between metrifonate (10 mg/kg every four months for one year) and praziquantel (40 mg/kg) curing light infections (626 participants, 1 trial, Analysis 7.1), but that this metrifonate dose was better at controlling heavy infections (615 participants, Analysis 7.2). Given that the subgroup was stratified after randomization, care should be taken in interpreting these results.

Egg reduction rate

Both metrifonate (two and three doses of 10 mg/kg) and praziquantel (single dose 40 mg/kg) led to reductions in egg excretion of over 98% in two trials (McMahon 1983; Doehring 1985), while in three trials a single dose of metrifonate (10 mg/kg) also resulted in an egg reduction of over 90% (Pugh 1983; Wilkins 1987a; Stephenson 1989) (Table 5).

Mean haemoglobin

Stephenson 1989 showed that participants in the metrifonate group had greater mean haemoglobin levels than those in the praziquantel group (RR 0.19, 95% CI 0.17 to 0.21; 208 participants, Analysis 6.2).

Adverse events

McMahon 1983 (54 participants) reported similar minor adverse events between metrifonate (10 mg/kg) and praziquantel (30 mg/kg), except for abdominal pain and vomiting, which occurred more frequently in the metrifonate group than the praziquantel group (40% versus 13% and 8% versus 0%). No serious adverse events were reported. Wilkins 1987a (184 participants) compared metrifonate (10 mg/kg x 1) versus praziquantel (40 mg/kg x 1) and reported no serious adverse event. Commonly reported adverse events for the combination treatment included headache, weakness, dizziness, nausea/vomiting, diarrhoea, abdominal pain, general malaise, and fever. Among these events, abdominal pain, general malaise, and fever were reported more frequently in those treated with praziquantel than metrifonate.

7. Metrifonate regimens: 5 mg/kg x 3, given in one day versus 7.5 mg/kg x 3, given fortnightly

One trial with 201 participants made this comparison (Aden Abdi 1989).

Parasitological failure

There was no significant difference in parasitological failure (201 participants, Analysis 8.1).

Egg reduction rate

Egg reduction rate (geometric mean) was 96% for the one-day regimen versus 97% for the fortnightly regimen (Table 5).

Adverse events

There was little difference in the percentage of mild adverse events reported for the fortnightly regimen (7%) versus the one-day regimen (9%) (Table 6).

8. Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg) versus praziquantel (40 mg/kg)

Wilkins 1987a showed that the combination was inferior to praziquantel at reducing parasitological failure (72 participants, Analysis 9.1). The same trial reported an egg reduction rate of over 90% for the combination therapy (Table 5).

9. Metrifonate (10 mg/kg x 1) versus metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg)

Wilkins 1987a showed no significant difference in parasitological failures with the two interventions (78 participants, Analysis 10.1).

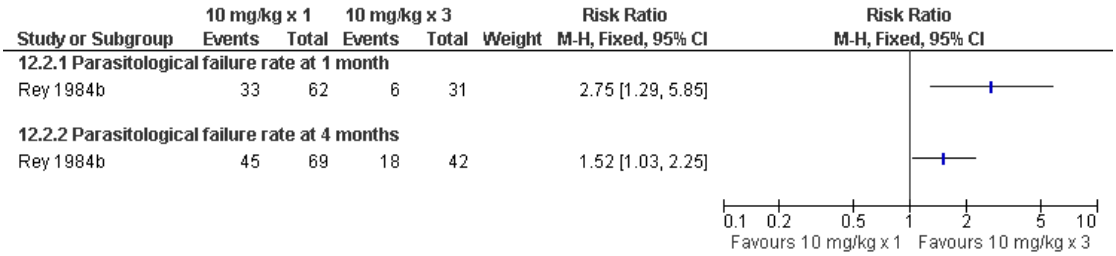
10. Artesunate plus praziquantel versus praziquantel alone

Borrmann 2001 showed no statistically significant difference between the combination and single treatment for parasitological failure (177 participants, Analysis 11.1). There was no obvious difference in egg reduction rates (ERR_{log} 1.9 versus 1.2). The trial reported 127 mild and six moderate adverse events, but they were not reported by intervention group (Table 6).

11. Different metrifonate doses

Rey 1984 compared three doses with one and two doses of 10 mg/kg metrifonate. There was no significant difference in the number of parasitological failure between two and three doses at one month and four months (Analysis 12.1). There were fewer parasitological failures with the three-dose regimen over the one-dose regimen at one month's follow up (RR 2.75, 95% CI 1.29 to 5.85; 93 participants) and four months' follow up (RR 1.52, 95% CI 1.03 to 2.25; 111 participants, Figure 2).

Figure 2. Metrifonate (10 mg/kg x 1) vs metrifonate (10 mg/kg x 3): Parasitological failure.



12. Different praziquantel doses versus standard dose (40 mg/kg x 1 oral)

Ten trials compared the standard dose with various other doses (McMahon 1979; Davis 1981; Oyediran 1981; Omer 1981; Rey 1983; Kardaman 1985; Wilkins 1987a; Taylor 1988; King 1989; King 2002).

Parasitological failure

There was no significant difference between the standard dose and 20 mg/kg x 2 (4 trials, Figure 3), 30 mg/kg (6 trials, Figure 4), and 20 mg/kg dose (2 trials, Figure 5); these results were similar for follow up at one, three, and six months.

Figure 3. Praziquantel (2 x 20 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure.

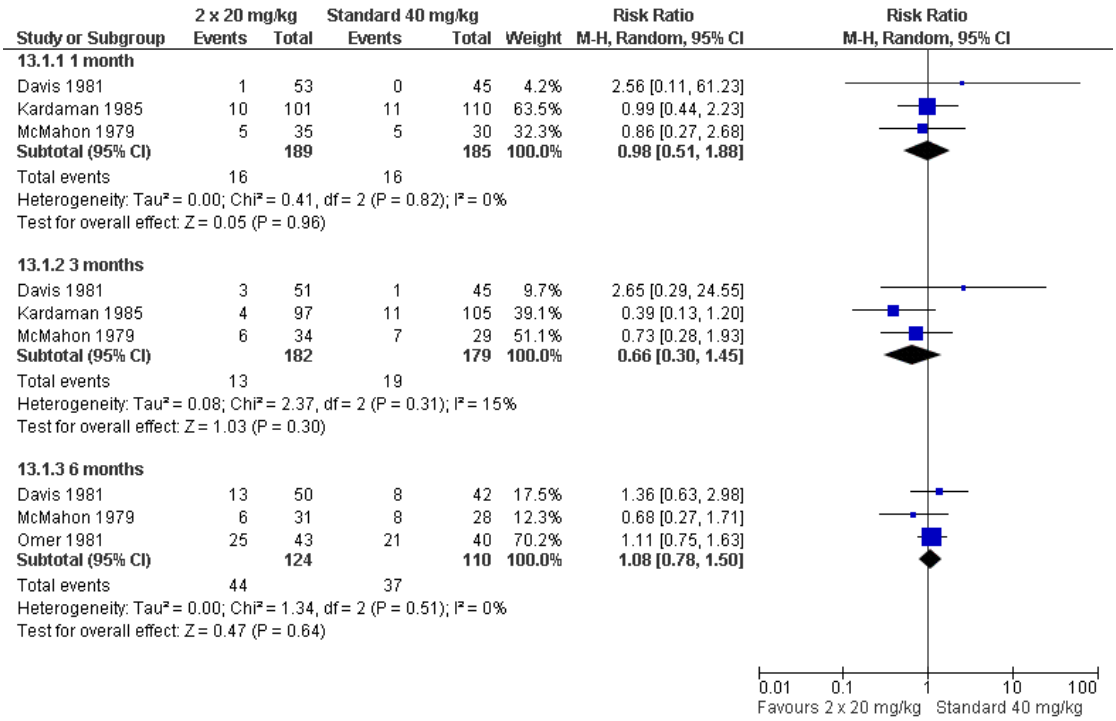


Figure 4. Praziquantel (30 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure.

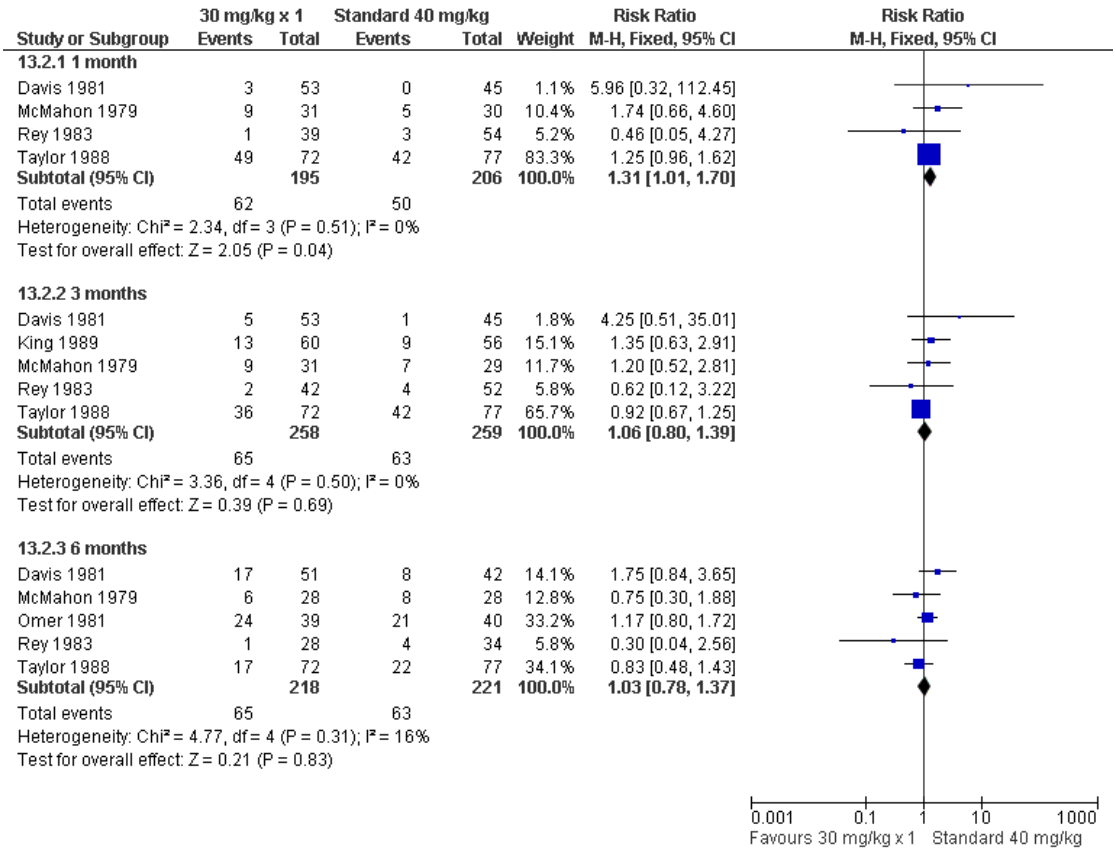
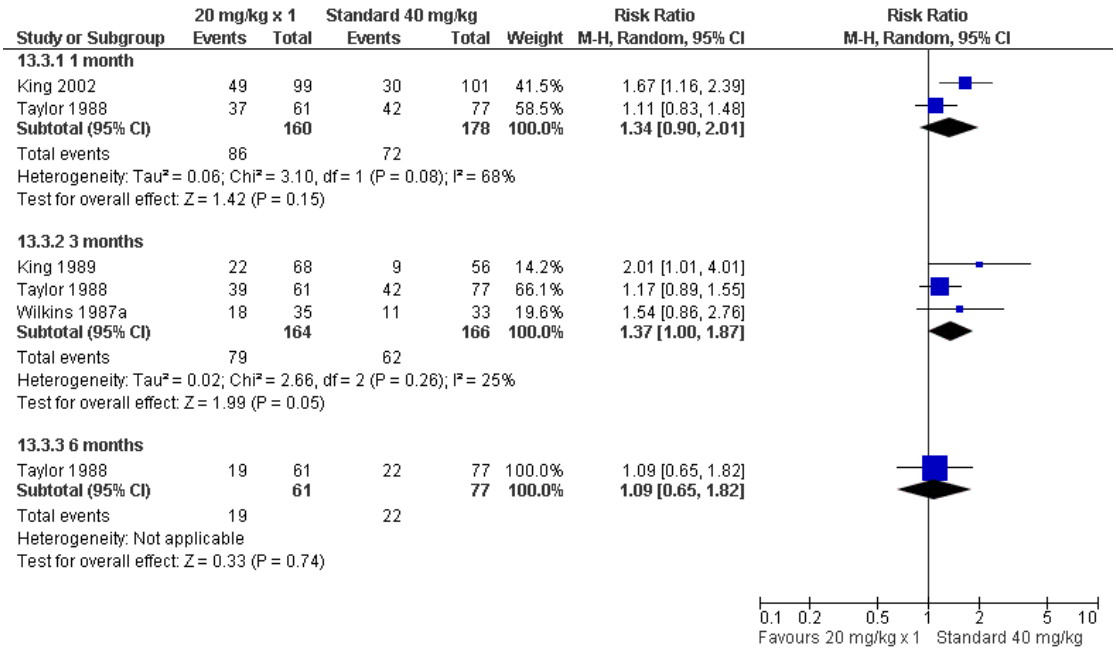


Figure 5. Praziquantel (20 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure.



Losses to follow up were generally high in some trials, but these did not differ across treatment and control groups within a single trial. There was no significant heterogeneity between the trials, and background endemicities did not seem to play a role; all trial sites had high endemicities except the trial by Davis 1981 (not specified). Examining for a differential effect between heavy and moderate or light infections with 30 mg/kg versus 40 mg/kg, a subgroup analysis of one small trial did not demonstrate a difference (116 participants, King 1989, Analysis 13.5). Here caution should be exercised in the interpretation of the data since the subgroup was selected after randomization.

Egg reduction rate

Five trials all showed no apparent differences in egg reduction rate (geometric mean); all had greater than 95% reduction in both arms, except for Oyediran 1981 in which the 30 mg/kg dose gave an 85.7% reduction compared with 97.7% for the standard dose (Table 5).

Haematuria

Two trials measured haematuria (King 1989; King 2002). King 1989 (117 participants) showed no difference in the rate of clearance between 30 mg/kg x 1 and the standard 40 mg/kg x 1 dose at three months (100% versus 99%). However, King 2002 (200 participants) showed a clear difference at six weeks' follow up between 20 mg/kg x 1 and the standard 40 mg/kg x 1 (40% versus 63%).

Adverse events

Davis 1981 recorded similar numbers of mild adverse events for each dose: 19%, 29%, and 17% for 30, 40, and 20 mg/kg x 2, respectively. Kardaman 1985 reported slightly higher rates with 20 mg/kg x 2 than the single dose of 40 mg/kg, but no numbers were reported. Neither trial reported serious adverse events (Table 6). Oyediran 1981 reported combined adverse events across 40, 30, and 20 mg/kg and recorded only two moderately severe events (umbilical pain). No serious adverse events were recorded.

DISCUSSION

Most of the 24 included trials were conducted many years ago, mostly in the 1970s and 1980s, and thus the standards of methodological quality did not reach the high standards that we would expect from trials carried out today; for example, only four out of the 24 trials used adequate methods to conceal allocation. However, effect sizes are so marked that it is unlikely that methodological quality will have caused such substantive biases to interfere with the marked effects and differences reported.

Both metrifonate and praziquantel showed good effects, but no trial compared the standard dose of each drug in a head-to-head comparison; instead trials compared different doses of each. Given that no trial compared the standard dose of metrifonate (7.5 to 10 mg/kg 3 times at 14-day intervals) with that of praziquantel (40 mg/kg) in a head-to-head assessment, discussion of adherence to treatment from currently available data is limited. However, the failure rate with the recommended standard dose of metrifonate (7.5 to 10 mg/kg 3 times at 14-day intervals) is 19% to 48%, while that of praziquantel (single 40 mg/kg oral dose) is 0% to 37% at one to three months' follow up. A dose of 7.5 mg/kg metrifonate produced more failures than 10 mg/kg, both doses administered three times at 14-day intervals. There appears to be no difference in effects of metrifonate 10 mg/kg given every four months for one year and the standard dose of praziquantel (40 mg/kg), but this may not be conclusive as the evidence came from only one trial (King 1988). Metrifonate (10 mg/kg 3 times at 14-day intervals) showed a similar effect to praziquantel (30 mg/kg). Public health programmes often recommend multiple-dose regimens, such as for metrifonate (3 doses of 7.5 to 10 mg/kg administered once every 14 days or every 4 months), but these are difficult to implement and might compromise overall compliance.

Both metrifonate and praziquantel showed high degrees of uncertainty around their effect estimates as shown by the wide confidence intervals. The small numbers in some of the trials may explain the levels of uncertainty. In this review we have analysed data mainly around infectivity and assumed statistical significance to be equal to clinical significance because it is not likely that small differences in effect of drugs being evaluated can mean large risks or clinical effects.

A single dose of 20 or 30 mg/kg of praziquantel was similarly efficacious compared to the standard dose of 40 mg/kg in terms of all outcomes measured in this review. Given current emphasis on controlling morbidity in high burden areas and morbidity, especially in children, is associated with the number of eggs in an individual (WHO 2002), this finding suggests lower doses of praziquantel may be effective in morbidity control. However, these results should be considered with caution. While it is true that parasite load (expressed by egg counts) is an important factor in both morbidity for the individual patient and environmental contamination (WHO 2002), a sub-curative dose may unduly put the drug under selective pressure and favour parasite resistance (Doenhoff 1998). Pharmacokinetic data of different doses of praziquantel are few and old, and have been obtained in healthy volunteers rather than in patients with schistosomiasis (Leopold 1978). An exponential increase was found in the area under the curve (AUC) with the praziquantel dose in the range of 5 to 50 mg/kg, with a six-fold increase from 20 to 50 mg/kg (Leopold 1978). However, these data do not come from infected patients, and hence cannot be extrapolated so easily. The artemisinins, best known for their use as antimalarial drugs, have been found to be effective against immature schistosomes in laboratory studies (Utzinger 2001a; Utzinger 2001c; Utzinger 2002). However, results from one low-quality trial show that artesunate is not effective when used alone or when combined with praziquantel. This may, to some extent, be explained by the fact that mature worms are less sensitive to the artemisinins (Utzinger 2007).

It has been suggested that there is a significant infection-associated loss of performance in a person with schistosomiasis that can be improved through antischistosomal treatment (Bergquist 2005; King 2005). This would necessitate any comprehensive assessment of antischistosomal drugs to include outcomes of subtle disease such as resolution of bladder or urinary tract pathology, growth, physical fitness, cognitive function, and educational achievement. Most trials did not investigate these outcome measures because the focus tended to be on measures of infectivity. However, we may include functional outcome measures in future updates if trials provide comprehensive data.

Adverse events

The rationale behind the widely spaced dosing interval of metrifonate treatment derives from its long-lasting effect on red blood cells and plasma cholinesterases (Plestina 1972). However, the clinical significance of this effect and why adverse events disappear during the first 12 to 24 hours but the recovery of the enzymes takes more than four to six weeks is not known (Plestina 1972). Safety studies have shown no serious adverse events in patients treated with 5 to 10 mg/kg metrifonate daily for six to 12 days (Snellen 1981), and various reviews of metrifonate's toxicology and pharmacology during its extensive use for urinary schistosomiasis in the 1970s concluded that it had very few adverse events (Holmstedt 1978). Also, metrifonate is currently used in Alzheimer's disease, which requires a high dose and extended regimen, and a systematic review has concluded an overall good tolerability with only mild to moderate adverse events (López-Arrieta 2006). In the current review, although adverse events were generally poorly assessed in the few trials measuring this, no trial recorded a serious adverse event, and no significant differences in the number and type of adverse events between metrifonate and praziquantel were recorded, except for abdominal pain where greater numbers of participants in the metrifonate group were reported with this adverse event.

AUTHORS' CONCLUSIONS

Implications for practice

Both praziquantel and metrifonate are efficacious (with few adverse events) for treating urinary schistosomiasis, but metrifonate requires multiple administrations and hence is operationally less convenient and more costly in community-based control programmes. However, leaving praziquantel as the only antischisto-

somal drug raises considerable concern in case resistance develops against this drug. We suggest metrifonate be reconsidered for the WHO Model List of Essential Medicines.

Implications for research

Well-designed trials are required to investigate the following areas.

- Different doses and regimens of metrifonate to identify appropriate doses for treatment and to facilitate adherence.

- Evaluation of the artemisinins (results are only available for artesunate and these are inconclusive).

- Combination therapy, ideally with drugs with unrelated mechanisms of action and targeting the different developmental stages of the schistosomes in the human host should be pursued; for example, praziquantel plus metrifonate, and praziquantel plus an artemisinin derivative.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aden Abdi 1989

Methods	Generation of allocation sequence: table of random numbers Allocation concealment: all doses kept in coded envelopes; drug distributor and participants unaware of type of treatment Blinding: investigators, participants, and assessors Inclusion of all randomized participants in the main analysis: 67% (201/300) Length of follow up: 1, 2, 3, and 6 months
Participants	Number randomized: 300 Inclusion criteria: excreting ≥ 20 eggs of *S. haematobium* per 10 mL urine; mostly children with mean age of 14 years Exclusion criteria: excreting < 20 eggs or found to have other concomitant diseases Diagnostic criteria: 10 mL of a single urine
Interventions	Metrifonate vs metrifonate: different doses 1. Standard 3 doses (7.5 mg/kg) given at 2-week intervals 2. Abbreviated doses (5 mg/kg) given 3 times in 1 day
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Adverse events
Notes	Location: Somalia Date of trial: not reported Endemicity: very high Number of communities: 5 Difficult monitoring adverse events as participants left soon after receiving treatment; information obtained when participants returned for next treatment; many participants could not be traced after taking the fifth dose Brand: metrifonate (Bilarcil, Bayer)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Beasley 1999

Methods	Generation of allocation sequence: random-number tables Allocation concealment: unclear Blinding: outcome assessors Inclusion of all randomized participants in the main analysis: 70% (250/357) Length of follow up: 15 weeks
Participants	Number randomized: 357 Inclusion criteria: children aged 7 to 12 years infected with *S. haematobium* and at least 1 geohelminth Exclusion criteria: very anaemic children (haemoglobin < 7.0 g/dL); heavy hookworm infection with egg count > 20,000 eggs per gram (epg); heavy *S. haematobium* infection with egg count > 2000 eggs/ 10 mL urine or Ascaris lumbricoides egg count > 200,000 epg; people who did not provide all baseline measurements; people not infected with both *S. haematobium* and a geohelminth Diagnostic criteria: 10 mL of single urine
Interventions	Albendazole plus praziquantel vs placebo 1. Albendazole (400 mg, single dose) plus praziquantel (40 mg/kg, single dose) 2. Placebo: magnesium sulfate and cellulose
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Anaemia (haemoglobin levels)
Notes	Location: Tanzania Date of trial: 1994 Endemicity: high (56%) Communities studied: 1 Dropouts equal in placebo and intervention groups Brand: albendazole (Zentel, Smithkline); praziquantel (Biltricide, Bayer)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Befidi-Mengue 1992

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: unclear Length of follow up: 6 months
Participants	Number randomized: 436 Inclusion criteria: school boys aged 6 to 15 years with mild to moderate *S. haematobium* infection Exclusion criteria: not stated Diagnostic criteria: 10 mL of a single urine

Befidi-Mengue 1992 (*Continued*)

Interventions	Praziquantel vs placebo 1. Praziquantel (40 mg/kg, single dose) 2. Placebo
Outcomes	1. Anaemia 2. Physical growth 3. Haematuria 4. Proteinuria
Notes	Location: Cameroon Date of trial: not reported Endemicity: not stated Communities studied: 1 Polyparasitism common in study area Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Borrmann 2001

Methods	Generation of allocation sequence: computer-generated randomization codes Allocation concealment: study drugs prepared in plastic bags and labelled sequentially with treatment numbers according to the randomization code Blinding: participants and investigators Inclusion of all randomized participants in the main analysis: 98.7% (296/300) Length of follow up: 8 weeks
Participants	Number randomized: 300 Inclusion criteria: children aged 5 to 13 years with asymptomatic *S. haematobium* infections Exclusion criteria: symptomatic schistosomiasis; recent adequate treatment for schistosomiasis; serious underlying diseases; and haemoglobin level < 7 g/dL Diagnostic criteria: 10 mL of 2 consecutive daily urines
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Artesunate (4 mg/kg/day for 3 days) 3. Praziquantel (40 mg/kg, single dose) plus artesunate (4 mg/kg/day over 3 days) 4. Artesunate placebo given over 3 days plus praziquantel placebo given once
Outcomes	1. Parasitological cure rate 2. Adverse events 3. Resolution of haematuria 4. Egg reduction rate

Borrmann 2001 (*Continued*)

Notes	Location: Gabon Date of trial: not reported Number in placebo group smaller than in the other groups (90:90:90:30); no explanation given Endemicity: very high (prevalence of 80%) Communities studied: 3 Adverse events defined as any changes in condition after treatment compared to baseline Brand: not stated

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Davis 1981

Methods	Generation of allocation sequence: random-numbers table Allocation concealment: tablets (active treatment and placebo) prepared in Germany were labelled as "A" or "B" and were physically similar and not known to the physicians or participants Blinding: participants, investigators, and outcome assessors Inclusion of all randomized participants in the main analysis: 92.4% (73/79) at 6 months; 83.5% (66/79) at 12 months; and 66% (52/79) at 24 months Length of follow up: 1, 6, 9, 12, 15, 18, and 24 months; up to 12 months' follow up included in review
Participants	Number randomized: 79 Inclusion criteria: children and young adults aged 7 to 22 years with *S. haematobium* infection excreting a minimum viable egg output of at least 50/10 mL urine Exclusion criteria: serious acute disease; no treatment within previous 6 months; > 6 years of age; females not pregnant or lactating Diagnostic criteria: 10 mL of 3 consecutive daily urine
Interventions	1. Praziquantel (20 mg/kg, single dose) 2. Praziquantel (30 mg/kg, single dose) 3. Praziquantel (40 mg/kg, single dose) 4. Praziquantel (20 mg/kg x 2 given at 4-h interval) 5. Placebo (same dose frequency as respective drug)
Outcomes	1. Adverse events 2. Parasitological cure rate 3. Mean haemoglobin
Notes	Location: Zambia Date of trial: not reported Trial setting: hospital Communities studied: 1 78% of participants had multiple parasitic infections, mainly hookworm, malaria, and *S. mansoni* Brand: not stated

Davis 1981 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Doehring 1985

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 100%; no losses to follow up Length of follow up: 1 month
Participants	Number randomized: 182 Inclusion criteria: boys aged 6 to 13 years with mixed *S. haematobium* and *S. mansoni* infections Exclusion criteria: not stated Diagnostic criteria: 10 mL of 3 consecutive daily urines and reagent strip for proteinuria
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Metrifonate (10 mg/kg, given at 2-week intervals) 3. Placebo (multivitamin tablet) Another arm consisted of oxamniquine (60 mg/kg, single dose), not part of current review All participants received a complete tetanus vaccine
Outcomes	1. Egg reduction rate 2. Proteinuria
Notes	Location: Sudan Date of trial: not reported Endemicity: very high Communities studied: 1 Brand: not stated

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Jewsbury 1977

Methods	Generation of allocation sequence: random numbers Allocation concealment: unclear Blinding: authors stated that all determinations were made blind, but unclear who were blinded Inclusion of all randomized participants in the main analysis: unclear Length of follow up: 6, 31, and 65 weeks after the third dose; up to 31 weeks included in review
Participants	Number randomized: 179 Inclusion criteria: children with *S. haematobium* infection or mixed *S. haematobium* and *S. mansoni* infection Exclusion criteria: not stated Diagnostic criteria: 10 mL of single urine at baseline, and 10 mL of 3 consecutive daily urines post-treatment
Interventions	1. Metrifonate (7.5 mg/kg, 3 doses fortnightly; called Group C in article) 2. Placebo (single 25 mg vitamin B6 tablet called Group B in article) 3 arms excluded from review: 3. Metrifonate therapy (7.5 mg/kg, 3 doses given fortnightly until 11 weeks) followed by metrifonate prophylaxis (7.5 mg/kg, 4 doses weekly); called Group A in article 4. Metrifonate prophylaxis (7.5 mg/kg, 4 doses given weekly); called Group D in article 5. No therapy or prophylaxis; called Group E in article Groups D and E consisted of children with no infection
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Adverse events
Notes	Location: Rhodesia (now Zimbabwe) Date of trial: not reported Endemicity: very high, prevalence of 80% Communities studied: 4 Where possible participants lost either before or during the trial were replaced with new children of appropriate sex, age group, and farm Brand: metrifonate (Bilarcil, Bayer)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Jinabhai 2001

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the main analysis: 84% (226/268) Length of follow up: 16 weeks
Participants	Number randomized: 268 Inclusion criteria: school children aged 8 to 10 years from 11 randomly selected schools Exclusion criteria: not stated Diagnostic criteria: microscopy by urine, but not stated how many urines
Interventions	1. Praziquantel (40 mg/kg, single dose) plus albendazole (400 mg, single dose) 2. Placebo Another arm consisted of albendazole (400 mg single dose) for intestinal helminths
Outcomes	1. Parasitological cure rate
Notes	Location: South Africa Date of trial: not reported Endemicity: high Communities studied: 11 Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kardaman 1985

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 92.8% (220/237) Length of follow up: 1, 3, 6, and 12 months
Participants	Number randomized: 237 Inclusion criteria: school children aged 7 to 11 years with mixed *S. haematobium* and *S. mansoni* infection Exclusion criteria: children receiving medication for other infections; received treatment for schistosomiasis during the preceding 6 months Diagnostic criteria: 2 positive urine samples (10 mL) for *S. haematobium* and 2 positive stool samples for *S. mansoni*
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Praziquantel (20 mg/kg x 2 given 4 to 6-h apart

Kardaman 1985 (*Continued*)

Outcomes	1. Adverse events 2. Parasitological cure rate 3. Egg reduction rate
Notes	Location: Sudan Date of trial: not reported Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

King 1988

Methods	Generation of allocation sequence: random-number tables Allocation concealment: unclear Blinding: participants and care providers Inclusion of randomized participants in the main analysis: 77% (1379/1787) Length of follow up: 36 months, but up to 12 months included in review
Participants	Number randomized: 2628 Inclusion criteria: school children and young adults (4 to 21 years) from an agricultural region infected with *S. haematobium* Exclusion criteria: not stated Presence of *S. haematobium* eggs measured by nucleopore filtration of urine: light infection (< 100 eggs/10 mL urine); moderate infection (100 to 400 eggs/10 mL urine); and heavy infection (> 400 eggs/10 mL urine)
Interventions	1. Metrifonate (10 mg/kg, 3 doses given at 4 months interval) 2. Praziquantel (40 mg/kg, single dose) followed by 2 doses of placebo each time the remaining doses of metrifonate were given
Outcomes	1. Haematuria measured with Chemstrip 5 indicator dipstick 2. Proteinuria measured with Chemstrip 5 indicator dipstick 3. Urinary tract abnormalities and changes 4. Prevalence of infection 5. Parasitological cure rate 6. Reinfection rate We included 1, 2, and 5 in this review
Notes	Location: Kenya Date of trial: not reported Brand: metrifonate (Bayer); praziquantel (Bayer)

Risk of bias

King 1988 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

King 1989

Methods	Generation of allocation sequence: randomized cards Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the main analysis: 86% (53/62), 91% (61/68), 87% (52/60), and 87% (47/56) from the 10, 20, 30, and 40 mg/kg treatment groups, respectively Length of follow up: 3 months
Participants	Number randomized: 280 (246 school children and 34 adults) Inclusion criteria: school children and adults infected with *S. haematobium* and excreting 50 eggs/10 mL of urine Exclusion criteria: not stated Diagnostic criteria: 10 mL of 2 daily consecutive urines, and reagent strips for haematuria and proteinuria
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Praziquantel (30 mg/kg, single dose) 3. Praziquantel (20 mg/kg, single dose) 4. Praziquantel (10 mg/kg, single dose)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria
Notes	Location: Kenya Date of trial: not reported Endemicity: very high

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

King 2002

Methods	Generation of allocation sequence: computer-generated sequence Allocation concealment: unclear Blinding: outcome assessors and clinicians Inclusion of randomized participants in the main analysis: 69% (200/291) Length of follow up: 6 weeks for parasitological cure, 9 months for ultrasound imaging
Participants	Number randomized: 291 Inclusion criteria: school children and young adults (age range 4 to 23 years) infected with *S. haematobium* Exclusion criteria: not stated Diagnostic criteria: 10 mL of 2 consecutive daily urines
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Praziquantel (20 mg/kg, single dose)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria
Notes	Location: Kenya Date of trial: 1993 Duration between trial and publication: 9 years Endemicity: very high, about 80% Communities studied: 2 Co-infection with geohelminths and malaria, but not *S. mansoni*, was common in the study area No other schistosomiasis control measures took place during the period of the study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

McMahon 1979

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 69% (125/183); 68% (123/183); 64% (117/183) lost to follow up at 1, 3, and 6 months, respectively Length of follow up: 1, 3, and 6 months
Participants	Number randomized: 183 Inclusion criteria: school children aged 7 to 15 years who presented 3 consecutive daily urines positive for *S. haematobium* with a geometric mean egg count of at least 250 miracidia per 10 mL urine Exclusion criteria: not stated Diagnostic criteria: 10 mL urine from 3 consecutive daily urines

McMahon 1979 (*Continued*)

Interventions	1. Praziquantel (30 mg/kg, single dose) 2. Praziquantel (40 mg/kg, single dose) 3. Praziquantel (20 mg/kg x 2 at 4-h intervals) 4. Placebo
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Adverse events
Notes	Location: Tanzania Date of trial: not reported Endemicity: not stated Communities studied: 1 Brand: praziquantel (Biltricide, Bayer)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

McMahon 1983

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 46/54 (86%) and 37/54 (69%) at 2 and 4 months, respectively Length of follow up: 2 and 4 months
Participants	Number randomized: 90 Inclusion criteria: people infected with *S. haematobium* with a geometric mean egg count of at least 250 miracidia per 10 mL urine Exclusion criteria: not stated Diagnostic criteria: 3 consecutive daily urines
Interventions	1. Metrifonate (10 mg/kg, 3 doses at 2-week intervals) 2. Praziquantel (30 mg/kg, single dose) A third arm consisting of niradazole was excluded
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Adverse events
Notes	Location: Tanzania Date of trial: not reported Endemicity: not stated Communities studied: 1

McMahon 1983 (*Continued*)

	Authors stated that any person who missed a dose was excluded from their final analysis Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Olds 1999

Methods	Generation of allocation sequence: randomized block design Allocation concealment: randomization code centrally kept and unique bottles were used with only codes Blinding: participants and outcome assessors Inclusion of randomized participants in the main analysis: 376/380 (99%), 376/380 (99%), 342/380 (90%), and 315/380 (83%) at 1.5, 3, 6, and 12 months
Participants	Number randomized: 380 Inclusion criteria: school children aged 4 to 18 years with *S. haematobium* infection Exclusion criteria: known allergy to praziquantel or albendazole; treatment with praziquantel or albendazole during the past 6 months; lack of consent; or females pregnant or suspected to be pregnant Diagnostic criteria: 10 mL of 2 consecutive daily urines at pre-treatment, but 10 mL of a single urine at post-treatment; dipstick for haematuria and proteinuria
Interventions	1. Praziquantel (40 mg/kg, single dose) plus albendazole (400 mg) 2. Praziquantel plus albendazole placebo 3. Albendazole plus praziquantel placebo 4. Both placebos
Outcomes	1. Physical growth measured in terms of height, skin-fold thickness at the subscapular, triceps, and abdominal positions; and mid-arm circumferences 2. Haemoglobin levels measured by fluorometry on a portable haemoglobinometer (Hemocue) 3. Failure rate 4. Egg reduction rate 5. Adverse effects
Notes	Location: Kenya Date of trial: not reported Endemicity: very high Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Omer 1981

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 80% (122/153) Length of follow up: 6 months
Participants	Number randomized: 153 Inclusion criteria: aged over 8 years with mixed infection of *S. haematobium* and *S. mansoni* either reporting to the hospital or detected during a field survey Exclusion criteria: aged below 8 years; advanced stage of disease; severe anaemia; and poor general health
Interventions	1. Praziquantel (30 mg/kg, single dose) 2. Praziquantel (40 mg/kg, single dose) 3. Praziquantel (20 mg/kg x 2, at 4-h apart)
Outcomes	1. Adverse events 2. Parasitological cure rate 3. Egg reduction rate
Notes	Location: Sudan Date of trial: 1978-9 Endemicity: very high Communities studied: 1 Brand: praziquantel (Biltricide, Bayer)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Oyediran 1981

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 68.3% (125/183), 67.2% (123/183), and 64% (117/183) at 1, 3, and 6 months, respectively Length of follow up: 1, 3, 6, 9, and 12 months, but we included up to 6 months since it reported only egg count data
Participants	Number randomized: 90 Inclusion criteria: school children aged 9 to 16 years with *S. haematobium* infection with a geometric mean egg count of viable eggs of at least 60 eggs/ 10 mL urine Exclusion criteria: aged below 6 years; concurrent acute or serious illness; and been treated with any antischistosomal drug within the past 6 months Diagnostic criteria: 10 mL of 3 consecutive daily urines

Oyediran 1981 (*Continued*)

Interventions	1. Praziquantel (30 mg/kg, single dose) 2. Praziquantel (40 mg/kg, single dose) 3. Praziquantel (20 mg/kg x 2, 4-h apart) 4. Placebo (40 mg/kg, single dose)
Outcomes	1. Egg reduction rate 2. Adverse events
Notes	Location: Nigeria Date of trial: not reported Endemicity: light to moderate Communities studied: 1 Brand: praziquantel (Biltricide, Bayer)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pugh 1983

Methods	Generation of allocation sequence: sequential Allocation concealment: unclear Blinding: authors stated double blind Inclusion of randomized participants in the main analysis: 97% (421/433) Length of follow up: 1, 3, and 6 months
Participants	Number randomized: 600 Inclusion criteria: school children (517 boys and 83 girls aged 5 to 18 years) with heavy haematuria by reagent strips Exclusion criteria: children with malaise, febrile illness, or who had received schistosomicidal drugs during the preceding 6 months of the trial Diagnostic criteria: 10 mL of single urine
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Metrifonate (10 mg/kg, single dose) 4. Placebo (ascorbic acid (300 mg, single dose) Placebo group special, selected light infections
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Adverse events (authors stated they evaluated adverse events, but not in detail)
Notes	Location: Malawi Date of trial: not reported Brand: metrifonate (Bilarcil, Bayer); praziquantel (Biltricide, Bayer)

Pugh 1983 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Rey 1983

Methods	Generation of allocation sequence: permutation table Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 93/103 (90.3%), 88/94 (93.6%), and 57/62 (91.9%) at 1, 3, and 6 months' follow up
Participants	Number randomized: 286 Inclusion criteria: individuals (all ages) infected with *S. haematobium* Exclusion criteria: not stated Diagnostic criteria: 10 mL of single urine
Interventions	1. Metrifonate (10 mg/kg, single dose) 2. Metrifonate (10 mg/kg, 2 doses given fortnightly) 3. Metrifonate (10 mg/kg, 3 doses given fortnightly)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate
Notes	Location: Niger Date of trial: not reported Endemicity: moderate (50%) Communities studied: 3 Study conducted during low transmission season Brand: not stated

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Rey 1984b

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the main analysis: 143/285 (50%) at 1 month follow up and 175/286 (61.2%) at 4 months
Participants	Number randomized: 286 Inclusion criteria: egg-positive individuals Exclusion criteria: not stated
Interventions	1. Metrifonate (10 mg/kg, single dose) 2. Metrifonate (10 mg/kg, 2 doses given fortnightly) 3. Metrifonate (10 mg/kg, 3 doses given fortnightly)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate
Notes	Location: Niger Date of trial: not reported Communities studies: 3 Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Stephenson 1985

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: outcome assessors Inclusion of all randomized participants in the main analysis: unclear Length of follow up: 8 months
Participants	Number randomized: 400 Inclusion criteria: children aged 6 to 15 years with light to moderate *S. haematobium* infections Exclusion criteria: heavy infection with *S. haematobium*; severe anaemia with haemoglobin < 8 g/dL Diagnostic criteria: 10 mL urine adjusted egg count of whole volume of urine
Interventions	1. Metrifonate (7.5 mg/kg, 3 times fortnightly) 2. Placebo (gelatine capsules containing lactose) Each child received a standard dose of bephenium hydroxynaphthoate (Alcopar 5 g sachet) to decrease the contribution of hookworm infections as a confounding variable in the subsequent analysis of haemoglobin change after metrifonate treatment

Stephenson 1985 (*Continued*)

Outcomes	1. Parasitological cure rate 2. Splenomegaly 3. Hepatomegaly 4. Egg reduction rate 5. Mean haemoglobin 6. Anthropometric measurements
Notes	Location: Kenya Date of trial: not reported Endemicity: moderate (46%) Communities studied: 1 Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Stephenson 1989

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: outcome assessors Inclusion of randomized participants in the main analysis: 90% (312/347) Length of follow up: 8 months
Participants	Number randomized: 347 Inclusion criteria: children in 3 primary schools with light to moderate *S. haematobium* infection who tested positive for haematuria by use of reagent strips Exclusion criteria: children with severe anaemia (haemoglobin < 8.0 g/dL) or heavy *S. haematobium* Diagnostic criteria: 10 mL urine adjusted egg count of whole volume of urine; by complete bladder voiding with egg count per 10 mL of urine adjusted for the total volume of each urine specimen by multiplying the egg count per slide by the actual specimen volume divided by 100 mL and are referred to as eggs per 10 mL adjusted
Interventions	1. Metrifonate (10 mg/kg, single dose) 2. Praziquantel (40 mg/kg, single dose) 3. Placebo (gelatine capsule containing lactulose, single dose)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate 3. Physical growth measured in terms of percentage change in weight, per cent weight-for-age, per cent weight-for-height, arm circumference, triceps, and subscapular skinfold thickness
Notes	Location: Kenya Date of trial: not reported Endemicity: high

Stephenson 1989 (*Continued*)

	Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Taylor 1988

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: participants and outcome assessors Inclusion of all randomized participants in the main analysis: unclear Length of follow up: 1, 3, and 6 months
Participants	Number randomized: 373 Inclusion criteria: school children aged 10 to 15 years with *S. haematobium* and *S. mansoni* mixed infection Exclusion criteria: not stated Diagnostic criteria: 10 mL of 3 consecutive daily urines
Interventions	1. Praziquantel (10 mg/kg, single dose) 2. Praziquantel (20 mg/kg, single dose) 3. Praziquantel (30 mg/kg, single dose) 4. Praziquantel (40 mg/kg, single dose) 5. Placebo (40 mg/kg, single dose)
Outcomes	1. Parasitological cure rate 2. Egg reduction rate
Notes	Location: Zimbabwe Date of trial: not reported Endemicity: very high (77%) Communities studied: 1 Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wilkins 1987a

Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: unclear Blinding: outcome assessors Inclusion of randomized participants in the main analysis: no losses reported Length of follow up: 3 months
Participants	Number randomized: 184 Inclusion criteria: children aged 2 to 19 years with light to moderate *S. haematobium* infection Exclusion criteria: not stated Diagnostic criteria: 10 mL of 3 consecutive daily urines
Interventions	1. Praziquantel (40 mg/kg, single dose) 2. Praziquantel (20 mg/kg, single dose) 3. Praziquantel (10 mg/kg, single dose) 4. Metrifonate (10 mg/kg, single dose) 5. Metrifonate (10 mg/kg, single dose) plus praziquantel (10 mg/kg, single dose)
Outcomes	1. Egg reduction rate 2. Adverse events
Notes	Location: The Gambia Date of trial: not reported Endemicity: very high Communities studied: 3 2 trials were reported (Simoto and Nyamanari trials), but only Nyamanari included in the review Egg count = log 10 (n+1) to include zeros Brand: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Study	Reason for exclusion
Aden-Abdi 1987	Participants not randomized
Boulanger 2007	No control group
De Clercq 2002	Selective treatment study (ie screening a whole or part of a population/community and treating all found infected), not randomized
Druilhe 1981	No control group

(*Continued*)

Inyang-Etoh 2004	Selective treatment study
Kardaman 1983	Participants not randomized
N'Goran 2003a	Selective treatment study
N'Goran 2003b	Trial used participants who tested negative for *S. haematobium* at baseline
Rey 1984	No control for metrifonate
Saif M 1981	Observational study
Schutte 1983	Matched controlled trial, not randomized
Snyman 1997	Follow-up time of 21 days falls outside our inclusion criteria
Taylor 2001	Children were assigned to treatment groups irrespective of their infection status at baseline (ie whether infected or not), and a prevalence study; also control group given treatment 3 months before the follow-up time at 6 months
Tchuem Tchuente 2004	Selective treatment study
Utzinger 2001a	Review data, not based on primary data
Utzinger 2003	Review data, the primary data were reported in De Clercq 2002 and Borrmann 2001
Wilkins 1987b	This refers to the Simoto trial, not randomized

DATA AND ANALYSES

Comparison 1. Metrifonate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 to 3 months	1	64	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.27, 0.64]
1.2 > 3 to 12 months	3	680	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.29, 0.95]
2 Change in mean haemoglobin (g/dL)	2	607	Mean Difference (IV, Fixed, 95% CI)	0.30 [0.28, 0.32]

Comparison 2. Praziquantel vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 to 3 months	4	534	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.27, 0.55]
1.2 > 3 to 12 months	3	433	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.14, 0.39]
2 Change in mean haemoglobin (g/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Artesunate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 2 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Praziquantel plus artesunate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 2 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Praziquantel plus albendazole vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 1 to 4 months	3	471	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.35, 0.59]
2 Change in mean haemoglobin (g/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Metrifonate (10 mg/kg, 1 dose) vs praziquantel (40 mg/kg, single dose) at 1 to 8 months	3	462	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.91, 5.82]
1.2 Metrifonate (10 mg/kg x 3 given fortnightly) vs praziquantel (30 mg/kg, single dose) at 2 months	1	54	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.60, 5.90]
1.3 Metrifonate (10 mg/kg every 4 months for 1 year) vs praziquantel (40 mg/kg, single dose) at 12 months	1	1241	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.94, 1.51]
2 Mean haemoglobin (g/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Metrifonate (10 mg/kg x 1) vs praziquantel (40 mg/kg, single dose)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 7. Metrifonate (10 mg/kg every 4 months for 1 year) vs standard praziquantel dose: effect on infection level

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 12 months: light infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Parasitological failure at 12 months: heavy infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. Metrifonate (5 mg/kg x 3, given 1 day) vs metrifonate (7.5 mg/kg x 3, fortnightly)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 1 month	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 9. Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg) vs praziquantel (40 mg/kg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 10. Metrifonate (10 mg/kg x 1) vs metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg x 1)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Artesunate plus praziquantel vs praziqunatel alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure at 2 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 12. Metrifonate: different doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 10 mg/kg x 2 vs 10 mg/kg x 3	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Parasitological failure rate at 1 month	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Parasitological failure rate at 4 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 10 mg/kg x 1 vs 10 mg/kg x 3	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Parasitological failure rate at 1 month	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Parasitological failure rate at 4 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 13. Praziquantel: different doses vs standard 40 mg/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure: 2 x 20 mg/kg	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 month	3	374	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.51, 1.88]
1.2 3 months	3	361	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.30, 1.45]
1.3 6 months	3	234	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.78, 1.50]
2 Parasitological failure: 30 mg/kg	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 1 month	4	401	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.01, 1.70]
2.2 3 months	5	517	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.39]
2.3 6 months	5	439	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.37]
3 Parasitolotical failure: 20 mg/kg	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 1 month	2	338	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.90, 2.01]
3.2 3 months	3	330	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.00, 1.87]
3.3 6 months	1	138	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.65, 1.82]
4 Proportion cleared of haematuria	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 2 x 20 mg/kg	2	308	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.95]
4.2 30 mg/kg	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.19]
5 Parasitiological failure: 30 mg/kg vs 40 mg/kg at 3 months' follow up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Light infection	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.2 Moderate infection	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 Heavy infection	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 14. Praziquantel: different doses vs standard 40 mg/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological failure rate at 1 to 12 months	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Failure rate: 2 x 20 mg/kg vs standard 40 mg/kg	4	457	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.77, 1.50]
1.2 Failure rate: 30 mg/kg vs standard 40 mg/kg	6	597	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.02, 1.53]
1.3 Failure rate: 20 mg/kg vs standard 40 mg/kg	4	530	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.09, 1.90]

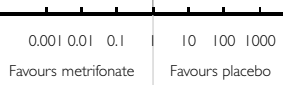
Analysis 1.1. Comparison 1 Metrifonate vs placebo, Outcome 1 Parasitological failure.

Review: Drugs for treating urinary schistosomiasis

Comparison: 1 Metrifonate vs placebo

Outcome: 1 Parasitological failure

Study or subgroup	Metrifonate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 1 to 3 months					
Jewsbury 1977	13/32	31/32		100.0 %	0.42 [0.27, 0.64]
Subtotal (95% CI)	**32**	**32**		**100.0 %**	**0.42 [0.27, 0.64]**
Total events: 13 (Metrifonate), 31 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.02 (P = 0.000058)					
2 > 3 to 12 months					
Jewsbury 1977	22/31	39/42		32.8 %	0.76 [0.60, 0.97]
Stephenson 1985	58/202	190/198		33.1 %	0.30 [0.24, 0.37]
Stephenson 1989	64/103	102/104		34.1 %	0.63 [0.54, 0.74]
Subtotal (95% CI)	**336**	**344**		**100.0 %**	**0.53 [0.29, 0.95]**
Total events: 144 (Metrifonate), 331 (Placebo)					
Heterogeneity: Tau² = 0.26; Chi² = 51.07, df = 2 (P<0.00001); I² =96%					
Test for overall effect: Z = 2.14 (P = 0.032)					



Analysis 1.2. Comparison 1 Metrifonate vs placebo, Outcome 2 Change in mean haemoglobin (g/dL).

Review: Drugs for treating urinary schistosomiasis

Comparison: 1 Metrifonate vs placebo

Outcome: 2 Change in mean haemoglobin (g/dL)

Study or subgroup	Metrifonate N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Stephenson 1985	202	1.3 (0.8)	198	1 (0.8)		2.4 %	0.30 [0.14, 0.46]
Stephenson 1989	103	0.14 (0.09)	104	-0.16 (0.09)		97.6 %	0.30 [0.28, 0.32]
Total (95% CI)	**305**		**302**			**100.0 %**	**0.30 [0.28, 0.32]**

Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 24.27 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Praziquantel vs placebo, Outcome 1 Parasitological failure.

Review: Drugs for treating urinary schistosomiasis

Comparison: 2 Praziquantel vs placebo

Outcome: 1 Parasitological failure

Study or subgroup	Praziquantel n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 1 to 3 months					
Borrmann 2001	24/89	24/30		25.7 %	0.34 [0.23, 0.50]
McMahon 1979	5/30	29/29		17.9 %	0.18 [0.08, 0.39]
Olds 1999	33/95	75/94		27.5 %	0.44 [0.32, 0.58]
Taylor 1988	42/77	90/90		28.9 %	0.55 [0.45, 0.67]
Subtotal (95% CI)	**291**	**243**		**100.0 %**	**0.39 [0.27, 0.55]**
Total events: 104 (Praziquantel), 218 (Placebo)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 12.15$, df = 3 (P = 0.01); $I^2 = 75\%$					
Test for overall effect: Z = 5.24 (P < 0.00001)					
2 > 3 to 12 months					
McMahon 1979	8/28	30/30		30.5 %	0.30 [0.17, 0.53]
Stephenson 1989	14/104	102/104		32.8 %	0.14 [0.08, 0.22]
Taylor 1988	22/77	87/90		36.7 %	0.30 [0.21, 0.42]
Subtotal (95% CI)	**209**	**224**		**100.0 %**	**0.23 [0.14, 0.39]**
Total events: 44 (Praziquantel), 219 (Placebo)					
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.36$, df = 2 (P = 0.03); $I^2 = 73\%$					
Test for overall effect: Z = 5.58 (P < 0.00001)					

Analysis 2.2. Comparison 2 Praziquantel vs placebo, Outcome 2 Change in mean haemoglobin (g/dL).

Review: Drugs for treating urinary schistosomiasis

Comparison: 2 Praziquantel vs placebo

Outcome: 2 Change in mean haemoglobin (g/dL)

Study or subgroup	Praziquantel N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Stephenson 1989	105	-0.05 (0.09)	104	-0.16 (0.09)		0.11 [0.09, 0.13]

Analysis 3.1. Comparison 3 Artesunate vs placebo, Outcome 1 Parasitological failure at 2 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 3 Artesunate vs placebo

Outcome: 1 Parasitological failure at 2 months

Study or subgroup	Artesunate n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Borrmann 2001	65/89	24/30		0.91 [0.73, 1.14]

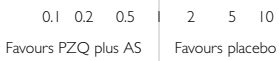
Analysis 4.1. Comparison 4 Praziquantel plus artesunate vs placebo, Outcome 1 Parasitological failure at 2 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 4 Praziquantel plus artesunate vs placebo

Outcome: 1 Parasitological failure at 2 months

Study or subgroup	PZQ plus AS n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Borrmann 2001	17/88	24/30		0.24 [0.15, 0.38]



Analysis 5.1. Comparison 5 Praziquantel plus albendazole vs placebo, Outcome 1 Parasitological failure at 1 to 4 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 5 Praziquantel plus albendazole vs placebo

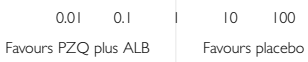
Outcome: 1 Parasitological failure at 1 to 4 months

Study or subgroup	PZQ plus ALB n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Beasley 1999	51/127	106/123		51.9 %	0.47 [0.37, 0.58]
Jinabhai 2001	2/18	9/11		3.7 %	0.14 [0.04, 0.52]
Olds 1999	38/98	75/94		44.4 %	0.49 [0.37, 0.64]
Total (95% CI)	**243**	**228**		**100.0 %**	**0.45 [0.35, 0.59]**

Total events: 91 (PZQ plus ALB), 190 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.42$, df = 2 (P = 0.18); $I^2 = 42\%$

Test for overall effect: Z = 5.90 (P < 0.00001)



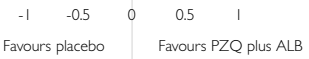
Analysis 5.2. Comparison 5 Praziquantel plus albendazole vs placebo, Outcome 2 Change in mean haemoglobin (g/dL).

Review: Drugs for treating urinary schistosomiasis

Comparison: 5 Praziquantel plus albendazole vs placebo

Outcome: 2 Change in mean haemoglobin (g/dL)

Study or subgroup	PZQ plus ALB N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Beasley 1999	127	-0.11 (0.07)	123	-0.35 (0.07)		0.24 [0.22, 0.26]



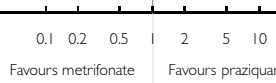
Analysis 6.1. Comparison 6 Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose), Outcome 1 Parasitological failure.

Review: Drugs for treating urinary schistosomiasis

Comparison: 6 Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose)

Outcome: 1 Parasitological failure

Study or subgroup	Metrifonate n/N	Praziquantel n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Metrifonate (10 mg/kg, 1 dose) vs praziquantel (40 mg/kg, single dose) at 1 to 8 months					
Pugh 1983	72/90	59/93		39.3 %	1.26 [1.05, 1.52]
Stephenson 1989	64/103	14/104		30.5 %	4.62 [2.77, 7.69]
Wilkins 1987a	29/39	11/33		30.3 %	2.23 [1.33, 3.74]
Subtotal (95% CI)	**232**	**230**		**100.0 %**	**2.31 [0.91, 5.82]**
Total events: 165 (Metrifonate), 84 (Praziquantel)					
Heterogeneity: $Tau^2 = 0.62$; $Chi^2 = 32.61$, df = 2 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 1.77 (P = 0.077)					
2 Metrifonate (10 mg/kg x 3 given fortnightly) vs praziquantel (30 mg/kg, single dose) at 2 months					
McMahon 1983	6/24	4/30		100.0 %	1.88 [0.60, 5.90]



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Study or subgroup	Metrifonate n/N	Praziquantel n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**24**	**30**		**100.0 %**	**1.88 [0.60, 5.90]**
Total events: 6 (Metrifonate), 4 (Praziquantel)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
3 Metrifonate (10 mg/kg every 4 months for 1 year) vs praziquantel (40 mg/kg, single dose) at 12 months					
King 1988	120/620	101/621		100.0 %	1.19 [0.94, 1.51]
Subtotal (95% CI)	**620**	**621**		**100.0 %**	**1.19 [0.94, 1.51]**
Total events: 120 (Metrifonate), 101 (Praziquantel)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					

Analysis 6.2. Comparison 6 Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose), Outcome 2 Mean haemoglobin (g/dL).

Review: Drugs for treating urinary schistosomiasis

Comparison: 6 Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose)

Outcome: 2 Mean haemoglobin (g/dL)

Study or subgroup	Metrifonate N	Mean(SD)	Praziquantel N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Metrifonate (10 mg/kg x 1) vs praziquantel (40 mg/kg, single dose)						
Stephenson 1989	103	0.14 (0.08)	105	-0.05 (0.08)		0.19 [0.17, 0.21]

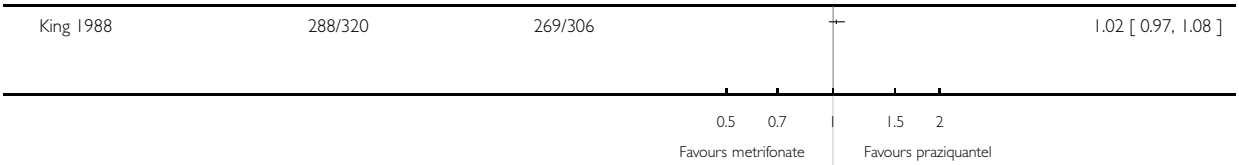
Analysis 7.1. Comparison 7 Metrifonate (10 mg/kg every 4 months for 1 year) vs standard praziquantel dose: effect on infection level, Outcome 1 Parasitological failure at 12 months: light infection.

Review: Drugs for treating urinary schistosomiasis

Comparison: 7 Metrifonate (10 mg/kg every 4 months for 1 year) vs standard praziquantel dose: effect on infection level

Outcome: 1 Parasitological failure at 12 months: light infection

Study or subgroup	Metrifonate n/N	Praziquantel n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
King 1988	288/320	269/306		1.02 [0.97, 1.08]



Analysis 7.2. Comparison 7 Metrifonate (10 mg/kg every 4 months for 1 year) vs standard praziquantel dose: effect on infection level, Outcome 2 Parasitological failure at 12 months: heavy infection.

Review: Drugs for treating urinary schistosomiasis

Comparison: 7 Metrifonate (10 mg/kg every 4 months for 1 year) vs standard praziquantel dose: effect on infection level

Outcome: 2 Parasitological failure at 12 months: heavy infection

Study or subgroup	Metrifonate n/N	Praziquantel n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
King 1988	211/300	252/315		0.88 [0.80, 0.96]

Analysis 8.1. Comparison 8 Metrifonate (5 mg/kg x 3, given 1 day) vs metrifonate (7.5 mg/kg x 3, fortnightly), Outcome 1 Parasitological failure at 1 month.

Review: Drugs for treating urinary schistosomiasis

Comparison: 8 Metrifonate (5 mg/kg x 3, given 1 day) vs metrifonate (7.5 mg/kg x 3, fortnightly)

Outcome: 1 Parasitological failure at 1 month

Study or subgroup	5 mg/kg x 3 n/N	7.5 mg/kg x 3 n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Aden Abdi 1989	54/101	48/100		1.11 [0.85, 1.46]

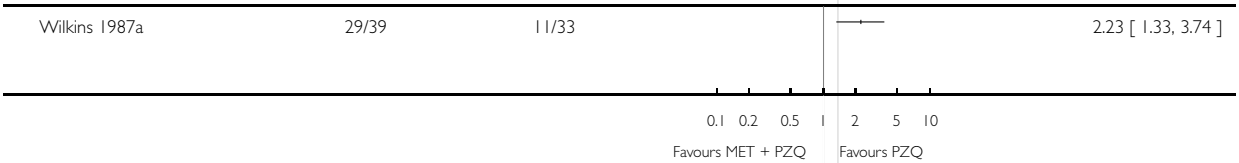
Analysis 9.1. Comparison 9 Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg) vs praziquantel (40 mg/kg), Outcome 1 Parasitological failure at 3 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 9 Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg) vs praziquantel (40 mg/kg)

Outcome: 1 Parasitological failure at 3 months

Study or subgroup	MET + PZQ n/N	PZQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Wilkins 1987a	29/39	11/33		2.23 [1.33, 3.74]



Analysis 10.1. Comparison 10 Metrifonate (10 mg/kg x 1) vs metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg x 1), Outcome 1 Parasitological failure at 3 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 10 Metrifonate (10 mg/kg x 1) vs metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg x 1)

Outcome: 1 Parasitological failure at 3 months

Study or subgroup	MET n/N	MET + PZQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Wilkins 1987a	29/39	22/39		1.32 [0.95, 1.84]

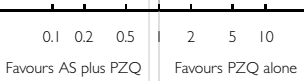
Analysis 11.1. Comparison 11 Artesunate plus praziquantel vs praziqunatel alone, Outcome 1 Parasitological failure at 2 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 11 Artesunate plus praziquantel vs praziqunatel alone

Outcome: 1 Parasitological failure at 2 months

Study or subgroup	AS plus PZQ n/N	PZQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Borrmann 2001	17/88	24/89		0.72 [0.41, 1.24]



Analysis 12.1. Comparison 12 Metrifonate: different doses, Outcome 1 10 mg/kg x 2 vs 10 mg/kg x 3.

Review: Drugs for treating urinary schistosomiasis

Comparison: 12 Metrifonate: different doses

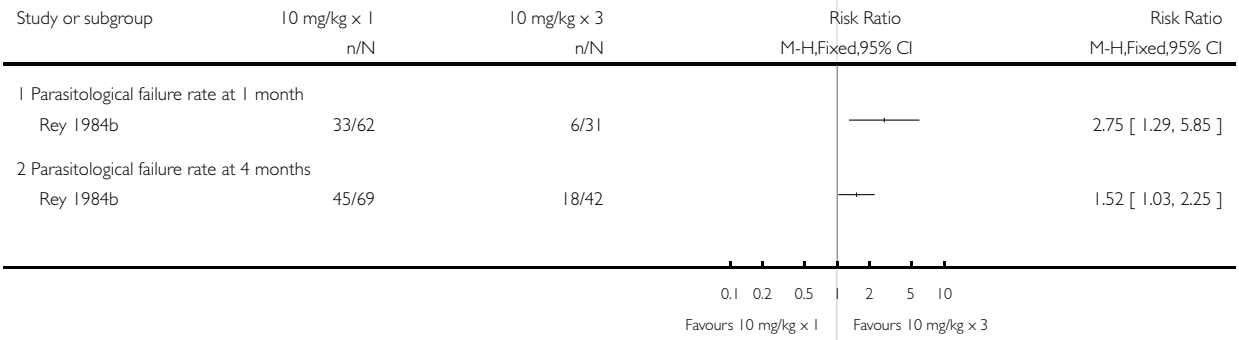
Outcome: 1 10 mg/kg x 2 vs 10 mg/kg x 3

Analysis 12.2. Comparison 12 Metrifonate: different doses, Outcome 2 10 mg/kg x 1 vs 10 mg/kg x 3.

Review: Drugs for treating urinary schistosomiasis

Comparison: 12 Metrifonate: different doses

Outcome: 2 10 mg/kg x 1 vs 10 mg/kg x 3

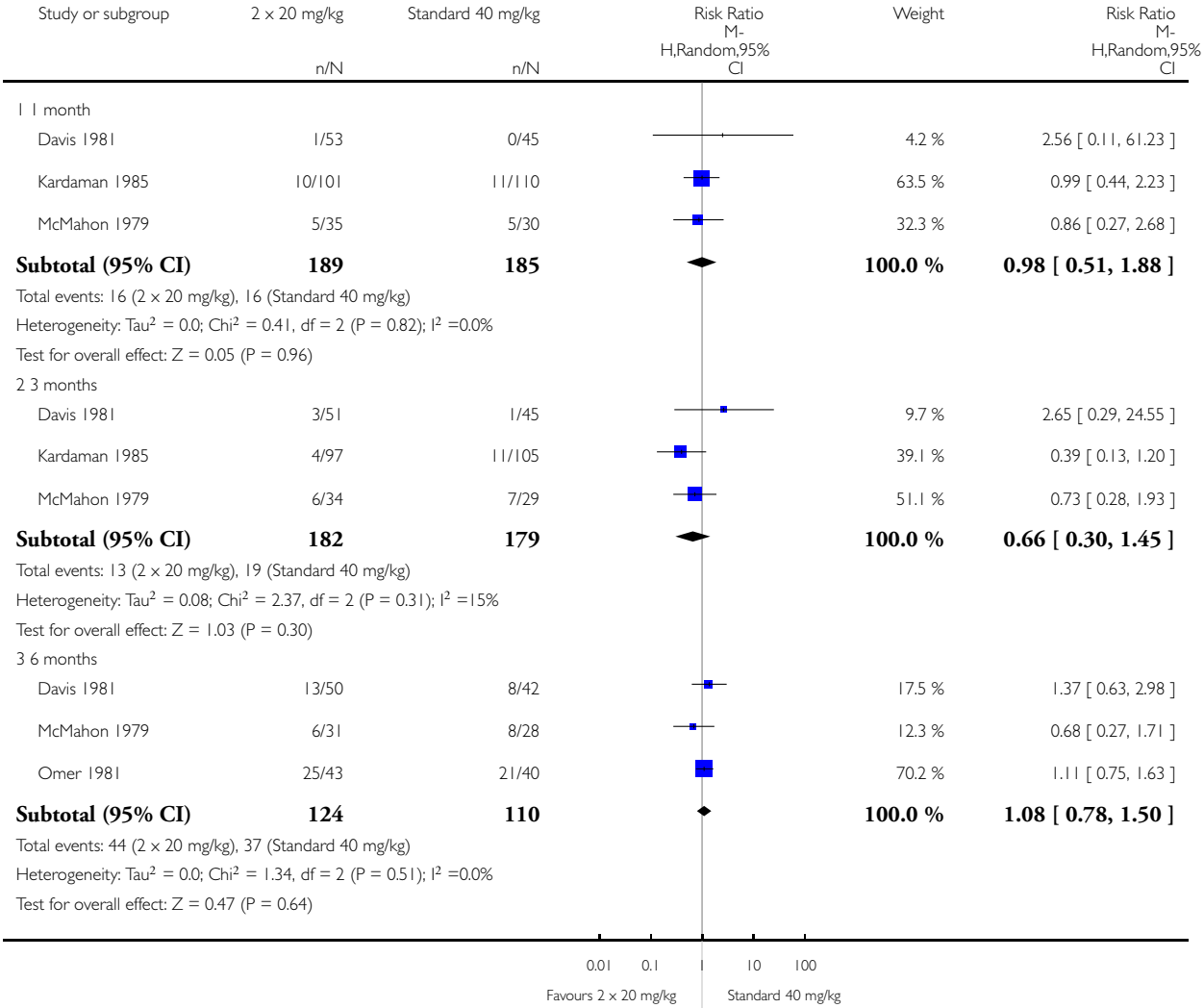


Analysis 13.1. Comparison 13 Praziquantel: different doses vs standard 40 mg/kg, Outcome 1 Parasitological failure: 2 x 20 mg/kg.

Review: Drugs for treating urinary schistosomiasis

Comparison: 13 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 1 Parasitological failure: 2 x 20 mg/kg



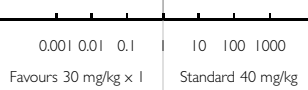
Analysis 13.2. Comparison 13 Praziquantel: different doses vs standard 40 mg/kg, Outcome 2 Parasitological failure: 30 mg/kg.

Review: Drugs for treating urinary schistosomiasis

Comparison: 13 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 2 Parasitological failure: 30 mg/kg

Study or subgroup	30 mg/kg x 1 n/N	Standard 40 mg/kg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 1 month					
Davis 1981	3/53	0/45		1.1 %	5.96 [0.32, 112.45]
McMahon 1979	9/31	5/30		10.4 %	1.74 [0.66, 4.60]
Rey 1983	1/39	3/54		5.2 %	0.46 [0.05, 4.27]
Taylor 1988	49/72	42/77		83.3 %	1.25 [0.96, 1.62]
Subtotal (95% CI)	**195**	**206**		**100.0 %**	**1.31 [1.01, 1.70]**
Total events: 62 (30 mg/kg x 1), 50 (Standard 40 mg/kg)					
Heterogeneity: Chi² = 2.34, df = 3 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 2.05 (P = 0.041)					
2 3 months					
Davis 1981	5/53	1/45		1.8 %	4.25 [0.51, 35.01]
King 1989	13/60	9/56		15.1 %	1.35 [0.63, 2.91]
McMahon 1979	9/31	7/29		11.7 %	1.20 [0.52, 2.81]
Rey 1983	2/42	4/52		5.8 %	0.62 [0.12, 3.22]
Taylor 1988	36/72	42/77		65.7 %	0.92 [0.67, 1.25]
Subtotal (95% CI)	**258**	**259**		**100.0 %**	**1.06 [0.80, 1.39]**
Total events: 65 (30 mg/kg x 1), 63 (Standard 40 mg/kg)					
Heterogeneity: Chi² = 3.36, df = 4 (P = 0.50); I² =0.0%					
Test for overall effect: Z = 0.39 (P = 0.69)					
3 6 months					
Davis 1981	17/51	8/42		14.1 %	1.75 [0.84, 3.65]
McMahon 1979	6/28	8/28		12.8 %	0.75 [0.30, 1.88]
Omer 1981	24/39	21/40		33.2 %	1.17 [0.80, 1.72]
Rey 1983	1/28	4/34		5.8 %	0.30 [0.04, 2.56]
Taylor 1988	17/72	22/77		34.1 %	0.83 [0.48, 1.43]
Subtotal (95% CI)	**218**	**221**		**100.0 %**	**1.03 [0.78, 1.37]**
Total events: 65 (30 mg/kg x 1), 63 (Standard 40 mg/kg)					
Heterogeneity: Chi² = 4.77, df = 4 (P = 0.31); I² =16%					
Test for overall effect: Z = 0.21 (P = 0.83)					

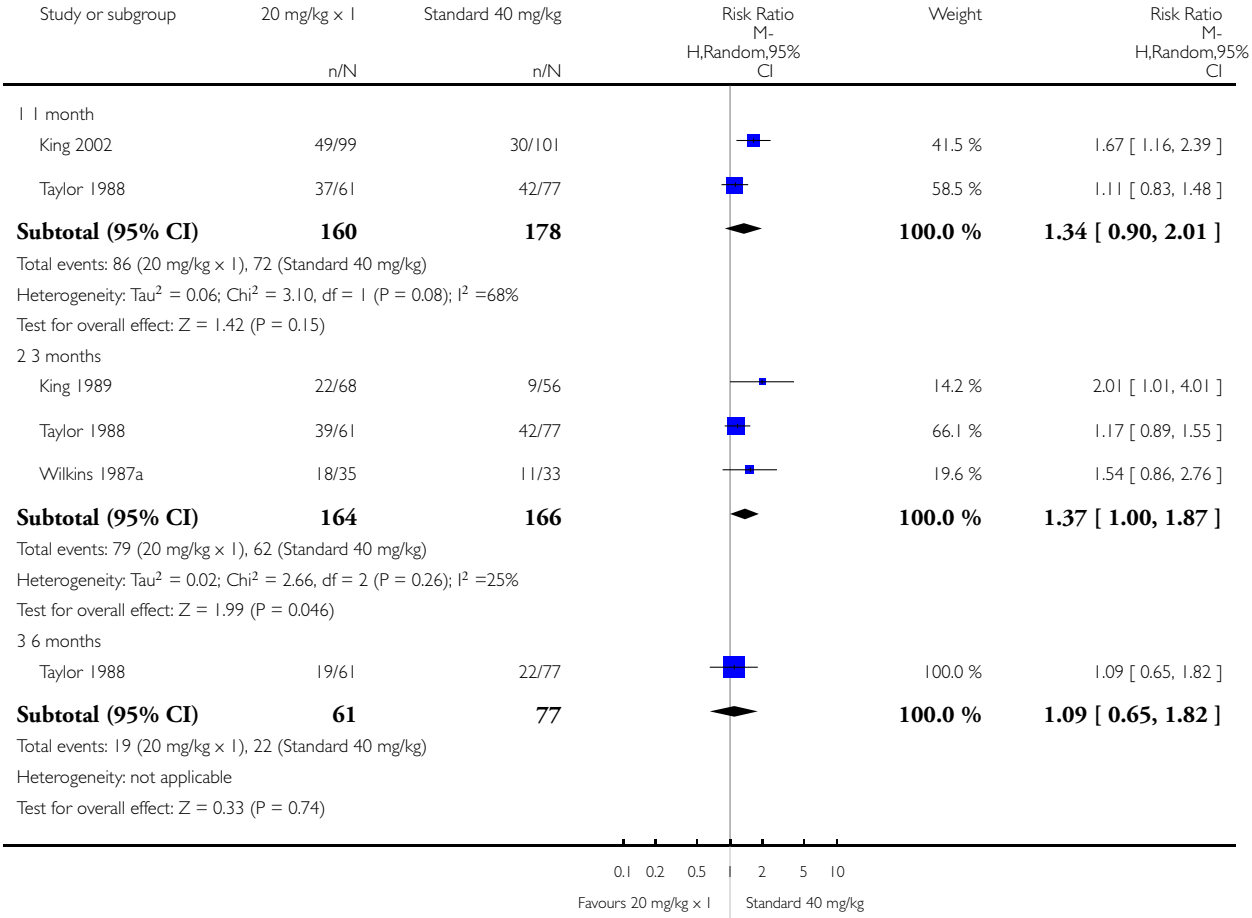


Analysis 13.3. Comparison 13 Praziquantel: different doses vs standard 40 mg/kg, Outcome 3 Parasitolotical failure: 20 mg/kg.

Review: Drugs for treating urinary schistosomiasis

Comparison: 13 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 3 Parasitolotical failure: 20 mg/kg



Analysis 13.4. Comparison 13 Praziquantel: different doses vs standard 40 mg/kg, Outcome 4 Proportion cleared of haematuria.

Review: Drugs for treating urinary schistosomiasis

Comparison: 13 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 4 Proportion cleared of haematuria

Study or subgroup	PZQ different dose n/N	Standard 40 mg/kg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 2 x 20 mg/kg					
King 1989	52/65	42/55		42.7 %	1.05 [0.87, 1.27]
King 2002	36/91	63/97		57.3 %	0.61 [0.45, 0.82]
Subtotal (95% CI)	**156**	**152**		**100.0 %**	**0.80 [0.67, 0.95]**
Total events: 88 (PZQ different dose), 105 (Standard 40 mg/kg)					
Heterogeneity: Chi^2 = 11.15, df = 1 (P = 0.00084); I^2 =91%					
Test for overall effect: Z = 2.56 (P = 0.010)					
2 30 mg/kg					
King 1989	45/61	42/55		100.0 %	0.97 [0.78, 1.19]
Subtotal (95% CI)	**61**	**55**		**100.0 %**	**0.97 [0.78, 1.19]**
Total events: 45 (PZQ different dose), 42 (Standard 40 mg/kg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					

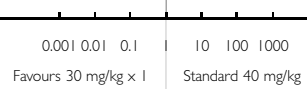
Analysis 13.5. Comparison 13 Praziquantel: different doses vs standard 40 mg/kg, Outcome 5 Parasitiological failure: 30 mg/kg vs 40 mg/kg at 3 months' follow up.

Review: Drugs for treating urinary schistosomiasis

Comparison: 13 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 5 Parasitiological failure: 30 mg/kg vs 40 mg/kg at 3 months' follow up

Study or subgroup	30 mg/kg x 1 n/N	Standard 40 mg/kg n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Light infection				
King 1989	2/18	1/9		1.00 [0.10, 9.61]
2 Moderate infection				
King 1989	7/27	3/29		2.51 [0.72, 8.72]
3 Heavy infection				
King 1989	6/15	6/18		1.20 [0.49, 2.95]



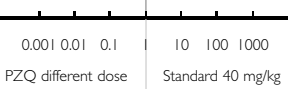
Analysis 14.1. Comparison 14 Praziquantel: different doses vs standard 40 mg/kg, Outcome 1 Parasitological failure rate at 1 to 12 months.

Review: Drugs for treating urinary schistosomiasis

Comparison: 14 Praziquantel: different doses vs standard 40 mg/kg

Outcome: 1 Parasitological failure rate at 1 to 12 months

Study or subgroup	PZQ different dose n/N	Standard 40 mg/kg n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Failure rate: 2 x 20 mg/kg vs standard 40 mg/kg					
Davis 1981	1/53	0/45		1.1 %	2.56 [0.11, 61.23]
Kardaman 1985	10/101	11/110		16.8 %	0.99 [0.44, 2.23]
McMahon 1979	5/35	5/30		8.6 %	0.86 [0.27, 2.68]
Omer 1981	25/43	21/40		73.5 %	1.11 [0.75, 1.63]
Subtotal (95% CI)	**232**	**225**		**100.0 %**	**1.07 [0.77, 1.50]**
Total events: 41 (PZQ different dose), 37 (Standard 40 mg/kg)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.50, df = 3 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
2 Failure rate: 30 mg/kg vs standard 40 mg/kg					
Davis 1981	3/53	0/45		0.5 %	5.96 [0.32, 112.45]
King 1989	13/60	9/56		6.8 %	1.35 [0.63, 2.91]
McMahon 1979	9/32	5/30		4.3 %	1.69 [0.64, 4.47]
Omer 1981	24/39	21/40		27.1 %	1.17 [0.80, 1.72]
Rey 1983	1/39	3/54		0.8 %	0.46 [0.05, 4.27]
Taylor 1988	49/72	42/77		60.5 %	1.25 [0.96, 1.62]
Subtotal (95% CI)	**295**	**302**		**100.0 %**	**1.25 [1.02, 1.53]**
Total events: 99 (PZQ different dose), 80 (Standard 40 mg/kg)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.41, df = 5 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 2.16 (P = 0.030)					
3 Failure rate: 20 mg/kg vs standard 40 mg/kg					
King 1989	22/68	9/56		8.4 %	2.01 [1.01, 4.01]
King 2002	49/99	30/101		31.0 %	1.67 [1.16, 2.39]
Taylor 1988	37/61	42/77		48.7 %	1.11 [0.83, 1.48]
Wilkins 1987a	18/35	11/33		11.9 %	1.54 [0.86, 2.76]
Subtotal (95% CI)	**263**	**267**		**100.0 %**	**1.44 [1.09, 1.90]**
Total events: 126 (PZQ different dose), 92 (Standard 40 mg/kg)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.81, df = 3 (P = 0.19); I^2 =38%					
Test for overall effect: Z = 2.60 (P = 0.0094)					



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	Schistosoma haematobium	SCHISTOSOMIASIS HAEMATOBIA	SCHISTOSOMA HAEMATOBIA	SCHISTOSOMA-HAEMATOBIA	Schistosoma haematobium
2	praziquantel	urinary schistosomiasis	urinary schistosomiasis	urinary schistosomiasis	urinary schistosomiasis
3	metrifonate	1 OR 2	1 OR 2	1 OR 2	1 or 2
4	albendazole	praziquantel	praziquantel	praziquantel	praziquantel
5	artesunate	metrifonate	metrifonate	metrifonate	metrifonate
6	artemether	albendazole	albendazole	albendazole	albendazole
7	2-6/OR	artesunate	artesunate	artesunate	artesunate
8	1 AND 7	artemether	artemether	artemether	artemether
9	-	4-8/OR	4-8/OR	4-8/OR	4-8/OR
10	-	3 AND 9	3 AND 9	3 AND 9	3 AND 9
11	-	-	Limit 10 to human	Limit 10 to human	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Diagnostic criteria pre- and post-treatment

Trial	Pre and post differ?	Diagnostic criteria
Aden Abdi 1989	No	10 mL of single urine
Beasley 1999	No	10 mL of single urine
Befidi-Mengue 1992	No	10 mL of single urine
Jewsbury 1977	Yes	10 mL of single urine vs 10 mL of 3 daily urines
Pugh 1983	No	10 mL of single urine
Omer 1981	No	10 mL of single urine

Table 2. Diagnostic criteria pre- and post-treatment (*Continued*)

Rey 1983	No	10 mL of single urine
Rey 1984	No	10 mL of single urine
Stephenson 1985	No	10 mL of urine adjusted for whole volume
Stephenson 1989	No	10 mL of urine adjusted for whole volume
Borrmann 2001	No	10 mL of 2 daily urines
Kardaman 1985	No	10 mL of 2 daily urines
King 1988	No	10 mL of 2 daily urines
King 1989	No	10 mL of 2 daily urines
King 2002	No	10 mL of 2 daily urines
Olds 1999	Yes	10 mL of 2 daily urines vs 10 mL of single urine
Davis 1981	No	10 mL of 3 daily urines
Doehring 1985	No	10 mL of 3 daily urines
McMahon 1979	No	10 mL of 3 daily urines
McMahon 1983	No	10 mL of 3 daily urines
Oyediran 1981	No	10 mL of 3 daily urines
Taylor 1988	No	10 mL of 3 daily urines
Wilkins 1987a	No	10 mL of 3 daily urines
Jinabhai 2001	Not stated	Not stated

Table 3. Intensity of infection categories: classifications used by trials

Trial	Light	Moderate	Heavy
King 1988	1 to 99	100 to 399	400+
King 1989	1 to 99	100 to 399	400+
King 2002	1 to 99	100 to 399	400+

Table 3. Intensity of infection categories: classifications used by trials (*Continued*)

McMahon 1983	250 to 500	501 to 1000	1000+
Omer 1981	60 to 249	250 to 499	500+
Rey 1984	1 to 5	6 to 50	51+
Stephenson 1985	1 to 29	30 to 99	100 to 500
Stephenson 1989	1 to 29	30 to 99	100 to 499
Taylor 1988	< 100	-	100+

Table 4. Risk of bias of included trials

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of randomized participants in analysis
Aden Abdi 1989	Adequate	Adequate	Assessors	Inadequate
Beasley 1999	Adequate	Unclear	Assessors	Inadequate
Befidi-Mengue 1992	Unclear	Unclear	Unclear	Unclear
Borrmann 2001	Adequate	Adequate	Participants and investigators	Adequate
Davis 1981	Adequate	Adequate	Participants, investigators, and assessors	Adequate
Doehring 1985	Unclear	Unclear	Unclear	Adequate
Jewsbury 1977	Adequate	Unclear	Unclear	Unclear
Jinabhai 2001	Unclear	Unclear	Unclear	Inadequate
Kardaman 1985	Unclear	Unclear	Unclear	Adequate
King 1988	Adequate	Unclear	Participants and care providers	Inadequate
King 1989	Adequate	Unclear	Unclear	Inadequate
King 2002	Adequate	Unclear	Assessors and clinicians	Inadequate
McMahon 1979	Unclear	Unclear	Unclear	Inadequate

Table 4. Risk of bias of included trials (*Continued*)

McMahon 1983	Unclear	Unclear	Unclear	Inadequate
Olds 1999	Adequate	Adequate	Participants and assessors	Adequate
Omer 1981	Unclear	Unclear	Unclear	Inadequate
Oyediran 1981	Unclear	Unclear	Unclear	Inadequate
Pugh 1983	Inadequate	Unclear	Participants, clinicians, and assessors	Adequate
Rey 1983	Adequate	Unclear	Unclear	Adequate
Rey 1984b	Unclear	Unclear	Unclear	Inadequate
Stephenson 1985	Unclear	Unclear	Assessors	Unclear
Stephenson 1989	Unclear	Unclear	Assessors	Adequate
Taylor 1988	Unclear	Unclear	Assessors	Unclear
Wilkins 1987a	Adequate	Unclear	Assessors	Adequate

Table 5. Egg reduction rate: 1 to 12 months

Comparison (intervention vs control)	Dose		Geometric mean		Median		Trial
	Intervention	Control	Intervention	Control	Intervention	Control	
Metrifonate vs placebo	10 mg/kg x 2	Placebo	-	-	99.5%	48.6%	Doehring 1985
	7.5 mg/kg x 3	”	-	-	91.3%	66.2% increase	Jewsbury 1977
	7.5 mg/kg x 3	“	94%	12.7% increase	-	-	Stephenson 1985
	10 mg/kg x 1	”	91.5%	5.3%	-	-	Stephenson 1989
Praziquantel vs placebo	40 mg/kg x 1	Placebo	99.6%	5.3%	-	-	Stephenson 1989
	40 mg/kg x 1	“	95%	64%	-	-	Befidi-Mengue 1992

Table 5. Egg reduction rate: 1 to 12 months (*Continued*)

	40 mg/kg x 1	”	-	-	98.7%	48.6%	Doehring 1985
	40 mg/kg x 1	“	98%	24%	-	-	Oyediran 1981
	20 mg/kg x 2	”	99%	24%	-	-	“
	30 mg/kg x 1	”	86%	24%	-	-	“
	40 mg/kg x 1	”	98%	23.4%	-	-	Taylor 1988
	30 mg/kg x 1	“	98.3%	23.4%	-	-	”
	20 mg/kg x 1	“	98.1%	23.4%	-	-	”
	40 mg/kg x 1	“	99.6%	20.3%	-	-	McMahon 1979
	20 mg/kg x 2	”	99.8%	20.3%	-	-	“
	30 mg/kg x 1	”	99.6%	20.3%	-	-	“
Praziquantel plus albendazole	Praziquantel: 40 mg/kg Albendazole: 400 mg	Praziquantel: 40 mg/kg Albendazole: 400 mg	99%	12% increase	-	-	Beasley 1999
Metrifonate vs praziquantel	10 mg/kg x 2	40 mg/kg x 1	-	-	99.5%	98.7%	Doehring 1985
	10 mg/kg x 3	”	98%	99%	-	-	McMahon 1983
	10 mg/kg x 1	“	96.3%	99.3%	-	-	Pugh 1983
	10 mg/kg x 1	”	91.5%	99.6%	-	-	Stephenson 1989
	10 mg/kg x 1	“	80.3%	99%	-	-	Wilkins 1987a
Different metrifonate doses	10 mg/kg x 3	10 mg/kg x 1	88.7%	37.1%	-	-	Rey 1984
	10 mg/kg x 2	”	81.9%	37.1%	-	-	“

Table 5. Egg reduction rate: 1 to 12 months (*Continued*)

Different metrifonate regimens	7.5 mg x 3 at 14-day intervals	5 mg/kg given 3 times in 1 day	97%	96%	-	-	Aden Abdi 1989
Different praziquantel doses	30 mg/kg	40 mg/kg x 1	99%	99.2%	-	-	King 1989
	20 mg/kg x 1	"	99%	99.2%	-	-	"
	20 mg/kg x 1	"	95%	98%	-	-	King 2002
	2 x 20 mg/kg x 1	"	99.8%	99.6%	-	-	McMahon 1979
	30 mg/kg x 1	"	99.6%	99.6%	-	-	"
	2 x 20 mg/kg x 1	"	98.7%	97.7%	-	-	Oyediran 1981
	30 mg/kg x 1	"	85.7%	97.7%	-	-	"
	30 mg/kg x 1	"	98.3%	98%	-	-	Taylor 1988
	20 mg/kg x 1	"	98.1%	98%	-	-	"
Combination of metrifonate plus praziquantel	Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg x 1)	"	90%	99%	-	-	Wilkins 1987a

Table 6. Adverse events

Comparison	Trial	Drug (dose)	Adverse events	No. participants	Remarks
Vs placebo	Jewsbury 1977	Metrifonate (7.5 mg/kg, 3 doses) Placebo	None reported	114	Investigated side effects as part of study, but none reported by participants
	Borrmann 2001	Praziquantel (40 mg/kg, single) Artesunate 4 mg/kg/day/3 days Praziquantel (40 mg/kg) plus artesunate 4 mg/kg/day/3 days	6 moderate and 127 mild events	300	Mild events but equally distributed among treatment groups with abdominal pain (14%) and headache (12%) the most frequent

Table 6. Adverse events (*Continued*)

	Olds 1999	Praziquantel (40 mg/kg, single dose) Praziquantel (40 mg/kg) plus albendazole (400 mg) Albendazole (400 mg)	15% 20% 14%	380	Adverse events mild to moderate
Metrifonate vs praziquantel	Wilkins 1987a	Praziquantel (40 mg/kg, 1 dose) Metrifonate (10 mg/kg, 1 dose)	See remarks	184	No serious adverse event. Commonly reported side effects included headache, weakness, dizziness, nausea/vomiting, diarrhoea, abdominal pain, general malaise, and fever. Among these events, abdominal pain, general malaise, and fever were reported more frequently in those treated with praziquantel, and others similar between groups
	McMahon 1983	Metrifonate (10 mg/kg, 3 doses) Praziquantel (30 mg/kg, single)	75% 30%	54	Adverse events were minor mostly abdominal pain but included nausea, vomiting, headache, fever, loose bowel, dizziness, itching, body pain
Metrifonate (different regimens)	Aden Abdi 1989	Metrifonate (7.5 mg/kg, 3 doses at 14-day intervals) Metrifonate (5 mg/kg given 3 times in 1 day)	7% 9%	201	Minor adverse events
Praziquantel (different doses)	Davis 1981	Praziquantel (30 mg/kg, single) Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	19% 29% 17%	151	Minor events, mostly abdominal discomfort

Table 6. Adverse events (*Continued*)

	Kardaman 1985	Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	See remarks	215	Minor adverse events, occurred slightly more with 20 mg/kg x 2 than single 40 mg/kg dose
	Oyediran 1981	Praziquantel (30 mg/kg, single) Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	3%	66	No serious adverse events, only 2 moderate events (umbilical pain) were recorded across all the dose categories. Adverse events were not reported separately for each dose category

WHAT'S NEW

Last assessed as up-to-date: 15 October 2007.

Date	Event	Description
16 October 2007	New citation required and conclusions have changed	2008, Issue 3: This review update has been prepared by new authors (A Danso-Appiah, J Utzinger, JP Liu, and P Olliaro). Each section of the review has been rewritten and updated, including the results and conclusions
16 October 2007	New search has been performed	2008, Issue 3: This review update, which is authored by a new author team (A Danso-Appiah, J Utzinger, JP Liu, and P Olliaro), is based on a new protocol (unpublished) with modified inclusion criteria, updated methods, and a new literature search. The review includes 24 trials and incorporates new comparisons. Each section of the review has been rewritten and updated, including the results and conclusions

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 2, 1997

Date	Event	Description
1 May 1997	New citation required and conclusions have changed	Review first published.

CONTRIBUTIONS OF AUTHORS

Anthony Danso-Appiah developed the protocol and carried out the systematic review; this included assessing methodological quality, analysing and interpreting the data, and drafting the manuscript. Jürg Utzinger, Jianping Liu, and Piero Olliaro assisted in the interpretation of the results and revising the text. All authors helped with revisions following the referees' comments.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.
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INDEX TERMS

Medical Subject Headings (MeSH)

Anthelmintics [*therapeutic use]; Praziquantel [therapeutic use]; Randomized Controlled Trials as Topic; Schistosomiasis haematobia [*drug therapy]; Trichlorfon [therapeutic use]

MeSH check words

Humans