

Treatment of urinary schistosomiasis: methodological issues and research needs identified through a Cochrane systematic review

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SUMMARY

Guidelines recommend praziquantel (PZQ) for the treatment and control of schistosomiasis, with no real alternative. Metrifonate was still widely used against *Schistosoma haematobium* in the 1990s, and then withdrawn. Experimental studies and clinical trials suggest that artemisinin compounds are active against *S. haematobium*. In a Cochrane systematic review assessing the efficacy and safety of drugs for treating urinary schistosomiasis, 24 randomized controlled trials ($n=6315$ individuals) met our inclusion criteria. These trials compared a variety of single agent and combination regimens with PZQ, metrifonate or artemisinin derivatives. The review confirmed that both the standard recommended doses of PZQ (single 40 mg/kg oral dose) and metrifonate ($3 \times 7.5\text{--}10$ mg/kg oral doses administered fortnightly) are efficacious and safe in treating urinary schistosomiasis, but there is no study comparing these two regimens head-to-head. There is currently not enough evidence to evaluate artemisinin compounds. Most of the studies included in the Cochrane systematic review were insufficiently powered, lacked standardization in assessing and reporting outcomes, and had a number of methodological limitations. In this paper we discuss the implications of these findings with respect to public health and research methodology and propose priority research needs.

Key words: schistosomiasis, urinary schistosomiasis, *Schistosoma haematobium*, systematic review, meta-analysis, praziquantel, metrifonate, artemisinin.

INTRODUCTION

Schistosomiasis is a common parasitic disease in the tropics and subtropics. An estimated 779 million individuals are at risk of acquiring schistosomiasis and more than 200 millions were infected in mid-2003 (Steinmann *et al.* 2006). The World Health Organization (WHO) estimates that the global burden due to schistosomiasis may be as high as 4.5 million disability-adjusted life years (DALYs) (WHO, 2002). However, a meta-analysis suggests that disability weights might be 2–15 times higher than those used in the global burden of disease study (King, Dickman and Tisch, 2005), and that the DALY underestimates the importance of chronic diseases like schistosomiasis (King and Bertino, 2008). This is further substantiated by the results of approaches using a quality of life questionnaire and decision-tree modelling (Jia *et al.* 2007; Finkelstein

et al. 2008). From a public health perspective, the three most important schistosome species are *Schistosoma haematobium* (causing urinary schistosomiasis), and *S. mansoni* and *S. japonicum* (causing intestinal schistosomiasis).

Two drugs, metrifonate and praziquantel (PZQ), have been used extensively for urinary schistosomiasis (Cioli, Pica-Mattocchia and Archer, 1995; Utzinger and Keiser, 2004). However, in the late 1990s, metrifonate was withdrawn from the WHO model list of essential medicines because it was considered clinically, economically and operationally inferior to PZQ as it is only active against *S. haematobium*, requires multiple administrations, and hence is less convenient in large-scale control programmes (Feldmeier and Chitsulo, 1999). Thus, PZQ remains the only drug for clinical management and community-based control of schistosomiasis (Cioli, 2000; Fenwick *et al.* 2003; Utzinger and Keiser, 2004; Caffrey, 2007; Doenhoff, Cioli and Utzinger, 2008). Large-scale morbidity control programmes became feasible as the price of PZQ fell from approximately US\$ 1.0 in the 1980s to less than US\$ 0.1 per 600 mg tablet (Fenwick *et al.* 2003;

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Fenwick, Keiser and Utzinger, 2006; Doenhoff *et al.* 2008). Paradoxically, this also stalled investments in the discovery and development of alternative control measures, such as other drugs, vaccines and diagnostics (Utzinger *et al.* 2007; Bergquist, Utzinger and McManus, 2008). Research carried out over the past 15 years revealed the antischistosomal properties of artemisinin derivatives, which act especially on the young developing stages of the parasites (for a recent review see Utzinger *et al.* 2007) as opposed to PZQ, which acts against the adult worms and the very young schistosomula just after skin penetration (Sabah *et al.* 1986; Utzinger *et al.* 2007).

The use of PZQ has increased considerably after the 54th World Health Assembly set the target of at least 75% of school-aged children and other high-risk groups to be treated regularly with PZQ by 2010 in areas where the disease is highly endemic (WHO, 2002). At least 17 million doses of PZQ have been administered, primarily to school-aged children in selected African countries, since the launch of the 'Schistosomiasis Control Initiative' in 2003 (Fenwick *et al.* 2006). Relying on praziquantel alone for controlling a disease that affects millions of people is risky should resistance develop against this drug (Danso-Appiah and de Vlas, 2002; Doenhoff *et al.* 2008).

In the light of this, we assessed the effects of PZQ and other antischistosomal treatments by conducting a Cochrane systematic review, including comparisons between PZQ and metrifonate and trials of combination treatments. During this process, we identified a number of methodological issues relevant to the interpretation of existing data that might help researchers to design more appropriate trials in the future. The full review is available on the Cochrane Library (Danso-Appiah *et al.* 2008). In this paper we highlight key findings of the review, discuss implications of various methodological limitations and consider future research needs.

SUMMARY OF COCHRANE SYSTEMATIC REVIEW

Inclusion criteria and search strategy

To qualify for inclusion, a study was (1) to be controlled, randomized or quasi-randomized, enrolling individuals infected with *S. haematobium*, as determined microscopically for *S. haematobium* eggs in a standard filtrate of 10 ml of urine or by haematuria (Feldmeier and Poggensee, 1993); and (2) to treat patients with either PZQ, metrifonate or artemisinin derivatives. An extensive, standard search was carried out, which included MEDLINE (1966 to August 2007), EMBASE (1974 to August 2007), LILACS (1982 to August 2007), conference proceedings and contacting specialists in the field (Danso-Appiah *et al.* 2008).

Data retrieval, quality assessment and analysis

Eligibility and methodological quality of the identified trials were assessed by the authors and the data analysed using Review Manager 4.2 (The Cochrane Collaboration, 2003). The main outcome measure was failure rate (the proportion of individuals remaining positive for eggs in their urine at follow-up). Comparisons between groups were expressed as relative risk (RR) with 95% confidence intervals (CIs) for both individual studies and on aggregate. The secondary parameter was egg reduction rate and was analysed using weighted mean difference with standard error. The proportion of patients with adverse events was compared between treatment and control arms.

Key findings of the Cochrane systematic review

The search identified 24 randomised controlled trials that together involved 6315 participants. Table 1 summarises key characteristics of these 24 trials. When used as monotherapy, both metrifonate and PZQ showed obvious benefit in terms of parasitological outcomes (Danso-Appiah *et al.* 2008). One trial (120 participants) of artesunate showed no obvious benefit over placebo.

For combination treatments, one trial studied the combination of PZQ with artesunate, but there was no obvious advantage over PZQ alone.

Metrifonate versus PZQ: comparisons and dose effects

Fig. 1 summarises the failure rate of metrifonate versus PZQ in the five trials meeting our inclusion criteria (McMahon, 1983; Pugh and Teesdale, 1983; Wilkins and Moore, 1987; King *et al.* 1988; Stephenson *et al.* 1989).

When metrifonate was introduced, some early studies investigated a single dose of 10 mg/kg (the standard dose is 7.5 to 10 mg/kg three times at 14-day intervals) versus the standard single dose of 40 mg/kg PZQ. Although the single metrifonate dose was inferior in three trials measuring failure at one to eight months, the 95% CIs were too wide for statistical significance (RR = 2.31, 95% CI: 0.91–5.82; $n = 462$ participants). This lack of significance is due to significant heterogeneity between trials ($I^2 = 94%$) likely to be associated with the duration of follow-up: the RR was 1.26 at one month of follow-up (Pugh and Teesdale, 1983), 2.23 at three months (Wilkins and Moore, 1987) and 4.62 at eight months (Stephenson *et al.* 1989).

There was no significant difference in failure rates when metrifonate given as multiple doses (3×10 mg/kg fortnightly) was compared with PZQ (30 mg/kg) in a small trial involving 54 participants (McMahon, 1983). A trial comparing three doses

Table 1. Summary of the characteristics of randomised controlled trials included in our Cochrane systematic review (Danso-Appiah *et al.* 2008) evaluating antischistosomal drugs, used alone or in combination, for treating urinary schistosomiasis

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Aden Abdi and Gustafsson (1989); Somalia	Not reported	5	Children: mean age of 14 years	Urine filtration (10 ml; 1 specimen)	Very high	300	1. Metrifonate (7.5 mg/kg × 3 given at 2-week intervals) 2. Metrifonate (5 mg/kg × 3 given in 1 day)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer)	1, 2, 3 and 6	Adequate	Adequate	Investigators, participants and assessors	33% at 2 months
Beasley <i>et al.</i> (1999); Tanzania	1994	1	Children: 7–12 years	Urine filtration (10 ml; 1 specimen)	High (56%)	357	1. PZQ (40 mg/kg × 1) plus albendazole (400mg × 1) 2. Placebo	1. Cure rate 2. Egg reduction rate 3. Mean haemoglobin	PZQ (Biltricide, Bayer)	3-75	Adequate	Unclear	Outcome assessors	30%
Befidi-Mengue <i>et al.</i> (1992); Cameroon	Not reported	1	Boys: 6–15 years	Urine filtration (10 ml; 1 specimen)	Not reported	436	1. PZQ (40 mg/kg × 1) 2. Placebo	1. Anaemia 2. Physical growth 3. Haematuria 4. Proteinuria	Not stated	6	Unclear	Unclear	Unclear	Unclear
Borrmann <i>et al.</i> (2001); Gabon	Not reported	3	Children: 5–13 years	Urine filtration (10 ml; 2 specimens)	Very high (80%)	300	1. PZQ (40 mg/kg × 1) 2. Artesunate (4 mg/kg/day for 3 days) 3. PZQ (40 mg/kg × 1) plus artesunate (4 mg/kg/day over 3 days) 4. Placebo	1. Cure rate 2. Adverse events 3. Resolution of haematuria 4. Egg reduction rate	Not stated	8	Adequate	Adequate	Participants and investigators	1.3%
Davis <i>et al.</i> (1981); Zambia	Not reported	1	Children and young adults: 7–22 years	Urine filtration (10 ml; 3 specimens)	Not reported	79	1. PZQ (20 mg/kg × 1) 2. PZQ (30 mg/kg × 1) 3. PZQ (40 mg/kg × 1) 4. PZQ (20 mg/kg × 2) 5. Placebo	1. Adverse events 2. Cure rate 3. Mean haemoglobin	Not stated	1, 6, 9 and 12	Adequate	Adequate	Participants, investigators and outcome assessors	7.6% and 16.5% at 6 and 12 months, respectively
Doehring <i>et al.</i> (1985); Sudan	Not reported	1	Boys: 6–13 years	Urine filtration (10 ml; 3 specimens)	Very high	182	1. PZQ (40 mg/kg × 1) 2. Metrifonate (10 mg/kg × 3 given at 2-week intervals) 3. Placebo	1. Egg reduction rate 2. Proteinuria	Not stated	1	Unclear	Unclear	Unclear	0%
Jewsbury and Cooke (1976); Zimbabwe	Not reported	4	Children (age not specified)	Urine filtration (10 ml; 1 specimen vs. 3 specimens)	Very high (80%)	179	1. Metrifonate (7.5 mg/kg × 3 given at 2-week intervals) 2. Placebo (Third arm excluded from current review)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer)	1.2, 7 and 16	Adequate	Unclear	Unclear	Not reported
Jinabhai <i>et al.</i> (2001); South Africa	Not reported	11	Children: 8–10 years	Not stated	High	268	1. PZQ (40 mg/kg × 1) plus albendazole (400 mg × 1) 2. Placebo (Another arm consisted of albendazole (400 mg × 1) for intestinal helminths)	1. Cure rate	Not stated	4	Unclear	Unclear	Unclear	Not reported

Table 1. (cont.)

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Kardaman <i>et al.</i> (1985); Sudan	Not reported	Not reported	Children: 7–11 years	Urine filtration (10 ml; 2 specimens)	Not reported	237	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 2)	1. Adverse events 2. Cure rate 3. Egg reduction rate	Not reported	1, 3, 6 and 12	Unclear	Unclear	Unclear	7.3%
King <i>et al.</i> (1988); Kenya	Not reported	Not reported	Children and young adults: 4–21 years	Urine filtration (10 ml; 2 specimens)	Not reported	2628	1. Metrifonate (10 mg/kg × 3 given at 4-month intervals) 2. PZQ (40 mg/kg × 1)	1. Haematuria 2. Proteinuria (Other arms not relevant for current review, hence were excluded)	Metrifonate (Bilarcil, Bayer); PZQ (Biltricide Bayer)	12	Adequate	Unclear	Participants and assessors	23%
King <i>et al.</i> (1989); Kenya	Not reported	Not reported	Children and adults (age not specified)	Urine filtration (10 ml; 2 specimens)	Very high	280	1. PZQ (40 mg/kg × 1) 2. PZQ (30 mg/kg × 1) 3. PZQ (20 mg/kg × 1) 4. PZQ (10 mg/kg × 1)	1. Cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria	Not reported	3	Adequate	Unclear	Unclear	14%
King <i>et al.</i> (2002); Kenya	1993	2	Children and young adults: 4–23 years	Urine filtration (10 ml; 2 specimens)	Very high (80%)	291	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 1)	1. Cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria	Not reported	2.5 and 9	Adequate	Unclear	Clinicians and assessors	31%
McMahon and Kolstrup (1979); Tanzania	Not reported	1	Children: 7–15 years	Urine filtration (10 ml; 3 specimens)	Not reported	183	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2) 4. Placebo	1. Cure rate 2. Egg reduction rate 3. Adverse events	PZQ (Biltricide, Bayer)	1, 3 and 6	Unclear	Unclear	Unclear	31%, 32% and 36% at 1, 3 and 6 months, respectively
McMahon (1983); Tanzania	Not reported	1	Children and adults (age not specified)	Urine filtration (10 ml; 3 specimens)	Not reported	90	1. Metrifonate (10 mg/kg × 3 given at 2-week intervals) 2. PZQ (30 mg/kg × 1) (Third arm consisting of niradazole was excluded)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Not reported	2 and 4	Unclear	Unclear	Unclear	14% and 31% at 2 and 4 months, respectively
Olds <i>et al.</i> (1999); Kenya	Not reported	1	Children: 4–18 years	Urine filtration (10 ml; 2 specimen vs. 10 ml; 1 specimen)	Very high	380	1. PZQ (40 mg/kg × 1) plus albendazole (400 mg × 1) 2. PZQ plus albendazole placebo 3. Albendazole plus PZQ placebo 4. Both placebos	1. Physical growth 2. Haemoglobin 3. Failure rate 4. Egg reduction rate 5. Adverse effects	Not reported	1.5, 3, 6 and 12	Adequate	Adequate	Participants and assessors	1%, 1%, 10% and 17% at 1.5, 3, 6 and 12 months, respectively
Omer (1981); Sudan	1978–79	1	Children (> 8 years) and adults	Urine filtration (10 ml; 1 specimen)	Very high	153	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2)	1. Adverse events 2. Cure rate 3. Egg reduction rate	PZQ (Biltricide, Bayer)	6	Unclear	Unclear	Unclear	20%
Oyediran <i>et al.</i> (1981); Nigeria	Not reported	1	Children: 9–16 years	Urine filtration (10 ml; 3 specimens)	Light to moderate	90	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2) 4. Placebo	1. Egg reduction rate 2. Adverse events	PZQ (Biltricide, Bayer)	1, 3 and 6	Unclear	Unclear	Unclear	31.7%, 32.3% and 36% at 1, 3 and 6 months, respectively

Table 1. (cont.)

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Pugh and Teesdale (1983); Malawi	Not reported	Not reported	Children: 5–18 years	Urine filtration (10 ml; 1 specimen)	Not reported	600	1. PZQ (40 mg/kg × 1) 2. Metrifonate (10 mg/kg × 1) 3. Placebo	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer); PZQ (Biltricide, Bayer)	1, 3 and 6	Inadequate	Unclear	Participants, clinicians and assessors	3% at 1 month
Rey <i>et al.</i> (1983); Niger	Not reported	3	Children and adults (age not specified)	Urine filtration (10 ml; 1 specimen)	High (50%)	103	1. Metrifonate (10 mg/kg × 1) 2. Metrifonate (10 mg/kg × 2 given fortnightly) 3. Metrifonate (10 mg/kg × 3 given fortnightly)	1. Cure rate 2. Egg reduction rate	Not reported	1, 3 and 6	Adequate	Unclear	Unclear	9.7%, 6.4% and 8.1% at 1, 3 and 6 months, respectively
Rey, Nhouhou and Sellin (1984); Niger	Not reported	3	Children and adults (age not specified)	Urine filtration (10 ml; 1 specimen)	Not reported	286	1. Metrifonate (10 mg/kg × 1) 2. Metrifonate (10 mg/kg × 2 given fortnightly) 3. Metrifonate (10 mg/kg × 3 given fortnightly)	1. Cure rate 2. Egg reduction rate	Not reported	2 and 4	Unclear	Unclear	Unclear	50% and 38.8% at 2 and 4 months, respectively
Stephenson <i>et al.</i> (1985); Kenya	Not reported	1	Children: 6–15 years	Urine filtration (10 ml of urine adjusted for whole volume)	Moderate (46%)	400	1. Metrifonate (7.5 mg/kg × 3 given fortnightly) 2. Placebo	1. Cure rate 2. Splenomegaly 3. Hepatomegaly 4. Egg reduction rate 5. Haemoglobin 6. Anthropometric measurements	Not reported	8	Unclear	Unclear	Assessors	Not reported
Stephenson <i>et al.</i> (1989); Kenya	Not reported	Not reported	Children (age not specified)	Urine filtration (10 ml of urine adjusted for whole volume)	Light to moderate	347	1. Metrifonate (10 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. Placebo	1. Cure rate 2. Egg reduction rate 3. Physical growth	Not reported	8	Unclear	Unclear	Assessors	10%
Taylor, Murare and Manomano (1988); Zimbabwe	Not reported	1	Children: 10–15 years	Urine filtration (10 ml; 3 specimens)	Very high (77%)	373	1. PZQ (10 mg/kg × 1) 2. PZQ (20 mg/kg × 1) 3. PZQ (30 mg/kg × 1) 4. PZQ (40 mg/kg × 1) 5. Placebo	1. Cure rate 2. Egg reduction rate	Not reported	1, 3 and 6	Unclear	Unclear	Assessors	No losses reported
Wilkins and Moore (1987); Gambia	Not reported	3	Children: 2–19 years	Urine filtration (10 ml; 3 specimens)	Very high	184	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 1) 3. PZQ (10 mg/kg × 1) 4. Metrifonate (10 mg/kg × 1) 5. Metrifonate (10 mg/kg × 1) plus PZQ (10 mg/kg × 1)	1. Egg reduction rate 2. Adverse events	Not reported	3	Adequate	Unclear	Assessors	No losses reported

* N – Number of communities involved in the trial.

** For urine filtration, 10 ml; 3 specimen *vs.* 10 ml; 1 specimen means pre- and post-treatment diagnosis varied; i.e. pre-treatment diagnosis involved 10 ml and 3 specimen but 10 ml and 1 specimen for post-treatment assessment.

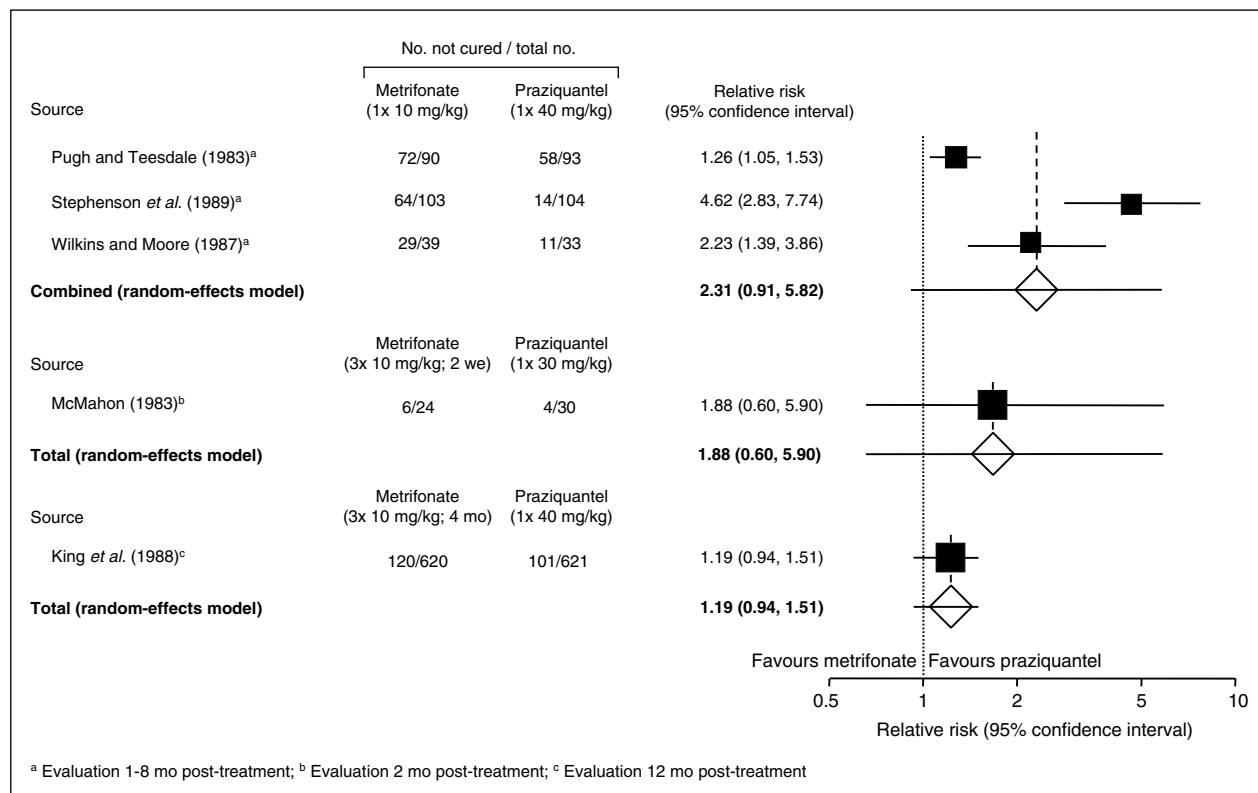


Fig. 1. Risk ratio estimates (combined or total) of randomized controlled trial(s) of metrifonate (different regimens) versus PZQ (single dose, 30 mg/kg or 40 mg/kg) against *S. haematobium*. Rectangles represent risk ratios and sizes of the rectangles denote the weight given to each trial in the meta-analysis. Diamond and vertical broken line indicate combined (total) relative risk (RR). Horizontal lines indicate 95% confidence intervals. The dashed vertical line is the null value (RR = 1; neither favouring metrifonate nor PZQ). Abbreviations: mo, month; we, week.

of metrifonate at 10 mg/kg given once every four months with the standard 40 mg/kg PZQ (single dose) in school-aged children in Kenya detected no difference overall, but metrifonate was superior in the subgroup of children with a heavy infection (RR = 0.88, 95% CI: 0.80–0.96; $n = 615$ participants). However, as the subgroup was stratified after randomisation, this result should be interpreted with caution. Both metrifonate (two and three doses of 10 mg/kg) and PZQ (single dose 40 mg/kg) led to very high reductions in egg excretion (> 98%) in two trials (McMahon, 1983; Doehring *et al.* 1985).

One trial ($n = 54$ participants) compared adverse events and reported similar minor events between metrifonate (3×10 mg/kg) and PZQ (30 mg/kg); no serious adverse events were noted (McMahon, 1983). Mild and transient abdominal pain was more common with triplicate metrifonate than single dose PZQ (75% versus 30%), but the dose of PZQ used (30 mg/kg) was lower than the one currently recommended (40 mg/kg) (WHO, 2002).

Metrifonate: dose comparisons

One trial with 201 participants compared 3×5 mg/kg metrifonate administered in a single day to 3×7.5 mg/kg given fortnightly (Aden Abdi and Gustafsson, 1989). There was no significant difference

in parasitological failure and egg reduction rate; the geometric mean egg reduction rate was 96% for the one-day regimen and 97% for the fortnightly regimen. There was little difference in the percentage of patients with mild adverse events reported for the fortnightly regimen (7%) versus the one-day regimen (9%).

Three doses of metrifonate (10 mg/kg) were compared with one and two doses (Rey, Nouhou and Sellin, 1984). There was no significant difference in parasitological failure rates between two and three doses at one month and four months follow-up. Similarly, no significant differences in failure rate and egg reduction rates were detected between two and three doses of 10 mg/kg, given fortnightly in a trial of 81 participants (Rey *et al.* 1984). By contrast, there were fewer parasitological failures with the three-dose regimen over the one dose regimen at the one month follow-up (RR = 2.75, 95% CI: 1.29–5.85; $n = 93$ participants) and the four-month follow-up (RR = 1.52, 95% CI: 1.03–2.25; $n = 111$ participants).

Different PZQ doses versus standard regimen (1 × 40 mg/kg)

Ten trials compared the standard regimen of PZQ (single dose of 40 mg/kg) to various other doses (McMahon and Kolstrup, 1979; Davis *et al.* 1981;

Omer, 1981; Oyediran *et al.* 1981; Rey *et al.* 1983; Kardaman *et al.* 1985; Wilkins and Moore, 1987; Taylor, Murare and Manomano, 1988; King *et al.* 1989, 2002). In terms of parasitological failure, there was no significant difference between the standard regimen and 2×20 mg/kg (4 trials), a single dose of 30 mg/kg (6 trials), and a single dose of 20 mg/kg (2 trials). Similar results were found at one, three and six months follow-up. Losses to follow-up were generally high, but these did not differ across treatment and control groups within a single trial. There was no significant heterogeneity between the trials, and background endemicity did not seem to play a role. Examining for a differential effect between heavy and moderate or light infections with 30 mg/kg *versus* standard 40 mg/kg, a subgroup analysis of one small trial (King *et al.* 1989) did not show any difference ($n=116$ participants). Five trials showed no apparent differences in egg reduction rate (geometric mean); all had greater than 95% reduction in both arms.

Artesunate

Thus far, only one randomised controlled trial conducted in Gabon in schoolchildren compared the effects of artesunate combined with PZQ to each individual drug given as monotherapy (Borrmann *et al.* 2001). Whilst the artesunate-PZQ combination resulted in a relatively higher egg reduction rate, it was not possible to identify an effect of artesunate, as no significant difference was observed in cure rates when compared to PZQ alone.

METHODOLOGICAL LIMITATIONS

Lack of standardization and quality data for the assessment of efficacy and safety of antischistosomal drugs was reported previously for *S. mansoni* (Danso-Appiah and de Vlas, 2002). In this Cochrane systematic review (Danso-Appiah *et al.* 2008), we identified a number of methodological limitations that raise issues with trial quality and the potential for bias, outlined below. Some of the shortcomings have implications for the interpretation of trials in schistosomiasis and other tropical diseases (responses to methodological limitations summarised in Box 1).

(1) Some trials had no proper sample size calculation: this suggests the authors may not have considered whether their study was sufficiently powered to answer the question being posed. (2) Randomisation quality was not high: only four out of 24 trials (17%) met quality standards for adequate concealment of allocation and described the methods used (for quality standards see Jüni, Altman and Egger (2001) and Higgins and Green (2008). Trials conducted in the early 1990s and earlier did not conceal allocation except one (Davis *et al.* 1981). Generation of allocation sequence was adequate in less than

Box 1. Responses to methodological limitations of trials included in a Cochrane review of drugs for treating urinary schistosomiasis (Danso-Appiah *et al.* 2008)

Design issues

1. There is the need for a unified study methodology in the design, collection and reporting of trials.
2. Trialists should be sensitized to the importance of proper sample size calculation to ensure that trials are sufficiently powered. High losses to follow-up in trials with small sample sizes further compromise the statistical power.
3. There is the need to describe the randomisation procedure clearly.
4. There is a need for standardized, quality-controlled diagnostic criteria within and between trials.
5. In high endemicity areas a follow-up time of 4 to 8 weeks is appropriate when investigating cure rates to avoid eggs released from dead worms and minimise the effect of re-infection.

Interpretation and reporting

6. Intensity of infection and egg reduction rate (ERR) should be reported in geometric mean, and intensity of infection should be based on egg count of only the positive cases and reported using the standard classification by the WHO (WHO, 2002).
7. Treatment outcomes need to be clearly defined and standardised across trials. Parasitological outcomes should be reported with; (a) level of endemicity, (b) diagnostic criteria, (c) dose used, (d) age of participants and (e) follow-up time.

half of the trials included in our meta-analysis. For the others, the method used was unclear although all were reported as randomized controlled trials. (3) Losses to follow-up were often high in some trials, and increased proportionally with the duration of follow-up: 17 trials registered losses of <10% for short-term evaluations at one to three months, but losses reached up to 50% in some trials when follow-up time was longer than three months. (4) Diagnostic criteria were varied, vague and not standardised: among the trials included in our meta-analysis, the criteria for diagnosis varied greatly; some trials used three urine specimens on three consecutive days for microscopic examination, whilst others used a single specimen (Table 1). In some trials sampling criteria varied even between pre- and post-treatment using microscopy (e.g. three urine specimens for the pre-treatment diagnosis but only one for post-treatment follow-up assessment) while other trials lacked any criteria for diagnosis. (5) Classification of infection intensities lacked standardization: Table 2 shows considerable variation in the classification of infection

Table 2. Classification of different *S. haematobium* infection intensities in clinical trials included in a Cochrane systematic review (Danso-Appiah *et al.* 2008), n.c. not classified

<i>S. haematobium</i> infection intensity (eggs/10 ml urine)			
Light	Moderate	Heavy	Reference
60–249	250–499	≥ 500	Omer (1981)
250–500	501–1000	≥ 1000	McMahon (1983)
1–5	6–50	> 50	Rey, Nouhou and Sellin (1984)
1–29	30–99	100–500	Stephenson <i>et al.</i> (1985)
1–99	100–399	≥ 400	King <i>et al.</i> (1988)
< 100	n.c.	≥ 100	Taylor, Murare and Manomano (1988)
1–29	30–99	100–499	Stephenson <i>et al.</i> (1989)
1–99	100–399	≥ 400	King <i>et al.</i> (1989); King <i>et al.</i> (2002)
1–49	n.c.	≥ 50	WHO (2002)

intensity across trials. According to current WHO guidelines, infection intensity of *S. haematobium* is either light (1–49 eggs/10 ml of urine) or heavy (≥ 50 eggs/10 ml of urine) (WHO, 2002). In the trials included in our meta-analysis, however, light infections were variably classified as 1–5, 1–29, 1–99, 60–249 or even 250–500 eggs/10 ml of urine. Accordingly, moderate and heavy infections varied from one trial to another. (6) Outcomes were reported in a variety of ways: in our review we defined primary outcomes as (i) parasitological failure and (ii) egg reduction rate. However, these two measures were variably reported as cure rate, failure rate, cumulative failure rate or prevalence for parasitological failure, and as a median, arithmetic mean or geometric mean for egg reduction rate. Even the calculation of geometric mean varied; some investigators considered only the egg-positive individuals, whilst others included the negatives and introduced a correction factor of plus 1. The latter becomes problematic after treatment when most of the remaining infections are light, as it may overestimate egg count values. (7) Timing of post-treatment assessments varied greatly: the majority of trials evaluated cure and egg reduction rate within one to three months; however, some trials did so at three weeks or earlier, or only six or even 12 months post-treatment. Results from studies on urinary schistosomiasis assessing outcomes earlier than three weeks or beyond three months post-treatment should be considered with caution. The reasons are that the development of *S. haematobium* worms takes approximately two months (Ghandour, 1978); shorter follow-up is confounded by eggs of killed worms still being excreted, longer follow-up by re-infections, particularly in highly endemic settings (N'Goran *et al.* 2001; Tchuem Tchuente *et al.* 2004; Satayathum *et al.* 2006). Noteworthy, most of the trials in this review were conducted in high endemicity areas and there was no way in differentiating between re-infection and recrudescence.

DISCUSSION

Public health implications

Despite the above-mentioned methodological limitations, the findings of our Cochrane systematic review have important public health implications. One of the most important findings is that both PZQ and metrifonate are efficacious and safe (Danso-Appiah *et al.* 2008). The failure rate with the recommended standard dose of PZQ (40 mg/kg) is 0–37%, whilst that of metrifonate (3 × 7.5–10 mg/kg given fortnightly) is 19–48% at one to three months follow-up. However, no trial included in our analysis directly compared the above-mentioned standard doses, therefore precluding any head-to-head assessment of the two treatments from currently available data.

Although the effects of PZQ against placebo are obvious, for some comparisons between regimens with both PZQ and metrifonate there was uncertainty around their effect estimates as shown by the wide 95% CIs. The small sample size in some of the trials may explain the levels of uncertainty. However, the magnitude of the effect is at times so dramatic that it is unlikely that methodological quality alone will have caused substantive biases to interfere with the marked effects and differences reported.

No difference was demonstrated with a single dose of 20 or 30 mg/kg of PZQ compared to the standard regimen (single oral dose of 40 mg/kg) in terms of all outcomes measured in this review. Given the current emphasis on controlling morbidity in high-burden areas (WHO, 2002), and morbidity, especially among school-aged children, being associated with the number of eggs in an individual, this finding suggests lower doses of PZQ may be effective in morbidity control. However, these results should be considered with caution as detection error can play a role, especially when the studies are few and sample sizes are small. While it is true that parasite load (with egg counts often used as a proxy measure) 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; Doenhoff *et al.* 2008). Pharmacokinetic data of different doses of PZQ are few and old, and have been obtained in healthy volunteers rather than in schistosome-infected patients (Leopold *et al.* 1978). An exponential increase was found in the area under the curve (AUC) with the PZQ dose in the range of 5 to 50 mg/kg, with a six-fold increase from 20 to 50 mg/kg (Leopold *et al.* 1978). However, these data do not come from infected patients, and hence cannot be extrapolated so easily. This calls for well designed trials incorporating also pharmacokinetic assessment, possibly with sparse sampling and population kinetic assessment. These trials should also control for food intake, as the bioavailability of PZQ depends upon taking it with food and the type of food matters (Mandour *et al.* 1990; Castro *et al.* 2000).

The rationale behind the widely spaced dosing intervals of metrifonate treatment derives from its long-lasting effect on red blood cells and plasma cholinesterases (Plestina, Davis and Bailey, 1972). However, the clinical significance of this effect and why side effects disappear during the first 12–24 hours whereas the recovery of the enzymes takes more than 4–6 weeks is not known (Plestina *et al.* 1972). Safety studies have shown no serious adverse events in patients treated with 5–10 mg/kg metrifonate daily for 6–12 days (Snellen, 1981), and various reviews of the toxicology and pharmacology of metrifonate during its extensive use for urinary schistosomiasis in the 1970s concluded that it had very few adverse events (Holmstedt *et al.* 1978; Feldmeier and Doehring, 1987; Cioli *et al.* 1995). Also, metrifonate is currently used in Alzheimer's disease in extended regimens, and a systematic review has concluded that overall tolerability is good with only mild to moderate adverse events (López-Arrieta and Schneider, 2006). In the current review, although drug safety was generally poorly reported and assessed in few trials, no trial recorded a serious adverse event, and no significant differences in the number and type of adverse events between metrifonate and PZQ were recorded, except for abdominal pain that was more frequent after metrifonate. Optimizing metrifonate treatment may provide a means of easing drug pressure exerted on schistosomes by the wide deployment of PZQ.

Immature schistosomes are less sensitive to PZQ than adult worms (Sabah *et al.* 1986), which has raised concern about controlling schistosomiasis effectively with this drug. Artemisinin derivatives proved to be effective against immature schistosomes in laboratory studies (Utzinger *et al.* 2003, 2007). However, this review shows that artesunate was not effective against *S. haematobium* infections (though evidence was derived from a single trial (Borrmann

et al. 2001)), and combining artesunate and 40 mg/kg PZQ did not improve efficacy over PZQ alone. In two non-randomised trials involving artesunate alone, results were relatively better (De Clercq *et al.* 2002; Inyang-Etoh *et al.* 2004). The latter findings were confirmed in a recent trial; artesunate alone (4 mg/kg) resulted in a cure rate of 70.5%, whereas an artesunate-PZQ combination obtained a cure rate of 88.6% (Inyang-Etoh *et al.* 2009). Finally, a recent trial in children under six years of age who were co-infected with *Plasmodium falciparum* and *S. haematobium* and who were treated with two different artemisinin-based combinations for malaria therapy showed good effects on *S. haematobium*. This trial, however, could not be included in the current analysis because there was no control group (Boulanger *et al.* 2007).

The need for good trial methods

The validity of randomized controlled trials rests in part on adequate allocation concealment and minimal losses to follow-up, and weaknesses in both these aspects were found in the trials included in the current meta-analysis (Table 1). Without adequate allocation concealment properly developed random allocation sequences can be subverted (Schulz and Grimes, 2002). A likely explanation for only four trials (17%) included in our final analyses adequately concealing allocation is that this had not been identified as a particularly relevant issue at the time the trials were conducted (20–30 years ago). Even after the publication of the CONSORT statement (Begg *et al.* 1996) and despite continued educational efforts, the quality of reporting of randomized controlled trials still needs improvement (Altman *et al.* 2001; Moher, Schulz and Altman, 2001).

The effect of losing patients during follow-up on randomisation is crucial as this relates to the internal validity and the power of the trial. In our systematic review we could not do a sensitivity analysis to evaluate the effect of loss to follow-up because data were not sufficient. We encourage trialists to take particular note of this issue and ensure that losses are minimised and power is preserved in future trials. Also, we welcome debate on the most appropriate timing of follow-up in evaluating drug trials of both urinary and intestinal schistosomiasis. The biology of schistosomes suggests that treatment effects with antischistosomal drugs on parasitological parameters should be evaluated during a window of four to eight weeks post-treatment to avoid detecting the tail of eggs released from dead worms on one side, and re-infections on the other side. A first attempt has been made to evaluate this for intestinal schistosomiasis due to *S. mansoni*, and the authors concluded that three weeks after PZQ administration is an appropriate timing for drug efficacy evaluation (Scherrer *et al.* 2009).

Safety is generally overlooked and when data are available they are poorly reported. It is important that trialists realise the importance of adequately documenting and reporting on tolerability.

Diagnostic concerns

The quality of diagnosis can influence the observed cure rates as clearly shown for both *S. mansoni* (de Vlas and Gryseels, 1992; Booth *et al.* 2003) and *S. haematobium* (N'Goran *et al.* 2003). Sensitivity will affect in particular the detection of light infections during follow-up. We found considerable variation in diagnostic criteria not only between, but also within trials, also with regard to infection intensity. This may be explained by the fact that the WHO classification as light (1–49 eggs/10 ml urine) and heavy infection intensity (≥ 50 eggs/10 ml urine) was endorsed only recently (WHO, 2002) and was not in use when the trials summarized here. Because of the different thresholds used for infection intensity, it was not possible to combine and analyse the data according to heavy infections, which is relevant to morbidity control.

Study population issues

The age of participants enrolled in randomized controlled trials may also influence results. Here, 22 trials out of 24 recruited school-aged children. Hence the overall effect estimates as reported in this review may be lower than studies including all-age subjects, as adults usually show lower infection intensities than school-aged children and, conversely, higher treatment efficacies. This issue has been documented for *S. mansoni* (Raso *et al.* 2004), and it is conceivable that the same holds for *S. haematobium*. It should also be noted that restricting treatment to school-aged children leaves untreated adults and pre-school children still excreting eggs to maintain transmission, if indeed transmission is a function of egg output. This brings us to two important sets of considerations. First, data should be reported separately for children and adults before, if necessary, pooling the data to assess overall effects. Second, the purpose of studies depends on the target population. Studies in children receiving antischistosomal treatment are more apt to assess the 'true' efficacy of the drug because drugs such as PZQ have an immune response-dependent component (Doenhoff *et al.* 1987), which is more active in adults, while whole-population studies are more suited to assess the programmatic effectiveness and effects of control interventions.

IMPLICATIONS FOR POLICY

Both PZQ and metrifonate are effective and safe for treating urinary schistosomiasis. Our systematic

review and that of López-Arrieta and Schneider (2006) indicate that metrifonate is well tolerated. Although in schistosomiasis control metrifonate has operational drawbacks, notably multiple administrations, which make it less convenient for large-scale morbidity control programmes than a single dose of PZQ, the two drugs have similar efficacy profiles. Furthermore, considering that schistosomes are under intense and growing drug pressure by PZQ and the inherent vulnerability of schistosomiasis control to parasite resistance, we suggest metrifonate should be reconsidered for the treatment of urinary schistosomiasis, to ease the drug pressure on PZQ. This implies continued availability (production and distribution) of the drug. It is also important to have an alternative drug for treating urinary schistosomiasis should PZQ resistance emerge.

Most of the trials contributing to this review were conducted more than a decade ago, and entail a series of methodological limitations. The new schistosomiasis trials must be conducted to contemporary standards of clinical research paying particular attention to quality issues we have raised, and adopt commonly agreed criteria.

Our findings point to new approaches worth being explored in well-designed trials such as: (1) reassessing appropriate dosing schedules for metrifonate, including compliance and feasibility in control programmes; (2) comparing standard metrifonate (3×7.5 – 10 mg/kg given fortnightly) and PZQ (1×40 mg/kg) doses; (3) evaluating artemisinin-based regimens and combination treatments where appropriate (areas where malaria and schistosomiasis are not co-endemic); and (4) obtaining pharmacokinetic/pharmacodynamic correlates for PZQ.

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DISCLAIMER

The opinions expressed in this paper are those of the authors and may not reflect those of their employing organizations. PLO is a staff member of the WHO; the authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHO.

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