Overview of the evidence for safety and efficacy of medicines for the treatment of neglected tropical diseases in children

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## Acronyms

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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ALB</td>
<td>Albendazole</td>
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<tr>
<td>DEC</td>
<td>Diethylcarbamazine</td>
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<td>EMLc</td>
<td>Essential Medicines List for Children</td>
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<tr>
<td>HAT</td>
<td>Human African Trypanosomiasis</td>
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<td>IVM</td>
<td>Ivermectin</td>
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<td>LEV</td>
<td>Levamisole</td>
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<td>LVM</td>
<td>Levamisole</td>
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<td>MBD</td>
<td>Mebendazole</td>
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<td>MBZ</td>
<td>Mebendazole</td>
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<td>MSF</td>
<td>Médecins sans Frontières</td>
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<td>NTDs</td>
<td>Neglected tropical diseases</td>
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<td>PSAC</td>
<td>Pre-school age children</td>
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<td>PYR</td>
<td>Pyrantel</td>
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<td>PZQ</td>
<td>Praziquantel</td>
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<td>RCT</td>
<td>Randomized controlled trials</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

In October 2008\(^1\) the Subcommittee of the Expert Committee for the Selection and Use of Essential Medicines reviewed the following medicines:

– Antischistosomal and antitrematode medications
– Antiamoebic and anti-giardiasis medications
– Antitrypanosomal medicines

The lack of new medicines for treatment options was highlighted, as well as the lack of information (particularly in relation to the antitrypanosomal medications) about efficacy and safety for their use in the paediatric population. The Subcommittee therefore requested that the clinical evidence for these medicines should be reviewed. This recommendation was subsequently endorsed by the Expert Committee.

Neglected tropical diseases (NTDs) are a group of communicable diseases which thrive in impoverished settings and blight the lives of around one billion people worldwide, while threatening the health of millions more. Despite the numbers affected by tropical diseases there is currently very little in the way of new treatments to offer old diseases. WHO recently published a report that focuses on 17 neglected tropical diseases and disease groups.\(^1\) The report found that there are currently 149 countries and territories where neglected tropical diseases are endemic, at least 100 of which are endemic for 2 or more of these diseases, and 30 countries that are endemic for 6 or more.

The diseases identified in the report as the main NTDs are:

Dengue
Rabies
Trachoma
Buruli ulcer
Endemic treponematoses (including yaws)
Leprosy
Chagas disease (American trypanosomiasis)
Human African trypanosomiasis (sleeping sickness)
Leishmaniasis
Cysticercosis
Dracunculiasis (guinea-worm disease)
Echinococcosis
Foodborne trematode infections
Lymphatic filariasis (elephantiasis)
Onchocerciasis (river blindness)
Schistosomiasis (bilharziasis)
Soil-transmitted helminthiases (intestinal parasitic worms)

The World Health Organization (WHO) recommends five public-health strategies for the prevention and control of neglected tropical diseases:

1. Expansion of preventive chemotherapy
2. Intensified case-detection and case management
3. Improved vector control
4. Appropriate veterinary public health measures
5. Provision of safe water, sanitation and hygiene

The purpose of this review is to identify existing evidence for the medicines currently included in the WHO Model List of Essential Medicines for Children and recommended for the treatment of schistosomiasis, soil-transmitted helminthiasis, filarial diseases, amoebiasis, giardiasis, Human African trypanosomiasis and Chagas disease (American trypanosomiasis), in the paediatric population.2-5

**Objective**

To identify evidence to support the use of medicines currently listed in the WHO Model List of Essential Medicines for Children for the treatment of the specified neglected tropical diseases in children 0-18 years of age, with a particular focus on use in children less than 4 years of age.
What is the evidence for safety and efficacy of medicines for the treatment of neglected tropical diseases in children?

Methods

Search strategy

To identify efficacy and safety data for the specified medicines in children a systematic search of the literature was performed using the following electronic databases: the Cochrane Trials Register, Cochrane Database of Systematic Reviews, Medline/Pubmed (1950-present), Embase (1980-present), Public Library of Science (PLoS) open access, WHO database, Royal Society of Medicine online catalogue, JAMA, Bulletin of the World Health Organization and Memórias do Instituto Oswaldo Cruz. In addition reference lists of the most relevant articles were searched. The full search strategy can be founding Appendix B.

Individual drugs and terms searched: (Appropriate MeSH terms and subject headings were identified for each database)

- **Mebendazole, levamisole, pyrantel, niclosamide**: helminths (including individual helminthic species).
- **Praziquantel, triclabendazole, oxamniquine**: helminth, schistosomiasis (S. Mansoni, S. Japonicum, S. Haematobium).
- **Ivermectin, diethylcarbamazine**: filariasis (individual species), lymphatic filariasis, onchocerciasis, loasis.
- **Diloxanide**: amoebiasis, *Entamoeba histolytica*.
- **Metronidazole**: giardiasis, neonates, sepsis.
- **Pentamidine**: *Trypanosoma brucei gambiense*, sleeping sickness, Human African Trypanosomiasis.
- **Suramin sodium**: *Trypanosoma brucei rhodesiense* (and terms as for pentamidine).
- **Eflornithine, melarsoprol**: As above.
- **Benznidazole, nifurtimox**: Chagas disease, American trypanosomiasis, *Trypanosoma Cruzi*.

The individual drug, relevant pathogen and neglected tropical disease search terms (as shown above) were then combined individually with the following: (children OR paediatrics OR neonates OR pre-school age children) AND (safety OR efficacy) AND (pharmacokinetics OR pharmacodynamics) AND (dosing OR scheduling).

Selection criteria

To assess clinical efficacy all interventional studies with or without a control group (using either differing doses for comparison or other appropriate drugs) were deemed eligible for inclusion. With respect to safety data, all study designs where considered eligible for inclusion.
Inclusion criteria:

- Studies including children (0-18 years), from which paediatric data could be extracted.
- Studies published in the English language.
- Randomized controlled trials (RCT), quasi RCT, cohort studies, case control studies, case series, observational studies.

Exclusion criteria:

- Non-English studies.
- Studies including data for adults and children, where paediatric data were not reported separately.
- Studies reporting adult data only.

Results

A summary of the available paediatric specific efficacy and safety data for each of the individual medicines is provided below (all tables can be found in Appendix A).

Table 1 provides an overview of the evidence.
What is the evidence for safety and efficacy of medicines for the treatment of neglected tropical diseases in children?

<table>
<thead>
<tr>
<th>Drug Name(s)</th>
<th>Studies reporting data for children</th>
<th>Efficacy data</th>
<th>Safety data</th>
<th>PK data</th>
<th>Doses reported</th>
<th>Formulation(s) reported</th>
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<tr>
<td>Mebendazole (MBZ)</td>
<td>10 studies (9 RCTs[^6-14], 1 observational[^15]; n=6856, age range 6 mos to 70 yrs) 2 studies included children &lt;3 years[^6,9]</td>
<td>All studies, except Flohr et al. 2007[^7] showed treatment with MBZ to be effective</td>
<td>3 studies reported adverse events as an outcome.[^6,8,9] No serious adverse events reported. Main problems: nausea, abdominal distension and discomfort</td>
<td>No</td>
<td>200 mg tds; 500 mg od (most commonly used); 600 mg multiple doses</td>
<td>Tablet 500 mg chewable tablet No other information provided</td>
</tr>
<tr>
<td>Levamisole (LVM)</td>
<td>3 studies (2 RCTs[^8,16], 1 observational[^17]; n=1633; age range 1 to 19 yrs) 2 studies included children &lt;4 yrs[^16,17]</td>
<td>All studies showed efficacy based on reduction in egg counts. Albonico et al. 2003 showed LVM to have smaller effect on egg clearance compared to MBZ or MBZ+LVM</td>
<td>Adverse events occurring once in different patients (temperature rise, loose stools, convulsion) not reported to be directly related to LVM. No other adverse events reported</td>
<td>No</td>
<td>&lt; 3 yrs 40 mg 3-9 yrs 60 mg &gt;9 yrs 80 mg</td>
<td>Tablet</td>
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<tr>
<td>Pyrantel (PYR)</td>
<td>4 studies (3 RCTs[^11,12,20], 1 observational study[^14]) 3 included only children[^12,14,20] (n=2074; age range 2 yrs to 10 yrs 1 included adults and children[^11] (n=147; age range 3 yrs to 70 yrs)</td>
<td>Effective in treating ascaris lumbricoides Poor efficacy for treating hookworm infections Higher cure rate than MBZ for trichuriasis infection, but less effective than albendazole</td>
<td>None of the studies provided any information about adverse events/safety</td>
<td>No</td>
<td>10 mg/kg/day 11 mg/kg/day 12.5 mg/kg/day 15-20 kg: 150 mg 21-30 kg: 300 mg 31-40 kg: 450mg</td>
<td>Tablet</td>
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<tr>
<td>Drug Name (s)</td>
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<tr>
<td>Niclosamide</td>
<td>No</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Diethylcarbamizine (DEC)</td>
<td>6 studies (3 RCTs25,28,29; 3 observational studies30,31,33; n= &gt;12000; age range 1 to 87 years)</td>
<td>All studies showed efficacy with a reduction in mf and antigenaemia</td>
<td>Mild adverse events reported (nausea, vomiting, fever, headache). No cessation of treatment required</td>
<td>No</td>
<td>6 mg/kg</td>
<td>No information reported</td>
</tr>
<tr>
<td>Ivermectin (IVM)</td>
<td>7 studies (4 RCTs24,26,27,29; 1 comparative field trial34, 1 follow up study32, 1 safety study35; n= age range 3 yrs to 87 yrs) 2 studies included children &lt;4 yrs29,32</td>
<td>IVM treatment alone had lower mf clearance rates than combination therapy (IVM + albendazole)</td>
<td>No serious adverse events reported. Most frequently reported side effects: headache, swellings, arthralgia and fever</td>
<td>No</td>
<td>Dose ranged from 150 mcg/kg to 400 mcg/kg</td>
<td>3 mg tablets</td>
</tr>
<tr>
<td>Praziquantel (PZQ)</td>
<td>13 studies (8 RCTs30-46; 1 safety pilot study48, 1 observational study51, 1 clinical efficacy trial49,50, 1 quasi RCT52) 8 studies included only children30,41,44-46,49-51 (n = 5181; age range 4 yrs to 18 yrs) 5 studies included adults and children40,42,43,47,49 (n = 5710; age range 7 yrs to 60 yrs)</td>
<td>Efficacy against S. haematobium (cure rate of 88.5%; egg reduction rate 98.2%) PZA more efficacious than Niridazole, Metrifonate and placebo with ascorbic acid</td>
<td>7 studies reported adverse events as an outcome43,46,47,49. Generally side effects were mild and transient (dizziness, headache, abdominal pain, vomiting, diarrhoea). No cessation of treatment required</td>
<td>No</td>
<td>20 mg/kg single oral dose 20 mg/kg 2 oral doses 20 mg/kg 3 oral doses 40 mg/kg single dose 60 mg/kg split dose 3 hrs apart</td>
<td>200 mg tablet</td>
</tr>
<tr>
<td>Praziquantel (PZQ) Additional information from unpublished studies</td>
<td>5 observational studies 4 studies included pre-school age children48-50 (n= 1748; age range 1 mth to 6 yrs) 1 study included primary school children47 (n = 5700 age range 6 yrs to 12 yrs).</td>
<td>All studies showed efficacy of PZQ tablets and PZQ syrup with reduction in egg counts in consecutive stool/</td>
<td>All studies reported adverse events as an outcome. In general, PZA tablets and/or syrup were well tolerated, with mild, transient side effects.</td>
<td>No</td>
<td>40 mg/kg 1-3 yrs: 518 mg; 1 tablet &gt;3-5 yrs: 740 mg; 11/4 tablet &gt;5-6yrs: 977 mg; 12/3 tablet</td>
<td>Tablet 600mg (crushed and mixed with orange juice for younger children unable to swallow tablets;</td>
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</tbody>
</table>
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<tr>
<td>Oxamniquine</td>
<td>9 studies (4 RCTs, 4 clinical efficacy trials, 1 follow up study)</td>
<td>urine samples. Although, efficacy of PZQ tablets shown to be greater than efficacy of PZQ syrup. PZA treatment resulted in significant reduction in overall infection prevalence (29.5% to 5.68%) and infection intensity 19.7 to 1.39 eggs/10ml urine.</td>
<td>Reported side effects: fatigue, dizziness, drowsiness, headache, loss of appetite and stomach ache. 1 study showed symptoms were significantly higher among uninfected children compared to those with S.mansoni</td>
<td>No</td>
<td>10 mg/kg bd for 1 day or 2 days, 20 mg/kg single oral dose or bd for 1 day or 3 days, 800 mg/m²/day in 2 divided doses (approx. 60 mg/kg)</td>
<td>required dosage was broken into smaller pieces or crushed using mortar and pestle. A honey based solution was added to make a suspension for some of the children. Syrup (EPIQUANTEL®)</td>
</tr>
<tr>
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<tr>
<td>Triclabendazole</td>
<td>3 studies (1 pilot study&lt;sup&gt;50&lt;/sup&gt;; 1 community dose comparison study&lt;sup&gt;52&lt;/sup&gt;; 1 case series&lt;sup&gt;53&lt;/sup&gt;, n= 184; age range 2 yrs to 62 yrs). All the studies included adults and children.</td>
<td>Cure rate with single dose 74.9%. Higher cure rate (93.9%) with 2 doses.</td>
<td>No significant adverse events. Good tolerability</td>
<td>No</td>
<td>10 mg/kg od or bd</td>
<td>Oral No other information reported</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>5 studies (1 RCT&lt;sup&gt;69&lt;/sup&gt;; 1 prospective open label randomized trial&lt;sup&gt;70&lt;/sup&gt;; 1 survey of efficacy and adverse events&lt;sup&gt;71&lt;/sup&gt;; 2 comparative trials&lt;sup&gt;72,73&lt;/sup&gt;; n= age range 7 mos to 12 yrs). Only 1 study included children &lt;2 yrs&lt;sup&gt;79&lt;/sup&gt;</td>
<td>All studies showed efficacy by parasitological assessment of stool samples. Cure rates ranged from 80% to 97%</td>
<td>Adverse events mild, transient and did not require cessation of treatment. Reported side effects included: anorexia, nausea, vomiting, malaise and metallic taste</td>
<td>4 studies. Preterm and term infants have a lower total body clearance and prolonged half-life, whereas children over 4 have PK parameters similar to adults. Dose should be decreased in malnourished children.</td>
<td>15 mg/kg in 3 divided doses for 7 days 20 mg/kg/day for 5 days 30 mg/kg bd for 7 days</td>
<td>Oral route of administration. No other information provided</td>
</tr>
<tr>
<td>Diloxanide</td>
<td>2 studies (1 comparative trial&lt;sup&gt;79&lt;/sup&gt;, n= 39; age range 7 mos to 10 yrs; 1 retrospective study&lt;sup&gt;80&lt;/sup&gt; n= 4371 treatment)</td>
<td>Unable to determine efficacy data from information</td>
<td>Most commonly reported side effect: flatulence. Fewer adverse events reported</td>
<td>No</td>
<td>25 mg/kg od for 10 days</td>
<td>Oral. No other information provided</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Pentamidine</td>
<td>courses from 1977 to 1990)</td>
<td>reported in comparative trial</td>
<td>in those aged 20 mos to 10 yrs than those aged &gt;10 yrs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Suramin</td>
<td>No</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Melarsoprol</td>
<td>4 studies (2 RCT, 1 phase II clinical trial, 1 retrospective analysis; n = 3035; age range 0 to 62 yrs. All the studies included both adults and children)</td>
<td>melarsoprol + eflornithine not as effective as nifurtimox + eflornithine (cure rates 44% vs. 94% respectively)</td>
<td>Significantly toxic. Some deaths attributable to complications of treatment. Poorly tolerated by all age groups. Very young (&lt;2 yrs) more prone to jaundice and rash than adults. Lower incidence of encephalopathic syndrome in PSAC, but higher mortality rate in those that did develop it</td>
<td>No</td>
<td>Over 26 days: 3 series of 4 daily i.v infusions starting at 1.2 mg/kg, increasing to 3.6 mg/kg with a 7 day interval between series 1.8 mg/kg/d for 10 days 2.2 mg/kg/d for 10 days</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Eflornithine</td>
<td>5 studies (3 RCTs, 1 retrospective study, 1 clinical trial; n = 3509; age range 0 to 77 yrs) 2 studies included children &lt; 2 yrs</td>
<td>Eflornithine has equal efficacy to melarsoprol</td>
<td>Number of adverse events increased with longer duration of treatment, but only statistically significant for diarrhea and infections. Less toxic than</td>
<td>No</td>
<td>100 mg/kg 6 hourly for either 7 or 14 days 200mg/kg 12 hourly for 14 days 100 mg/kg i.v 6 hourly for 14 days, followed by 75</td>
<td>Oral Intravenous infusion</td>
</tr>
<tr>
<td>Drug Name (s)</td>
<td>Studies reporting data for children</td>
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<tr>
<td>Benznidazole</td>
<td>7 studies (4 RCTs\textsuperscript{80,93}, 1 follow up study\textsuperscript{94}, 1 observational study\textsuperscript{95}, 1 control program study\textsuperscript{96} (MSF project); n= age range newborn to 18 yrs)</td>
<td>3 studies\textsuperscript{80,92} showed efficacy in comparison to placebo in children with indeterminate or early stage trypanosome cruzi</td>
<td>Minor adverse events (gastrointestinal disorders; rash). No deaths reported</td>
<td>No</td>
<td>2.5 mg/kg bd for 60 days 5 mg/kg/d 7.5 g/kg once daily for 30 or 60 days 7.5 mg/kg bd or tds for 60 days Maximum dose 300 mg/d</td>
<td>Tablets 100 mg tablets ground up and capsules filled with 8, 10, 13 and 15 mg powder to treat neonates according to weight</td>
</tr>
<tr>
<td>Nifurtimox (N)</td>
<td>2 studies (2 RCTs\textsuperscript{82,85}; n&gt; 54; age range 5 yrs to 62 yrs). Not possible to extract paediatric specific data from either study</td>
<td>Only used in combination with eflornithine (E) or melarsoprol (M) N+E more effective than M+E (cure rates 94% vs. 44% respectively)</td>
<td>Combination of N+E well tolerated. Low fatality rate compared to melarsoprol (0.76% vs. 6%)</td>
<td>No</td>
<td>15 mg/kg/d 8 hourly for 10 days 20 mg/kg/d 8 hourly for 10 days</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Abbreviations used in table: RCT = randomized controlled trial; mos = months; yrs = years; tds = 3 time daily; od = once daily; bd = twice daily; mf = microfilarial load; d = day
Mebendazole (MBZ) for the treatment of soil transmitted helminth infections

Ten studies were identified that included children' nine RCTs (4 of which were double blinded and placebo controlled)\textsuperscript{6-14} and one observational study.\textsuperscript{15} The age of participants ranged from 6 months to 18 years; the number of participants ranged from 96 to 3028 (Refer to Table 2). Only 2 studies, Montresor et al.\textsuperscript{9} and Stoltzfus et al.\textsuperscript{8} included children in the preschool age group (starting from 6 months of age).

A variety of different doses were used across the studies:

- MBZ 500 mg tablet (described as oral intake) single dose.
- MBZ 200 mg taken 3 times daily orally.
- MBZ 600 mg taken orally "multiple doses".

The 500 mg dose of MBZ was the most commonly used (8/10 studies).\textsuperscript{6,9,11-12,14} None of the studies provided evidence for the dosing and scheduling of MBZ in children. The pharmacokinetic data identified referred only to adults. The only formulation that was used in the studies was a tablet dosage form (regardless of patient age). Only one study reported using a chewable tablet (Stoltzfus et al).\textsuperscript{8} No information was provided in the studies regarding how the tablets were administered to the different age groups.

All the studies, with one exception (Flohr et al.\textsuperscript{7}), showed treatment with MBZ to be effective with a reduction in prevalence and intensity of STH infections. Efficacy was measured by reduction or absence of helminth eggs in the faeces.

Three studies (Albonico et al.\textsuperscript{8}, Montresor et al.\textsuperscript{9}, Cañete et al.\textsuperscript{13}) reported adverse events as well as efficacy. No serious adverse events were noted in any of the studies. The adverse events that were documented required no medical intervention and were mainly symptoms of nausea, abdominal distension and discomfort.

Despite an informal consultation by the WHO in 2002 evaluating the evidence for safety and efficacy of MBZ use in the under 24 months age group there have been no new randomized controlled trials since that of Montresor et al. 2002.\textsuperscript{9} There was one observational study by Morrone et al.\textsuperscript{15} in 96 preschool age children, but the results were not stratified into age groups. The aim of this study was to determine use and frequency of chemotherapeutic agents within that age group, and efficacy and safety was not specifically evaluated.

Levamisole (LVM) for the treatment of soil transmitted helminth infections

Three studies were identified that included children' two RCTs (Albonico et al.\textsuperscript{8} and Thein-Lang et al.\textsuperscript{10}) and one observational study (Lionel et al.\textsuperscript{17}). Both the RCTs used a valid method of randomization, but only Albonico et al.\textsuperscript{8} had a placebo control arm. Both studies were non-blinded. The age of participants ranged from 1 to 19 years. In the case series study by Lionel et al.\textsuperscript{17} nine children under 2 were included, but the lower limit of the age range was not reported (Table 3).

Doses of LVM used in the studies ranged from 40 mg to 80 mg depending on the child’s age. In one study (Thein-Lang 10) the dose used was not reported - only documented as "per manufacturers guidelines”. No information was given about how the tablets were administered to the children.
All studies showed there was efficacy based on reduction in egg counts. Albonico et al.8 (n=914, age range 7-18 years) that LVM had a smaller effect on egg clearance when compared to treatment with MBZ or combined MBZ/LVM.

At the dosages reported above few adverse events were reported. Thein-Lang et al.16 reported a temperature rise, loose stools and convulsions occurring once in different patients; on each occasion it was found to not be related to LVM.

There are data describing the long-term effects of LVM use in childhood nephrotic syndrome18-19 indirectly giving further evidence of safety of its use in children. The studies showed LVM to be well tolerated with minimal side effects. These studies were reviewed, but not reported in Table 3 as dosing regimens, scheduling and efficacy outcomes were unrelated to aim of this review.

**Pyrantel (PYR) for the treatment of soil transmitted helminth infections**

Four studies were found that reported efficacy data for children’ three RCTs and one longitudinal evaluation (Table 4). Forrester et al20, Albonico et al.12 and Northrop-Clewes et al.14 recruited children for their studies, age range 2 to 10 years. Sacko et al.11 included children and adults, with an age range of 3 to 70 years. The number of participants ranged from 147 to 1329.

The reported dose of pyrantel used in the studies varied from 10 mg/kg/day to 12.5 mg/kg/day. One study12 stratified the dosing by weight bands: 15 to 20 kg – 150 mg tablet; 21 to 30 kg - 300 mg tablet and 31 to 40 kg - 450 mg tablet. The range across the different weights is therefore 10 mg/kg to 14.5 mg/kg.

The only formulation reported in the studies was a tablet. Pyrantel overall showed good efficacy in the treatment of soil transmitted helminths, but in the study by Forrester et al.20 it was found to be less effective against Trichuriasis infection compared with albendazole. In the other studies pyrantel was shown to have comparative cure rates to mebendazole in treatment of A. Lumbricoides, Trichuria trichuris and human hookworm infections.

None of the studies reviewed reported adverse events.

**Niclosamide for the treatment of soil transmitted helminth infections**

No studies were identified that met the inclusion criteria.

**Systematic reviews of antihelminthics**

A systematic review by Keiser et al.21 reviewed the efficacy of single oral albendazole, mebendazole, levamisole, and pyrantel against A. lumbricoides, hookworm and T. trichuria infections. Twenty RCTs were included in the systematic review, of which 9 included children. The review concluded that treatment success was dependent on the type of soil transmitted nematode that was being treated. Albendazole, mebendazole and pyrantel were
all effective at curing *A. lumbricoides* (cure rate 88-93%), but were less successful in producing cure rates for *T. trichuria* and human hookworm infections (15-36%).

Taylor-Robinson et al. evaluated the effects of treatment on school performance. Adverse events were reported as a secondary outcome. Adverse events were found to be mild and transient and not requiring cessation of treatment. Nausea and abdominal discomfort were the most commonly reported side effects.

Albonico et al. did a review summarizing the data available to support the use of antihelminthics in pre-school age children. They reviewed 17 published reports on the prevalence of STH in pre-school age children and evaluated the safety and efficacy of medication used in children. The review highlighted issues that needed to be addressed urgently:

1. Monitoring safe administration
2. Monitoring efficacy
3. Need for paediatric formulations.

Refer to Table 5 for further details.

**Diethylcarbamazine (DEC) for the treatment of filarial diseases**

Six studies reported efficacy and/or safety data for the use of DEC in children. Three RCTs, One study, although initially a double-blinded placebo controlled RCT, had its placebo arm terminated early when efficacy of treatment became evident. The remaining 3 studies were monitoring/evaluation studies of the impact of community mass drug administration programmes and included both adults and children (Table 6).

The reported dose of DEC administered in all the studies was 6 mg/kg. The age range across the studies was 1 to 87 years, with sample sizes ranging from 82 to 18,415 participants. A monitoring study by Weil et al. reported the impact of mass drug administration with DEC and albendazole in the 2-5 year age group. All the studies using DEC as a treatment arm showed efficacy with a reduction in microfilaria and antiginaemia in the younger age groups. Babu et al. reported adverse events of nausea, vomiting, fever, headache, however no cessation of treatment was required. Kshirsaga et al. assessed the safety of DEC in 5-12 year olds. They concluded that there was a good safety profile with good tolerability. However, it was not possible to determine the type and frequency of the adverse events from what was reported in the study.

Despite the inclusion of children in the community mass drug administration evaluation and monitoring studies, children under six years of age frequently did not have blood tests to determine microfilaria load. The burden of microfilaria in those less than six years was not reported and the evaluation of the impact of mass drug administration on microfilaria in these children was not possible following subsequent rounds of treatment.

Apart from the dose, no information was reported about how the medicine was administered to pre school age children. Data for efficacy and safety for children under 4
years of age could not be extracted as results were not stratified by age. No studies were found that reported pharmacokinetic data for the paediatric population (specifically in those <4 years)

### Ivermectin (IVM) for the treatment of filarial diseases

Seven studies were identified that included children in treatment groups. Four RCTs, 1 follow up study, 1 comparative field trial, and 1 safety study. Only two studies included children less than 4 years (Ramaiah et al. and Ndyomugyeni et al.). Results were stratified for Ramaiah et al. as percentage microfilaria in the 0-5 age range and as <10 years in the Ndyomugyeni et al. study. Two RCTs (Beach et al. and Simonsen et al.) evaluated IVM efficacy in children aged 5 to 18 years (Table 6).

The age range of participants across the studies was 3 to 87 years and the number of participants ranged from 182 to 5,055 participants. The dosage of IVM used in the studies ranged from 150 mcg/kg to 400 mcg/kg. Tablets were the only formulation mentioned. No information was provided about how the tablets were administered to younger children.

Efficacy was measured in terms of microfilarial clearance. IVM treatment alone compared to combination therapy had lower microfilarial clearance rates. Four studies specifically mentioned adverse events associated with treatment (Simonsen et al., Asio et al., Vyungumana et al., Mohammed et al.) but only Vyungumana et al. reported the frequency and type of adverse events. The most frequently reported side effects were headache, swellings, arthralgia and fever. In general side effects were mild and transient and all the studies described ivermectin as well tolerated.

### Systematic reviews for antifilarials

The systematic review by Adinarayan et al. evaluated the effect of DEC medicated salt on infection with lymphatic nematodes. Twenty-one RCTs were included. Extraction of paediatric data from the review was difficult, since the study descriptions lacked details of age ranges. Outcomes measured were microfilaria prevalence, adverse events, disease status, and change in vector infection or infectivity rates. The authors concluded that DEC-medicated salt was an effective intervention with minimal side effects and good tolerability. Tisch et al. examined what drug interventions were most effective in reducing circulating microfilaria. Forty-three RCTs and fourteen field trials were included. No age range was specified, but it was assumed that children had been included in the community trials. Safety and tolerability of the drugs were not reported (Table 7).

A review by Olsen of 31 studies and 2 abstracts evaluated the efficacy and safety of combinations of various medicines, including of albendazole (ALB)-praziquantel (PZQ), ivermectin (IVM), diethylcarbamazine (DEC) and mebendazole, in the treatment of schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis or onchocerciasis. Sample size across the studies ranged from 25 to 2000; age range 2 to 98 years. There were no significant pharmacokinetic interactions when ALB-PZQ, ALB-DEC, ALB-IVM or ALB-IVM-PZQ were co-administered. Efficacy of IVM in the treatment of lymphatic filariasis was enhanced by combination with DEC.
No systematic review of studies exclusively in the paediatric population was identified.

**Praziquantel (PZQ) for the treatment of schistosomiasis**

Thirteen studies were identified with efficacy and or safety data reported separately for children (Table 8): 8 randomized blinded placebo controlled trials, 1 study was described as a RCT, but the method used for randomization was not reported, 1 safety pilot study, 2 clinical trials of efficacy and 1 longitudinal intervention study.

The age range across the studies was 4 to 60 years; sample size ranged from 80 to 5,055 participants. The majority of the studies only included children; exceptions were: Hou et al., Ferrari et al., Mohammed et al., Davis et al. and Inyang-Etoh et al. However, in the study by Davis et al. (n=80) only 4 out of 80 participants were >16 (age range 7-22 years). None of the trials included children under the age of four.

Dosages of PZQ used varied from 20-60 mg/kg/dose, administered as either a single dose or divided into 2-3 doses over the course of either a single day or over a course of several weeks (refer to Table 8 for further details). The medication was administered orally and only available in tablet form. Davis et al. evaluated the effectiveness of different doses of PZQ (single dose versus 2 doses versus 3 doses, each "dose" 20 mg/kg). All the doses showed high efficacy in clearance of *S. haematobium* and no serious adverse effects were reported.

Efficacy of treatment was determined by intensity and prevalence of infection (egg counts in faeces/urine or hatching test). Of the 13 studies reviewed 7 reported adverse events as an outcome (Ferrari et al., Sissoko et al., Hou et al., Midzi et al., Inyang-Etoh et al., Keiser et al. and Davis et al.). These 7 studies reported that adverse events were minimal, with no need to withdraw treatment. Side effects such as dizziness, headache, abdominal pain, vomiting and diarrhoea were described as transient and mild, not requiring cessation of treatment. No studies were identified that reported pharmacokinetic data for PZQ in children.

**Additional information following a WHO meeting to review results from studies on the treatment of young children for schistosomiasis**

A meeting was held at WHO-HQ on 13th-14th September 2010 to discuss the results from 5 observational studies undertaken in 5 different countries (Egypt, Sudan, Niger, Zimbabwe and Uganda) investigating safety and efficacy of PZA treatment in young children with schistosomiasis (n= 7448; age range 0.1 mth to 12 years). All studies showed efficacy of PZQ tablets and/or PZQ syrup with reduction in egg counts in consecutive stool and urine samples. However, cure rates were lower among Egyptian school children treated with PZQ suspension than those treated with PZQ tablets under all circumstances (Barakat et al.). Egg reduction rates were the same regardless of whether child received suspension or tablet.

All studies reported adverse events as an outcome (see Table 8). In general, PZA tablets and/or syrup were well tolerated, with mild, transient side effects. Reported side effects included fatigue, dizziness, drowsiness, headache, loss of appetite and stomach ache. One study (Kabatereine et al.) showed reported symptoms post treatment to be significantly higher among uninfected children compared to those with *S. mansoni.*
Administration of praziquantel to pre-school-age children was shown to be acceptable, safe and efficacious in the context of individual case management and large group settings.

**Oxamniquine for the treatment of schistosomiasis**

Nine studies were identified that reported paediatric safety and/or efficacy data: 4 RCTs, 4 clinical trials of efficacy and one 2-year follow up study of an efficacy trial. The studies by Ayele et al., Axton et al., Katz et al. and Lambertucci et al. only included children, age range 6 to 16 years. The remaining trials recruited both adults and children, age range across the studies 2 to >20 years. The number of participants ranged from 57 to 1,138 (Table 9).

Doses of oxamniquine ranged from 10 mg/kg to 60 mg/kg across the various studies. The mode of administration was oral, either in a capsule form or suspension for the young children. The age of those receiving suspension rather than tablet form was not reported. The doses were given once daily or in divided doses either over several hours or over 2 days. Reported adverse events were mild and transient: dizziness and drowsiness were the most frequently.

Oxamniquine in children at lower doses did not appear to be as effective as in adults in achieving cure rates. The higher doses were associated with an increase in adverse events. The optimal dose for treatment as determined by Ayele et al. was 30 mg/kg over 2 days. The consensus from the studies that included both adult and children was that oxamniquine was better tolerated and more effective in the adult groups. No studies were identified that reported pharmacokinetic data for the use of oxamniquine in children.

**Triclabendazole for the treatment of schistosomiasis**

Three studies reported data relating to efficacy and safety of triclabendazole: 1 pilot study, 1 community dose comparison study, 1 case series. All the studies included a mixture of adult and paediatric participants but none of the studies stratified the results by age. The age range of participants in the studies was 2 to 62 years of age, with the number of participants ranging from 10 to 134 participants (Table 10). None of the studies were randomized or had a control arm. The studies found that triclabendazole was effective for the clearance of fascioliasis cysts. The study by El-Morshedy et al. provided more convincing efficacy data, as the sample group was larger (134 participants). Cure rates for single dose and 2 doses 24 hours apart were 74.9% and 93.9% respectively. Tolerability was reported to be good and no significant adverse events were reported.

A case series by El-Karaksy et al. looked at the effectiveness and tolerability of triclabendazole for the treatment of fasciola hepatica in Egyptian children. The series demonstrated that a 78% cure rate was achievable with minimal side effects. The age range of this population was 4 to 15 years of age.
Systematic reviews for treatment of schistosomiasis

Saconata et al.\textsuperscript{64} analysed thirteen RCTs in their systematic review. The aim was to determine the efficacy of PZQ and oxamniquine in the treatment of \textit{S. mansoni}. The conclusion was that both treatments were effective treatment options with minimal adverse events documented. Paediatric data were difficult to extract.

Danso-Appia et al.\textsuperscript{65} reviewed treatment options of PZQ, metrifonate, artemisinin derivatives or albendazole alone or in combination for urinary schistosomiasis. Twenty-four trials were included; 19 of which reported the use of PZQ in children >5 years. Only one trial in the review described treatment of children <5 years (Wilkins et al.\textsuperscript{66}) but information about administration of treatment for those under 5 years could not be extracted. Refer to Table 11 for further details.

Metronidazole for the treatment of amoebiasis and giardiasis

Six studies were identified with extractable paediatric data: 1 prospective open labelled randomized trial, 1 RCT\textsuperscript{69}, 1 prospective open label randomized trial\textsuperscript{70}, 1 survey study of efficacy and adverse events\textsuperscript{71}, and 3 comparative studies\textsuperscript{72,73,79}. The studies reported treatment outcomes for either amoebiasis or giardiasis. The age range of the participants in the reviewed studies was 7 months to 12 years of age, with a sample size of 39 to 122 participants. Only one study by Rubidge et al.\textsuperscript{79} included children under the age of 2 years (Table 13). Dosing regimens for metronidazole were different in all the studies; 15 mg/kg in 3 divided doses for 7 days, 20 mg/kg/day for 5 days and 30 mg/kg twice daily for 7 days. Dosing appeared to be via the oral route, but it was difficult to ascertain from some studies and no further information about formulation was reported. Treatment with metronidazole was assessed by parasitological clearance of cysts in all the studies. Adverse events were considered mild, transient and did not require cessation of treatment. Adverse events of anorexia, nausea, vomiting, malaise, and metallic taste were reported by Sadjjadi et al.\textsuperscript{73}, the other studies mentioned nausea as the most frequently reported side effect. Refer to tablets 12 and 13 for more information.

Studies reporting the metabolism or pharmacokinetics of metronidazole:

Alestig et al.\textsuperscript{74} (1980) measured serum concentrations and urinary excretion of metronidazole after single dose therapy in patients with giardiasis in 10 adults and 6 children (ages not stated). Results were reported as an average of all participants and not age specific.

Lares-Asseff et al.\textsuperscript{75} (1992) published a study evaluating at the pharmacokinetics of metronidazole in severely malnourished and nutritionally rehabilitated children that suggested that the dose of metronidazole should be reduce in malnourished children.

Lau et al.\textsuperscript{76} (1992) (only abstract available) reviewed the historical pharmacokinetic studies for metronidazole, including data obtained from specific chromatographic techniques to measure parent drug and metabolite activity. The main finding of the review was that preterm and term infants have a lower total body clearance and prolonged half-life, whereas children over 4 have pharmacokinetic parameters similar to adults. Children who were
malnourished also had delayed clearance of the drug. The study found that also the oral bioavailability is close to 100%.

There have been suggestions that infants as young as 6 weeks metabolize metronidazole in a similar manner to adults. Amon et al. 1983 assessed children aged 6 weeks to 14 years in whom treatment with metronidazole was started and their findings suggested that there was little difference in kinetic parameters between children and adults.

**Diloxanide for the treatment of amoebiasis**

Two relevant studies were found from which paediatric data could be extracted, 1 randomized comparative trial and 1 retrospective analysis of efficacy and safety data (Table 13). A comparative trial by Rubidge et al. evaluated children (n= 39) between 7 months to 10 years of age. Twenty participants received treatment with metronidazole, with the remaining participants being given a combination of treatments, one of which was diloxanide. It was not possible to extract efficacy and safety data for diloxanide from this study; however the author concluded that metronidazole was an effective and well-tolerated treatment.

A study by McCauley et al. analysed efficacy and adverse event data associated with diloxanide treatment and found that fewer adverse effects were reported for persons aged 20 months to 10 years than for persons aged > 10 years (6/206 versus 89/763) with 86% of those treated achieving parasitological cure. Reported adverse events included flatulence, dizziness, diarrhoea or cramping, nausea and headache. No cessation of treatment was required. The study demonstrated that diloxanide was a safe and effective treatment in children for clearance of *E. Histolytica* cysts.

**Systematic reviews for antiamoebic and antigiardiasis medicines**

A systematic review by Gonzales evaluated antiamoebic medicines for treating amoebic colitis (37 studies, n= 4487). Of those trials, 10 included only children (<15 years) and 10 included both adults and children. Results for children alone were not extractable from the review. The overall finding of the review was that tinidazole reduced clinical failure compared to metronidazole (8 studies, n=477) and caused fewer side effects. The trials reviewed were reported to be inadequate or unclear in methodological quality (Table 14).

**Pentamidine for the treatment of 1st stage African trypanosomiasis, (Trypanosoma brucei gambiense infection)**

Three efficacy studies including children, were identified, 1 clinical study, 1 clinical trial (phase ii), and 1 retrospective analysis (Table 15). Sample sizes ranged from 523 to 1952; age range of participants ranged from 0 to 15 years. Only 1 study (Eperon et al) stratified the participants by age groups and reported the results according to these age stratifications. The dose of pentamidine administered in all the studies was 4 mg/kg given intramuscularly. The overall results showed use of pentamidine in all age groups was safe and effective with no reports of serious adverse events.
Suramin for the treatment of the initial phase of Trypanosomal *brucei rhodensiense* infection

No studies from which paediatric data could be extracted were found.

**Melarsoprol for the treatment of 2nd stage African trypanosomiasis**

Four studies were found with extractable safety and efficacy data for children, 2 randomized clinical trials\(^82,84\), 1 phase II clinical trial\(^87\) and 1 retrospective comparative analysis.\(^88\) The age range across the studies was 0 to 62 years and sample sizes ranged from 52 to 1958 patients (Table 15). Eperon et al.\(^88\) was the only study to present results specifically for pre-school age children.

The dose of melarsoprol used varied from 1.2 mg/kg to 3.6 mg/kg, with the most commonly used dose of 2.2 mg/kg being administered as an intravenous infusion. The results from all the reviewed studies showed that melarsoprol was poorly tolerated by all age groups, with the very young (<2 years) being prone to jaundice and rash more commonly than the adults treated.\(^88\) Eperon et al.\(^88\) found that there was a lower incidence of encephalopathic syndrome in pre-school age children, but those who did develop it had a higher mortality rate. All studies found melarsoprol to be significantly toxic, with some deaths attributable to the complication of adverse effects of the treatment.

Ongoing studies are currently evaluating alternatives to treatment for late stage Human African Trypanosomiasis, which include the combination of nifurtimox and eflorehnine compared to melarsoprol in children as well.

**Eflornithine for the treatment of 2nd stage African Trypanosomiasis (Trypanosomiasis *brucei gambiense*)**

Five studies were identified that had extractable safety and efficacy data for children, 3 RCTS, 1 retrospective study and 1 clinical efficacy trial.\(^82,83,85,88-89\) Two studies (Eperon et al.\(^88\) and Milord et al.\(^89\)) included children under the age of 2 years. The age range of participants was 0 to 77 years. The population size ranged from 54 to 1928 participants. Each study used a different dose of eflornithine (Table 15).

Adverse events were noted in all studies, however the overall conclusion was that eflornithine was an effective treatment with less toxic side effects to melarsoprol. Only Eperon et al.\(^88\) stratified the results by the different age groups. Further trials are underway examining combination therapy of nifurtimox and eflornithine as a more effective treatment with a lower toxicity profile as shown by Priotto et al.\(^82\).

Pepin et al.\(^83\) studied different dosage scheduling for eflornithine and found that a 7-day treatment duration was effective for treatment and with an improved adverse event profile (i.e. diarrhoea and infections) in comparison to the longer 14-day treatment duration that has been used in previous studies.
**Gap analysis**

**Systematic reviews for the treatment of Human African Trypanosomiasis (HAT)**

There are currently no published systematic reviews on African trypanosomiasis. There is an ongoing NECT trial in the Democratic Republic of Congo that includes children of all ages.

**Benznidazole for the treatment of American trypanosomiasis**

Seven studies were reviewed looking at the efficacy and safety of benznidazole use. Paediatric data was extractable from all the studies, 4 RCTs\(^{90-93}\), 1 follow up study of the Andrade et al. 1996 RCT\(^{94}\), 1 observational trial\(^{95}\) and 1 control program study\(^{96}\) (Médecins sans Frontières’ project). The age of participants ranged from newborn to 18 years of age, and the number of participants ranged from 106 to 2,444. Dosages varied from 2.5 mg/kg twice a day for 60 days to 7.5 mg/kg once a day for 30 days or twice a day for 60 days. Trials by Sosa-Estani et al.\(^{90}\), Andrade et al.\(^{91}\) and Galvão et al.\(^{92}\) were able to show efficacy of benznidazole in comparison to a placebo treatment in children with both indeterminate stage or early stage *trypanosome cruzi* infection (Table 16).

Chippaux et al.\(^{93}\) studied 253 newborns using antibody titres as a marker for cure. No adverse events were noted with treatment in this age group, but antibody titres were noted to be present in non parasataemic infants of seropositive mothers for a period of up to 8 months. Escriba et al.\(^{95}\) examined children between 9 months to 12 years and noted minor adverse events, such as gastrointestinal disorders and rash. They noted that those <10 years of age tended to take longer to seroconvert.

Administration of treatment was oral, with tablets being crushed to the nearest appropriate dose. No further information was provided regarding different formulations.

**Nifurtimox for the treatment of American trypanosomiasis**

No studies were found describing the use of nifurtomox in the treatment of American trypanosomiasis in children. Two studies were identified that reported us of nifurtimox in combination with eflornithine for the treatment of late stage HAT *gambiense* (n= 54, age range 5 to 62 years)\(^{82,83}\). It was not possible to extract paediatric data from either study (Table 16).

**Systematic reviews of treatment of American trypanosomiasis (Chagas disease)**

There were no systematic reviews describing treatment in children. The only two paediatric studies that were included in reviews of Chagas disease treatment were by Sosa-Estani et al.\(^{90}\) and Andrade et al.\(^{91}\), described above. The reviews concluded that there was a lack of sufficient evidence regarding treatment, dosing schedules and a paucity of RCTs evaluating treatment of chronic and indeterminate Chagasic disease (Table 17).

**Gaps in evidence**

Only a limited number of RCTs/clinical trials evaluating the safety and efficacy for each NTD medicine in the paediatric population were identified. Some relevant studies may have been missed due to the fact that the search was limited to English language papers. Several potentially relevant studies in Spanish or Portuguese were not reviewed.
The gaps identified in the evidence for use of these medicines in children include:

- Lack pharmacokinetic and pharmacodynamic data for these medicines in the paediatric population, especially <4-year age group.
- In all medicine groups most of the studies poorly described and/or reported age stratification within the participant groups.
- In many of the community studies there was a lack of stratification of the results according to different age groups.
- The method of administration of the medicine to children, especially the younger age groups, not clearly described.
- Lack of paediatric friendly formulations (benznidazole is an example of where crushed tablets are being used to treat neonates).

**Future research requirements have been identified as:**

1. Pharmacokinetic data in the paediatric population, especially pre-school age children (<4 years).
2. Improved reporting of paediatric data in clinical trials and community MDA programmes. All data for children should be stratified and reported by age group.

**Conclusion**

The purpose of this review was to determine whether or not there was sufficient evidence to support the use of the current dosages and formulations of medicines included on the WHO Essential Medicine List for the treatment of neglected tropical diseases in the paediatric population. In general it was found that there is a lack of high quality clinical trials in the paediatric population and there is a paucity of pharmacokinetic data for the reviewed medicines within the 0-5 age group.
References


APPENDICES

Appendix A:

WHO Model List of Essential Medicines for children³

Levamisole: tablet 50 mg; 150 mg (as hydrochloride)
Mebendazole: tablet (chewable) 100 mg; 500 mg
Niclosamide: tablet (chewable) 500 mg (listed for use when praziquantel treatment fails)
Praziquantel: tablet 150 mg; 600 mg
Pyrantel: oral liquid 50 mg (as embonate)/ml; tablet (chewable) 250 mg (as embonate)
Ivermectin: tablet (scored) 3 mg, 6 mg
Diethycarbamazine (complementary list): tablet 50 mg; 100 mg (dihydrogen citrate)
Triclabendazole: tablet 250 mg
Oxamniquine (complementary list): capsule 250 mg; oral liquid 250 mg/5ml (for use when praziquantel treatment fails)
Diloxanide: tablet 500 mg (furoate) >25 kg
Metronidazole: injection 500 mg in 100ml vial; oral liquid 200 mg (as benzoate)/5 ml; tablet 200 mg to 500 mg

Medicines for treatment of 1st stage of African Trypanosomiasis

Pentamidine: powder for injection 200 mg (pentamidine isetionate) in vial.
Suramin Sodium: powder for injection 1g in vial

Medicines for the treatment of 2nd stage African Trypanosomiasis

Eflornithine: Injection 200 mg (hydrochloride)/ml in 100ml bottle
Melarsoprol: Injection 3.6% solution in 5 ml ampoule (180 mg of active compound)
Benznidazole: tablet 100 mg
Nifurtimox: tablet 30 mg; 120 mg; 250 mg
Current WHO dosing guidelines from the manual of preventative chemotherapy in human helminthiasis\textsuperscript{4,5,6}:

**Preschool age children (1-5 years)**

- Albendazole (ALB) 200 mg for children aged 12-23 months
- Mebendazole (MBD) 500 mg for children ≥1 year
- Levamisole (LVM) 2.5 mg/kg for children ≥1 year
- Pyrantel (PYR) 10 mg/kg for children aged ≥1 year
- Niclosamide if ≤2 years 500 mg, 2-6 years 1 g
- Praziquantel (PZQ) for >4 years 10-25 mg/kg depending on infection up to 50 mg/kg in 3 daily divided doses for cysticercosis

**School-age children (aged 6-15 years) and adults (aged >15 years)**

- ALB 400 mg
- MBD 500 mg
- LEV 2.5 mg/kg standard dose for school-age children 80 mg
- PYR 10 mg/kg
- PZQ according to height starting from >94 cm

For further details on dosing and scheduling details were taken from the WHO Model Formulary\textsuperscript{6}. 
Summary of evidence tables
<table>
<thead>
<tr>
<th>Drug Name (s)</th>
<th>Studies reporting data for children</th>
<th>Efficacy data</th>
<th>Safety data</th>
<th>PK data</th>
<th>Doses reported</th>
<th>Formulation(s) reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole (MBZ)</td>
<td>10 studies (9 RCTs(^{6,14}), 1 observational(^{15}); n=6856, age range 6 mos to 70 yrs) 2 studies included children &lt;3 years(^{8,9})</td>
<td>All studies, except Flohr et al. 2007(^{7}) showed treatment with MBZ to be effective</td>
<td>3 studies reported adverse events as an outcome.(^{6,8,9}) No serious adverse events reported. Main problems: nausea, abdominal distension and discomfort</td>
<td>No</td>
<td>200 mg tds; 500 mg od (most commonly used); 600 mg multiple doses</td>
<td>Tablet 500 mg chewable tablet No other information provided</td>
</tr>
<tr>
<td>Levamisole (LVM)</td>
<td>3 studies (2 RCTs(^{8,16}), 1 observational(^{17}); n=1633; age range 1 to 19 yrs) 2 studies included children &lt;4 yrs(^{16,17})</td>
<td>All studies showed efficacy based on reduction in egg counts. Albonico et al. 2003 showed LVM to have smaller effect on egg clearance compared to MBZ or MBZ+LVM</td>
<td>Adverse events occurring once in different patients (temperature rise, loose stools, convulsion) not reported to be directly related to LVM. No other adverse events reported</td>
<td>No</td>
<td>&lt;3 yrs 40 mg 3-9 yrs 60 mg &gt;9 yrs 80 mg</td>
<td>Tablet</td>
</tr>
<tr>
<td>Pyrantel (PYR)</td>
<td>4 studies (3 RCTs(^{11,12,20}), 1 observational study(^{14})) 3 included only children(^{12,14,20}) (n= 2074; age range 2 yrs to 10</td>
<td>Effective in treating ascaris lumbricoides Poor efficacy for treating hookworm</td>
<td>None of the studies provided any information about adverse events/safety</td>
<td>No</td>
<td>10 mg/kg/day 11 mg/kg/day 12.5 mg/kg/day 15-20 kg; 150 mg</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

Table 1 Summary of available evidence
<table>
<thead>
<tr>
<th>Drug Name(s)</th>
<th>Studies reporting data for children</th>
<th>Efficacy data</th>
<th>Safety data</th>
<th>PK data</th>
<th>Doses reported</th>
<th>Formulation(s) reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niclosamide</td>
<td>yrs 1 included adults and children(^{11}) (n=147; age range 3 yrs to 70 yrs)</td>
<td>infections</td>
<td></td>
<td></td>
<td>21-30 kg: 300 mg 31-40 kg: 450mg</td>
<td></td>
</tr>
<tr>
<td>Diethylcarbamazine  (DEC)</td>
<td>6 studies (3 RCTs(^{25,28,29}), 3 observational studies(^{30,31,33}); n= &gt;12000; age range 1 to 87 years</td>
<td>All studies showed efficacy with a reduction in mf and antiginaemia</td>
<td>Mild adverse events reported (nausea, vomiting, fever, headache). No cessation of treatment required</td>
<td>No</td>
<td>6 mg/kg</td>
<td>No information reported</td>
</tr>
<tr>
<td>Ivermectin (IVM)</td>
<td>7 studies (4 RCTs(^{24,26,27,29}); 1 comparative field trial(^{32}), 1 follow up study(^{32}), 1 safety study(^{35}); n= age range 3 yrs to 87 yrs; 2 studies included children &lt;4 yrs(^{29,32})</td>
<td>IVM treatment alone had lower mf clearance rates than combination therapy (IVM + albendazole)</td>
<td>No serious adverse events reported. Most frequently reported side effects: headache, swellings, arthralgia and fever</td>
<td>No</td>
<td>Dose ranged from 150 mcg/kg to 400 mcg/kg</td>
<td>3 mg tablets</td>
</tr>
<tr>
<td>Praziquantel (PZQ)</td>
<td>13 studies (8 RCTs(^{39-46}), 1 safety pilot study(^{48}), 1 observational study(^{51}), 1 clinical efficacy trial(^{49,50})</td>
<td>Efficacy against S. haematobium (cure rate of 88.5%; egg reduction rate 98.2%)</td>
<td>7 studies reported adverse events as an outcome(^{40-43,46,47,49}). Generally side effects were mild and transient</td>
<td>No</td>
<td>20 mg/kg single oral dose 20 mg/kg 2 oral doses 20 mg/kg 3 oral doses</td>
<td>200 mg tablet</td>
</tr>
<tr>
<td>Drug Name (s)</td>
<td>Studies reporting data for children</td>
<td>Efficacy data</td>
<td>Safety data</td>
<td>PK data</td>
<td>Doses reported</td>
<td>Formulation(s) reported</td>
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<tr>
<td>----------------------------------</td>
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</tr>
<tr>
<td></td>
<td>8 studies included only children[^39,41,44-46,49-51] (n = 5181; age range 4 yrs to 18 yrs)</td>
<td>PZA more efficacious than Niridazole, Metrifonate and placebo with ascorbic acid</td>
<td>(dizziness, headache, abdominal pain, vomiting, diarrhoea). No cessation of treatment required</td>
<td></td>
<td>40 mg/kg single dose 60 mg/kg split dose 3 hrs apart</td>
<td>Tablet 600mg (crushed and mixed with orange juice for younger children unable to swallow tablets; required dosage was broken into smaller pieces or crushed using mortar and pestle. A honey based solution was added to make a suspension for some of the children )</td>
</tr>
<tr>
<td></td>
<td>5 studies included adults and children[^40,42,43,47,48] (n= 5710; age range 7 yrs to 60 yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Praziquantel (PZQ)</td>
<td>5 observational studies 4 studies included pre-school age children[^96-101] (n= 1748; age range 1 mth to 6 yrs) 1 study included primary school children[^97] (n= 5700 age range 6 yrs to 12 yrs).</td>
<td>All studies showed efficacy of PZQ tablets and PZQ syrup with reduction in egg counts in consecutive stool/urine samples. Although, efficacy of PZQ tablets shown to be greater than efficacy of PZQ syrup. PZA treatment resulted in significant reduction in overall infection prevalence (29.5%)</td>
<td>All studies reported adverse events as an outcome. In general, PZA tablets and/or syrup were well tolerated, with mild, transient side effects. Reported side effects: fatigue, dizziness, drowsiness, headache, loss of appetite and stomach ache. 1 study showed symptoms were significantly higher among uninfected children compared</td>
<td>No</td>
<td>40 mg/kg 1-3 yrs: 518 mg; 1 tablet &gt;3-5 yrs: 740 mg; 1(\frac{1}{2}) tablet &gt;5-6yrs: 977 mg; 1(\frac{2}{3}) tablet</td>
<td></td>
</tr>
<tr>
<td>Drug Name (s)</td>
<td>Studies reporting data for children</td>
<td>Efficacy data</td>
<td>Safety data</td>
<td>PK data</td>
<td>Doses reported</td>
<td>Formulation(s) reported</td>
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</tr>
</tbody>
</table>
| Oxfendazole   | 9 studies (4 RCTs\(^{52-54,58,59}\), 4 clinical efficacy trials\(^{55-57,59}\), 1 follow up study\(^{60}\))
4 studies only included children\(^{52,53,57,58}\) (n=510; age range 2 yrs to 16 yrs)
5 studies included adults and children\(^{53,54,56,59,60}\) (n > 1261; age range 2 yrs to >20 yrs) | More effective at treating S. Mansoni infection than S. Haematobium
In children, lower doses, not as successful in achieving cure as same doses in adults. Higher doses associated with an increase in adverse events.
Better tolerated and more effective in adult groups | Adverse events generally mild and transient.
Dizziness, headache and drowsiness were the most commonly reported side effects. | No | 10 mg/kg bd for 1 day or 2 days
15 mg/kg single dose or bd for 1 day, 2 days or 8 days
20 mg/kg single oral dose or bd for 1 day or 3 days
800 mg/m\(^2\)/day in 2 divided doses (approx. 60 mg/kg)
Optimal dose for children reported to be 30 mg/kg over 2 days (Ayele et al 1986, n=162; age < 15 yrs) | Capsule Suspension |
| Triclabendazole | 3 studies (1 pilot study\(^{61}\), 1 community dose comparison study\(^{62}\); 1 case series\(^{63}\) | Cure rate with single dose 74.9%
Higher cure rate (93.9%) with 2 | No significant adverse events.
Good tolerability | No | 10 mg/kg od or bd | Oral
No other information reported |
<table>
<thead>
<tr>
<th>Drug Name(s)</th>
<th>Studies reporting data for children</th>
<th>Efficacy data</th>
<th>Safety data</th>
<th>PK data</th>
<th>Doses reported</th>
<th>Formulation(s) reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>5 studies (1 RCT; 1 prospective open label randomized trial; 1 survey of efficacy and adverse events; 2 comparative trials; n= age range 7 mos to 12 yrs). Only 1 study included children &lt;2 yrs.</td>
<td>All studies showed efficacy by parasitological assessment of stool samples. Cure rates ranged from 80% to 97%</td>
<td>Adverse events mild, transient and did not require cessation of treatment. Reported side effects included: anorexia, nausea, vomiting, malaise and metallic taste</td>
<td>4 studies. Preterm and term infants have a lower total body clearance and prolonged half-life, whereas children over 4 have PK parameters similar to adults. Dose should be decreased in malnourished children.</td>
<td>15 mg/kg in 3 divided doses for 7 days 20 mg/kg/day for 5 days 30 mg/kg bd for 7 days</td>
<td>Oral route of administration. No other information provided</td>
</tr>
<tr>
<td>Diloxanide</td>
<td>2 studies (1 comparative trial; n= 39; age range 7 mos to 10 yrs; 1 retrospective study) n= 4371 treatment courses</td>
<td>Unable to determine efficacy data from information reported in comparative trial</td>
<td>Most commonly reported side effect: flatulence. Fewer adverse events reported in those aged 20 mos to 10</td>
<td>No</td>
<td>25 mg/kg od for 10 days</td>
<td>Oral. No other information provided</td>
</tr>
<tr>
<td>Drug Name (s)</td>
<td>Studies reporting data for children</td>
<td>Efficacy data</td>
<td>Safety data</td>
<td>PK data</td>
<td>Doses reported</td>
<td>Formulation(s) reported</td>
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</tr>
<tr>
<td>Pentamidine</td>
<td>3 studies (1 clinical study\textsuperscript{66}, 1 phase II clinical trial\textsuperscript{97}, 1 retrospective study\textsuperscript{88}; n = 3133; age range 0 to &gt; 15yrs)</td>
<td>Not reported</td>
<td>No serious adverse events reported</td>
<td>No</td>
<td>4 mg/kg i.m once daily for 7 days</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>Suramin</td>
<td>No</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Melarsoprol</td>
<td>4 studies (2 RCT\textsuperscript{82,84}, 1 phase II clinical trial\textsuperscript{87}, 1 retrospective analysis\textsuperscript{88}; n = 3035; age range 0 to 62 yrs. All the studies included both adults and children) melarsoprol + eflornithine not as effective as nifurtimox + eflornithine (cure rates 44% vs. 94% respectively)</td>
<td>Significantly toxic. Some deaths attributable to complications of treatment. Poorly tolerated by all age groups. Very young (&lt;2 yrs) more prone to jaundice and rash than adults. Lower incidence of encephalopathic syndrome in PSAC, but higher mortality rate in those that did develop it</td>
<td>No</td>
<td>Over 26 days: 3 series of 4 daily i.v infusions starting at 1.2 mg/kg, increasing to 3.6 mg/kg with a 7 day interval between series 1.8 mg/kg/d for 10 days 2.2 mg/kg/d for 10 days</td>
<td>Intravenous infusion</td>
<td></td>
</tr>
<tr>
<td>Eflornithine</td>
<td>5 studies (3 RCT\textsuperscript{82,83,85}, 1 retrospective study\textsuperscript{88}, 1 clinical) Eflornithine has equal efficacy to melarsoprol</td>
<td>Number of adverse events increased with longer duration of</td>
<td>No</td>
<td>100 mg/kg 6 hourly for either 7 or 14 days</td>
<td>Oral Intravenous infusion</td>
<td></td>
</tr>
<tr>
<td>Drug Name (s)</td>
<td>Studies reporting data for children</td>
<td>Efficacy data</td>
<td>Safety data</td>
<td>PK data</td>
<td>Doses reported</td>
<td>Formulation(s) reported</td>
</tr>
<tr>
<td>--------------</td>
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<td>--------------</td>
<td>-------------</td>
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<td>----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Benznidazole</td>
<td>7 studies (4 RCTs, 1 follow up study, 1 observational study, 1 control program study (MSF project); n= age range newborn to 18 yrs)</td>
<td>3 studies showed efficacy in comparison to placebo in children with indeterminate or early stage trypanosome cruzi</td>
<td>Minor adverse events (gastrointestinal disorders; rash). No deaths reported</td>
<td>No</td>
<td>2.5 mg/kg bd for 60 days 5 mg/kg/d 7.5 mg/kg/d oral daily for 30 or 60 days 7.5 mg/kg bd or tds for 60 days Maximum dose 300mg/d</td>
<td>Tablets 100 mg tablets ground up and capsules filled with 8, 10, 13 and 15 mg powder to treat neonates according to weight</td>
</tr>
<tr>
<td>Nifurtimox (N)</td>
<td>2 studies (2 RCTs; n&gt; 54; age range 5 yrs to 62 yrs). Not possible to extract paediatric specific data from either study</td>
<td>Only used in combination with eflornithine (E) or melarsoprol (M) N+E more effective than M+E (cure rates 94% vs. 44% respectively)</td>
<td>Combination of N+E well tolerated. Low fatality rate compared to melarsoprol (0.76% vs. 6%)</td>
<td>No</td>
<td>15 mg/kg/d 8 hourly for 10 days 20 mg/kg/d 8 hourly for 10 days</td>
<td>Oral</td>
</tr>
</tbody>
</table>
Abbreviations used in table: RCT = randomized controlled trial; mos = months; yrs = years; tds = 3 time daily; od = once daily; bd = twice daily; mf = microfilarial load; d = day
### Appendix B: Details of search strategy

<table>
<thead>
<tr>
<th>Search Set</th>
<th>PubMed</th>
<th>EMBASE*</th>
<th>RSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Helminth*; AND/OR helminth; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
<td>Helminth*; AND/OR helminth; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
<td>Helminth*; AND/OR helminth; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
</tr>
<tr>
<td>2</td>
<td>Mebendazole*; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
<td>Mebendazole*; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
<td>Mebendazole*; AND/OR children/PSAC/Paediatrics; AND/OR safety and efficacy; pharmacokinetics/dynamics; all alone and in combination; individual helminth species used in search as well</td>
</tr>
<tr>
<td>3</td>
<td>Levamisole*; and all of the above search strategies used</td>
<td>Levamisole*; and all of the above search strategies used</td>
<td>Levamisole*; and all of the above search strategies used</td>
</tr>
<tr>
<td>4</td>
<td>Pyrantel*; and all of the above search strategies used</td>
<td>Pyrantel*; and all of the above search strategies used</td>
<td>Pyrantel*; and all of the above search strategies used</td>
</tr>
<tr>
<td>5</td>
<td>Niclosamide*; all of the above search strategies used</td>
<td>Niclosamide*; all of the above search strategies used</td>
<td>Niclosamide*; all of the above search strategies used</td>
</tr>
<tr>
<td>6</td>
<td>Praziquantel*; all of the above search strategies used; combination and single searches with schistosomiasis (different schistosome species)</td>
<td>Praziquantel*; all of the above search strategies used; combination and single searches with schistosomiasis (different schistosome species)</td>
<td>Praziquantel*; all of the above search strategies used; combination and single searches with schistosomiasis (different schistosome species)</td>
</tr>
<tr>
<td>7</td>
<td>Triclabendazole*; all of the above search categories used for PZQ</td>
<td>Triclabendazole*; all of the above search categories used for PZQ</td>
<td>Triclabendazole*; all of the above search categories used for PZQ</td>
</tr>
<tr>
<td>8</td>
<td>Oxamniquine*; all of the above search categories used for 7&amp;8</td>
<td>Oxamniquine*; all of the above search categories used for 7&amp;8</td>
<td>Oxamniquine*; all of the above search categories used for 7&amp;8</td>
</tr>
<tr>
<td>9</td>
<td>Ivermectin*; AND/OR children/PSAC; AND/OR filariasis (including individual searches for each species); lymphatic filariasis*; AND/OR onchocerciasis*; AND/OR Loasis*; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Ivermectin*; AND/OR children/PSAC; AND/OR filariasis (including individual searches for each species); lymphatic filariasis*; AND/OR onchocerciasis*; AND/OR Loasis*; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Ivermectin*; AND/OR children/PSAC; AND/OR filariasis (including individual searches for each species); lymphatic filariasis*; AND/OR onchocerciasis*; AND/OR Loasis*; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
</tr>
<tr>
<td>10</td>
<td>Diethylcarbamazine*; all of the search categories above used as <em>Onchoerca Volvulus</em></td>
<td>Diethylcarbamazine*; all of the search categories above used as <em>Onchoerca Volvulus</em></td>
<td>Diethylcarbamazine*; all of the search categories above used as <em>Onchoerca Volvulus</em></td>
</tr>
<tr>
<td>11</td>
<td>Diloxanide*; AND/OR children/PSAC; AND/OR amoebiasis; AND/OR entamoeba histolytica; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Diloxanide*; AND/OR children/PSAC; AND/OR amoebiasis; AND/OR entamoeba histolytica; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Diloxanide*; AND/OR children/PSAC; AND/OR amoebiasis; AND/OR entamoeba histolytica; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
</tr>
<tr>
<td>12</td>
<td>Metronidazole*; AND/OR children/PSAC; AND/OR neonates; AND/OR giardiasis; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Metronidazole*; AND/OR children/PSAC; AND/OR neonates; AND/OR giardiasis; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
<td>Metronidazole*; AND/OR children/PSAC; AND/OR neonates; AND/OR giardiasis; AND/OR safety and efficacy; AND/OR pharmacokinetics/pharmacodynamics</td>
</tr>
<tr>
<td>13</td>
<td>Pentamidine *; AND/OR T.b. gambiense; AND/OR sleeping sickness; AND/OR Human African Trypanosomiasis; AND/OR children/PSAC; AND/OR pharmacokinetics/dynamics; AND/OR safety and efficacy</td>
<td>Pentamidine *; AND/OR T.b. gambiense; AND/OR sleeping sickness; AND/OR Human African Trypanosomiasis; AND/OR children/PSAC; AND/OR pharmacokinetics/dynamics; AND/OR safety and efficacy</td>
<td>Pentamidine *; AND/OR T.b. gambiense; AND/OR sleeping sickness; AND/OR Human African Trypanosomiasis; AND/OR children/PSAC; AND/OR pharmacokinetics/dynamics; AND/OR safety and efficacy</td>
</tr>
</tbody>
</table>
With EMBASE and Pub Med the appropriate search terms were determined for input by first searching for the MeSH terms on Pub Med or for the appropriate subject heading and explosion on EMBASE.

The following search term was used in Pub Med when searching for children AND the drug of interest:

**PubMed**


**EMBASE**

c'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR 'childhood' OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pedia* OR paedi* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*
Appendix C: Flow diagrams for search results
Mebendazole Search Results

Records identified through database searching
n=706

Records after duplicates removed
N=204

Relevant records screened
N=57

Records excluded as not fitting inclusion criteria
N=46

Full text article assessed for eligibility
N=11

1 systematic review
9 RCT
1 prospective observational study
Records identified through database searching
n=175

Records after duplicates removed
N=75

Relevant records screened
N=12

Records excluded as not fitting inclusion criteria
N=6

Full text article assessed for eligibility
N=6

Full text article excluded as not part of inclusion criteria or relating to different disease process
N=2

1 systematic review
2 RCT
1 observational study
Pyranterl search results

Records identified through database searching
N=134

Records after duplicates removed
N=101

Relevant records screened

Records excluded as not fitting inclusion criteria
N=48

Full text article assessed for eligibility
N=5

1 systematic review
3 RCTs
1 observational study
Niclosamide search results

Records identified through database searching
N=29

Records after duplicates removed
N=12

Relevant records screened
N=12

Records excluded as not fitting inclusion criteria
N=12

No study found to fit inclusion criteria
Praziquantel search results

Records identified through database searching
N=452

Records after duplicates removed
N=140

Relevant records screened
N=140

Records excluded as not fitting inclusion criteria
N=107

Full text article assessed for eligibility
N=33

Records excluded as not fitting inclusion criteria
N=18

2 systematic reviews
8 RCT
1 RCT (randomization method not described)
2 clinical trials of efficacy
1 interventional longitudinal study
1 safety study (pilot study)
Triclabendazole search results

Records identified through database searching
N=26

Records after duplicates removed
N=21

Relevant records screened
N=14

Records excluded as not fitting inclusion criteria
N=7

Full text article assessed for eligibility
N=7

Records excluded as not fitting inclusion criteria
N=4

1 pilot study
1 community dose comparison study
1 case series
Oxamniquine search results

Records identified through database searching
N= 69

Records after duplicates removed
N= 48

Relevant records screened
N=22

Records excluded as not fitting inclusion criteria
N=9

Full text article assessed for eligibility
N=13

Records excluded as not fitting inclusion criteria
N=3

1 systematic review
4 RCTs
4 efficacy trials
1 follow up study
Ivermectin search results

Records identified through database searching
N=82

Records after duplicates removed
N=14

Relevant records screened
N= 14

Records excluded as not fitting inclusion criteria
N=3

Full text article assessed for eligibility
N=11

Full text article excluded as not part of inclusion criteria or relating to different disease process
N=4

4 RCTs
3 observational studies
Diethylcarbamazine search results

Records identified through database searching
N=208

Records after duplicates removed
N=126

Relevant records screened
N=86

Records excluded as not fitting inclusion criteria
N=63

Full text article assessed for eligibility
N=23

Full text article excluded as not part of inclusion criteria
N=17

3 RCTs
3 observational studies
Metronidazole search results

Records identified through database searching
N= 1556

Records after duplicates removed
N=700

Relevant records screened
N=350

Records excluded as not fitting inclusion criteria
N=318

Full text article assessed for eligibility
N=32

Full text article excluded as not part of inclusion criteria
N=22

1 systematic review
1 RCT
2 comparative clinical efficacy studies
1 survey of efficacy/adverse events
4 PK studies
1 prospective open label randomized trial
Diloxanide studies reviewed

Records identified through database searching
N= 11

Records after duplicates removed
N=6

Relevant records screened
N=6

Records excluded as not fitting inclusion criteria
N=4

1 comparative study
1 retrospective analysis
Pentamidine studies reviewed

Records identified through database searching
N=33

Records after duplicates removed
N=29

Relevant records screened
N=11

Records excluded as not fitting inclusion criteria
N=6

Full text article assessed for eligibility
N=5

Full text article excluded as not part of inclusion criteria
N=2

1 clinical study
1 phase ii clinical trial
1 retrospective analysis
Suramin studies reviewed

Records identified through database searching
N=30

Relevant records screened
N=11

Full text article assessed for eligibility
N=1

No paediatric studies identified
Melarsoprol studies reviewed

Records identified through database searching
N=23

Records after duplicates removed
N=17

Relevant records screened
N=11

Records excluded as not fitting inclusion criteria
N=4

Full text article assessed for eligibility
N=7

Full text article excluded as not part of inclusion criteria
N=3

2 RCT
1 clinical trial (phase II)
1 retrospective analysis
Eflornithine studies reviewed

Records identified through database searching
N=47

Records after duplicates removed
N=39

Relevant records screened
N=19

Records excluded as not fitting inclusion criteria
N=9

Full text article assessed for eligibility
N=10

Full text article excluded as not part of inclusion criteria
N=5

3 RCTs
1 retrospective analysis
1 open label trial
Benznidazole studies reviewed

Records identified through database searching
N= 36

Records after duplicates removed
N=32

Records screened
N=28

Records excluded as not fitting inclusion criteria
N=17

Full text article assessed for eligibility
N=11

Full text article excluded as not part of inclusion criteria
N=4

4 RCT
1 follow up study
1 observational study
1 control program study (MSF project)
Nifurtimox studies reviewed

Records identified through database searching
N=32

Records after duplicates removed
N=30

Records screened
N=9

Records excluded as not fitting inclusion criteria
N=9

No paediatric studies identified