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One hundred years of neglect in paediatric schistosomiasis

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SUMMARY

Early in the history of schistosomiasis research, children under five years of age were known to be infected. Although this problem was recognized over one hundred years ago, insufficient action has been taken to address this issue. Under current policy, such infected children only receive their first antiparasitic treatment (praziquantel-PZQ) upon entry into primary school as current mass drug administration (MDA) programmes typically target school-aged children. For many infected children, they will wait up to 6 years before receiving their first medication and significant schistosomiasis-related morbidity may have already established. This inequity would not be accepted for other diseases. To unveil some of the reasons behind this neglect, it is paramount to understand the intricate historical relationship between schistosomiasis and British Imperial medicine, to undertint its lasting influence on today's public health priorities. This review presents a perspective on the historical neglect of paediatric schistosomiasis, focusing on important gaps that persist from the early days after discovery of this parasite. Looking to end this inequity, we address several issues that need to be overcome to move forward towards the lasting success of schistosomiasis control and elimination efforts.

82 CHILDREN'S ROLE IN THE HISTORY OF SCHISTOSOMIASIS

83

84 As Farley has stated: "*Tropical medicine from 1898 to the 1970s was fundamentally*
85 *imperialistic in its basic assumptions, its methods, its goals and its priorities*" (Farley,
86 1991). He then elaborates on this point by stating that "*..the basic goal of tropical*
87 *medicine was to render the tropical world fit for white habitation and white investment*".
88 This period broadly overlaps the time of the discovery of the *Schistosoma* parasite and
89 the evolution in the biomedical community's understanding of the parasite's biology,
90 transmission, and disease manifestations (Fig.1). Robert T. Leiper, one of the most
91 prominent parasitologists of his time, detailed the African schistosome life cycle in
92 1916, enabling him to fulfill his mandate: to prevent the transmission of schistosomiasis
93 among British troops during World War I (Stothard *et al.*, 2016). He did so by promoting
94 activities to prevent contact with cercariae-infested waters. Although prevention
95 proved to be the most effective strategy for military troops, it was largely impracticable
96 for indigenous people whose lives depended on irrigation and farming along the Nile
97 Delta, and so could not be enforced.

98

99 In terms of the significance of disease in children, The British Colonial Office
100 recognized the inherent risks of raising children in tropical environments where, in
101 1893, schistosomiasis (*Bilharzia*) was known to be a common illness . British children
102 were advised to be sent home "*... or they will deteriorate physically and morally, grow up*
103 *slight, weedy, and delicate, with a general feebleness*" (Farley, 1991). This is one of the
104 first (indirect) descriptions of the disabling effects of schistosomiasis in children, albeit
105 European.

106

107 << Please insert Figure 1 here >>

108

109 There was a slow transition from the golden era of descriptive parasitology
110 (1850's-1920's), which had a particular interest in environmental practices for disease
111 control, toward disease-centered research, which enabled the discovery of effective
112 drugs. Nevertheless, human *Schistosoma*-related disease went without an available
113 treatment for over 50 years (Fig. 1). The species-specific description of
114 schistosomiasis-associated morbidity began early on, and necropsy studies primarily
115 contributed to this knowledge of chronic *Schistosoma* infection (Bustinduy, 2013) (Fig.

116 1). As a result, the most overt organ-level morbidities, such as hepatosplenomegaly,
117 peri-portal fibrosis, and subsequent portal hypertension with oesophageal varices, were
118 clearly linked to *S. mansoni* and *S. japonicum*. They thus became the primary focus of
119 population-based disease prevalence studies for intestinal forms of schistosomiasis.
120 Haematuria and renal tract pathology (bladder polyps, hydronephrosis and associations
121 to bladder cancer) were identified as complications of *S. haematobium* infection, and
122 these became the focus of efforts for prevention and control for this species (Bustinduy,
123 2013; Colley *et al.*, 2014). Unfortunately, it took over 100 years to recognize the more
124 widespread and disabling systemic morbidities of *Schistosoma* infection that affect the
125 youngest age groups (King & Dangerfield-Cha, 2008; Koukounari *et al.*, 2006;
126 Koukounari *et al.*, 2007; Mupfasoni *et al.*, 2009; Parraga *et al.*, 1996).

127

128 Michael Gelfand, a clinician stationed in Rhodesia (present day Zimbabwe) in the
129 early 1960's, was particularly influential in describing the morbidity of the disease in
130 children. In a detailed clinical description of intestinal schistosomiasis he reported:
131 "*This feature of tiredness stands out more in bilharziasis than in any other tropical*
132 *infestation. The lethargy of the child is often noticed by teachers, who sees him becoming*
133 *apathetic, falling behind in games and lacking enthusiasm.*" (Gelfand, 1967). At the time,
134 these careful clinical observations lacked metrics to accurately measure this 'fatigue'.
135 Moreover, there was no strategy to treat these children *en masse* (Farley, 1991). Much
136 later, the association between schistosomiasis and decreased physical fitness was
137 documented in Coastal Kenya among boys with urogenital schistosomiasis. This study,
138 although innovative, made use of the Harvard step-test, an instrument not validated for
139 children (Stephenson *et al.*, 1985b). Subsequent work in the same area has identified
140 the 20-meter shuttle run test as an accurate and easy-to-implement field fitness test
141 with excellent correlations between child poly-parasitic status, anaemia and decreased
142 aerobic capacity in over 2,000 children (Bustinduy *et al.*, 2011).

143

144 Infection in very young children was particularly well described in clinical
145 accounts from Rhodesia. Up to half of children as young as 2 years old were documented
146 as having egg-patent infection in endemic villages, but in an era of very expensive
147 injectable drug therapy, treating them was not even considered (Fig. 2). Only overt

148 morbidity was eligible for treatment and this mostly occurred among older children and
149 adults (Gelfand, 1967).

150

151 << Please insert Figure 2 here >>

152

153 In textbooks and policy literature, school-age children have been characterized
154 as the main transmitters of *Schistosoma* infection due to their high egg output (peaking
155 in mid-childhood between 10-15 years old) and increased water contact. Owing to their
156 “careless” water use practices, which include frequent wading, playing, and urinating or
157 defecating in or near the water, the *Schistosoma* transmission cycle is greatly bolstered
158 (Mott *et al.*, 1985; Webbe, 1982). Because detectable *Schistosoma*-specific morbidity due
159 to advanced organ fibrosis is mostly seen in early adulthood, children were not
160 considered as seriously affected by their infection status (Gryseels, 1989). In addition,
161 risk for disease was erroneously believed to be related only to high-intensity infections.
162 (Gryseels, 1989; Warren *et al.*, 1979) Recent studies across *Schistosoma* species have
163 discredited this paradigm by demonstrating that light-intensity infections already have
164 tangible negative health effects (Bustinduy *et al.*, 2013; Ezeamama *et al.*, 2005b; King,
165 2015).

166 In the first wave of population-based morbidity surveys in the 1960s and 1970s,
167 many children were wrongly classified as ‘uninfected’ due to insensitive diagnostic
168 methods (i.e., eggs were not found in urine or stool), and they were termed
169 ‘asymptomatic’ when overt anatomic morbidity was absent. (Mott, 2004; Mott & Cline,
170 1980) More refined seroprevalence studies have now demonstrated that almost all
171 children from highly endemic areas are infected by the time they reach puberty (Colley
172 *et al.*, 2014). Sadly, this misclassification of infection status has confounded accurate
173 burden of disease estimates and has delayed recognition of *Schistosoma* infection as a
174 major cause of disease/disability burden in endemic countries. (King, 2010; King, 2015)
175 Novel diagnostic assays, the Circulating Cathodic Antigen (CCA) and the Circulating
176 Anodic Antigen (CAA), which are able to detect circulating *Schistosoma* antigens from as
177 little as one worm pair, are now revealing clinically significant worm burdens in
178 individuals who were previously thought to be ‘uninfected’ based on egg-count testing.
179 (Colley *et al.*, 2013; van Dam *et al.*, 2015)

180

181 THE FIRST NUTRITIONAL STUDIES

182 The first nutritional studies in the 1980s were seminal in the field of paediatric
183 schistosomiasis. Conducted in Coastal Kenya by Stephenson and Latham, they opened
184 the door to rigorous research in this area. Epidemiological correlations were made
185 between parasitic infections, including *S. haematobium*, and delayed growth
186 (Stephenson *et al.*, 1985a). Children showed dramatic improvements in appetite and
187 physical fitness after a single dose of metrifonate, an drug effective against *S.*
188 *haematobium* that was used in that era. (Latham *et al.*, 1990) Unfortunately, little had
189 changed in the same area of Kenya over the next 25 years, when further studies,
190 applying more accurate morbidity metrics, confirmed that decreased fitness and
191 undernutrition were still highly prevalent among children infected with *S.*
192 *haematobium*. (Bustinduy *et al.*, 2013; Bustinduy *et al.*, 2011).

193 Progress in this field has been slow but steady. Nutritional studies of the impact
194 of *S. japonicum* infection led by McGarvey and colleagues at Brown University in
195 collaboration with researchers in the Philippines and China, have highlighted the
196 relationship between *S. japonicum* infection and increased systemic inflammation
197 within the human body, which is associated with a negative impact on growth.
198 (McGarvey *et al.*, 1992; McGarvey *et al.*, 1996). Later studies have shown (partial)
199 reversibility of malnutrition after treatment, particularly among those children who are
200 clinically wasted at baseline. (Coutinho *et al.*, 2006a)

201

202 FUNCTIONAL MORBIDITIES AFFECTING GROWTH

203 Advances in the knowledge of host-parasite immune responses have revealed that
204 schistosomiasis is fundamentally a chronic inflammatory disease that affects the entire
205 body. This has led to much wider recognition of morbidities that are linked to the pro-
206 inflammatory state that precedes fibrosis (Coutinho *et al.*, 2006b; Leenstra *et al.*, 2006;
207 Wamachi *et al.*, 2004). These so-called 'subtle' morbidities perhaps should be better
208 termed 'functional' morbidities, as they impair normal physiological functioning of an
209 infected child. The impact of infection on growth hormone (GH)/insulin-like growth
210 factor-1 (IGF-1) pathways is anabolic to the skeleton, and other inflammatory cytokines
211 also compromise bone growth (Farquharson & Ahmed, 2013). Linear growth can be
212 severely impaired by any chronic inflammation, including inflammation caused by
213 schistosomiasis, and this, in turn, leads to childhood growth stunting. Associated

214 anaemia of inflammation caused by infection with all species of *Schistosoma* impairs
215 iron storage release and utilization (Ezeamama *et al.*, 2005b; Koukounari *et al.*, 2006)
216 and this complication most readily manifests itself as decreased physical fitness
217 (Bustinduy *et al.*, 2011; Friedman *et al.*, 2005; Stephenson *et al.*, 1985b), poor
218 concentration, and diminished school performance (Ezeamama *et al.*, 2005a; Jukes *et al.*,
219 2002; Nokes *et al.*, 1999). If untreated, these manifestations become irreversible with
220 significant lifetime consequences: decreased work productivity as adults, altered
221 fertility in both men and women (Kjetland *et al.*, 2012) and decreased quality of life.
222 (Terer *et al.*, 2013) The misfortune behind the failure to recognize such ‘functional’
223 morbidities is that, because they are confounded by other co-endemic diseases,
224 particularly malaria, they are often not adequately recognized as schistosomiasis-
225 related manifestations.

226

227 There is a ‘magic window’ of opportunity to treat children who have suffered a
228 growth arrest. This is the ‘catch up’ growth period, when a child can accelerate growth
229 to achieve normal weight and height after an acute health insult, such as
230 schistosomiasis. (Gurarie *et al.*, 2011) This window closes when the growth plates fuse,
231 and therefore early intervention is essential to achieve normal height. (Fig. 3)

232

233 << Please insert Figure 3 here >>

234

235 ASSOCIATED DISABILITY IN CHILDREN

236 Why has the negative impact of paediatric schistosomiasis been undervalued? Part of
237 what makes schistosomiasis a ‘neglected’ disease (i.e., counted among the NTDs) is that
238 its perceived importance to health has been linked to its disability-adjusted life-year
239 (DALY) ranking in the WHO-World Bank Global Burden of Disease (GBD) system. In its
240 first iteration, the GBD program intentionally weighted disease impact by age, giving
241 much greater emphasis to diseases that affect 20-30 year olds, and much less to
242 diseases of children under five (Murray CJ, 1996). While this error has been corrected in
243 more recent GBD versions (Salomon *et al.*, 2012; Vos *et al.*, 2012) schistosomiasis has
244 always been assigned the health impact associated with ‘minor infections’ and given a
245 negligible 0.004-0.005 disability weight. Thus, although there are more than 250 million
246 persons with active (egg-positive) cases, and likely an equivalent number of people with

247 'egg-negative' *Schistosoma*-related disease, the calculated worldwide DALY impact of
248 schistosomiasis is perceived as less than one-tenth of that attributed to other, more
249 lethal diseases of childhood. In the eyes of many donors and policymakers, this lowers
250 its priority for control and prevention.

251

252 To correctly assess the disease burden of *Schistosoma* infection it is important to
253 recognize the lifetime *cumulative* impact of infection, not just in terms of individual
254 organ pathology and dysfunction, but also on the overall whole-body performance of
255 the growing child and young adult. Schistosomiasis that causes chronic anemia, growth
256 faltering, and poor cognitive performance is quite disabling in a setting where resources
257 are limited, and accommodation for disabilities is inadequate. Disease impact does not
258 end when *Schistosoma* infection ends, and the associated loss of schooling and/or
259 reduced growth cannot be reversed by childhood treatments if rapid reinfection is likely
260 where a child lives, plays, and works. Similarly, these losses cannot be reversed once a
261 person reaches adulthood. Once the child passes school age, most of these functional
262 pathologies become irreversible.

263

264 EARLY YEARS (< 5 YEARS OF AGE)

265 The institutional apathy regarding treatment of schistosomiasis in children under six is
266 in stark contrast to the recommendations for treatment of preschool children infected
267 with soil-transmitted helminths, a practice that has been at the forefront of paediatric
268 care and treatment campaigns for many years (World Health Organisation, 2007).
269 Children under five years of age are often daily exposed to infected water very early in
270 life, and although initial infection occurs 'silently', it generates inflammation that
271 predisposes to organ fibrosis, which will then endure for decades (Colley *et al.*, 2014)
272 **Fig 4.** This lack of recognition dates back to early WHO reports on schistosomiasis, in
273 which disease among very young children was described, but then appears to have been
274 forgotten in subsequent formulation of action plans (Mott, 1982). The justification for
275 this health policy gap was two-fold; firstly, young children were considered a lightly-
276 infected population and therefore thought to be at low-risk for schistosomiasis-
277 associated morbidity; secondly, there was no child-friendly formulation for oral
278 treatment that would decrease the risk of choking. Crushing tablets to treat younger
279 children was not considered practical for national programmes, although this approach

280 is widely performed for pill treatment of other diseases such as tuberculosis (Pineiro
281 Perez *et al.*, 2016). In essence, the under-fives weren't seriously considered at risk and
282 they were deemed too difficult and unsafe to treat, so they were excluded. It wasn't until
283 2010 that the first expert meeting on the inclusion of preschool children in
284 schistosomiasis control efforts was convened at the World Health Organisation (WHO).
285 (World Health Organization., 2011)

286

287 << Please insert Figure 4 here >>

288

289 From a modern perspective, stronger evidence is emerging that very young
290 preschool children do indeed harbor egg-patent infection. (Bosompem *et al.*, 2004;
291 Odogwu *et al.*, 2006; Sousa-Figueiredo *et al.*, 2008; Verani *et al.*, 2011) and also present
292 with early fibrosis, including hepatosplenic disease due to *S. mansoni* and early bladder
293 changes due to *S. haematobium* (**Fig 5**). Detection of these early fibrotic changes
294 however, may prove challenging.

295

296 A recent study in Gabon, piloting a novel protocol for clinical bedside '*Focused*
297 *Assessment with Sonography in Urogenital Schistosomiasis*' (FASUS), showed a 41%
298 prevalence of ultrasound detectable urinary tract morbidity in under-fives in a *S.*
299 *haematobium* endemic area (Jonathan Remppis *et al.*, manuscript in preparation). This
300 protocol was derived from the WHO's Niamey ultrasound protocol, widely used in
301 prevalence studies, but not validated as a clinical tool for morbidity assessment in
302 individual patients presenting with symptoms of *S. haematobium* infection. With the
303 increasing availability of low-cost ultrasound in endemic areas, this approach could
304 provide a point-of-care morbidity detection tool that could allow better definition of the
305 risk of early childhood pathology. (Belard *et al.*, 2016; Richter *et al.*, 2016)

306

307 << Please insert Figure 5 here >>

308

309 THE EVOLUTION OF ANTI-SCHISTOSOMAL TREATMENT

310 The first injectable anti-schistosomal treatment, potassium antimony tartrate, or tartar
311 emetic (TE), which contained trivalent antimony, was introduced in 1918 as a drug
312 initially used to treat visceral leishmaniasis. (Christopherson, 1924) (**Figure 1**)

313 Although promising at first, it had very limited efficacy and severe side effects (Jordan,
314 2000). Other drugs followed, including hycanthone, and oral niridazole each with
315 severe side effects and difficulties in administration. **Table 1** summarizes the different
316 anti-schistosomal treatments through time.

317

318 <<Please insert Table 1 here>>

319

320 Since 1984, praziquantel (PZQ), the current drug of choice, has displaced older drugs of
321 lesser effectiveness for all types of schistosomiasis. (Doenhoff *et al.*, 2008; King *et al.*,
322 1988; King & Mahmoud, 1989) Its full mechanism of action remains unclear, but it is
323 thought to act on the calcium ion channels of schistosome's tegument leading to
324 disruption of the parasite's surface, and exposing it to lethal damage by the host's
325 immune system (Doenhoff *et al.*, 2008). Adult dose finding studies in the 1970's and
326 1980's concluded that a single PZQ dose of 40 mg/kg was effective for treating *S.*
327 *haematobium* and *S. mansoni* (Davis *et al.*, 1979; Davis & Wegner, 1979; King *et al.*,
328 2002). However, in highly-endemic areas, a more intense, repeated dosing approach is
329 likely needed for optimal effect, particularly for *S. mansoni* (King *et al.*, 2011).

330

331 Since its introduction in the 1980s, praziquantel has been used safely in children.
332 However, their recommended dosages were directly extrapolated from
333 pharmacokinetic studies performed in adults (Kabatereine *et al.*, 2007; Mutapi *et al.*,
334 2011; Xiao, 2005). Work in Uganda in 2010 revealed sub-optimal PZQ cure rates for *S.*
335 *mansoni* among preschool children (Sousa-Figueiredo *et al.*, 2010). To explore the
336 appropriateness of age-adjusted dosing, the first pharmacokinetic/pharmacodynamic
337 PZQ study in children in Uganda was conducted in that same area. Results from this
338 recent study showed a very concerning risk of underdosing of children, particularly the
339 younger ones, if standard 40 mg/kg was given. Higher doses may be needed for treating
340 these and other children infected with *S. mansoni*. (Bustinduy *et al.*, 2016a)

341

342 << Please insert Figure 6 here>>

343

344

345

346 EXPANDING ACCESS TO PZQ FOR PRESCHOOL CHILDREN

347 In response to the recommendations from the WHO expert consultation in 2011, (World
348 Health Organization., 2011) an international, non-profit, public-private partnership,
349 called the Praziquantel Consortium has been formed
350 (www.paediatricpraziquantelconsortium.org). Its primary objective is to develop,
351 register, and provide access to a new and more palatable paediatric (orodispersible)
352 formulation of PZQ that can be used to treat young children, including infants and
353 toddlers under the age of 6 years. More importantly, data on the treatment of very
354 young children has been sparse and insufficient to define and confirm the best dosing
355 regimens for young children. These factors mandated the need for the Paediatric PZQ
356 Formulation Program to go through a full clinical drug development pathway. Currently,
357 a Phase 2 study is being conducted in infected preschool children in Ivory Coast. To
358 complement the product development aspects of the program, the consortium has also
359 started to explore means to provide access to the new paediatric treatment as soon as it
360 is marketed. (Bustinduy *et al.*, 2016b)

361

362 THE DOUBLE TREATMENT GAP IN MDA PROGRAMMES

363 The success of schistosomiasis control programmes has been very uneven over the last
364 century. Efficacy has varied largely depending on the baseline prevalence of infection.
365 (Jordan, 2000; Wang *et al.*, 2008). Success stories in Japan, Morocco, (Amarir *et al.*,
366 2011) Iran, and Tunisia give hope to less developed countries that are confronted by the
367 'trap' of self-perpetuating, disease-related poverty (Sacks, 2005). Economically
368 disadvantaged countries are only just now starting to prioritize NTD control (Savioli *et*
369 *al.*, 2009). To date, implementation of large-scale control efforts in highly endemic areas
370 has not shown permanent success, likely due to ecological factors favoring transmission
371 and human reinfection. Part of the unfortunate lack of success of many control efforts
372 stems from the complex reality of a disease that involves social interactions in hot spots
373 of high transmission. Campaigns frequently miss 'super-spreaders'- children and
374 individuals highly infected who act as reservoirs (King, 2009). The risk of reinfection or
375 're-worming' in high-transmission villages in Kenya was found to be as high as 50 %
376 over two years despite ongoing school-based MDA (Satayathum *et al.*, 2006). Even more
377 disheartening was the return to high prevalence in the same areas after control efforts
378 were interrupted for 8 years. (Wang *et al.*, 2012) Older control interventions, based on

379 better access to clean water and the use of molluscicides, may still have important
380 adjuvant roles to play as part of adaptive strategies in implementing more effective
381 schistosomiasis control programs. (Fenwick *et al.*, 2009; Garba *et al.*, 2009)

382

383 The WHO estimates that in the 52 countries in need of schistosomiasis control,
384 over 123 million of school-age children need preventive chemotherapy, out of which
385 only 43 million school age children (34.6 %) may actually receive it. (World Health
386 Organization., 2016) Therefore, there is a large treatment gap remaining among this age
387 group. Because current control strategies primarily target children who attend school,
388 those remaining at home, often with more severe disease, don't necessarily receive
389 treatment from MDA. A vicious cycle of heavier infection and more severe morbidity
390 ensues (Stothard, 2013; Stothard *et al.*, 2011). This double treatment gap (preschool
391 children and absent school age children) is a health inequality that should be a priority
392 in control program planning and implementation. Ambitious goals set by the WHO 2012
393 roadmap (Stothard *et al.*, 2014; World Health Organization., 2012) have increased
394 funding and raised the profile of schistosomiasis *control*, but this leaves a long road
395 ahead for true *elimination*.

396

397 CONCLUSIONS

398 While there has not been a failure to recognize early childhood *Schistosoma*-related
399 disease, treatment strategies have not been focused on this phase of infection and its
400 spectrum of disease. It is time for this to change. While MDA continues to lower
401 *Schistosoma* prevalence, the residual morbidity is significant and persistent low-level
402 worm burdens hinder the plans for elimination in many endemic areas. A more
403 comprehensive integrated management of schistosomiasis, including effective MDA of
404 both preschool and school age children, needs to be adopted as a better strategy for
405 control.

406

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878 **Table 1:** Different anti-schistosomal treatments through time.

Drug	Active for Species	Route of administration	Main Side effects	Severe Complications	Ref.
Tartar emetic (TE)	<i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Intravenous	<ul style="list-style-type: none"> • Nausea • Vomiting • Muscle, joint pain • T-wave inversion 	<ul style="list-style-type: none"> • Encephalopathy • Collapse • Rash • Hepatitis C 	(Christopherson, 1918; Davis, 1968; Frank <i>et al.</i> , 2000)
Lucanthone (Miracil D®)	<i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Oral	<ul style="list-style-type: none"> • Nausea • Vomiting • Anxiety 	<ul style="list-style-type: none"> • Lethargy 	(Blair <i>et al.</i> , 1949; Lees, 1966; Newsome & Halawani, 1950)
Hycanthione	<i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Intramuscular	<ul style="list-style-type: none"> • Nausea • Vomiting 	<ul style="list-style-type: none"> • Malignancy 	(Cook <i>et al.</i> , 1977; Moore, 1972; Warren <i>et al.</i> , 1978)
Niridazole (Ambilhar®)	<i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Oral	<ul style="list-style-type: none"> • Nausea • Vomiting • Headache • Vivid dreams • Acute confusion 	<ul style="list-style-type: none"> • Seizures • Malignancy • Death 	(Davis, 1966; Nicholson & McMahon, 1966)
Metrifonate	<i>S. haematobium</i>	Oral	<ul style="list-style-type: none"> • Nausea • Vomiting 	<ul style="list-style-type: none"> • Bronchospasm • Bradycardia • Ataxia • Respiratory paralysis 	(King <i>et al.</i> , 1988; King <i>et al.</i> , 1990)
Oxamniquine	<i>S. mansoni</i>	Oral	<ul style="list-style-type: none"> • Nausea • Vomiting • Dizziness • Drowsiness • Eosinophilia 	<ul style="list-style-type: none"> • Seizures • Hallucinations 	(da Silva <i>et al.</i> , 1975; Ferrari <i>et al.</i> , 2003)

Praziquantel	<i>S. mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i>	Oral	<ul style="list-style-type: none"> • Nausea • Vomiting • Abdominal pain • Headache • Dizziness • Drowsiness 	• Lethargy	(Davis <i>et al.</i> , 1979; King <i>et al.</i> , 2002)
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