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Paediatric and Maternal Schistosomiasis: Shifting the Paradigms

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Abstract

Background: In endemic area, schistosomiasis causes both overt and subclinical disease in young children and their mothers, as well as in returned travellers.

Sources of data: Key recently published literature.

Areas of agreement: An action plan for paediatric schistosomiasis and female genital schistosomiasis (FGS) is needed with expanded access to praziquantel (PZQ) required.

Areas of controversy: Schistosomiasis-related morbidity is underappreciated. Present and future demand for PZQ treatment is bottlenecked, imbalanced and inequitable. Current dosing, treatment algorithms and access plans are sub-optimal with treatment stalled during pregnancy in antenatal clinics.

Growing points: Raised dosing of PZQ (> 40 mg/kg) is being explored in young children. Surveillance of female genital schistosomiasis (FGS) is increasing. Use of PZQ in pregnancy is safe and guidelines for preventive chemotherapy are being revised in morbidity- and transmission-control settings.

Areas timely for developing research: Shifting focus of population-level control to individual-case management. Detection and prevention of FGS integrating PZQ delivery in child and women health services and antenatal clinics. Feasibility studies assessing alternative and expanded access to PZQ treatment to at-risk children and mothers and pregnant women.

Key words: praziquantel, PZQ, preventive chemotherapy, MDA, female genital schistosomiasis, FGS, pregnancy, HIV.

Running head: Paediatric and maternal schistosomiasis

Word count: 3,883

37 **Introduction**

38 Schistosomiasis is a water-borne disabling parasitic disease responsible for over 3.3 million
39 disability adjusted life years (DALY) worldwide. ¹ This figure is underestimated and in process
40 of upward revision in more recent burden of disease studies. ² Over 700 million people are at-
41 risk of acquiring an infection with any of the most relevant *Schistosoma* species and these
42 giving rise to two major clinical syndromes: 1- Intestinal schistosomiasis, caused by *S.*
43 *mansoni* (South America and sub-Saharan Africa (SSA)) and *S. japonicum* (China,
44 Philippines), and 2- Urogenital schistosomiasis caused by *S. haematobium* (SSA). Of the
45 currently recognised neglected tropical diseases caused by parasitic helminths³,
46 schistosomiasis can be considered unique as being the sole water-borne parasite able to
47 infect humans by per-cutaneous transmission⁴. Acute schistosomiasis, most commonly
48 associated with *S. japonicum*, is an infrequent manifestation of the disease and is also known
49 as 'Katayama fever', clinically presenting as a serum-sickness like syndrome. ⁵ More common
50 chronic manifestation of all types of schistosomiasis result from egg-deposition in target
51 organs and subsequent fibrosis impairing normal function. Less specific but more widely seen
52 clinical characteristics are those derived from the pro-inflammatory response triggered by the
53 parasite. These affect mostly children that are infected as early as infancy,⁶ and include
54 anaemia of inflammation, impaired linear growth, decreased physical fitness and decreased
55 quality of life. ⁷ Disease recognition is often overlooked and underappreciated, particularly in
56 younger children with early stages of schistosomiasis, as clinical features are shared and
57 masked with other endemic diseases such as malaria. ⁴ Recognition of all disease stages by
58 low-level skilled health workers is currently lacking and represents a hurdle to increase
59 praziquantel (PZQ) treatment coverage beyond community-based control programmes, the
60 mainstay of schistosomiasis control. A recent schistosomiasis clinical staging algorithm to aid
61 diagnosis in low-resource settings has recently been published. ⁸

62 Without anthelmintic treatment with PZQ, adult schistosomes may live for decades
63 within the host.⁹ By contrast, juvenile worms are tolerant to PZQ making this drug an imperfect

64 treatment tool against acute infection, which is difficult to diagnose unequivocally even with
65 modern biomarkers of infection¹⁰. On the other hand, as schistosome worms increase in
66 number, pair and mature to lay eggs subsequently through time, the diagnostic patency of
67 chronic schistosomiasis becomes ever more apparent; as does the congruency of a variety of
68 serological, molecular or parasitology methods¹¹. Using a selection of these markers it is
69 possible to monitor the efficacy of PZQ treatment¹¹ for which there are WHO guidelines that
70 measure the proportional reduction of schistosome eggs in excreta before and after treatment.
71 On the whole, the performance of PZQ is adequate according to those WHO standard
72 measures of cure.¹² However, measures of drug efficacy are poorer in younger children¹³ and
73 across all ages in high prevalence and transmission environments¹⁴.

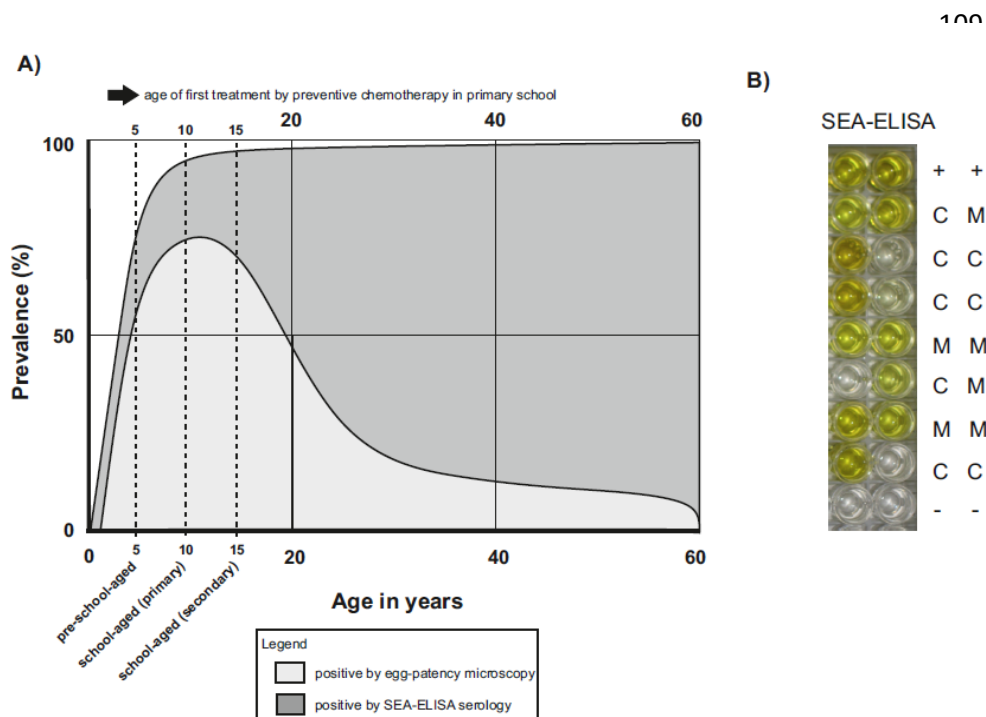
74 **Infected and overlooked**

75 *Children and mothers in the endemic setting*

76 The endemic transmission landscape of schistosomiasis is typically over-dispersed or focal
77 such that the disease can be very concentrated geographically around a given freshwater
78 habitat, while others nearby may experience no disease at all¹⁵. In such an area, e.g. a rural
79 village where there this schistosomiasis, the patency of infection varies by age and gender⁴.
80 Using traditional diagnostic methods based on egg-detection the most obvious infected group
81 are children, of either gender, in their late childhood and early adolescence⁴. This has been
82 the 'classic' view of the epidemiology of schistosomiasis in an endemic setting for many years
83 as shown in Figure 1A and discussed by Peter Jordan in this journal some 45 years ago¹⁶.
84 However since that time, a more extensive knowledge and appreciation of schistosomiasis
85 has been developed, now seen as a complex disease that may or may not coincide with
86 present egg-patent infection.² The traditional view based on egg-patency in the excreta gave
87 rise to the commonly held assumption that only heavy egg-patent infections were important
88 and those of light or moderate could be ignored¹⁷. This view is largely incorrect; if alternative
89 diagnostic methods are used such as serology or biomarkers, schistosomiasis is much more
90 pervasive in mothers and young children than previously thought¹⁸. Using a combination of

91 diagnostic assays has helped to better reveal the burden of disease in pre-school-aged
 92 children and their mothers¹⁹. But it's not only improved diagnostic accuracy for *Schistosoma*
 93 detection, morbidity detection methods have also been refined and thus schistosomiasis
 94 encompasses not only the chronic manifestations related to end-organ fibrosis (portal
 95 hypertension due to periportal fibrosis, bladder polyps and squamous cell carcinoma of the
 96 bladder), but it now includes more *functional* morbidities such as anaemia and arrested linear
 97 growth that are reversible only if treated early in childhood. The inputs used for the global
 98 Burden of Disease 2010 study underestimated the burden of the disability associated with
 99 *Schistosoma* infection.²⁰ These estimates did also not include late effects of the *functional*
 100 morbidities, of which growth stunting and cognitive impairment, infertility, dyspareunia and
 101 genital disease are now widely recognised as schistosomiasis-associated morbidities.
 102 Therefore the concept of an asymptomatic disease, historically describing children without
 103 overt clinical signs and symptoms, with no obvious chronic manifestations, can no longer be
 104 accepted.²

105 **Figure 1:** A schematic of (A) prevalence by age inferred by egg-count versus serology across
 106 an endemic population (i.e. in mothers and their children's) and (B) visual detection of
 107 antibodies to soluble eggs antigen (SEA) in mothers (M) and children (C) from lakeshore
 108 village on Lake Albert, Uganda. Positive (+) and negative (-) controls indicated.



112 There is an essential environmental transmission dynamic, as part of the schistosome
113 lifecycle, which is determined by the immediate presence of permissive freshwater snail hosts
114 and by unsafe water contact activities undertaken by the surrounding community, albeit from
115 local or visiting people. In principle, water contact can be broken down into two partially related
116 components, contamination- and exposure-related activities²¹. The transmission epidemiology
117 of schistosomiasis is intricately interwoven with the daily need for water as part of socio-
118 economic development and environmental hygiene. Until recently, as younger children are
119 often not directly seen in water, it was thought that their risk of infection was low and largely
120 in accordance with a low prevalence of egg-patent infection. However, this appraisal was
121 overturned as it is largely by passive water contact, such as *being* bathed in water collected
122 by the mother, often away from view within the homestead, that infants becomes first infected.
123 Such infections are best detected by serological methods. Figure 1B and data from novel
124 studies using global position system data suggest the levels of unsafe water contact of infants
125 and pre-school-aged children can be alarmingly high^{18, 22}. Furthermore, there is increasing
126 concern about the importance of maternal schistosomiasis²³ such that the disease should be
127 tackled simultaneously in both child and mother.

128 *Children and mothers within travel medicine*

129 Schistosomiasis is also a travel related disease for those that visit disease endemic locations
130 and knowingly or unknowingly undertake unsafe water contact activities. In the largest
131 returned traveller cohort published in the UK, the most common presenting symptom was
132 haematuria, related to urogenital schistosomiasis and almost half of the patients had
133 eosinophilia. ²⁴ A major difference in travel-related schistosomiasis is the age of the first
134 infection, typically in adults who have had little, if any, prior exposure to any helminthiasis.
135 This allows use of more general immunological markers of infection e.g. eosinophilia ²⁵.
136 Similarly, with a detailed travel history, the exact time and duration of most likely exposure can
137 be determined²⁶, setting aside these rather singular events of the traveller from the inevitable
138 daily routine of those that live in close proximity to unsafe water sources. The disease

139 spectrum that schistosomiasis also induces in travellers differs, typically with a greater number
140 of cerebrospinal complications, largely owing to ectopic egg laying sites, necessitating
141 advanced diagnostic imagery techniques and clinical management ²⁷.

142 It is interesting that significant disease can accrue in both young children and women
143 with relatively short durations of exposure and infection^{28, 29}. For example, there are numerous
144 case reports of maternal schistosomiasis³⁰ as well as individual cases where complications
145 have arisen from egg-based lesions within the Fallopian tubes ³⁰. Schistosomiasis within these
146 patients has been typically detected spuriously, for example, upon surgical encounter rather
147 than upon post-visit screening. In the UK, for example, there is no specific-screening
148 programme for schistosomiasis, and diagnostic tests are only requested when there is clinical
149 suspicion, however, awareness of the disease within general practice settings is typically low.
150 In addition, many of these travellers present with low-intensity infections, and current
151 diagnostics may be too insensitive for detection (egg counts in urine or stool). ²⁴ Serology can
152 not distinguish between acute or chronic infection, and cannot evaluate treatment efficacy due
153 to persistent IgG. New antigen diagnostic tests, the Circulating Anodic Antigen (CAA),
154 secreted across *Schistosoma* species is set to become a useful tool for low-level infections as
155 it can detect as little as one worm pair. ³¹

156 Pregnant travellers have seldom been reported in the literature. A recent retrospective
157 case series from Israel reported adverse foetal outcomes including low birth weight,
158 miscarriages and preterm labour, in pregnant women with schistosomiasis acquired during
159 travel that had not received PZQ at any given time after *Schistosoma* exposure compared to
160 those that had received PZQ during pregnancy and had normal birth outcomes. ²⁹

161 It is very plausible that many travellers returning to Europe will have schistosomiasis,
162 which will continue to go undetected until clinical manifestations develop. A good example is
163 the recent epidemic focus of urogenital schistosomiasis in Corsica that caught many general
164 practice surgeries by surprise³². The first case of urogenital schistosomiasis caused by
165 infection with *S. haematobium* in Corsica was observed in a 4-year old French child upon

166 presentation to Toulouse Hospital in March 2014 with a persistent history of haematuria. The
167 father of the child and other relatives from France were also found to have chronic haematuria,
168 pointing towards a then hitherto unknown *S. haematobium* transmission focus on the island.
169 Since then there has been a concerted effort to describe and curtail the disease which has
170 raised several concerns unique to this European setting and tourist destination³².

171 *Focus on female genital schistosomiasis (FGS)*

172 FGS is likely the most underestimated gynaecological disorder in the tropics. It manifests with
173 egg entrapment in the genital mucosa with granuloma formation and neovascular changes.³³
174 Pathognomonic lesions can be visually seen by colposcopy, but this method is costly and
175 requires high level training, frequently absent in endemic areas. A new visual diagnostic FGS
176 pocket atlas is freely available from WHO (<http://apps.who.int/iris/handle/10665/180863>) and
177 targeted to clinical health-care professionals and aiming to help with the identification of typical
178 cervical lesions. The main limitation of this promising tool is the need for a colposcope to
179 perform the gynaecological examination.

180 FGS affects women that are or have been infected with *S. haematobium* at any given
181 point in their lives. The exact onset of the lesions is unknown, as it is not ethically permissible
182 to conduct studies in girls that have not had their sexual debut. However genital
183 symptomatology has been linked to *S. haematobium* infection even in pre-pubertal girls,
184 suggesting early onset of FGS³⁴The consequences of the diagnostic difficulties for FGS get
185 reflected in the absence of accurate disease burden estimates in *S. haematobium* areas. This
186 is particularly troublesome when there is strong evidence of a fourfold increase in HIV in
187 women with *Schistosoma* infection.^{35, 36} The impact of FGS on women's reproductive life is
188 large with strong ties to infertility and subfertility.^{30 37} Cervical fibrotic lesions remain largely
189 unchanged months after PZQ treatment given following current recommended single-dose
190 guidelines.³⁸ This distressing reality highlights the importance of early treatment to prevent
191 established fibrotic morbidity.

192 **Current control of schistosomiasis with PZQ**

193 The mainstay of schistosomiasis control relies on preventive chemotherapy (PC) with PZQ, a
194 broad spectrum anti-parasitic drug delivered through mass drug administration programmes
195 to school-aged children. Programme regularity relies on background *Schistosoma* spp.
196 prevalence in each endemic country. PZQ is therefore delivered annually (egg-patent
197 prevalence $\geq 50\%$), every two years (prevalence $> 10-50\%$) or twice during primary schooling
198 time (prevalence $\geq 10\%$).³⁹ In 2012, it was estimated that across the world some 249 million
199 people were in need of regular PC, with 93% of those eligible to be found in sub-Saharan
200 Africa⁴⁰. Only 34% of all eligible school-aged children received PZQ in 2014.⁴¹

201 *Bottlenecks in global supply and delivery of PZQ*

202 It has been noted across many nations, and also formally reported, that Africa is desperate
203 for PZQ⁴², especially given that some 100 million school-aged children are eligible for
204 preventive chemotherapy⁴³. Since the development of PZQ in the 1970s, the large-scale
205 production and access plan for this drug has undergone several revisions^{44, 45}. The most
206 significant perhaps, was the drop in price from \$1.00 USD in 1998 to \$ 0.08 USD in 2003 per
207 tablet as then retailed by various pharmaceutical suppliers following from off-patent
208 production⁴⁶. This raw tablet price roughly equates to \$ 0.20 USD per 40 mg/kg treatment for
209 a typical school-aged child (i.e. 2.5 tablets) which also enabled simple *per capita* forecasting
210 of its supply as well as likely distribution costs for treatment of school-aged children in school.
211 This has been largely propelled forward by entities like the Schistosomiasis Control Initiative
212 (SCI)⁴⁷ operating since 2002. The SCI is a Bill & Melinda Gates Foundation project that has
213 also helped to solidify national actions against other diseases amenable to preventive
214 chemotherapy, for example, against soil-transmitted helminthiasis with co-delivery of
215 albendazole and PZQ to school-aged children using school-based logistical and delivery
216 systems⁴⁸.

217 In 2007, a change in this landscape started to take place upon the first pledged
218 donation *gratis* of PZQ to WHO by Merck-KGaA (Darmstadt, Germany) under their brand
219 name of CesolTM. Over the 2007-2010 period, 20 million PZQ tablets were donated annually,

220 prequalified by WHO and then shipped in-country to those national control programmes
221 requesting PZQ stocks for use in PC campaigns. Following on the London Declaration on
222 NTDs (<http://ntd-coalition.org>) in 2012, the Merck-KGaA donation was pledged to expand and
223 up-scale production to a total of 250 M tablets per year by 2020, achieving 103 M donated
224 tablets in 2015.

225 Since the London Declaration and the Merck-KGaA donation, the production market
226 of PZQ has not been stable, with certain companies reducing or stopping their production. An
227 unforeseen consequence of this is that the donation which is typically ring-fenced for use in
228 school-aged children, is coming under increasing pressure to be used to shore-up access to
229 PZQ in other groups. It is particularly noteworthy that the treatment needs of adults are not
230 factored into the donation, and are largely catered for by Ministries of Health within their
231 procurement of essential drugs.

232 **Expanded access for preventive chemotherapy and treatment to vulnerable** 233 **populations**

234 *Paediatric praziquantel formulation*

235 It is astonishing that the PZQ treatment needs of school-aged children had so long eclipsed
236 those of younger, preschool-aged children who today are considered just as vulnerable, if not
237 more so, than their older counterparts⁴⁵. As recently highlighted, this oversight is concomitant
238 with a general neglect of paediatrics within tropical medicine.⁴⁹ From today's perspective, it is
239 unethical to withhold safe medical treatment to those that need it, especially children.
240 Importantly, PZQ has been safely delivered off-license through crushed tablets to hundreds of
241 children under four years of age across different settings.⁵⁰ The first pharmacokinetic-
242 pharmacodynamic study in young Ugandan children with *S. mansoni* infection using crushed
243 tablets of PZQ found that raised dosing to 60 mg/kg was favourable to the WHO recommended
244 single dosing of 40 mg/kg⁵¹ which was in contrast to results of a multi-country meta-analysis
245 that only included school-age children⁵². Worryingly, no child achieved bloodstream antigenic
246 clearance based on schistosome circulating anodic antigen (CAA). Given that many of these

247 children had very high levels of CAA before treatment, to remove this substantial worm burden
248 would require repeated treatments⁵¹.

249 Current control programmes unduly focus attention on school-aged children that
250 harbour highest intensity egg-patent infection. This is further skewed by the fact that traditional
251 diagnostic methods may miss moderate-light infections that are more commonly seen in the
252 youngest children.¹¹ This approach downplays the clinical importance of these early infections
253 that require more sensitive diagnostic methods.^{53, 54} Ultrasound detectable morbidity is already
254 present in children and lesions responds to higher PZQ doses.⁵⁵

255 Over the last decade with a greater focus on disease surveillance in children under
256 five years of age, there is a much wider appreciation of their treatment needs^{18, 50}. Addressing
257 this, in 2010 WHO held an informal review of the available evidence for treating preschool
258 aged children (PSAC) with schistosomiasis. The recommendations of this meeting concluded
259 that it was possible to use crushed or broken tablets for treatment in the interim until a children-
260 friendly paediatric formulation of PZQ was developed. In response, a public-private-
261 partnership was formed in July 2012 and entitled the paediatric praziquantel consortium
262 (PPC). This was tasked to develop, register and provide an oral dispersible tablet (ODT) for
263 use in future treatment campaigns to supplement the existing Cesol® 600 mg tablet donation.
264 ⁵⁶

265 Several important decisions first had to be addressed in the development of an
266 appropriate PZQ formulation, its optimal dosing and associated product access plan. Results
267 from ongoing bioavailability studies in the PPC were presented at an additional meeting of the
268 WHO in September 2015 to further assess treatment needs and guidelines for PSAC.^{56, 57}
269 The optimal delivery platform to roll-out this new paediatric formulation has yet to be evaluated.
270 As a feasible product delivery plan, PSAC PZQ preventive treatment could be integrated within
271 the ongoing maternal-child health visits as part of the integrated management of childhood
272 illnesses (IMCI), a comprehensive primary health care delivery plan endorsed by WHO.¹⁷

273 *PZQ in pregnancy*

274 An estimated 40 million women of reproductive age are infected with Schistosomiasis. At the
275 time of its release in 1979, PZQ was never formally studied in pregnant or lactating women
276 and remains a United States Federal Drug Administration pregnancy Class B drug. Its Class
277 B designation was based on numerous animal studies supporting its safety,^{58, 59} but a lack of
278 well-controlled trials during human pregnancy.⁶⁰

279 In 2002, the World Health Organization (WHO) sponsored an “Informal Consultation”
280 on the use of PZQ during pregnancy and lactation. The report emanating from that meeting
281 recommended that all schistosomiasis infected pregnant and lactating women be considered
282 high-risk groups and offered treatment with praziquantel individually or during treatment
283 campaigns.⁶¹⁻⁶³ This recommendation was reissued in 2006 as part of the WHO’s *Guidelines*
284 *for Preventative Chemotherapy for Helminthiasis*³⁹ in which it was recommended that
285 pregnant and lactating women be included in mass drug administration (MDA) campaigns.
286 ³⁹Importantly, at the time of these reports, no randomized controlled trials of praziquantel
287 during human pregnancy had been conducted. Addressing the safety of expanded use, the
288 authors cited demonstrated PZQ’s safety in animal models, post-market surveillance data,
289 and PZQ use for the treatment of cysticercosis during pregnancy. With respect to efficacy, the
290 recommendations were based on both demonstrated reversibility of end organ damage and
291 anemia with more frequent treatment, among non-pregnant populations. Many nations did not
292 initially adopt these guidelines citing lack of sufficient safety data from controlled trials.

293 *Praziquantel and human pregnancy: results of two randomized controlled trials (RCTs)*

294 Two randomized, double blind, placebo controlled trials have been completed since the most
295 recent WHO Guidelines addressing the treatment of pregnant women with PZQ.^{64, 65} One
296 randomized, controlled trial conducted in Uganda, assigned women attending a hospital-
297 based antenatal clinic into one of four groups: placebo, albendazole, praziquantel, or
298 praziquantel + albendazole. The study agent(s) were given during the second or third trimester

299 (mean gestational age 26.6 weeks).⁶⁴ This large trial did not demonstrate a significant impact
300 of PZQ on maternal anemia or birth weight, even among the approximately 18% of women
301 who were infected with *S. mansoni*.

302 A second RCT, conducted in Leyte, The Philippines, recruited only women who were
303 infected with *S. japonicum* at the time of enrolment. Women (N=360) were treated at 12-16
304 weeks gestation with 60 mg/kg of Praziquantel given as a split dose over 4 hours or placebo.
305 PZQ did not significantly impact the primary outcome, birth weight, nor other secondary
306 outcomes including prevalence of low birth weight, prematurity, and intra-uterine growth
307 restriction. PZQ treatment did culminate in increased maternal serum ferritin levels at 32
308 weeks gestation with a trend toward improved new born iron endowment. In addition, pregnant
309 women were successfully treated as defined by parasitological cure at 22 weeks gestation.
310 Treatment was well tolerated with reactogenicity rates similar to that observed in non-pregnant
311 subjects. Importantly, there were no significant differences in key safety outcomes including
312 abortion, foetal death *in utero* and congenital anomalies.⁶⁵

313 *Policy implications/Future Directions*

314 Though some nations, reassured by results of RCTs, have recently adopted recommendations
315 to include pregnant women in PZQ MDA campaigns,^{64, 65} many nations still have not.⁶⁶ For
316 example, in Zanzibar, where local guidelines did not recommend treatment of pregnant
317 women, two of the most commonly reasons cited by individuals for not receiving PZQ during
318 community treatment campaigns were pregnancy and breast feeding.⁶⁷ Furthermore, there is
319 concern that even in nations that have adopted these recommendations, limited dissemination
320 of information to schistosomiasis program managers and health care providers has led to
321 continued exclusion. Across these nations, millions of women of reproductive age are not
322 treated for many years during repeated cycles of pregnancy and lactation. An unfortunate
323 implication of this creates an obvious refugia for schistosomes within the human populace
324 ultimately facilitating environmental transmission.

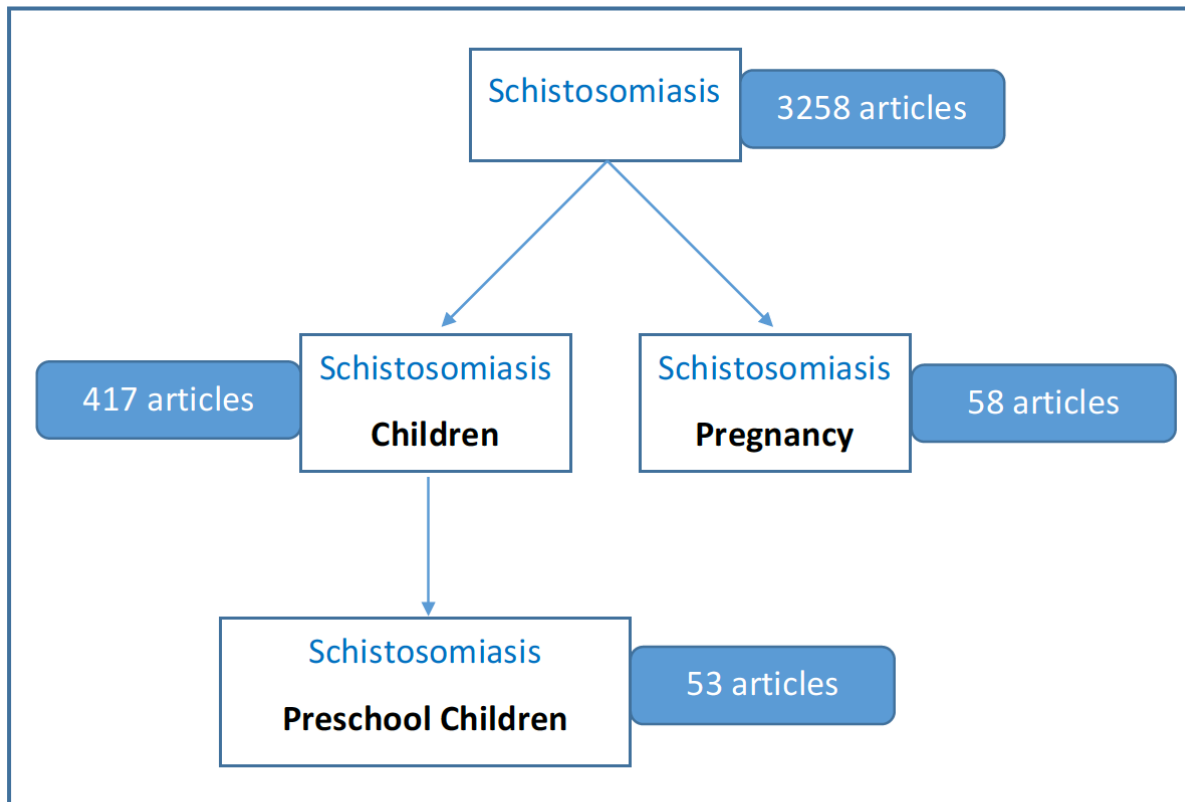
325 **Conclusions**

326 The exclusion of two of the most vulnerable infected populations (pregnant women, PSAC)
327 from schistosomiasis control programmes is detrimental not only to their own health present
328 and future, but it also precludes the elimination of this parasitic disease in endemic areas. This
329 inequality is also reflected in the research effort dedicated to these groups as shown in **Figure**
330 **2**. There is a disproportionate amount of evidence derived from other aspects of
331 schistosomiasis in detriment of PSAC and pregnancy data, notwithstanding returned
332 travellers. Paradigm shifts are not only needed to acknowledge light infections as pernicious
333 to health and moving away from heavy worm burdens as the only accurate morbidity indexes.
334 It is also indispensable to think of alternative PZQ delivery platforms to target at-risk
335 populations that can synergise with ongoing MDA efforts. One model could include PZQ
336 delivery at antenatal clinics and maternal-child health visits.

337 Some interventions that can help address these issues include education to programme
338 managers in endemic regions that lead MDA campaigns on the safety of PZQ in pregnancy.
339 Clinical officers and nurses in clinics can be educated on the safe delivery of PZQ in PSAC.
340 In addition, women, who have been told for decades that they cannot be treated when
341 pregnant or breast feeding, will likely need targeted re-education. Finally, co-authors of the
342 Philippines RCT and regulatory program staff at the United States' (US) National Institutes of
343 Health/National Institute of Allergy and Infectious Diseases, are collaborating with the US
344 Federal Drug Administration to change PZQ's class designation from B to A, indicating safe
345 use during human pregnancy as supported by well controlled studies.

346 Within the existing PZQ supply constraints the commitment from national control
347 programmes has to expand its views and operate on an evidence-based agenda, without
348 neglecting at-risk populations in need of treatment. It will take a coordinated effort between
349 national and international agencies and strong advocacy to achieve this, but the time is right
350 to make these changes.

Figure 2: Articles published and indexed in Pubmed in the last 10 years on schistosomiasis in pregnant women, children and preschool children.*



* MeSH search terms used: 'schistosomiasis and human'; 'schistosomiasis and pregnancy'; 'schistosomiasis and children, not adults' and 'schistosomiasis and child, preschool not adults'.

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354 **Conflict of interest statement**

355 The authors have no potential conflicts of interest

356

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361

362 **Figure legends**

363

364 **Figure 1:** A schematic of (A) prevalence by age inferred by egg-count versus serology across
365 an endemic population (i.e. in mothers and their children's) and (B) visual detection of

366 antibodies to soluble eggs antigen (SEA) in mothers (M) and children (C) from lakeshore
367 village on Lake Albert, Uganda. Positive (+) and negative (-) controls indicated.

368

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