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.
Introduction

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

Without anthelminthic treatment with PZQ, adult schistosomes may live for decades within the host. By contrast, juvenile worms are tolerant to PZQ making this drug an imperfect
treatment tool against acute infection, which is difficult to diagnose unequivocally even with modern biomarkers of infection. On the other hand, as schistosome worms increase in number, pair and mature to lay eggs subsequently through time, the diagnostic patency of chronic schistosomiasis becomes ever more apparent; as does the congruency of a variety of serological, molecular or parasitology methods. Using a selection of these markers it is possible to monitor the efficacy of PZQ treatment for which there are WHO guidelines that measure the proportional reduction of schistosome eggs in excreta before and after treatment. On the whole, the performance of PZQ is adequate according to those WHO standard measures of cure. However, measures of drug efficacy are poorer in younger children and across all ages in high prevalence and transmission environments.

**Infected and overlooked**

*Children and mothers in the endemic setting*

The endemic transmission landscape of schistosomiasis is typically over-dispersed or focal such that the disease can be very concentrated geographically around a given freshwater habitat, while others nearby may experience no disease at all. In such an area, e.g. a rural village where there this schistosomiasis, the patency of infection varies by age and gender. Using traditional diagnostic methods based on egg-detection the most obvious infected group are children, of either gender, in their late childhood and early adolescence. This has been the ‘classic’ view of the epidemiology of schistosomiasis in an endemic setting for many years as shown in Figure 1A and discussed by Peter Jordan in this journal some 45 years ago. However since that time, a more extensive knowledge and appreciation of schistosomiasis has been developed, now seen as a complex disease that may or may not coincide with present egg-patent infection. The traditional view based on egg-patency in the excreta gave rise to the commonly held assumption that only heavy egg-patent infections were important and those of light or moderate could be ignored. This view is largely incorrect; if alternative diagnostic methods are used such as serology or biomarkers, schistosomiasis is much more pervasive in mothers and young children than previously thought. Using a combination of
diagnostic assays has helped to better reveal the burden of disease in pre-school-aged children and their mothers\textsuperscript{19}. But it’s not only improved diagnostic accuracy for \textit{Schistosoma} detection, morbidity detection methods have also been refined and thus schistosomiasis encompasses not only the chronic manifestations related to end-organ fibrosis (portal hypertension due to periportal fibrosis, bladder polyps and squamous cell carcinoma of the bladder), but it now includes more \textit{functional} morbidities such as anaemia and arrested linear growth that are reversible only if treated early in childhood. The inputs used for the global Burden of Disease 2010 study underestimated the burden of the disability associated with \textit{Schistosoma} infection.\textsuperscript{20} These estimates did also not include late effects of the \textit{functional} morbidities, of which growth stunting and cognitive impairment, infertility, dyspareunia and genital disease are now widely recognised as schistosomiasis-associated morbidities. Therefore the concept of an asymptomatic disease, historically describing children without overt clinical signs and symptoms, with no obvious chronic manifestations, can no longer be accepted.\textsuperscript{2}

\textbf{Figure 1:} A schematic of (A) prevalence by age inferred by egg-count versus serology across an endemic population (i.e. in mothers and their children’s) and (B) visual detection of antibodies to soluble eggs antigen (SEA) in mothers (M) and children (C) from lakeshore village on Lake Albert, Uganda. Positive (+) and negative (-) controls indicated.
There is an essential environmental transmission dynamic, as part of the schistosome lifecycle, which is determined by the immediate presence of permissive freshwater snail hosts and by unsafe water contact activities undertaken by the surrounding community, albeit from local or visiting people. In principle, water contact can be broken down into two partially related components, contamination- and exposure-related activities\(^2\). The transmission epidemiology of schistosomiasis is intricately interwoven with the daily need for water as part of socio-economic development and environmental hygiene. Until recently, as younger children are often not directly seen in water, it was thought that their risk of infection was low and largely in accordance with a low prevalence of egg-patent infection. However, this appraisal was overturned as it is largely by passive water contact, such as being bathed in water collected by the mother, often away from view within the homestead, that infants becomes first infected. Such infections are best detected by serological methods. Figure 1B and data from novel studies using global position system data suggest the levels of unsafe water contact of infants and pre-school-aged children can be alarmingly high\(^{18, 22}\). Furthermore, there is increasing concern about the importance of maternal schistosomiasis\(^2\) such that the disease should be tackled simultaneously in both child and mother.

**Children and mothers within travel medicine**

Schistosomiasis is also a travel related disease for those that visit disease endemic locations and knowingly or unknowingly undertake unsafe water contact activities. In the largest returned traveller cohort published in the UK, the most common presenting symptom was haematuria, related to urogenital schistosomiasis and almost half of the patients had eosinophilia.\(^2\) A major difference in travel-related schistosomiasis is the age of the first infection, typically in adults who have had little, if any, prior exposure to any helminthiasis. This allows use of more general immunological markers of infection e.g. eosinophilia\(^2\). Similarly, with a detailed travel history, the exact time and duration of most likely exposure can be determined\(^2\), setting aside these rather singular events of the traveller from the inevitable daily routine of those that live in close proximity to unsafe water sources. The disease
spectrum that schistosomiasis also induces in travellers differs, typically with a greater number
of cerebrospinal complications, largely owing to ectopic egg laying sites, necessitating
advanced diagnostic imagery techniques and clinical management.  

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

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

It is very plausible that many travellers returning to Europe will have schistosomiasis,
which will continue to go undetected until clinical manifestations develop. A good example is
the recent epidemic focus of urogenital schistosomiasis in Corsica that caught many general
practice surgeries by surprise. The first case of urogenital schistosomiasis caused by
infection with S. haematobium in Corsica was observed in a 4-year old French child upon
presentation to Toulouse Hospital in March 2014 with a persistent history of haematuria. The father of the child and other relatives from France were also found to have chronic haematuria, pointing towards a then hitherto unknown *S. haematobium* transmission focus on the island. Since then there has been a concerted effort to describe and curtail the disease which has raised several concerns unique to this European setting and tourist destination.  

*Focus on female genital schistosomiasis (FGS)*

FGS is likely the most underestimated gynaecological disorder in the tropics. It manifests with egg entrapment in the genital mucosa with granuloma formation and neovascular changes. Pathognomonic lesions can be visually seen by colposcopy, but this method is costly and requires high level training, frequently absent in endemic areas. A new visual diagnostic FGS pocket atlas is freely available from WHO ([http://apps.who.int/iris/handle/10665/1180863](http://apps.who.int/iris/handle/10665/1180863)) and targeted to clinical health-care professionals and aiming to help with the identification of typical cervical lesions. The main limitation of this promising tool is the need for a colposcope to perform the gynaecological examination.

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

*Current control of schistosomiasis with PZQ*
The mainstay of schistosomiasis control relies on preventive chemotherapy (PC) with PZQ, a broad spectrum anti-parasitic drug delivered through mass drug administration programmes to school-aged children. Programme regularity relies on background *Schistosoma* spp. prevalence in each endemic country. PZQ is therefore delivered annually (egg-patent prevalence ≥ 50%), every two years (prevalence > 10-50 %) or twice during primary schooling time (prevalence ≥ 10%). In 2012, it was estimated that across the world some 249 million people were in need of regular PC, with 93% of those eligible to be found in sub-Saharan Africa. Only 34% of all eligible school-aged children received PZQ in 2014.

*Bottlenecks in global supply and delivery of PZQ*

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

In 2007, a change in this landscape started to take place upon the first pledged donation *gratis* of PZQ to WHO by Merck-KGaA (Darmstadt, Germany) under their brand name of Cesol™. Over the 2007-2010 period, 20 million PZQ tablets were donated annually,
prequalified by WHO and then shipped in-country to those national control programmes requesting PZQ stocks for use in PC campaigns. Following on the London Declaration on NTDs (http://ntd-coalition.org) in 2012, the Merck-KGaA donation was pledged to expand and up-scale production to a total of 250 M tablets per year by 2020, achieving 103 M donated tablets in 2015.

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

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

*Paediatric praziquantel formulation*

It is astonishing that the PZQ treatment needs of school-aged children had so long eclipsed those of younger, preschool-aged children who today are considered just as vulnerable, if not more so, than their older counterparts. As recently highlighted, this oversight is concomitant with a general neglect of paediatrics within tropical medicine. From today’s perspective, it is unethical to withhold safe medical treatment to those that need it, especially children. Importantly, PZQ has been safely delivered off-license through crushed tablets to hundreds of children under four years of age across different settings. The first pharmacokinetic-pharmacodynamic study in young Ugandan children with *S. mansoni* infection using crushed tablets of PZQ found that raised dosing to 60 mg/kg was favourable to the WHO recommended single dosing of 40 mg/kg which was in contrast to results of a multi-country meta-analysis that only included school-age children. Worryingly, no child achieved bloodstream antigenic clearance based on schistosome circulating anodic antigen (CAA). Given that many of these
children had very high levels of CAA before treatment, to remove this substantial worm burden
would require repeated treatments\textsuperscript{51}.

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

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

Several important decisions first had to be addressed in the development of an
appropriate PZQ formulation, its optimal dosing and associated product access plan. Results
from ongoing bioavailability studies in the PPC were presented at an additional meeting of the
WHO in September 2015 to further assess treatment needs and guidelines for PSAC. \textsuperscript{56, 57}
The optimal delivery platform to roll-out this new paediatric formulation has yet to be evaluated.
As a feasible product delivery plan, PSAC PZQ preventive treatment could be integrated within
the ongoing maternal-child health visits as part of the integrated management of childhood
illnesses (IMCI), a comprehensive primary health care delivery plan endorsed by WHO. \textsuperscript{17}
An estimated 40 million women of reproductive age are infected with Schistosomiasis. At the time of its release in 1979, PZQ was never formally studied in pregnant or lactating women and remains a United States Federal Drug Administration pregnancy Class B drug. Its Class B designation was based on numerous animal studies supporting its safety, but a lack of well-controlled trials during human pregnancy. 

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

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

Two randomized, double blind, placebo controlled trials have been completed since the most recent WHO Guidelines addressing the treatment of pregnant women with PZQ. One randomized, controlled trial conducted in Uganda, assigned women attending a hospital-based antenatal clinic into one of four groups: placebo, albendazole, praziquantel, or praziquantel + albendazole. The study agent(s) were given during the second or third trimester.
(mean gestational age 26.6 weeks). This large trial did not demonstrate a significant impact of PZQ on maternal anemia or birth weight, even among the approximately 18% of women who were infected with *S. mansoni*.

A second RCT, conducted in Leyte, The Philippines, recruited only women who were infected with *S. japonicum* at the time of enrolment. Women (*N*=360) were treated at 12-16 weeks gestation with 60 mg/kg of Praziquantel given as a split dose over 4 hours or placebo.

PZQ did not significantly impact the primary outcome, birth weight, nor other secondary outcomes including prevalence of low birth weight, prematurity, and intra-uterine growth restriction. PZQ treatment did culminate in increased maternal serum ferritin levels at 32 weeks gestation with a trend toward improved new born iron endowment. In addition, pregnant women were successfully treated as defined by parasitological cure at 22 weeks gestation.

Treatment was well tolerated with reactogenicity rates similar to that observed in non-pregnant subjects. Importantly, there were no significant differences in key safety outcomes including abortion, foetal death *in utero* and congenital anomalies.

**Policy implications/Future Directions**

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

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

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

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

The authors have no potential conflicts of interest

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Figure legends

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

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

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