One hundred years of neglect in paediatric schistosomiasis

AMAYA L. BUSTINDUY[1]*, STEPHEN WRIGHT[2], ELIZABETH C. JOEKES[3], NARCIS B. KABATEREINE[4], JUTTA REINHARD-RUPP[5], CHARLES H. KING[6] *and* J. RUSSELL STOTHARD[7]

[1] *Department of Clinical Research, London School Of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK*
[2] *Hospital for Tropical Diseases, Mortimer Market Centre, Mortimer Market, London WC1E 6JD, UK*
[3] *Department of Radiology, The Royal Liverpool University Hospitals NHS Trust, Liverpool L78XP, UK*
[4] *Schistosomiasis Control Initiative, Imperial College of London, 1 Norfolk Place, Paddington, London W2 1PG, UK*
[5] *Global Health R&D Department (route de la Verrerie 6, 1267 Coinsins, Switzerland) being part of the Biopharma Business of Merck KGaA, Darmstadt, Germany*
[6] *Center for Global Health and Diseases, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio, 44106, USA*
[7] *Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, UK*

(*Received 11 September 2016; revised 22 December 2016; accepted 2 January 2017; first published online 1 March 2017*)

SUMMARY

Early in the history of schistosomiasis research, children under 5 years of age were known to be infected. Although this problem was recognized over 100 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 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 underline 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.

Key words: paediatrics, schistosomiasis, *Schistosoma*, praziquantel, intestinal schistosomiasis, urogenital schistosomiasis, ultrasound.

CHILDREN'S ROLE IN THE HISTORY OF SCHISTOSOMIASIS

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

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

There was a slow transition from the golden era of descriptive parasitology (1850s–1920s), which had a particular interest in environmental practices for disease control, towards disease-centred research, which enabled the discovery of effective drugs.

* Corresponding author: Department of Clinical Research, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. E-mail: Amaya.Bustinduy@lshtm.ac.uk

Parasitology (2017), **144**, 1613–1623.
doi:10.1017/S0031182017000014

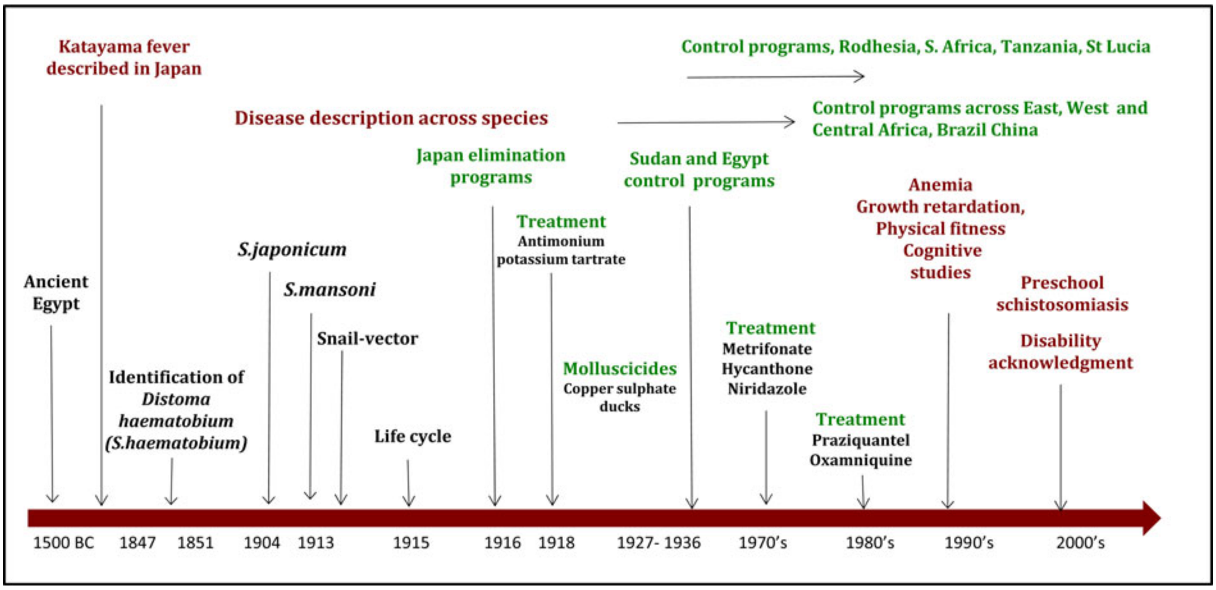

Fig. 1. A brief timeline summary of the more important events in the history of schistosomiasis. In black, discoveries in parasite biology; in red, clinical studies; in green, schistosomiasis control efforts.

Nevertheless, human *Schistosoma*-related disease went without an available treatment for over 50 years (Fig. 1). The species-specific description of schistosomiasis-associated morbidity began early on, and necropsy studies primarily contributed to this knowledge of chronic *Schistosoma* infection (Bustinduy and King, 2013) (Fig. 1). As a result, the most overt organ-level morbidities, such as hepatosplenomegaly, peri-portal fibrosis, and subsequent portal hypertension with oesophageal varices, were clearly linked to *Schistosoma mansoni* and *Schistosoma japonicum*. They thus became the primary focus of population-based disease prevalence studies for intestinal forms of schistosomiasis. Haematuria and renal tract pathology (bladder polyps, hydronephrosis and associations to bladder cancer) were identified as complications of *Schistosoma haematobium* infection, and these became the focus of efforts for prevention and control for this species (Bustinduy and King, 2013; Colley *et al*. 2014). Unfortunately, it took over 100 years to recognize the more widespread and disabling systemic morbidities of *Schistosoma* infection that affect the youngest age groups (Parraga *et al*., 1996; Koukounari *et al*., 2006, 2007; King and Dangerfield-Cha, 2008; Mupfasoni *et al*., 2009).

Michael Gelfand, a clinician stationed in Rhodesia (present-day Zimbabwe) in the early 1960s, was particularly influential in describing the morbidity of the disease in children. In a detailed clinical description of intestinal schistosomiasis, he reported: '*This feature of tiredness stands out more in bilharziasis than in any other tropical infestation. The lethargy of the child is often noticed by teachers, who sees him becoming apathetic, falling behind in games and lacking enthusiasm*.' (Gelfand, 1967). At the time, these careful clinical observations lacked metrics to accurately measure this 'fatigue'. Moreover, there was no strategy to treat these children *en masse* (Farley, 1991). Much later, the association between schistosomiasis and decreased physical fitness was documented in Coastal Kenya among boys with urogenital schistosomiasis. This study, although innovative, made use of the Harvard step-test, an instrument not validated for children (Stephenson *et al*. 1985*b*). Subsequent work in the same area has identified the 20-m shuttle run test as an accurate and easy-to-implement field fitness test with excellent correlations between child poly-parasitic status, anaemia and decreased aerobic capacity in over 2000 children (Bustinduy *et al*. 2011).

Infection in very young children was particularly well described in clinical accounts from Rhodesia. Up to half of children as young as 2 years old were documented as having egg-patent infection in endemic villages, but in an era of very expensive injectable drug therapy, treating them was not even considered (Fig. 2). Only overt morbidity was eligible for treatment and this mostly occurred among older children and adults (Gelfand, 1967).

In textbooks and policy literature, school-age children have been characterized as the main transmitters of *Schistosoma* infection due to their high egg output (peaking in mid-childhood between 10 and 15 years old) and increased water contact. Owing to their 'careless' water use practices, which include frequent wading, playing and urinating or defecating in or near the water, the *Schistosoma* transmission cycle is greatly bolstered (Webbe, 1982; Mott *et al*. 1985). Because detectable *Schistosoma*-specific morbidity due to advanced organ fibrosis is mostly seen in early adulthood, children were not considered as

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

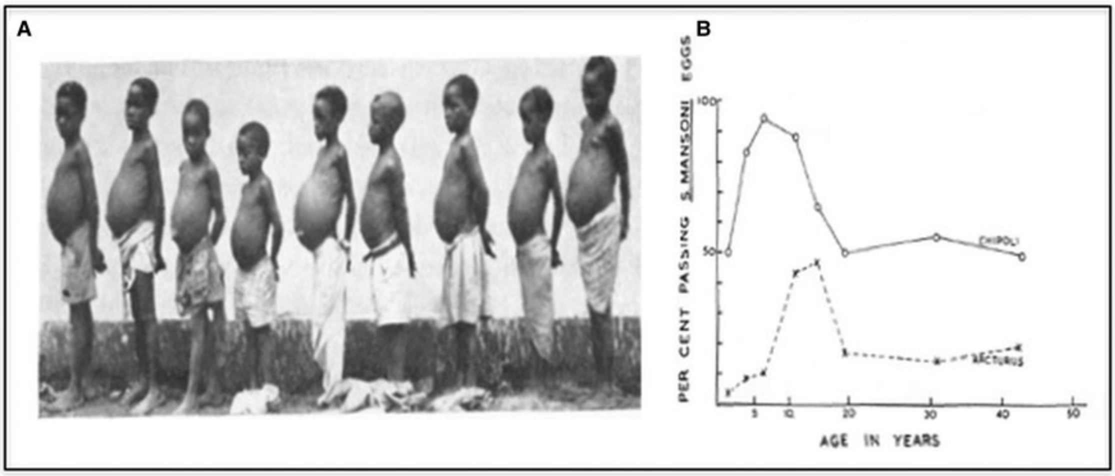

Fig. 2. Often overlooked aspects of schistosomiasis previously identified decades ago. (A) Young children with severe hepatosplenomegaly in Zimbabwe (Rhodesia). (B) Age distribution of egg-patent *S. mansoni* infection in a high-(Chipoli) and low-(Arcturus) transmission villages, with significant involvement of children under 5 (50% prevalence in Chipoli). Adapted from Gelfand (1967).

seriously affected by their infection status (Gryseels, 1989). In addition, risk for disease was erroneously believed to be related only to high-intensity infections. (Warren *et al*. 1979; Gryseels, 1989) Recent studies across *Schistosoma* species have discredited this paradigm by demonstrating that light-intensity infections already have tangible negative health effects (Ezeamama *et al*. 2005*b*; Bustinduy *et al*. 2013; King, 2015).

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

THE FIRST NUTRITIONAL STUDIES

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

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

FUNCTIONAL MORBIDITIES AFFECTING GROWTH

Advances in the knowledge of host–parasite immune responses have revealed that schistosomiasis is fundamentally a chronic inflammatory disease that affects the entire body. This has led to much wider recognition of morbidities that are linked to the pro-inflammatory state that precedes fibrosis

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

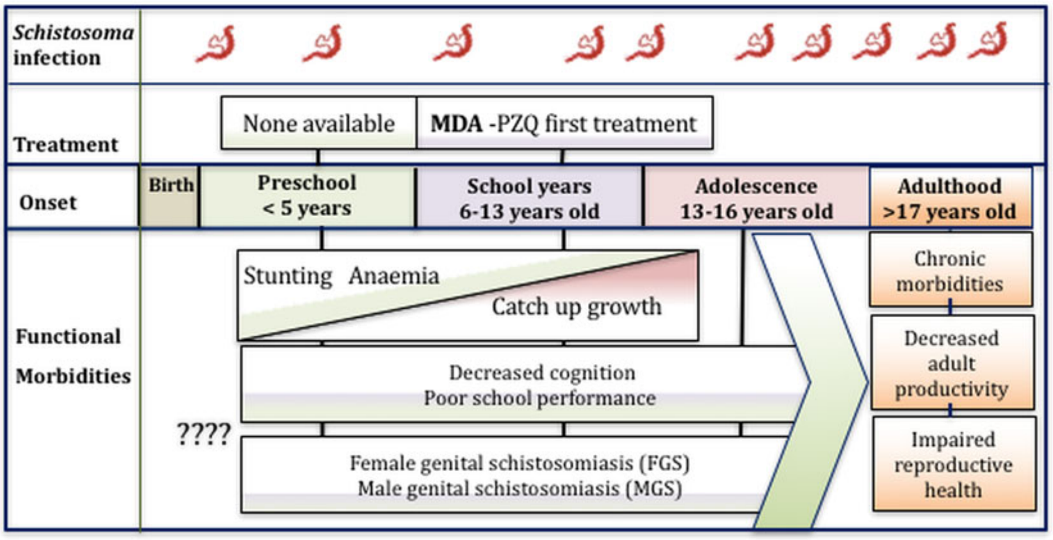

Fig. 3. Timing of the onset of different schistosomiasis-associated morbidities. Pro-inflammatory state due to *Schistosoma* infection impairs normal linear growth and development (functional morbidity) and manifests as stunting and anaemia starting <2 years of age. The catch-up growth window can only occur before growth plates fuse. First treatment occurs at school entry but chronic infection can already be present years before, and re-infection may be rapid. The onset of first FGS/MGS manifestations is unknown.

(Wamachi *et al*. 2004; Coutinho *et al*. 2006*b*; Leenstra *et al*. 2006). These so-called 'subtle' morbidities perhaps should be better termed 'functional' morbidities, as they impair normal physiological functioning of an infected child. The impact of infection on growth hormone/insulin-like growth factor-1 pathways is anabolic to the skeleton, and other inflammatory cytokines also compromise bone growth (Farquharson and Ahmed, 2013). Linear growth can be severely impaired by any chronic inflammation, including inflammation caused by schistosomiasis, and this, in turn, leads to childhood growth stunting. Associated anaemia of inflammation caused by infection with all species of *Schistosoma* impairs iron storage release and utilization (Ezeamama *et al*. 2005*b*; Koukounari *et al*. 2006) and this complication most readily manifests itself as decreased physical fitness (Stephenson *et al*. 1985*b*; Friedman *et al*. 2005; Bustinduy *et al*. 2011), poor concentration and diminished school performance (Nokes *et al*. 1999; Jukes *et al*. 2002; Ezeamama *et al*. 2005*a*). If untreated, these manifestations become irreversible with significant lifetime consequences: decreased work productivity as adults, altered fertility in both men and women (Kjetland *et al*. 2012) and decreased quality of life. (Terer *et al*. 2013) The misfortune behind the failure to recognize such 'functional' morbidities is that, because they are confounded by other co-endemic diseases, particularly malaria, they are often not adequately recognized as schistosomiasis-related manifestations.

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

ASSOCIATED DISABILITY IN CHILDREN

Why has the negative impact of paediatric schistosomiasis been undervalued? Part of what makes schistosomiasis a 'neglected' disease [i.e. counted among the Neglected Tropical Diseases (NTDs)] is that its perceived importance to health has been linked to its disability-adjusted life-year (DALY) ranking in the WHO–World Bank Global Burden of Disease (GBD) system. In its first iteration, the GBD program intentionally weighted disease impact by age, giving much greater emphasis to diseases that affect 20–30 year olds, and much less to diseases of children under 5 (Murray, 1996). While this error has been corrected in more recent GBD versions (Salomon and Jonas, 2012; Vos and Memish, 2012) schistosomiasis has always been assigned the health impact associated with 'minor infections' and given a negligible 0·004–0·005 disability weight. Thus, although there are more than 250 million persons with active (egg-positive) cases, and likely an equivalent number of people with 'egg-negative' *Schistosoma*-related disease, the calculated worldwide DALY impact of schistosomiasis is perceived as less than one-tenth of that attributed to other, more lethal diseases of childhood. In the eyes of many donors and policymakers, this lowers its priority for control and prevention.

To correctly assess the disease burden of *Schistosoma* infection it is important to recognize

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

Fig. 4. Photographs of young children suffering from schistosomiasis. (A) Early chronic morbidity (hepatosplenomegaly) in child under 5 years of age with intestinal schistosomiasis; (B) A preschool child collecting water and being exposed to cercariae-infested freshwater.

the lifetime *cumulative* impact of infection, not just in terms of individual organ pathology and dysfunction, but also on the overall whole-body performance of the growing child and young adults. Schistosomiasis that causes chronic anaemia, growth faltering and poor cognitive performance is quite disabling in a setting where resources are limited, and accommodation for disabilities is inadequate. Disease impact does not end when *Schistosoma* infection ends, and the associated loss of schooling and/or reduced growth cannot be reversed by childhood treatments if rapid reinfection is likely where a child lives, plays and works. Similarly, these losses cannot be reversed once a person reaches adulthood. Once the child passes school age, most of these functional pathologies become irreversible.

EARLY YEARS (<5 YEARS OF AGE)

The institutional apathy regarding treatment of schistosomiasis in children under six is in stark contrast to the recommendations for treatment of preschool children infected with soil-transmitted helminths, a practice that has been at the forefront of paediatric care and treatment campaigns for many years (World Health Organisation, 2007). Children under 5 years of age are often daily exposed to infected water very early in life, and although initial infection occurs 'silently', it generates inflammation that predisposes to organ fibrosis, which will then endure for decades (Colley *et al*. 2014) Fig. 4. This lack of recognition dates back to early WHO reports on schistosomiasis, in which disease among very young children was described, but then appears to have been forgotten in subsequent formulation of action plans (Mott, 1982). The justification for this health policy gap was 2-fold; firstly, young children were considered a lightly infected population and therefore thought to be at low risk for schistosomiasis-associated morbidity; secondly, there was no child-friendly formulation for oral treatment that would decrease the risk of choking. Crushing tablets to treat younger children was not considered practical for national programmes, although this approach is widely performed for pill treatment of other diseases such as tuberculosis (Pineiro Perez *et al*. 2016). In essence, the under-fives were not seriously considered at risk and they were deemed too difficult and unsafe to treat, so they were excluded. It was not until 2010 that the first expert meeting on the inclusion of preschool children in schistosomiasis control efforts was convened at the World Health Organisation (WHO) (World Health Organization, 2011).

From a modern perspective, stronger evidence is emerging that very young preschool children do indeed harbour egg-patent infection (Bosompem *et al*. 2004; Odogwu *et al*. 2006; Sousa-Figueiredo

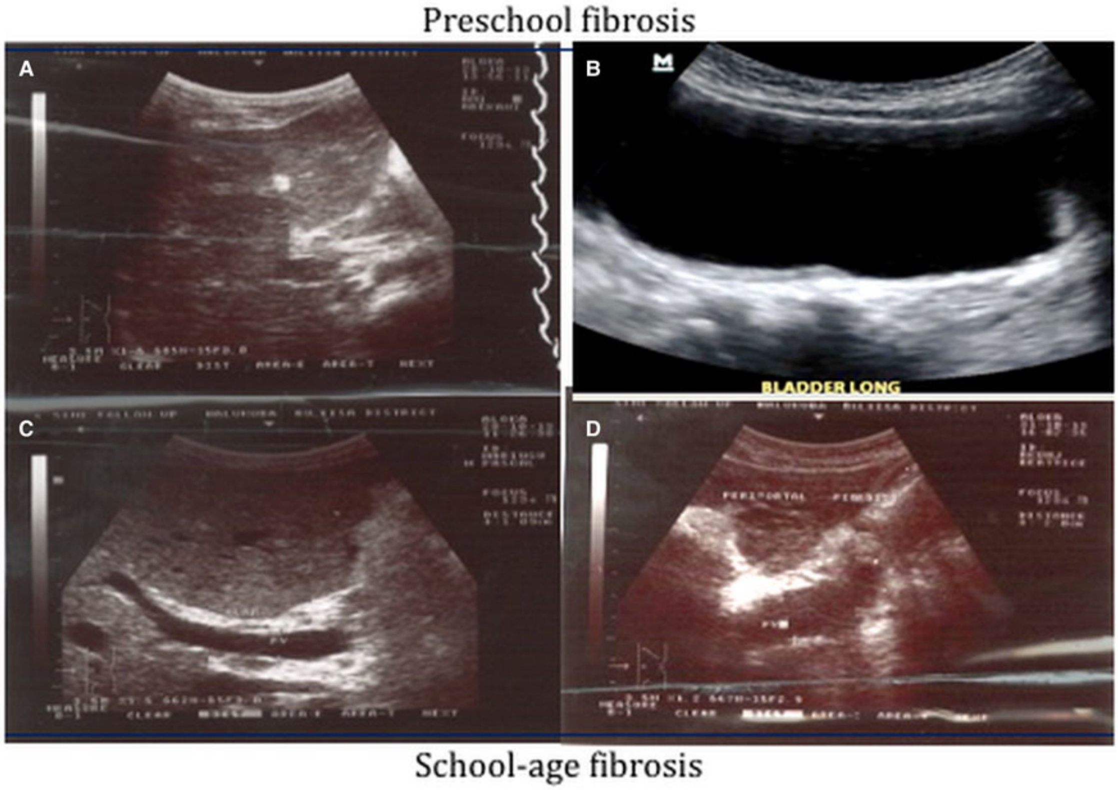

Fig. 5. Ultrasound findings by WHO classification. Preschool children in (A): Uganda – Liver fibrosis-stage C on a 4-year-old girl and (B): Gabon – early bladder polyp and bladder thickening in a 2-year-old boy. School-aged children (C): Uganda – 12-year-old boy with stage D fibrosis (D): 16-year-old girl with stage E fibrosis. N.B. Image B – courtesy of Dr. Jonathan Rempiss.

et al. 2008; Verani *et al.* 2011). and also present with early fibrosis, including hepatosplenic disease due to *S. mansoni* and early bladder changes due to *S. haematobium* (Fig. 5). Detection of these early fibrotic changes, however, may prove challenging.

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

THE EVOLUTION OF ANTI-SCHISTOSOMAL TREATMENT

The first injectable anti-schistosomal treatment, potassium antimony tartrate, or tartar emetic (TE), which contained trivalent antimony, was introduced in 1918 as a drug initially used to treat visceral leishmaniasis (Christopherson, 1924) (Fig. 1). Although promising at first, it had very limited efficacy and severe side-effects (Jordan, 2000). Other drugs followed, including hycanthone and oral niridazole each with severe side-effects and difficulties in administration. Table 1 summarizes the different anti-schistosomal treatments through time.

Since 1984, praziquantel (PZQ), the current drug of choice, has displaced older drugs of lesser effectiveness for all types of schistosomiasis (King *et al.* 1988; King and Mahmoud, 1989; Doenhoff *et al.* 2008). Its full mechanism of action remains unclear, but it is thought to act on the calcium ion channels of schistosome's tegument leading to disruption of the parasite's surface, and exposing it to lethal damage by the host's immune system (Doenhoff *et al.* 2008). Adult dose finding studies in the 1970s and 1980s concluded that a single PZQ dose of 40 mg kg^{-1} was effective for treating *S. haematobium* and *S. mansoni* (Davis *et al.* 1979; Davis and Wegner, 1979; King *et al.* 2002). However, in highly endemic areas, a more intense, repeated dosing approach is likely needed for optimal effect, particularly for *S. mansoni* (King *et al.* 2011).

Since its introduction in the 1980s, PZQ has been used safely in children. However, their recommended dosages were directly extrapolated from pharmacokinetic studies performed in adults (Xiao, 2005;

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

Table 1. Different anti-schistosomal treatments through time

Drug	Active for species	Route of administration	Main side effects	Severe complications	Ref.
Tartar emetic (TE)	*S. mansoni* *S. haematobium* *S. japonicum*	Intravenous	• Nausea • Vomiting • Muscle, joint pain • T-wave inversion	• Encephalopathy • Collapse • Rash • Hepatitis C	(Christopherson, 1918; Davis, 1968; Frank *et al*. 2000)
Lucanthone (Miracil D ®)	*S. mansoni* *S. haematobium* *S. japonicum*	Oral	• Nausea • Vomiting • Anxiety	• Lethargy	(Blair *et al*. 1949; Newsome and Halawani, 1950; Lees, 1966)
Hycanthone	*S. mansoni* *S. haematobium* *S. japonicum*	Intramuscular	• Nausea • Vomiting	• Malignancy	(Moore, 1972; Cook *et al*. 1977; Warren *et al*. 1978)
Niridazole (Ambilhar®)	*S. mansoni* *S. haematobium* *S. japonicum*	Oral	• Nausea • Vomiting • Headache • Vivid dreams • Acute confusion	• Seizures • Malignancy • Death	(Davis, 1966; Nicholson and McMahon, 1966)
Metrifonate	*S. haematobium*	Oral	• Nausea • Vomiting	• Bronchospasm • Bradycardia • Ataxia • Respiratory paralysis	(King *et al*. 1988; King *et al*. 1990)
Oxamniquine	*S. mansoni*	Oral	• Nausea • Vomiting • Dizziness • Drowsiness • Eosinophilia	• Seizures • Hallucinations	(da Silva *et al*. 1975; Ferrari *et al*. 2003)
Praziquantel	*S. mansoni* *S. haematobium* *S. japonicum*	Oral	• Nausea • Vomiting • Abdominal pain • Headache • Dizziness • Drowsiness	• Lethargy	(Davis *et al*. 1979; King *et al*. 2002)

Kabatereine *et al*. 2007; Mutapi *et al*. 2011). Work in Uganda in 2010 revealed sub-optimal PZQ cure rates for *S. mansoni* among preschool children (Sousa-Figueiredo *et al*. 2010). To explore the appropriateness of age-adjusted dosing, the first pharmacokinetic/pharmacodynamic PZQ study in children in Uganda was conducted in that same area. Results from this recent study showed a very concerning risk of underdosing of children, particularly the younger ones, if standard 40 mg kg^{-1} was given. Higher doses may be needed for treating these and other children infected with *S. mansoni* (Bustinduy *et al*. 2016*a*) Fig. 6.

EXPANDING ACCESS TO PZQ FOR PRESCHOOL CHILDREN

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

THE DOUBLE-TREATMENT GAP IN MDA PROGRAMMES

The success of schistosomiasis control programmes has been very uneven over the last century. Efficacy has varied largely depending on the baseline

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

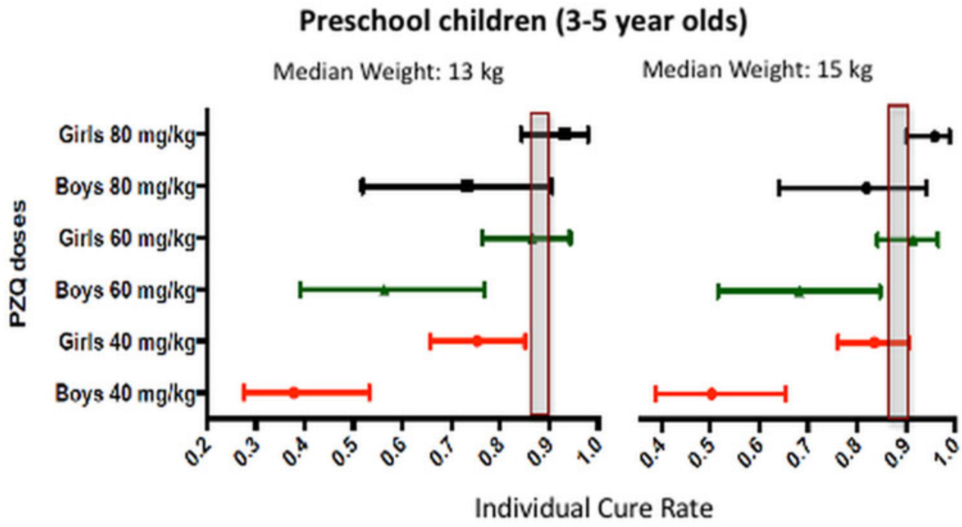

Fig. 6. Individual cure rate by different PZQ doses as modelled in 5000 patients in scale 0·0 (total failure) to 1·0 (complete cure) at 24 days post-single dose PZQ. Median weights-for-age were used to calculate the plots. Adapted from (Bustinduy *et al*. 2016*a*).

prevalence of infection (Jordan, 2000; Wang *et al*. 2008). Success stories in Japan, Morocco (Amarir *et al*. 2011), Iran and Tunisia give hope to less developed countries that are confronted by the 'trap' of self-perpetuating, disease-related poverty (Sacks, 2005). Economically disadvantaged countries are only just now starting to prioritize NTD control (Savioli *et al*. 2009). To date, implementation of large-scale control efforts in highly endemic areas has not shown permanent success, likely due to ecological factors favouring transmission and human reinfection. Part of the unfortunate lack of success of many control efforts stems from the complex reality of a disease that involves social interactions in hot spots of high transmission. Campaigns frequently miss 'super-spreaders'– children and individuals highly infected who act as reservoirs (King, 2009). The risk of reinfection or 're-worming' in high-transmission villages in Kenya was found to be as high as 50% over 2 years despite ongoing school-based mass drug administration (MDA) (Satayathum *et al*. 2006). Even more disheartening was the return to high prevalence in the same areas after control efforts were interrupted for 8 years (Wang *et al*. 2012). Older control interventions, based on better access to clean water and the use of molluscicides, may still have important adjuvant roles to play as part of adaptive strategies in implementing more effective schistosomiasis control programmes (Fenwick *et al*. 2009; Garba *et al*. 2009).

The WHO estimates that in the 52 countries in need of schistosomiasis control, over 123 million of school-age children need preventive chemotherapy, out of which only 43 million school age children (34·6%) may actually receive it (World Health Organization, 2016). Therefore, there is a large treatment gap remaining among this age group. Because current control strategies primarily target children who attend school, those remaining at home, often with more severe disease, do not necessarily receive treatment from MDA. A vicious cycle of heavier infection and more severe morbidity ensues (Stothard *et al*. 2011; Stothard *et al*., 2013). This double-treatment gap (preschool children and absent school age children) is a health inequality that should be a priority in control programme planning and implementation. Ambitious goals set by the WHO, 2012 roadmap (World Health Organization, 2012; Stothard *et al*. 2014) have increased funding and raised the profile of schistosomiasis *control*, but this leaves a long road ahead for true *elimination*.

CONCLUDING REMARKS

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

ACKNOWLEDGEMENTS

We would like to thank Jonathan Remppis and Anais Verheyden for contributing their data on preschool children from Gabon. We thank the University for Glasgow for hosting the meeting on celebration of Leiper, Leishman and Robertson. J.R.S. is Director of

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

COUNTDOWN, an implementation research consortium funded by DFID, UK.

FINANCIAL SUPPORT

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

REFERENCES

Amarir, F., El Mansouri, B., Fellah, H., Sebti, F., Mohammed, L., Handali, S., Wilkins, P., El Idrissi, A. L., Sadak, A. and Rhajaoui, M. (2011). National serologic survey of Haematobium schistosomiasis in Morocco: evidence for elimination. *American Journal of Tropical Medicine and Hygiene* **84**, 15–19.

Belard, S., Tamarozzi, F., Bustinduy, A. L., Wallrauch, C., Grobusch, M. P., Kuhn, W., Brunetti, E., Joekes, E. and Heller, T. (2016). Point-of-care ultrasound assessment of tropical infectious diseases – a review of applications and perspectives. *American Journal of Tropical Medicine and Hygiene* **94**, 8–21.

Blair, D. M., Meeser, C. V., Loveridge, F. G., Ross, W. F. (1949). Urinary schistosomiasis treated with miracil D. *Lancet* **1**, 344–346.

Bosompem, K. M., Bentum, I. A., Otchere, J., Anyan, W. K., Brown, C. A., Osada, Y., Takeo, S., Kojima, S. and Ohta, N. (2004). Infant schistosomiasis in Ghana: a survey in an irrigation community. *Tropical Medicine and International Health* **9**, 917–922.

Bustinduy, A. L., King, C. H. (2013). Schistosomiasis. In *Manson's Tropical Diseases* (ed. Farrar, J., Hotez, P. J., Junghanss, T., Kang, G., Lalloo, D. and White, N. J.), pp. 698–725. Elsevier.

Bustinduy, A. L., Thomas, C. L., Fiutem, J. J., Parraga, I. M., Mungai, P. L., Muchiri, E. M., Mutuku, F., Kitron, U. and King, C. H. (2011). Measuring fitness of Kenyan children with polyparasitic infections using the 20-meter shuttle run test as a morbidity metric. *PLoS Neglected Tropical Diseases* **5**, e1213.

Bustinduy, A. L., Parraga, I. M., Thomas, C. L., Mungai, P. L., Mutuku, F., Muchiri, E. M., Kitron, U. and King, C. H. (2013). Impact of polyparasitic infections on anemia and undernutrition among Kenyan children living in a *Schistosoma haematobium*-endemic area. *American Journal of Tropical Medicine and Hygiene* **88**, 433–440.

Bustinduy, A., Waterhouse, D., de Sousa-Figueiredo, J., Roberts, S. A., Atuhaire, A., Van Dam, G. J., Corstjens, P. A., Scott, J. T., Stanton, M. C., Kabatereine, N. B., Ward, S., Hope, W. H., Stothard, J. R. (2016*a*). Population pharmacokinetics and pharmacodynamics of praziquantel in Ugandan children with intestinal schistosomiasis: higher dosages are required for maximal efficacy. *MBio* **7**, e00227–16.

Bustinduy, A. L., Friedman, J. F., Kjetland, E. F., Ezeamama, A. E., Kabatereine, N. B., Stothard, J. R. and King, C. H. (2016*b*). Expanding praziquantel (PZQ) access beyond mass drug administration programs: paving a way forward for a pediatric PZQ formulation for schistosomiasis. *PLoS Neglected Tropical Diseases* **10**, e0004946.

Christopherson, J. B. (1918). Intravenous injections of antimonium tartaratum in Bilharziosis. *British Medical Journal* **2**, 652–653.

Christopherson, J. B. (1924). Longevity of parasitic worms. The term of living existence of *Schistosoma haematobium* in the human body. *Lancet* 742–743.

Colley, D. G., Binder, S., Campbell, C., King, C. H., Tchuem Tchuente, L. A., N'Goran, E. K., Erko, B., Karanja, D. M., Kabatereine, N. B., van Lieshout, L. and Rathbun, S. (2013). A five-country evaluation of a point-of-care circulating cathodic antigen urine assay for the prevalence of *Schistosoma mansoni*. *American Journal of Tropical Medicine and Hygiene* **88**, 426–432.

Colley, D. G., Bustinduy, A. L., Secor, W. E. and King, C. H. (2014). Human schistosomiasis. *Lancet* **383**, 2253–2264.

Cook, J. A., Jordan, P., Woodstock, L. and Pilgrim, V. (1977). A controlled trial of hycanthone and placebo in *Schistosomiasis mansoni* in St. Lucia. *Annals of Tropical Medicine and Parasitology* **71**, 197–202.

Coutinho, H. M., Acosta, L. P., McGarvey, S. T., Jarilla, B., Jiz, M., Pablo, A., Su, L., Manalo, D. L., Olveda, R. M., Kurtis, J. D. and Friedman, J. F. (2006*a*). Nutritional status improves after treatment of *Schistosoma japonicum*-infected children and adolescents. *Journal of Nutrition* **136**, 183–188.

Coutinho, H. M., Leenstra, T., Acosta, L. P., Su, L., Jarilla, B., Jiz, M. A., Langdon, G. C., Olveda, R. M., McGarvey, S. T., Kurtis, J. D. and Friedman, J. F. (2006*b*). Pro-inflammatory cytokines and C-reactive protein are associated with undernutrition in the context of *Schistosoma japonicum* infection. *American Journal of Tropical Medicine and Hygiene* **75**, 720–726.

da Silva, L. C., Sette, H., Jr., Chamone, D. A., Saez-Alquezar, A., Punskas, J. A. and Raia, S. (1975). Further clinical trials with oxamniquine (UK 4271), a new anti-schistosomal agent. *Revista do Instituto de Medicina Tropical de Sao Paulo* **17**, 307–311.

Davis, A. (1966). Field trials of ambilhar in the treatment of urinary bilharziasis in schoolchildren. *Bulletin of the World Health Organisation* **35**, 827–835.

Davis, A. (1968). Comparative trials of antimonial drugs in urinary schistosomiasis. *Bulletin of the World Health Organisation* **38**, 197–227.

Davis, A. and Wegner, D. H. (1979). Multicentre trials of praziquantel in human schistosomiasis: design and techniques. *Bulletin of the World Health Organisation* **57**, 767–771.

Davis, A., Biles, J. E. and Ulrich, A. M. (1979). Initial experiences with praziquantel in the treatment of human infections due to *Schistosoma haematobium*. *Bulletin of the World Health Organisation* **57**, 773–779.

Doenhoff, M. J., Cioli, D. and Utzinger, J. (2008). Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Current Opinion in Infectious Diseases* **21**, 659–667.

Ezeamama, A. E., Friedman, J. F., Acosta, L. P., Bellinger, D. C., Langdon, G. C., Manalo, D. L., Olveda, R. M., Kurtis, J. D. and McGarvey, S. T. (2005*a*). Helminth infection and cognitive impairment among Filipino children. *American Journal of Tropical Medicine and Hygiene* **72**, 540–548.

Ezeamama, A. E., Friedman, J. F., Olveda, R. M., Acosta, L. P., Kurtis, J. D., Mor, V. and McGarvey, S. T. (2005*b*). Functional significance of low-intensity polyparasite helminth infections in anemia. *Journal of Infectious Diseases* **192**, 2160–2170.

Farley, J. (1991). *Bilharzia: A History of Imperial Tropical Medicine*, Cambridge University Press, Cambridge, MA.

Farquharson, C. and Ahmed, S. F. (2013). Inflammation and linear bone growth: the inhibitory role of SOCS2 on GH/IGF-1 signaling. *Pediatric Nephrology* **28**, 547–556.

Fenwick, A., Webster, J. P., Bosque-Oliva, E., Blair, L., Fleming, F. M., Zhang, Y., Garba, A., Stothard, J. R., Gabrielli, A. F., Clements, A. C., Kabatereine, N. B., Toure, S., Dembele, R., Nyandindi, U., Mwansa, J. and Koukounari, A. (2009). The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. *Parasitology* **136**, 1719–1730.

Ferrari, M. L., Coelho, P. M., Antunes, C. M., Tavares, C. A. and da Cunha, A. S. (2003). Efficacy of oxamniquine and praziquantel in the treatment of *Schistosoma mansoni* infection: a controlled trial. *Bulletin of the World Health Organisation* **81**, 190–196.

Frank, C., Mohamed, M. K., Strickland, G. T., Lavanchy, D., Arthur, R. R., Magder, L. S., El Khoby, T., Abdel-Wahab, Y., Aly Ohn, E. S., Anwar, W. and Sallam, I. (2000). The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* **355**, 887–891.

Friedman, J. F., Kanzaria, H. K. and McGarvey, S. T. (2005). Human schistosomiasis and anemia: the relationship and potential mechanisms. *Trends in Parasitology* **21**, 386–392.

Garba, A., Toure, S., Dembele, R., Boisier, P., Tohon, Z., Bosque-Oliva, E., Koukounari, A. and Fenwick, A. (2009). Present and future schistosomiasis control activities with support from the Schistosomiasis control initiative in West Africa. *Parasitology* **136**, 1731–1737.

Gelfand, M. (1967). *A Clinical Study of Intestinal Bilharziasis (Schistosoma Mansoni) in Africa*. Edward Arnold (Publishers) Ltd, London, UK.

Gryseels, B. (1989). The relevance of schistosomiasis for public health. *Annals of Tropical Medicine and Parasitology* **40**, 134–142.

Gurarie, D., Wang, X., Bustinduy, A. L. and King, C. H. (2011). Modeling the effect of chronic schistosomiasis on childhood development and the potential for catch-up growth with different drug treatment strategies promoted for control of endemic schistosomiasis. *American Journal of Tropical Medicine & Hygiene* **84**, 773–781.

Jordan, P. (2000). From katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. *Acta Tropica* **77**, 9–40.

Jukes, M. C., Nokes, C. A., Alcock, K. J., Lambo, J. K., Kihamia, C., Ngorosho, N., Mbise, A., Lorri, W., Yona, E., Mwanri, L., Baddeley, A. D., Hall, A., Bundy, D. A. and Partnership for Child, D. (2002). Heavy schistosomiasis associated with poor short-term memory and slower reaction times in Tanzanian schoolchildren. *Tropical Medicine and International Health* **7**, 104–117.

Kabatereine, N. B., Brooker, S., Koukounari, A., Kazibwe, F., Tukahebwa, E. M., Fleming, F. M., Zhang, Y., Webster, J. P., Stothard, J. R. and Fenwick, A. (2007). Impact of a national helminth control programme on infection and morbidity in Ugandan schoolchildren. *Bulletin of the World Health Organisation* **85**, 91–99.

King, C. H. (2009). Toward the elimination of schistosomiasis. *New England Journal of Medicine* **360**, 106–109.

King, C. H. (2010). Parasites and poverty: the case of schistosomiasis. *Acta Tropica* **113**, 95–104.
King, C. H. (2015). It's time to dispel the myth of "asymptomatic" schistosomiasis. *PloS Neglected Tropical Diseases* **9**, e0003504.
King, C. H. and Dangerfield-Cha, M. (2008). The unacknowledged impact of chronic schistosomiasis. *Chronic Illness* **4**, 65–79.
King, C. H. and Mahmoud, A. A. (1989). Drugs five years later: praziquantel. *Annals of Internal Medicine* **110**, 290–296.
King, C. H., Lombardi, G., Lombardi, C., Greenblatt, R., Hodder, S., Kinyanjui, H., Ouma, J., Odiambo, O., Bryan, P. J., Muruka, J., Magak, P., Weinert, D., Ransohoff, D., Houser, H., Koech, D., Arap Siongok, T. K. and Mahmoud, A. A. F. (1988). Chemotherapy-based control of schistosomiasis haematobia. I. Metrifonate versus praziquantel in control of intensity and prevalence of infection. *American Journal of Tropical Medicine and Hygiene* **39**, 295–305.
King, C. H., Lombardi, G., Lombardi, C., Greenblatt, R., Hodder, S., Kinyanjui, H., Ouma, J., Odiambo, O., Bryan, P. J., Muruka, J. *et al*. (1990). Chemotherapy-based control of schistosomiasis haematobia. II. Metrifonate vs. praziquantel in control of infection-associated morbidity. *American Journal of Tropical Medicine and Hygiene* **42**, 587–595.
King, C. H., Muchiri, E. M., Mungai, P., Ouma, J. H., Kadzo, H., Magak, P. and Koech, D. K. (2002). Randomized comparison of low-dose versus standard-dose praziquantel therapy in treatment of urinary tract morbidity due to *Schistosoma haematobium* infection. *American Journal of Tropical Medicine and Hygiene* **66**, 725–730.
King, C. H., Olbrych, S. K., Soon, M., Singer, M. E., Carter, J. and Colley, D. G. (2011). Utility of repeated praziquantel dosing in the treatment of schistosomiasis in high-risk communities in Africa: a systematic review. *PloS Neglected Tropical Diseases* **5**, e1321.
Kjetland, E. F., Leutscher, P. D. and Ndhlovu, P. D. (2012). A review of female genital schistosomiasis. *Trends in Parasitology* **28**, 58–65.
Koukounari, A., Fenwick, A., Whawell, S., Kabatereine, N. B., Kazibwe, F., Tukahebwa, E. M., Stothard, J. R., Donnelly, C. A. and Webster, J. P. (2006). Morbidity indicators of *Schistosoma mansoni*: relationship between infection and anemia in Ugandan schoolchildren before and after praziquantel and albendazole chemotherapy. *American Journal of Tropical Medicine and Hygiene* **75**, 278–286.
Koukounari, A., Gabrielli, A. F., Toure, S., Bosque-Oliva, E., Zhang, Y., Sellin, B., Donnelly, C. A., Fenwick, A. and Webster, J. P. (2007). *Schistosoma haematobium* infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. *Journal of Infectious Diseases* **196**, 659–669.
Latham, M. C., Stephenson, L. S., Kurz, K. M. and Kinoti, S. N. (1990). Metrifonate or praziquantel treatment improves physical fitness and appetite of Kenyan schoolboys with *Schistosoma haematobium* and hookworm infections. *American Journal of Tropical Medicine and Hygiene* **43**, 170–179.
Leenstra, T., Coutinho, H. M., Acosta, L. P., Langdon, G. C., Su, L., Olveda, R. M., McGarvey, S. T., Kurtis, J. D. and Friedman, J. F. (2006). *Schistosoma japonicum* reinfection after praziquantel treatment causes anemia associated with inflammation. *Infection and Immunity* **74**, 6398–6407.
Lees, R. E. (1966). Lucanthone hydrochloride in the treatment of *Schistosoma mansoni* infection. *Transactions of the Royal Society of Tropical Medicine & Hygiene* **60**, 233–236.
McGarvey, S. T., Aligui, G., Daniel, B. L., Peters, P., Olveda, R. and Olds, G. R. (1992). Child growth and schistosomiasis japonica in northeastern Leyte, the Philippines: cross-sectional results. *American Journal of Tropical Medicine and Hygiene* **46**, 571–581.
McGarvey, S. T., Aligui, G., Graham, K. K., Peters, P., Olds, G. R. and Olveda, R. (1996). Schistosomiasis japonica and childhood nutritional status in northeastern Leyte, the Philippines: a randomized trial of praziquantel versus placebo. *American Journal of Tropical Medicine and Hygiene* **54**, 498–502.
Moore, J. A. (1972). Teratogenicity of hycanthone in mice. *Nature* **239**, 107–109.
Mott, K. E. (1982). "Control of schistosomiasis": morbidity-reduction and chemotherapy. *Acta Leidensia* **49**, 101–111.
Mott, K. E. (2004). Schistosomiasis. In *Global Epidemiology of Infectious Diseases* (ed. Murray, C. J. L., Lopez, A. and Mathers, C. D.), pp. 341–391. World Health Organisation, Geneva, Switzerland.
Mott, K. E. and Cline, B. L. (1980). Advances in epidemiology survey methodology and techniques in schistosomiasis. *Bulletin of the World Health Organisation* **58**, 639–647.
Mott, K. E., Dixon, H., Osei-Tutu, E., England, E. C. and Davis, A. (1985). Effect of praziquantel on hematuria and proteinuria in urinary schistosomiasis. *American Journal of Tropical Medicine and Hygiene* **34**, 1119–1126.
Mupfasoni, D., Karibushi, B., Koukounari, A., Ruberanziza, E., Kaberuka, T., Kramer, M. H., Mukabayire, O., Kabera, M., Nizeyimana, V., Deville, M. A., Ruxin, J., Webster, J. P. and Fenwick, A. (2009). Polyparasite helminth infections and their association to anaemia and undernutrition in northern Rwanda. *PloS Neglected Tropical Diseases* **3**, e517.
Murray, C. J. L. A. (1996). *Rethinking DALYs;The Global Burden of Disease*. Harvard School of Public Health/World Bank, Cambridge, MA, 1–98.
Mutapi, F., Rujeni, N., Bourke, C., Mitchell, K., Appleby, L., Nausch, N., Midzi, N. and Mduluza, T. (2011). *Schistosoma haematobium* treatment in 1–5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PloS Neglected Tropical Diseases* **5**, e1143.
Newsome, J. and Halawani, A. (1950). The treatment of urinary bilharzia in Egypt by miracil D. *Transactions of the Royal Society of Tropical Medicine & Hygiene* **44**, 67–76.
Nicholson, N. G. and McMahon, J. E. (1966). Death following ambilhar therapy. *British Medical Journal* **2**, 1261.
Nokes, C., McGarvey, S. T., Shiue, L., Wu, G., Wu, H., Bundy, D. A. and Olds, G. R. (1999). Evidence for an improvement in cognitive function following treatment of *Schistosoma japonicum* infection in Chinese primary schoolchildren. *American Journal of Tropical Medicine and Hygiene* **60**, 556–565.
Odogwu, S. E., Ramamurthy, N. K., Kabatereine, N. B., Kazibwe, F., Tukahebwa, E., Webster, J. P., Fenwick, A. and Stothard, J. R. (2006). *Schistosoma mansoni* in infants (aged < 3 years) along the Ugandan shoreline of Lake Victoria. *Annals of Tropical Medicine and Parasitology* **100**, 315–326.
Parraga, I. M., Assis, A. M., Prado, M. S., Barreto, M. L., Reis, M. G., King, C. H. and Blanton, R. E. (1996). Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. *American Journal of Tropical Medicine and Hygiene* **55**, 150–156.
Pineiro Perez, R., Santiago Garcia, B., Fernandez Llamazares, C. M., Baquero Artigao, F., Noguera Julian, A., Mellado Pena, M. J. and en representacion de p, T. (2016). [The challenge of administering anti-tuberculosis treatment in infants and pre-school children. pTBred Magistral Project]. Anales de Pediatria(***Barcelona***) **85, 4–12.**
Richter, J., Botelho, M. C., Holtfreter, M. C., Akpata, R., El Scheich, T., Neumayr, A., Brunetti, E., Hatz, C., Dong, Y. and Dietrich, C. F. (2016). Ultrasound assessment of schistosomiasis. *Zeitschrift für Gastroenterologie* **54**, 653–660.
Sacks, J. (2005). *The End of Poverty: Economic Possibilities for our Time*. Penguin Press, London.
Salomon, J. A., Vos, T., Hogan, D. R., Gagnon, M., Naghavi, M., Mokdad, A., Begum, N., Shah, R., Karyana, M., Kosen, S., Farje, M. R., Moncada, G., Dutta, A., Sazawal, S., Dyer, A., Seiler, J., Aboyans, V., Baker, L., Baxter, A., Benjamin, E. J., Bhalla, K., Bin Abdulhak, A., Blyth, F., Bourne, R., Braithwaite, T., Brooks, P., Brugha, T. S., Bryan-Hancock, C., Buchbinder, R., Burney, P. *et al*. (2012). Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* **380**, 2129–2143.
Satayathum, S. A., Muchiri, E. M., Ouma, J. H., Whalen, C. C. and King, C. H. (2006). Factors affecting infection or reinfection with *Schistosoma haematobium* in coastal Kenya: survival analysis during a nine-year, school-based treatment program. *American Journal of Tropical Medicine and Hygiene* **75**, 83–92.
Savioli, L., Gabrielli, A. F., Montresor, A., Chitsulo, L. and Engels, D. (2009). Schistosomiasis control in Africa: 8 years after World Health Assembly Resolution 54·19. *Parasitology* **136**, 1677–1681.
Sousa-Figueiredo, J. C., Basanez, M. G., Mgeni, A. F., Khamis, I. S., Rollinson, D. and Stothard, J. R. (2008). A parasitological survey, in rural Zanzibar, of pre-school children and their mothers for urinary schistosomiasis, soil-transmitted helminthiases and malaria, with observations on the prevalence of anaemia. *Annals of Tropical Medicine and Parasitology* **102**, 679–692.
Sousa-Figueiredo, J. C., Pleasant, J., Day, M., Betson, M., Rollinson, D., Montresor, A., Kazibwe, F., Kabatereine, N. B. and Stothard, J. R. (2010). Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. *International Health* **2**, 103–113.
Stephenson, L. S., Latham, M. C., Kurz, K. M., Kinoti, S. N., Oduori, M. L. and Crompton, D. W. (1985*a*). Relationships of *Schistosoma haematobium*, hookworm and malarial infections and metrifonate treatment to growth of Kenyan school children. *American Journal of Tropical Medicine and Hygiene* **34**, 1109–1118.

https://doi.org/10.1017/S0031182017000014 Published online by Cambridge University Press

Stephenson, L. S., Latham, M. C., Kurz, K. M., Miller, D., Kinoti, S. N. and Oduori, M. L. (1985*b*). Urinary iron loss and physical fitness of Kenyan children with urinary schistosomiasis. *American Journal of Tropical Medicine and Hygiene* **34**, 322–330.

Stothard, J. R., Sousa-Figueiredo, J. C., Betson, M., Green, H. K., Seto, E. Y., Garba, A., Sacko, M., Mutapi, F., Vaz Nery, S., Amin, M. A., Mutumba-Nakalembe, M., Navaratnam, A., Fenwick, A., Kabatereine, N. B., Gabrielli, A. F. and Montresor, A. (2011). Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology* **138**, 1593–1606.

Stothard, J. R., Sousa-Figueiredo, J. C., Betson, M., Bustinduy, A. and Reinhard-Rupp, J. (2013). Schistosomiasis in African infants and preschool children: let them now be treated! *Trends in Parasitology* **29**, 197–205.

Stothard, J. R., Stanton, M. C., Bustinduy, A. L., Sousa-Figueiredo, J. C., Van Dam, G. J., Betson, M., Waterhouse, D., Ward, S., Allan, F., Hassan, A. A., Al-Helal, M. A., Memish, Z. A. and Rollinson, D. (2014). Diagnostics for schistosomiasis in Africa and Arabia: a review of present options in control and future needs for elimination. *Parasitology* **141**, 1947–1961.

Stothard, J. R., Kabatereine, N. B., Archer, J., Al-Shehri, H., Tchuem-Tchuente, L. A., Gyapong, M. and Bustinduy, A. L. (2016). A centenary of Robert T. Leiper's lasting legacy on schistosomiasis and a COUNTDOWN on control of neglected tropical diseases. *Parasitology* 1–11. doi: 10.1017/S0031182016000998.

Terer, C. C., Bustinduy, A. L., Magtanong, R. V., Muhoho, N., Mungai, P. L., Muchiri, E. M., Kitron, U., King, C. H. and Mutuku, F. M. (2013). Evaluation of the health-related quality of life of children in *Schistosoma haematobium*-endemic communities in Kenya: a cross-sectional study. *PloS Neglected Tropical Diseases* **7**, e2106.

Van Dam, G. J., Xu, J., Bergquist, R., de Dood, C. J., Utzinger, J., Qin, Z. Q., Guan, W., Feng, T., Yu, X. L., Zhou, J., Zheng, M., Zhou, X. N. and Corstjens, P. L. (2015). An ultra-sensitive assay targeting the circulating anodic antigen for the diagnosis of *Schistosoma japonicum* in a low-endemic area, People's Republic of China. *Acta Tropica* **141**, 190–197.

Verani, J. R., Abudho, B., Montgomery, S. P., Mwinzi, P. N., Shane, H. L., Butler, S. E., Karanja, D. M. and Secor, W. E. (2011). Schistosomiasis among young children in Usoma, Kenya. *American Journal of Tropical Medicine and Hygiene* **84**, 787–791.

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., Baddour, L. M., Bahalim, A. N., Barker-Collo, S., Barrero, L. H., Bartels, D. H., Basanez, M. G., Baxter, A., Bell, M. L., Benjamin, E. J., Bennett, D. *et al*. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2163–2196.

Wamachi, A. N., Mayadev, J. S., Mungai, P. L., Magak, P. L., Ouma, J. H., Magambo, J. K., Muchiri, E. M., Koech, D. K., King, C. H. and King, C. L. (2004). Increased ratio of tumor necrosis factor-alpha to interleukin-10 production is associated with *Schistosoma haematobium*-induced urinary-tract morbidity. *Journal of Infectious Diseases* **190**, 2020–2030.

Wang, L., Utzinger, J. and Zhou, X. N. (2008). Schistosomiasis control: experiences and lessons from China. *Lancet* **372**, 1793–1795.

Wang, X., Gurarie, D., Mungai, P. L., Muchiri, E. M., Kitron, U. and King, C. H. (2012). Projecting the long-term impact of school- or community-based mass-treatment interventions for control of *Schistosoma* infection. *PloS Neglected Tropical Diseases* **6**, e1903.

Warren, K. S., Siongok, T. K., Ouma, J. H. and Houser, H. B. (1978). Hycanthone dose-response in *Schistosoma mansoni* infection in Kenya. *Lancet* **1**, 352–354.

Warren, K. S., Mahmoud, A. A., Muruka, J. F., Whittaker, L. R., Ouma, J. H. and Arap Siongok, T. K. (1979). Schistosomiasis haematobia in coast province Kenya. Relationship between egg output and morbidity. *American Journal of Tropical Medicine and Hygiene* **28**, 864–870.

Webbe, G. (1982). The intermediate hosts and host-parasite relationships. In *Schistosomiasis Epidemiology, Treatment and Control* (eds. Jordan, P. and Webbe, G.), pp. 16–49. Heinemann, London.

World Health Organization. (2007). *Integrated Management of Childhood Illnesses*, World Health Organization, Geneva, Switzerland.

World Health Organization. (2011). *Report of a Meeting to Review the Results of Studies on the Treatment of Schistosomiasis in Preschool-aged Children*. World Health Organization, Geneva, Switzerland.

World Health Organization. (2012). *Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases : A Roadmap for Implementation: Executive Summary*, World Health Organization, Geneva, Switzerland.

World Health Organization. (2016). Schistosomiasis: number of people treated worldwide in 2014. *The Weekly Epidemiological Record* **91**, 53–60. World Health Organization, Geneva, Switzerland.

Xiao, S. H. (2005). Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Tropica* **96**, 153–167.