FEMALE GENITAL SCHISTOSOMIASIS
The Most Neglected Gynaecological Disease

The International Society for Neglected Tropical Diseases
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1 SUMMARY

Schistosomiasis (aka bilharzia) is a devastating poverty-related neglected tropical disease (NTD) which affects over 200 million people across more than 50 countries. The vast majority (>90%) of cases are found in Sub-Saharan Africa (SSA) and more than half of those infected are school-aged children. The causative agent is a blood fluke, of the genus *Schistosoma*. The larvae of this parasite are transmitted by snails in human fresh water sources, acting as intermediate hosts. Following ingestion by humans, schistosome larvae develop into worms in the body and colonise organs and tissues. Egg deposition by adult worms leads to an inflammatory response in affected tissues and potentially serious clinical consequences which can include anaemia, liver enlargement, abdominal pain and diarrhea. Depending on the species of parasite (there are five main types), infections are primarily intestinal or urogenital in nature. Schistosomiasis has the highest global burden of disease among the recognized NTDs, according to the WHO. Female genital schistosomiasis (FGS) is a specific disease entity which affects at least 20 million girls and women (epidemiological information is scant; another prevalence estimate is substantially higher, at up to 150 million). FGS results from infection by *S. haematobium*, the most common species of schistosome parasite. In FGS, egg embolisation results in fibrotic nodules in the uterus, cervix and lower genital tracts. This in turn can result in a variety of serious symptoms including bleeding, pain during intercourse, impaired reproduction (encompassing ectopic pregnancies, infertility, spontaneous abortions and premature births), social stigma, depression and cervical lesions. Of particular concern is the growing body of evidence linking FGS with increased HIV transmission and disease progression in African women. Treatment for schistosomiasis is available in the form of the anti-parasitic drug praziquantel (donated by Merck KGaA), which is highly effective at killing adult worms. However, the standard single dose regimen is not thought to be sufficient to prevent and destroy all the eggs associated with FGS such that preventative treatment, beginning in childhood, may be needed. In this regard, a circa 6,500 patient study is underway in South Africa to assess the impact of annual preventative praziquantel treatment on the prevalence and severity of FGS, together with the prevalence of HIV infection, among pre- and post-pubertal schoolgirls, with estimated primary completion in December 2018. An additional barrier to effective treatment of FGS is lack of capacity to effectively diagnose and case manage patients: as noted in the most substantive review of the literature (Christinet *et al*; Int J Parasitology 46 (2016) 395-404), “proper clinical and laboratory diagnosis of
FGS remains a significant issue and bottleneck” and “recognition and treatment of schistosomiasis genital tract lesions requires well trained physicians and specialized infrastructure which are not readily available in most schistosomiasis endemic settings”. Finally, the lack of a child-friendly formulation of praziquantel represents a barrier to uptake of treatment of pre-school girls with FGS. In the latter case, there is optimism that this may be addressed by the efforts of the Pediatric Praziquantel Consortium which plans to file a palatable, orally dispersible formulation for registration in 2019. It would be wrong not to recognize the major progress over the past decade in the treatment and control of schistosomiasis as a whole, led by the WHO. This is evident in the trebling of praziquantel treatment coverage of school-aged children in affected countries between 2008 and 2015, to 45%. However, coverage is still below the WHO goal of “at least 75%” by 2020. Furthermore, the specific complexities surrounding recognition, diagnosis and treatment of FGS continue to constitute major additional challenges. Accordingly, much more needs to be done by the global health community and affected nations to address this common source of acute and chronic suffering in girls and women, best summarised in the words of Christinet: “the scarcity of integrated approaches to address FGS calls for more concerted action in its detection, treatment and prevention, otherwise it will remain a neglected gynaecological disease.”

2 SCHISTOSOMIASIS AND FGS: OVERVIEW

Schistosomiasis was first described in Egypt in 1851 by Theodor Bilharz (giving rise to the traditional name of the disease of bilharzia). It is a water-borne, poverty-related parasitic disease for which the causative agent is a blood fluke (trematode worm) of the genus *Schistosoma*. Schistosomiasis has the highest global burden of disease among the recognized NTDs, according to the WHO, with an estimated 218 million people requiring treatment in 2015 across 52 countries and c.700 million living in endemic areas. Over 90% of infections occur in SSA but parts of Latin America and Asia are also prone to disease. Children are especially susceptible: more than half of those requiring treatment in 2015 were school-aged children and a large proportion of the under-14 age group in endemic countries are infected.

The life cycle of the *Schistosoma* parasite involves freshwater snails, as intermediate hosts, which pass larvae (known as cercariae) into the water. Ingestion of the larvae from water sources results in infection of humans, which ultimately pass parasite eggs back into the water via urine or faeces. The eggs migrate to and infect snails, perpetuating the cycle. Within humans, the schistosome larvae develop into adult worms which colonise organs and tissues and produce eggs. It is the inflammatory response to deposited eggs which gives rise to the multiple symptoms of schistosomiasis which can include anaemia, liver enlargement, abdominal pain and diarrhea. The adult worms can live for years in the veins which drain the human urogenital tract and intestines, resulting in chronic disease. There are five main types of schistosome parasite: *S. haematobium*, the most common species (accounting for around two-thirds of schistosomiasis infections in SSA), is associated with urogenital infections while *S. mansoni* (the second most common species), *S. japonicum*, *S. mekongi*, and *S. guineensis* are associated with intestinal infections.

Female genital schistosomiasis (FGS) is a specific type of schistosomiasis which results from infection of girls and women by *S. haematobium*. Described by the Public Library of Science (PLOS) as “this ancient scourge of girls and women”, FGS is characterized by embolization of deposited parasite
eggs and the development of fibrotic nodules in the uterus, cervix and lower genital tracts. This in turn may result in a variety of serious symptoms including:

- vaginal bleeding
- pain during intercourse
- impaired reproductive capability (with a spectrum of possible adverse outcomes including ectopic pregnancy, infertility, spontaneous abortion, premature birth and low birth weight)
- social stigma
- depression
- cervical lesions (and potentially cervical cancer)

FGS is estimated to affect at least 20 million girls and women, predominantly in SSA. However, this figure could be a dramatic under-estimate as the scientific literature notes the paucity of validated epidemiological information on the disease. PLOS for example, suggests that the prevalence of FGS could be substantially higher, at up to 150 million affected girls and women. In either case, FGS represents a major under-recognised gynaecological health burden.

An additional, critically-important dimension to this disease is that there is an increasing body of clinical evidence associating FGS with increased risk of HIV infection. A recent paper by Downs et al. in PLOS demonstrated that pre-existing schistosomiasis infection in a rural region of Tanzania increased the risk for HIV infection nearly three-fold in women, while there was no impact on risk in men. The authors concluded that “schistosomiasis may play a role in HIV transmission and disease progression in African countries”. It is hypothesized that ulcerated lesions and inflammation in the urogenital tract resulting from FGS infection increase mucosal susceptibility to HIV following sexual exposure.

Figure 1 on the following page summarises key elements of the pathology, prevalence, treatment options and WHO targets for schistosomiasis and FGS.
### Figure 1: Schistosomiasis and FGS overview

| Cause | Infection with blood flukes (trematode worms; genus: Schistosoma) from contaminated fresh water (usually where sanitation is inadequate). Snails act as hosts, passing larvae (cercariae) into the water. The cycle is perpetuated when infected humans pass eggs from female worms into fresh water sources, via urine or faeces, facilitating the migration of the eggs to snails. There are five main species of schistosomiasis parasite. The most common, accounting for ~67% of schistosomiasis cases in Sub-Saharan Africa (SSA), is *S. haematobium* which is responsible for urogenital infections. The four other main schistosome species each result in intestinal infections and include *S. mansoni* (the most common of the four), *S. japonicum*, *S. mekongi*, *S. guineensis*.
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| Clinical manifestation | Adult worms live in the veins which drain the human urogenital tract and intestines. Chronic damage is typically caused by the inflammatory immune reaction to eggs which become trapped in bodily tissues and organs. This can result in a variety of symptoms including anaemia, malnutrition, abdominal pain, liver and bladder damage. Female genital schistosomiasis (FGS) is a specific disease entity which results from the embolisation of *S. haematobium* eggs to form fibrotic nodules in the uterus, cervix and lower genital tracts of girls and women. This can result in bleeding, pain, impaired reproduction (including ectopic pregnancies, spontaneous abortions and premature births), social stigma, cervical lesions (possibly cervical cancer) and an increased risk of HIV/AIDS infection (up to 3-fold in a recent paper).
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| Affected regions | According to the WHO, 78 countries are affected by schistosomiasis of which 52 require preventative chemotherapy (see ‘Treatment’ below). Globally ~700m people live in endemic regions and an estimated 218m infected people required preventative treatment in 2015. The vast majority (>90%) of people affected by schistosomiasis live in SSA, including a large proportion of children aged under-14 (more than half of those requiring preventative treatment in 2015 were school-aged children). Schistosomiasis is also found in Asia, Latin America and occasionally elsewhere (eg, an outbreak took place in Corsica, France in 2013). Within this total, the prevalence of FGS in girls and young women is estimated to be at least 20m.
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| Treatment | The antiparasitic drug praziquantel (principally donated by Merck KGaA), administered as a single dose of 40mg/kg, is used to successfully treat schistosomiasis. Praziquantel can also be safely used in conjunction with albendazole and/or ivermectin in populations at risk from a wide range of helminthic parasites (lymphatic filariasis, onchocerciasis and soil transmitted helminthiasis). A child-friendly version of praziquantel has not been available thus far but a palatable, orally dispersible formulation is undergoing clinical development by the Pediatric Praziquantel Consortium: the target is to file this paediatric formulation for registration in 2019, so that the 25m pre-school age children suffering from schistosomiasis in SSA can receive suitable treatment. Additional strategies recommended by WHO to prevent and treat schistosomiasis include hygiene education, improving fresh water sanitation and snail control.
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| Progress to date | The WHO has used praziquantel for preventative control since 2006 (although the drug has been in use in schistosomiasis since 1984). As part of the London Declaration on NTDs in January 2012, Merck KGaA committed to donate up to 250m praziquantel tablets pa for an unlimited period (a ten-fold expansion, from 25m tablets pa previously). Increased availability of effective medication has helped to facilitate significantly increased treatment coverage levels: in 2015, ~45% of school-aged children in target countries had treatment coverage, representing around two-thirds of the WHO target of at least 75% by 2020 (see ‘WHO targets’ below) and around three-times the level of coverage (14%) achieved in 2008. The availability of a child-friendly formulation of praziquantel is expected to help to expand coverage further given the high prevalence of children among those infected.
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| WHO targets | The WHO Roadmap aims to control morbidity from schistosomiasis and achieve treatment coverage of at least 75% of all school-aged children by 2020. The WHO concedes that additional targets for regional elimination (prevention of transmission) by 2020 are “unlikely to be achieved”.

Source: WHO website, miscellaneous medical websites (eg, PLOS)
3 CURRENT AND FUTURE TREATMENT OPTIONS

The standard treatment for schistosomiasis is the anti-parasitic drug praziquantel, administered as a single dose of 40mg/kg. This is highly effective at killing adult worms (although it may not be sufficient to completely eliminate eggs in FGS – see section 4 below). Praziquantel has the added advantage that it can be safely used in conjunction with other recommended anti-worming drugs, albendazole and/or ivermectin, in populations at risk from a wide range of helminthic parasites (lymphatic filariasis, onchocerciasis and soil transmitted helminthiasis).

The WHO has recommended praziquantel for preventative control of schistosomiasis since 2006 (although the drug has been in use to treat the disease since 1984). The German-based pharmaceutical company Merck KGaA supplies the drug free of charge to the WHO and, as part of the London Declaration on NTDs in January 2012, the company committed to donate up to 250 million tablets pa for an unlimited period. This represented a ten-fold expansion in supply, from 25 million tablets pa previously. The increased availability of praziquantel, together with educational and other efforts to raise disease awareness by the global health community (including the WHO, the Schistosomiasis Control Initiative, USAID and DFID, amongst others), has helped to facilitate significantly increased treatment coverage levels; in 2015, around 45% of school-aged children in target countries had treatment coverage, representing around two-thirds of the WHO target of “at least 75%” by 2020 and around three-times the level of coverage (14%) achieved in 2008.

To date, a child-friendly version of praziquantel has not been available. However, a palatable, orally dispersible formulation is undergoing clinical development by the international non-profit Pediatric Praziquantel Consortium: the target is to file a paediatric formulation for registration in 2019, so that the 25 million pre-school age children suffering from schistosomiasis in SSA can receive suitable treatment. The Consortium was founded in 2012 and now includes Merck KGaA, Astellas Pharma Inc., Swiss Tropical and Public Health Institute (Swiss TPH), Lygature, Farmanguinhos, Simcyp and the UK-based Schistosomiasis Control Institute (SCI). Two alternative tablet formulations (one containing racemic praziquantel and the other the clinically active L-isomer) are currently undergoing a Phase II trial in preschool-age children age 6 years or below in the Ivory Coast (the study started in June 2016) in an effort to find the optimal dosage format. A Phase III registrational study is planned to start in 2018, based on the outcome of the Phase II trial.

Non-pharmaceutical strategies recommended by the WHO to prevent and treat schistosomiasis include hygiene education, improving fresh water sanitation and snail control.
4 SPECIFIC ISSUES FOR FGS

FGS presents specific complexities that demand a greater focus from the global health community and affected nations. First, as noted, the standard single dose regimen of praziquantel is not thought to be sufficient to prevent and destroy all the eggs associated with FGS, based on a number of scientific papers. As a consequence, it has been proposed that preventative treatment, beginning in childhood, may be needed to fully prevent and control FGS. In this regard, a circa 6,500 patient study is underway in South Africa to assess the impact of annual preventative praziquantel treatment on the prevalence and severity of FGS, together with the prevalence of HIV infection, among pre- and post-pubertal schoolgirls. This study (“Prevention of Female Genital Schistosomiasis (FGS) in Rural High-Endemic South Africa (VIBE-FGS); clinicaltrials.gov identifier, NCT01154907) has an estimated primary completion date of December 2018, suggesting that first results will become available during 2019. The authors of the study (which is sponsored by Oslo University Hospital) note that the results “can be of use in current schistosomiasis control programs in the near term resulting in improved strategies for treatment” and that “preventing or reducing the risk of FGS and genital lesions will lead to improved reproductive health among women living in schistosomiasis endemic areas”.

Secondly, the lack of a child-friendly formulation of praziquantel represents a barrier to uptake of treatment of pre-school girls with FGS. As noted above, however, there is optimism that this may be addressed by the efforts of the Pediatric Praziquantel Consortium.

Perhaps the greatest barrier, however, to the effective treatment and control of FGS is lack of capacity in affected countries to effectively diagnose and case manage patients. This is highlighted in a substantive and impressive review of the literature on FGS (“Female Genital Schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease”; Christinet et al; Int J Parasitology 46 (2016) 395-404). The author, Vanessa Christinet, notes that “proper clinical and laboratory diagnosis of FGS remains a significant issue and bottleneck”. As a result “women suffering from FGS approach healthcare providers with complaints about bleeding, infertility or suspicion of having sexually transmitted infections, however little attention is provided because the recognition and treatment of schistosomiasis genital tract lesions requires well trained physicians and specialized infrastructure which are not readily available in most schistosomiasis endemic settings”.

The WHO has attempted to improve the ease of diagnosis by publishing a user-friendly reference document on FGS (“Female genital schistosomiasis – A pocket atlas for clinical health-care professionals”; 2015). This 49-page booklet provides straightforward criteria and clear schematics to aid in the diagnosis of FGS-associated lesions in the uterine cervix and vagina. However, to put this fully into operation at scale requires training of medical staff and appropriate diagnostic equipment (digital cameras, colposcopes), which are often not readily available in affected regions. Consequently, investment in capacity and health system strengthening in endemic areas is desperately needed if the barriers are to be more effectively addressed.
The prevalence of FGS, at anywhere between 20 million and 150 million, alone justifies greater focus on the part of the global health community. However, if this prevalence is considered also in the context of the seriousness of the consequences of infection - from bleeding and pain to severely compromised reproductive health – and the fact that in many cases it is young girls affected, the urgency with which this NTD should be addressed is amplified many times over. The need to address this disease becomes more acute still when we take into account the growing body of evidence suggesting that schistosomiasis infection may play an important role in HIV transmission and disease progression among women in Africa.

The 2030 Sustainable Development Goals (SDGs) seek, amongst others, to “ensure healthy lives and promote well-being for all at all ages”, including a focus on ending NTDs as well as improving reproductive health. If the SDGs are to be taken at all seriously, a concerted approach must be a priority for the global health community and affected nations to address this common and entirely unnecessary source of suffering in girls and women.

An integrated approach involving investment in medical education and training, improved diagnosis, validated preventative treatment regimens (including child-friendly medication), a greater focus on water sanitation (for prevention), and overall health system strengthening is needed. Efforts to control and eliminate other tropical diseases (for example, malaria) already benefit from such an integrated, holistic strategy across supra-national health organisations, NGOs, other donors and endemic nations. To close with the words of Christinet: “the scarcity of integrated approaches to address FGS calls for more concerted action in its detection, treatment and prevention, otherwise it will remain a neglected gynaecological disease.”
KEY SOURCES


WHO website information pages on schistosomiasis (August 2017); http://www.who.int/schistosomiasis/en/

‘Female genital schistosomiasis – A pocket atlas for clinical health-care professionals’ (WHO; 2015)

‘Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease’; Christinet et al; International Journal for Parasitology 46 (2016) 395–404

‘Female Genital Schistosomiasis (FGS): Sub-Saharan Africa’s Secret Scourge of Girls and Women’; Hotez (2013); Blog from PLOS (Public Library of Science) website

Effects of schistosomiasis on susceptibility to HIV-1 infection and HIV-1 viral load at HIV-1 seroconversion: A nested case-control study


‘Schistosomiasis Control Initiative and Pediatric Praziquantel Consortium join forces in the fight against schistosomiasis’ (12 October 2016; https://www.pediatricpraziquantelconsortium.org/)

www.clinicaltrials.gov

ABOUT THE AUTHOR

Mark Clark is a 30-year veteran analyst of the pharmaceutical industry and has since 2015 divided his time between his consultancy practice (BIApharma LLP) and volunteering for health-related charities. Mark is a Trustee of Malaria Consortium and a member of its Finance, Audit & Risk Committee. He has also volunteered for Malaria No More UK and authored the ISNTD Disease Briefs, ‘Benchtop to Barrios: the challenge of developing new drugs for Chagas disease’ and ‘Mycetoma: the case for a new entrant to the WHO’s list of neglected tropical diseases (NTDs)’.