Chapter 6

Global Control Efforts of Schistosomiasis and Soil-Transmitted Helminthiasis

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Additional information is available at the end of the chapter

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Abstract

Schistosomiasis is a waterborne disease whose life cycle involves freshwater sources conducive for the survival and reproduction of aquatic snails that form a connective link between man and water in the life cycle and transmission of schistosomiasis. The African region has network of rivers with freshwater suggesting the presence of schistosomiasis and difficulty to control. Some communities, due to socioeconomic challenges, have inadequate sanitation and water supply; use of bush toilets for excretion is commonly practiced. These conditions in Africa also promote transmission of soil-transmitted helminthiasis. The World Health Organization (WHO), in response to the public health and socioeconomic impact of neglected tropical diseases, is coordinating strategies for the control and elimination of the diseases including schistosomiasis and soil-transmitted helminthiasis. As one of the milestones, mapping of neglected tropical diseases in the African region has been prioritized for the implementation of control strategies. In countries where mapping has been completed, WHO and its partners are supplying medicines required for annual mass treatment for preventive chemotherapy and encourage countries to take ownership in implementing complementary strategies for morbidity control, elimination and eradication of country-specific neglected tropical diseases. The mainstay of helminthiasis control is preventive chemotherapy, targeting school age children to prevent morbidity and development of pathological manifestations, including urogenital schistosomiasis that is understood to contribute to HIV transmission. Vaccines are still to be discovered and designed, with many possible antigen candidates, but however the immune responses are still to be fully understood. There is need to understand the subtle link between each component of the immune responses and the host immunogenetics impacting on the translated immunological response of cytokines that are delicately controlled for cellular immunity and antibody production. Currently, preventive chemotherapy treatment is the only

control method in concert with health education in an attempt to cut the helminthiasis life cycle.

Keywords: control, schistosomiasis, soil-transmitted helminthiasis, mass drug administration, chemotherapy

1. Introduction

Parasitic worms (helminths) are responsible for chronic infections of over two billion people worldwide and impose a huge public health burden. The hallmark of helminth infection is immune modulation of the host's immune response, which both limits immunopathology in the host while allowing the worms to evade host immune attack. The immune modulation of host responses during helminth infection has attracted much interest in terms to understand the generation of protective immunity. Unfortunately, the immune modulation occurring during helminth infection also interferes with the expression of naturally acquired protective immunity against the parasites, resulting in an accumulation of parasites in the host. Experimental Studies suggest manipulating host regulatory responses can enhance helminths vaccine efficacy. In human schistosomiasis, the health impact is not confined to immunopathology but extends to physical damage resulting from the presence of the parasites and the passage of parasite eggs as they are excreted from the host via urine or stool. In the case of urogenital schistosomiasis, infection interferes with child development and health, diminishes female reproductive health and increases susceptibility to sexually transmitted diseases including HIV and can lead to bladder cancer.

Currently available control method is treatment of infected people with the antihelminthic drug praziquantel. Field studies have already demonstrated that praziquantel treatment can induce protective immunity in chronically infected children, while treatment if conducted earlier in life would mean children benefit from the effects of praziquantel earlier, thus avoiding the health costs associated with chronic infections. Praziquantel treatment imparts on molecular and immune responses, mediating resistance in individuals previously with chronic schistosome who became resistant against reinfection by the parasites. This concept of infection-treatment as immunization is used in some veterinary diseases. There is need to investigate the transcriptional and post-translational characteristics underlying resistance to schistosome. Subsequently, regular childhood treatment may induce protective immune responses, that is, treatment of primary infections before it becomes chronic, induces regulatory responses that may reduce the efficacy of the effector responses. More studies are required to understand the activation of regulatory, pro- and anti-inflammatory responses in individuals who remain susceptible to re-infection and the mechanisms by which these regulatory responses modulate effector functions. Such knowledge is important to improving current and future helminth interventions as well as the development of novel therapeutics against immune-mediated pathology arising from parasitic infection or immune dysfunction.

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An important constraint for helminths vaccine development is the paucity of information on the induction of appropriate effector pathways mediating protective immunity over the regulatory responses, which modulate them, as well as on mechanisms by which vaccine efficacy and longevity can be enhanced. Experimental studies of other helminths suggest that vaccine efficacy can be improved beyond the typical low protection level by neutralizing immunomodulatory processes. There is missing evidence to identify the key immunomodulators and their functional mechanisms, which can be manipulated to improve the efficacy of helminths vaccines and pathways that can be manipulated to enhance the longevity of vaccine-induced resistance. In addition, there is currently lack of consensus on markers of vaccine-induced protection. However, in the meantime, preventive chemotherapy is the only alternative in concert with health education.

1.1. Human helminthiasis as neglected tropical diseases

Human helminthiasis are part of the neglected tropical diseases (NTDs), which are a diverse group of parasitic, viral and bacterial diseases with distinct characteristics, that thrive mainly among the poorest populations, hinder socioeconomic development and cause substantial illness for more than one billion people globally [1]. Seventeen NTDs (**Figure 1**) have been specified by the World Health Organization (WHO) and these include dengue, buruli ulcer, cutaneous leishmaniasis, taeniasis/cysticercosis and echinococcosis/hydatidosis, foodborne trematode infections, soil-transmitted helminthiasis (STH), intestinal worms, rabies, blinding trachoma, endemic treponematoses (yaws), leprosy, Chagas disease, Human African trypanosomiasis, visceral leishmaniasis, dracunculiasis, lymphatic filariasis, onchocerciasis and schistosomiasis [2]. These NTDs impair physical and intellectual capacities of the affected persons, thereby perpetuating the cycle of poverty [1]. Forty-seven countries in the African region are endemic to at least one NTD and 37 of them (79%) are coendemic for at least five of these diseases [3].

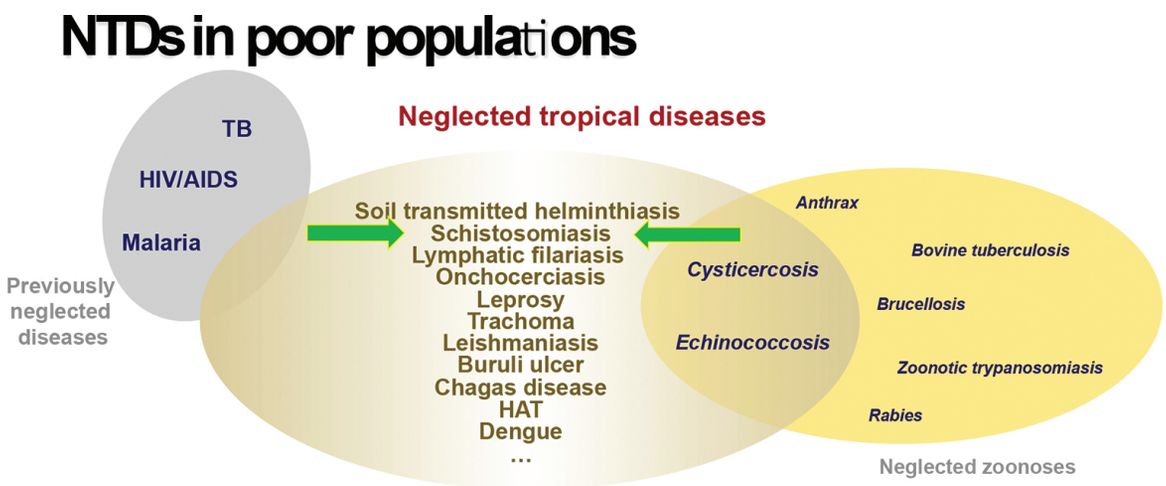

Figure 1. A list of neglected tropical diseases. Much attention is given to the previously neglected diseases being Malaria, HIV/AIDS and TB. While schistosomiasis and soil transmitted helminthiasis continue to be neglected. Included are neglected zoonosis diseases that come about the interactions of humans and their animals.

Five of the 17 NTDs [lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis (STH) and trachoma] are amenable to preventive chemotherapy. Thus, targeting such disease for control and elimination using available safe medicines and supported by complementary interventions could provide a noticeable quick win on NTD for the African region and in particular for the endemic countries. STHs have been specified as endemic in many countries even though the data collection methods used could be at variance from those recommended by WHO [3]. Countries in the African region through their Ministries of Health have not only endorsed the adoption of the resolutions on NTD by the World Health Assembly (WHA) in 2013, but they also expressed their commitment to scaling up interventions against the major NTDs [1]. With such an increased momentum to eliminate NTDs, it is critical that WHO member states implement NTD strategies demonstrating their commitments.

2. Disease transmission

Schistosomiasis transmission begins most often when people come into contact with bodies of freshwater in which infected people have urinated or defecated and there is a stage of the life cycle in intermediate snail host [4]. Transmission is linked to the life cycle of the schistosome (e.g., egg, miracidium larval form, sporocyst, cercaria, schistosomule, adult schistosome), when an egg comes in contact with freshwater, where it hatches and releases a miracidium. The miracidium swims by ciliary movement toward the snail intermediate host and penetrates its soft tissue. The *Schistosoma* species are transmitted by different freshwater snails that serve as intermediate hosts (**Figure 2**). The miracidium penetrated the snail and develops into sporocyst that migrates to the hepatic and gonadal tissue of the intermediate snail host. After 2–4 weeks, the sporocysts develop into cercariae [4]. Hundreds of the fork-tailed cercariae leave the snail intermediate host under the stimulation of light, swimming in the water until they find definitive mammalian hosts. The cercariae enters the skin using both mechanical activity and proteolytic enzymes [5], losing the tail and develops into schistosomules that migrate via the blood or lymphatic vessels [4]. The schistosomules then migrate to the portal circulation where they mature into adult worms. Adult *S. japonicum, S. mekongi* and *S. intercalatum* worms stay in the portal and mesenteric vessels, while *S. haematobium* worms migrate and live in the vesical plexus. The adult worms mate, with the male adult schistosome embracing the female worm into its gynaecophoric canal [5]. Four to 6 weeks after the cercaria has penetrated the human skin, the embraced female adult worm starts producing eggs, except for *S. haematobium* worms that take about 60–63 days before oviposition [6]. The adult female worms continue producing eggs throughout their lifetime, with about half the number of eggs produced are excreted with feces or urine, while the rest remain trapped in the tissues causing immunopathology (**Figure 2**) [7].

2.1. Global public health significance of schistosomiasis

Schistosomiasis remains one of the most prevalent parasitic diseases in the world, found endemic in 76 countries and is a public health concern in the developing world [8]. Schistoso-

miasis is a chronic disease, poorly recognized at early stages and if untreated the disease debilitates men and women during their most reproductive years. The disease is typically common in areas of the economically disadvantaged people living in areas that have no access to proper sanitation and good water supply systems. The high-risk groups for schistosomiasis are school age children, adolescents, reproductive women and also those whose occupations involve contact with water, for example fishermen, farmers, irrigation workers and women in their domestic tasks [8]. It is estimated that about 652 million people are at risk of infection from the five human schistosome species (*S. haematobium, S. mansoni, S. japonicum, S. intercalatum and S. mekongi*) and that 193 million are infected of which 85% are on the African continent [8]. Children between 5 and 15 years of age are the high-risk group and suffer most from morbidity due to high intensities of infection [9]. Though schistosomiasis has been intensively investigated over the past half a century, alone or in combination with other infectious diseases, a lot needs to be understood. **Figure 3** gives a detailed analysis of the effects of infection, the clinical evolution and the resultant severe diseases resolution and manifestations. Progression to disease severity is compounded by many other conditions that include the host genetics, coinfections by other parasites, intensity and duration of infection. However, other conditions such as malnutritional status of the host that is common in resource-limited areas may also aggravate the infections to severe diseases condition.

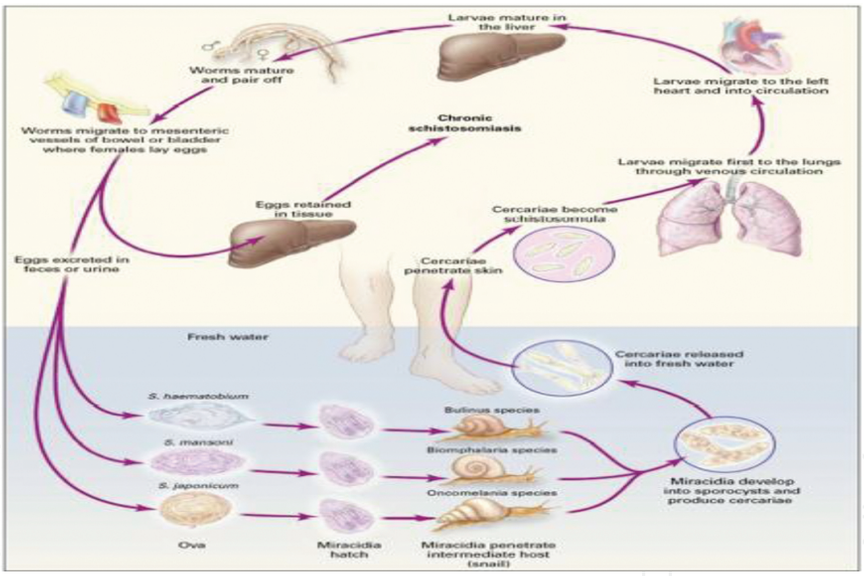

Figure 2. A general life cycle of *schistosome* species [7]. The life cycle shows the different shell morphology of the intermediate host and the morphological appearance of the ova that is important for diagnosis.

The number of individuals with hydronephrosis due to *S. haematobium* infection has been estimated to be close to 20 million, while about 70 million mainly school–age children suffer from hematuria due to their water contact activities [8]. Indirect measurement of morbidity is important in children, ranging from malnutrition, anemia, growth retardation, irritability and cognitive impairment that result in poor performance in school. Sick children are often absent from school, leading to loss in school performance and participation. Chronic irreversible

sequelae, such as liver fibrosis, urinary tract obstruction and bladder cancer, become apparent in schistosomiasis in adult age as a result of heavy infection that occurs during childhood. This underscores the importance of repeated chemotherapy at regular intervals of young children living in endemic areas in order to prevent development of irreversible sequelae in adulthood.

Genital schistosomiasis is also common in both males and females in endemic areas. Female genital schistosomiasis (FGS) described as the presence of schistosome eggs on the upper or lower part of the reproductive tract has been demonstrated in up to 75% of females living in schistosomiasis endemic communities (**Figure 4A** and **B**) in Africa [10–12]. Reproductive complications due to FGS include low birthweight, abortions, ectopic pregnancies, primary and secondary infertility [13–16]. In African cultures, infertility in married couples is often blamed on women. This leads to rejection by husbands, family and kinship group. The society may not accept women who do not get pregnant [16]. It is also hypothesized that FGS facilitates transmission of HIV [12, 17]. The far-reaching consequences of schistosomiasis infection also include reduced national economic growth and persistent poverty. However, treatment using a single dose is now available, effective and safe to be taken by uninfected children or pregnant mothers and, can easily be incorporated into regular field activities [18]. Any initiative to control schistosomiasis will not only contribute towards morbidity reduction but also to the control of HIV transmission, improvement of school health and performance of children, national economic growth and poverty alleviation.

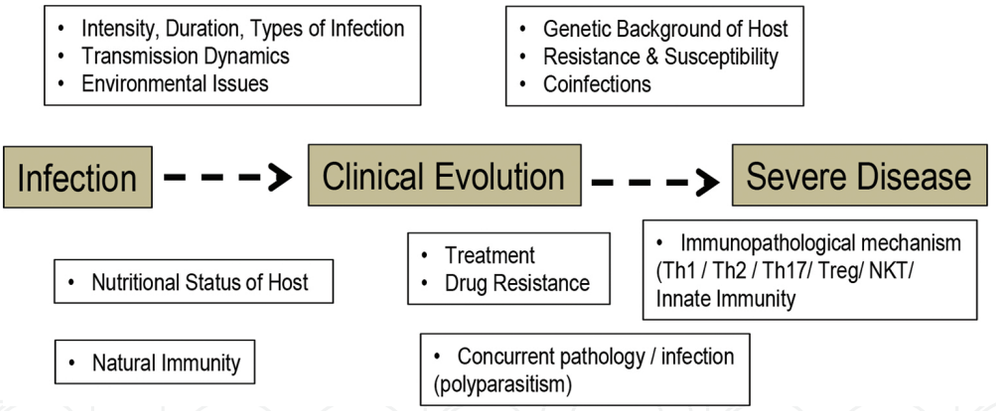

Figure 3. Indicating the contributing factors that drive one parasitic infection to clinical evolution and ultimately leading to severe diseases.

2.2. Soil-transmitted helminthiasis

Soil-transmitted helminthiases are nematodes transmitted from the soil to humans. These include hookworms (*Ancylostoms*), round worms (Ascaris *lumbricoides*) and whip worms (*Trichuris trichiura*). Like schistosomiasis, soil transmitted helminthes (STHs) are widely distributed in economically disadvantaged communities who do not have sanitary facilities [19]. The burden of the disease associated with STHs is enormous. Over two billion people are infected worldwide and 135,000 people die annually from STHs infection [2, 19]. Again like schistosomiasis, the most susceptible groups are primary and preschool-aged children (5–15

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years). About 400 million school age children worldwide are infected with STHs [3]. Hookworm infection is picked at the age of two years when children are frequently left to play on contaminated soil and infection increases with age, age range (5–15 years) being the most high-risk group [19, 20]. Hookworm infection causes iron-deficient anemia [21]. The intestinal stage hookworms feed on blood and cause further hemorrhage when they stop feeding because they release anticoagulant compounds. A single adult hookworm is estimated to cause a daily blood loss into the gut of from 0.03 to 0.15 ml [21, 22]. Intestinal stage hookworms change position every 4–6 h as they seek new sites for blood meal [23]. This mode of feeding is a major cause of morbidity in young children and pregnant women who have high demand of iron or are malnourished. Other effects of hookworm infection include itchy rash, cough, fever, bloody sputum, and loss of appetite, nausea, vomiting, diarrhea, abdominal discomfort, paleness, fatigue and blood in the stool [21].

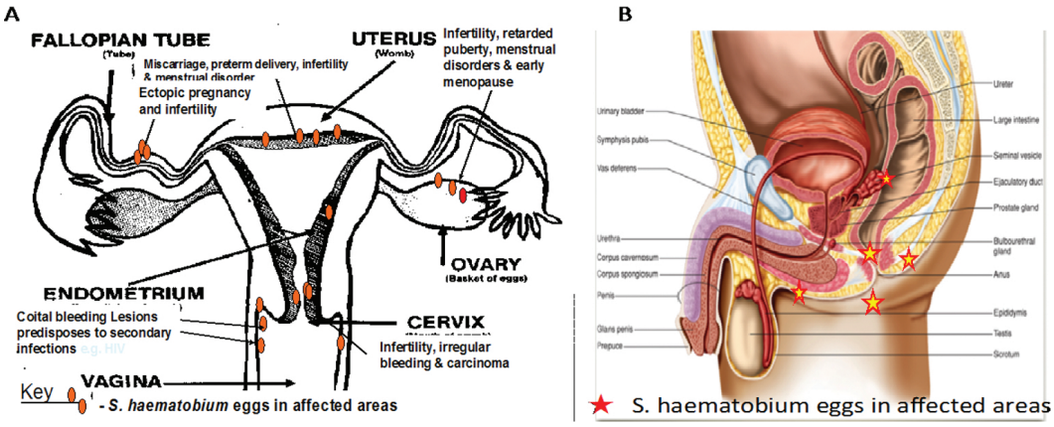

Figure 4. Illustration of the female (A) and male (B) genital schistosomiasis affected areas. The affected areas may facilitate easy transmission of HIV besides causing other reproductive complication leading to infertility.

Ascaris lumbricoides infection causes diarrhea, intestinal obstruction, reduced food intake, abdominal pains, impaired fat digestion and Vitamin A absorption (leading to nutritional deficiency). Infected children contaminate the soil by their indiscriminate defecation. Infection causes reduced appetite leading to malnutrition, which in turn result in reduced host immune resistance to other infections. Other effects include vomiting, jaundice, disturbed sleep, dry skin and pneumonitis during larval passage in lungs. *Trichuris trichiura* (whipworm) cause blood loss in the form of hemorrhage associated with trichuriasis dysentery syndrome or rectal prolapse [22]. More commonly blood loss is believed to be part of an exudation from the damaged epithelium and is proportional to parasite burden. Other effects of whipworm infection include: diarrhea and pain in the right lower abdomen, anemia secondary to blood loss and impaired learning (cognitive) ability [23]. Transmission of *Ascaris lumbricoides* and *Trichuris trichiura* is through oral fecal route by ingestion of infective eggs. Children who are most frequently exposed to contaminated soils are mostly infected than adults.

The conditions that support transmission of STH are similar to those favoring transmission of schistosomiasis (poor sanitation, contamination of the environment with human excreta,

poverty leading to lack of protective clothing and safe water supply). These conditions could create an overlap of epidemiological distribution of schistosomiasis and STHs in some regions. There is a high risk of morbidity exacerbation due to mixed infection from schistosomes and STHs. At least 50% of severely ill people due to worm infestation are school age children [19, 24], and infection from STHs and schistosomiasis represent more than 40% of the disease burden due to all tropical diseases, excluding malaria [25]. But these diseases are treatable. The public health significance of schistosomiasis and STH has triggered response from WHO, which in the 54.19th WHA 2001, demanded that all member state endemic to these NTDs should provide regular mass treatment to primary school children at risk of morbidity due to schistosomiasis and STH, with praziquantel and albendazole. There is a major shift in the policy for the control of Preventative Chemotherapeutic Treatment of NTDs to that of control/elimination [3].

2.3. Diagnosis

The standard diagnosis for schistosomiasis is detection of viable eggs in urine (*S. haematobium*), feces (*S. japonicum, S. mansoni*), or tissue biopsies. Currently, the presence of infecting schistosomes cannot be ruled out definitively if no ova are detected in urine or feces, because of the low sensitivity of the standard urine and fecal examinations [26]. Molecular techniques to detect schistosome DNA in fecal specimens have greater sensitivity than microscopy, but the techniques still suffer from sampling limitations because of the irregular distribution of eggs in the excreta. Schistosome DNA detection in serum or urine is being evaluated [27]. Serological assays have proven useful for diagnosis as the techniques detect schistosome-antigen–specific antibodies in symptomatic individuals. However, for individuals in endemic areas for schistosomiasis, the serology is unable to discriminate between active infection and past exposure. The main challenge of the serological assays is the inability to distinguish between past and current active infection. However, a negative test can rule out infection in endemic population, while another drawback is the test positivity over prolonged periods after therapy making the tests unreliable for post-treatment follow-up [27]. Better diagnostic tests for schistosomiasis are still needed for both in the field and in the clinic and new technologies are being studied. Advances for drug development is also essential for diseases elimination programs and vaccine assessment in which infection follow-up post-treatment must be accurately monitored over time. Currently, there is a lack of true gold standard for quantitative correlations to the actual worm burden [26]. An important public health aspect of monitoring control and elimination programs would be detection of schistosome infections in the snail host. Snail xenodiagnosis would enable the identification of environmental contamination especially during the control and elimination programs by the use of snails located at selected sentinel sites or assessing wild snails at common water contact sites [27]. The snail infections are usually detected by inducing cercarial shedding, while prepatent infections can be identified using histological examination of snail tissues and molecular parasitological techniques such as polymerase chain reaction (PCR) or loop-mediated isothermal amplification assays [28].

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2.4. Global control of helminthiasis

2.4.1. Vector control

The three major species of schistosomes that infect humans, *S. mansoni*, *S. haematobium* and *S. japonicum*, are transmitted by specific genera of snails; *Biomphalaria spp.*, *Bulinus spp*. and *Oncomelania spp*., respectively. Vector control has most commonly been done through the use of chemical molluscicides such as niclosamide [29]. The chemicals that kill snails are nonspecific and are also toxic for other aquatic life such as fish. Fish toxicity and yellowing of treated water by niclosamide decrease the acceptability of mollusciciding by the communities [30]. The chemicals are expensive, while they can rapidly be washed down streams following rains or diluted to nontoxic concentrations in larger water bodies, thereby demanding frequent reapplication. Furthermore, training for personnel who apply molluscicides is required who would understand the environmental conditions such as water hardness and temperature.

Indigenous plant extracts are an attractive alternative to chemicals for killing snails. These have low costs due to local availability and the extracts are less toxic to other forms of aquatic life [31]. The plant *Phytolacca dodecandra* has received some attention but has not been effectively employed for schistosomiasis control. The intervention requires community involvement that is dependent on participation rates that is affected by perceived importance of the intervention, the ability to observe impact or personal benefits and the degree of input the population has in designing the intervention [32]. Biological control is another approach to reducing snail populations and impacting transmission of schistosomiasis. Prawns and crawfish can be used to reduce snail populations, for example, *M. vollenhovenii* and *Procambarus clarkii* are voracious consumers of snails. Certain species of fish are also predators for the snails that transmit schistosomiasis. Cichlid populations are molluscivores that preferentially feed on *Bulinus spp*. compared to snails with thicker shells [33]. Other attempts to alter snail populations include environmental alterations such as removal of vegetation on which they feed, lining canals with cement or draining water bodies where they live [34]. Attempts to directly remove snails that included financial incentives for numbers of snails collected have been employed but with increased infection risk to persons doing the work [35]. The applicability and efficacy of this method in African settings is not appropriate. While in areas of high schistosomiasis transmission, it has been reported that the number of infected snails is usually low, suggesting that only a few infected snails maintain the life cycle [36]. Snails that are nonhosts for human schistosomiasis and compete with or predate on intermediate host snails can be used for control. Introduction of ampullarid (e.g., *Marisa cornuarietis*) or thiarid (e.g., *Melanoides tuberculata*) snails in endemic areas in the Caribbean region was reported to successfully displace populations of *Biomphalaria spp*. leading to reduction and interruption of *S. mansoni* of transmission [37].

2.4.2. Health education

Health education is an important component of effective schistosomiasis prevention and control. Developing health education programs requires that the design, administration and outcomes be adapted to different socioeconomic and cultural settings [38]. Several studies have

shown that the individual's behavioral changes facilitating disease prevention and control. Behavior cannot be changed simply with the acquisition of knowledge that can be obtained from health education [39]. Health education programs end up not successful when the socioeconomic and cultural context of communities is not considered. Individuals and communities have to be considered in full their environment and education when developing programs for the control of diseases in an area. The success of programs in reducing high-risk behavior and promoting health-enhancing behavior depends to a considerable degree on whether the life cycle and other biomedical concepts and information are presented in an appropriate, emotional, social, economic and cultural context of target populations. Consideration should be taken when people do not have the means for changing their behavior, for example, inadequate health services, no access to proper sanitation and clean water supply, unavailability of antihelminthic medications and unaffordability of modern treatment.

Observations were made in a longitudinal study conducted in Zimbabwe over 33 months in which parasitology follow-up examination and treatment was done every 6 months for the first year, then a break for almost 24 months. The reinfection was observed to take place in such an endemic setting rising to almost half the levels before treatment (**Figures 5A–D**). However, after a long break of 24 months, the prevalence was seen to rise to almost pretreatment levels, even though infection intensity was drastically reduced.

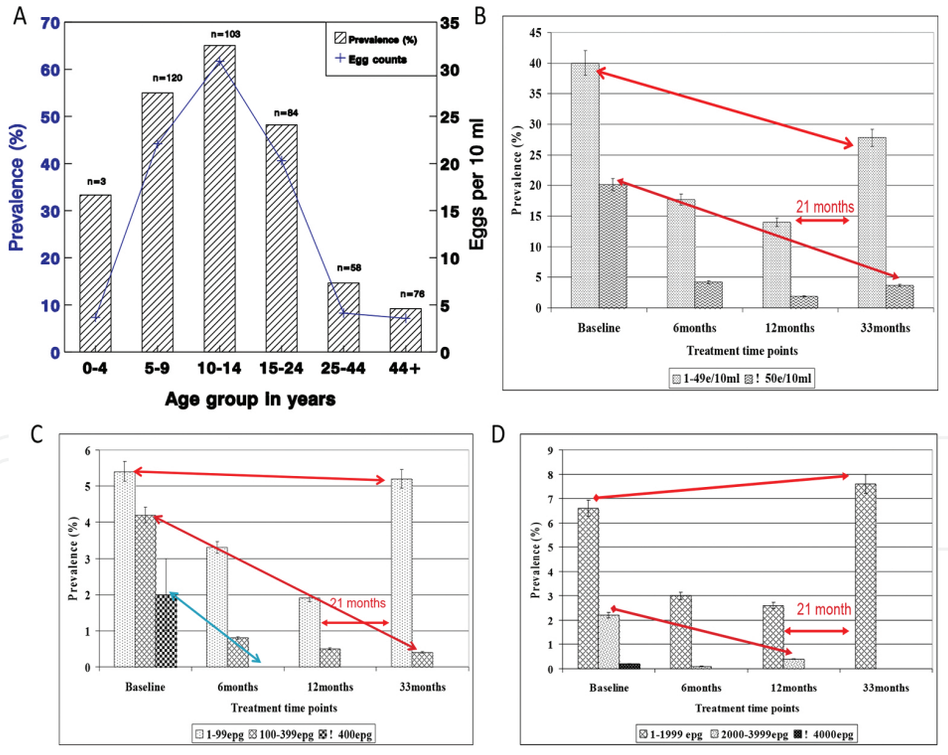

Figure 5. Showing a typical infection re-infection longitudinal study conducted in Zimbabwe at 6 monthly observations in the first year and then another examination after 24 months. **Panel A**: A typical age prevalence/egg intensity curve in a community before treatment. Showing a peak within the 10–14-year-old age group. **Panel B**: *S. haematobium*; **Panel C**: *S. mansoni* and **Panel D**: Soil-transmitted helminths; infection prevalence and intensity of infection with follow-up time point. Regular treatment was observed to be effective in prevention of heavy infections.

2.4.3. Vaccines

Despite several years of mass antiparasitic drug therapy programs and other control measures, helminthiasis still continues to exist. The discovery of a vaccine still remains a pipe dream for the control of human helminthiasis. A vaccine would contribute to the reduction of schistosomiasis morbidity through immune modulation leading to a decrease in parasite load and reduced egg production. A lot of research has been done with a view of controlling and preventing schistosomiasis. Researchers have focused on vaccines, host genetic predisposition, coinfections, autoimmunity and improved diagnostics for surveillance.

Several candidate human schistosomiasis vaccines are in different stages of preclinical and clinical development. The most eligible candidates are egg antigens and the schistosomula tegument membrane antigens (Sm 23, SmTSP-2 and Sm29) [40] of *S. haematobium* and *S. mansoni*. Two recombinant *S. mansoni* vaccines; *Sm*-TSP-2 and *Sm*-14 are being tested, while *Sm*p80 (calpain) is undergoing testing in nonhuman primates [40]. The *Sh*28GST, also known as Bilhvax is in advanced clinical development for *S. haematobium* infection. These vaccines were selected on the basis of their protective immunity in preclinical challenge models, through human immune-epidemiological studies or both [41]. The vaccine candidate development and evaluations are being advanced through collaboration of academic research institutions, nonprofit vaccine product development partnerships, biotechnology companies, and developing country vaccine manufacturers. The success in developing promising vaccine candidates has been possible from screening schistosome *OMICs* databases using DNA microarray profiling, proteomics, glycomics and immunomics [42] and the application of RNA interference (RNAi) technology that has allowed investigators to ascribe specific functions to the parasite molecules and the role in parasite survival [43]. A potential strategy that could accelerate the achievement of an effective vaccine would be the association of different recombinant antigens that previously resulted in partial protection or the use of pools of antigens known as multivalent or multiepitope vaccines [42].

The vaccine development strategies are bedeviled with many biological bottlenecks such as the lack of reliable surrogates of protection in humans; immune interactions in coinfections with other diseases in endemic areas; the potential risk of IgE responses to antigens in endemic populations; and paucity of appropriate vaccine efficacy studies in nonhuman primate models. Research is also needed on the role of modern adjuvants targeting specific parts of the innate immune system to tailor a potent and protective immune response for lead schistosome vaccine candidates with the long-term aim to achieve curative worm reduction [44].

3. Immunology

Immune responses during schistosomiasis can be considered in terms of three broad aspects of immunopathogenesis, resistance to reinfection and immunodiagnostics. The development and establishment of chronic infection is impacted by the presence of chronic antigenic exposure as illustrated in **Figure 2** and summarized in **Figure 3**. The immunological regulation associated with the morbidity of schistosomiasis has been studied without completely

understanding the impact [45, 46] of the immunological components involved that contribute to failure to design successful vaccines. However, the immune mechanisms related to resistance to reinfection and in response to candidate parasite antigens are not well defined. Adult worms are known to be refractory to immune attack; while immature and developing worms, skin-stage and lung-stage schistosomulae are the probable targets of protective immunity [46, 47] that are safe from drug effects. Whether a protective resistance to reinfection exists is still not well characterized and understood [47, 48], but evidence suggests that such resistance may develop rather slowly [46, 47]. The induction of protective immunity has been shown through immunization of various experimental hosts with irradiated cercariae to work for a short period of time. Data from endemic populations suggest that age-associated decreases in infection result from the development of antiparasite immunity, rather than reduced contact with water [24]. Although the responsible antigens and host immune responses are not fully defined, resistance to reinfection is believed to be associated with IgE antibodies against worm antigens, with low concentrations of IgG4 antibodies to worm antigens and high blood eosinophilia. Resistance to reinfection is partial, which means that protective sterile immunity either does not develop or is rare. Treatment of schistosomiasis increases common correlates of resistance: eosinophilia, parasite-specific IgE and interleukin 5 production in response to worm antigens, while repeated treatment to prevent reinfections can lead to longer intervals before reinfection, even accounting for similar exposure patterns in highly exposed participants [48].

3.1. Coinfections

Neglected tropical diseases are found in areas that have conducive environmental conditions. Schistosomiasis and soil-transmitted helminthiasis often occur alongside each other and with other tropical infectious diseases and with a wide range of coinfecting organisms. In addition to the direct morbidities, schistosomiasis can affect immunological and physiological responses of the host and the coinfecting pathogens. Thus, better control of schistosomiasis could provide adjunctive benefits towards other coinfecting organisms in such areas. The most studied and compelling example is the effect of schistosomiasis on susceptibility to HIV infection. Among women with female genital schistosomiasis, the inflammation of the genital epithelial tissue can lead to a compromised physical barrier to exposure to HIV through sexual activity. In population-based studies, female genital schistosomiasis has been associated with a three to four times increased risk of HIV infection [10–12, 16, 17, 49].

Schistosomiasis alters immune responses directed towards coinfecting pathogens, allergens or vaccines. The immunoregulatory responses during schistosome infection could downregulate T-helper type-1 immune response associated with the control of viral or protozoan infections or interfere with immunization generally made available to children living in affected tropical areas. In one of many studies of schistosomiasis and malaria coinfections it seems to indicate that schistosomiasis modulates malaria; however, studies have yielded conflicting results [50–54]. In some cases, malaria prevalence, anemia and pathological effects are higher in children with schistosomiasis than in children without schistosomiasis, whereas antimalarial immune responses are diminished [51]. However, other studies report no protec-

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tive effect of schistosome infection on malaria that can be accompanied by increased immune responses [53, 54]. Schistosome and malaria-related antigens can cross react to some extent, further complicating the situation. However, within the host there is need for a delicate but subtle interplay between pro- and anti-inflammatory cytokines that play a major controlling effector role on the antibody production and the cell-mediated antibody dependent cytotoxicity (**Figure 6A** and **B**).

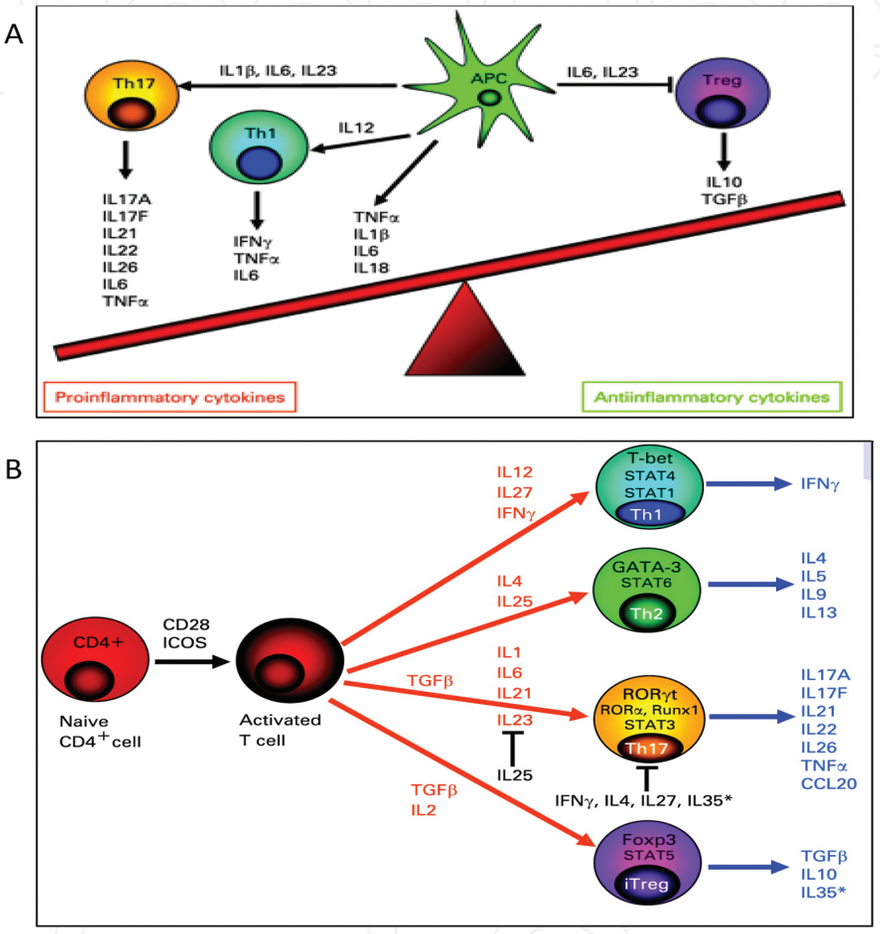

Figure 6. Plate A, Pro- and anti-inflammatory cytokines involved in a delicate balances that play an important role in down regulating deleterious effector response to helminthiasis invasion. **Plate B**, Illustrating the key T-helper subsets that are important in helminthiasis infections, control and regulation to avoid development of immunopathology.

3.2. Host immunogenetics

The development of genetic epidemiology methods using recent human genetic mapping information has led to major advances in the identification of host genes in human schistosomiasis and other infections [55]. Determining the role of host genetics in schistosomiasis is complicated by the numerous parasite and environmental factors involved in transmission. Two immunological and pathological phenotypes have been studied so far as schistosomiasis infection levels on the host-parasite as consequences measured by the fecal egg counts and the severe hepatic fibrosis assessed by ultrasound examination. The first study was performed on

Brazilian pedigrees and provided strong evidence for a major gene controlling infection levels by *S. mansoni* denoted as SM1, which was mapped to chromosome 5q31-q33 [55]. This region contains several candidate genes involved in the regulation of the Th1/Th2 responses. The direct role of cytokine polymorphisms located within these genes further elucidation. Another study conducted in Sudan showed the presence of a major gene influencing the development of severe hepatic fibrosis during *S. mansoni* infection denoted as SM2. This gene is located on chromosome 6q22-q23 and is closely linked to the IFN-gamma receptor 1 gene encoding the receptor of the strongly antifibrogenic cytokine interferon-gamma. There is also evidence for the genetic control of pathology due to *S. mansoni*, where the linkage is reported on a region containing the gene for the interferon-gamma receptor 1 subunit. Numerous association studies have also provided evidence for major histocompatibility complex control of pathology in schistosomiasis through cytokine polymorphisms [55–57]. Host immunogenetics is important in driving the host immune effector mechanisms such that cytokine polymorphisms may be crucial in the expression of resistance or susceptibility to a host of infections [57, 58]. Any impact on the underlying immune genetics (**Figure 7**), would impact the cytokines expression and antibody production [58].

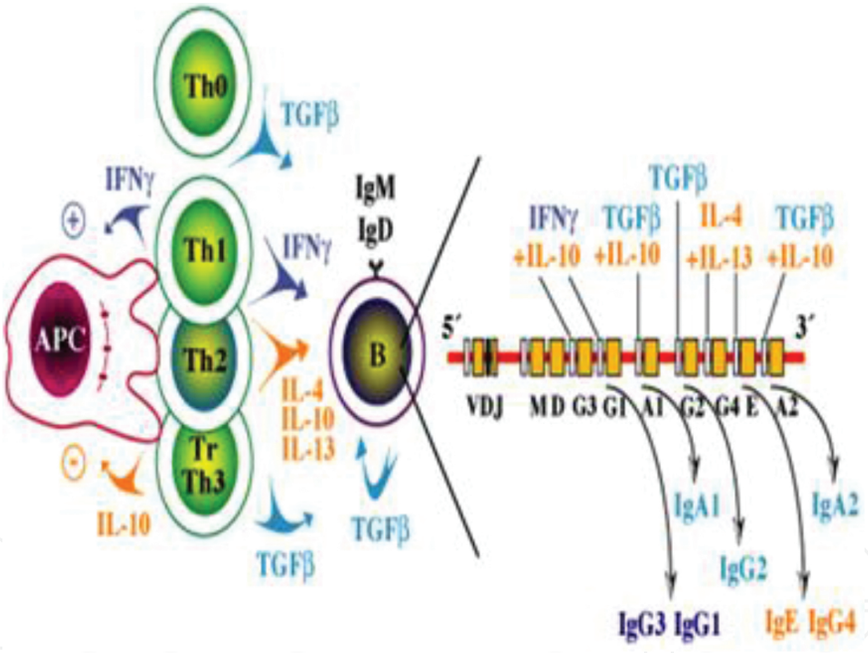

Figure 7. Showing the link of the antigen presentation to the T-helper cell subsets including T-regulatory cells. The T-helper cells produce a barrage of cytokines that selectively influence B cells at gene level to class switch antibody production leading to the synthesis of either protective or blocking antibodies [58].

4. Mass drug administration (MDA)

Mass drug administrations (MDA) in affected populations or communities form the basis of current schistosomiasis and soil-transmitted helminthiasis (STH) control and/or management.

The MDAs can follow one or more of the following approaches; house-to-house administrations (i.e., mobile teams), booth distribution (i.e., fixed teams), administering drugs in special population groups (e.g., school age children, etc.) and/or areas of community gatherings (e.g., marketplaces, stations, etc.) [2]. Such chemotherapeutic prevention and management strategies of infectious diseases in endemic areas have some significant shortcomings, chief among them being re-infections [59, 60], due to untreated human and animal reservoirs. Prophylactic measures in these areas are difficult as that would mean people will have to take the medicines frequently for life, thus exposing them to potential life-threatening adverse drug events and development of drug resistance. In endemic areas during a five-year round of annual mass treatment of school going age children, before and post-treatment checks revealed that re-infection always takes place (**Figure 5**). Reinfections were most common in cases where MDA was not accompanied with adequate environmental and health promotion/education interventions. Successful MDA in endemic areas has to be conducted in all age groups. For better coverage, the World Health Organization recommends the utilization of all available medicine distribution channels especially in countries with high levels of infections [60–64].

Repeated MDAs have helped some countries to significantly reduce the disease burden. An example is the 84% reduction of baseline levels of schistosomiasis in a moderately highly endemic region of the northeast of Sierra Leone, with MDA interventions repeated yearly over three years [61]. Communities in Zanzibar, Tanzania also recorded significant reductions in infections levels of soil-transmitted helminthiasis (90–98%) and scabies (68–98%) as additional benefits associated with the annual mass drug administration of ivermectin and albendazole for lymphatic filariasis. Modeling done by Anderson *et al*. [62] noted that it was possible to even eliminate *S. mansoni* by WHO's MDA guidelines at least in areas with lower transmission levels if high coverage is attained and maintained beyond above 75% coverage [64]. The noted disease burden reductions also have positive impact on morbidities and comorbidities like anemia, malaria and HIV [49, 64].

Despite significant contributions, great optimism and positive outlook; MDA may not lead to total elimination on its own [63]. There is a great need for critical assessments of all MDAs for more positive effects to be realized. Significant community effectiveness of MDA programs stand challenged by issues around; very low coverage (<75%) as about a third of those that really require treatment and/or chemoprophylaxis are receiving it [64, 65]; the utilization of volunteers and/or underpaid workers to distribute or administer medicines; overly relying on fragile healthcare systems in marginalized communities or countries; lack of health and/or pharmacoeconomic evaluations; sustainability questions associated with all chemo-prophylaxis interventions; belief systems, socioeconomic status and general community acceptance; lack of evidence of wider safety and effectiveness of medicines involved in different communities and fears of exerting unnecessary selection pressure, thus promoting drug resistance [63–65]. Despite the noted negative concerns, MDA remain popular in the prevention and/or management of schistosomiasis and soil transmitted helminthiasis. As highlighted above WHO suggests ways by which wider coverage can be attained like utilization of all available medicine distribution channels. Also because in almost all affected and/or poor countries developmental partners and international pharmaceutical companies finance the MDAs, as

such the programs remain cost-effective at least from a governmental perspective of pharmacoeconomic evaluations. Issues to do with community acceptance may be addressed by adequate promotional and/or educational programs to clearly explain the aims and objectives of each MDA intervention. Critical evaluation of each MDA intervention on issues to do with safety, drug effectiveness, cost-effectiveness/benefit, sustainability and political will positively feed into the subsequent interventions.

4.1. Helminthiasis management

For schistosomiasis, WHO recommends praziquantel with doses of 40–60 mg/kg body weight in one and/or 2–3 divided dose(s). Praziquantel is effective against all five important species of schistosomes, that is, *Schistosoma mansoni, S. haematobium, S. japonicum, S. intercalatum* and *S. mekongi*. Praziquantel 'the first antihelminthic drug to fulfill the World Health Organization's requirements for population-based chemotherapy of a broad range of parasitic infections' is also effective against clonorchiasis, opisthorchiasis, paragonimiasis, taeniasis and intestinal trematodiases. Other drugs with recognizable effectiveness against schistosomiasis are metrifonate and oxamniquine. Metrifonate is an organophosphate cholinesterase inhibitor thus it has significant safety issues. Oxamniquine has a complicated manufacturing process, which drives manufacturing cost up [65]. Thus, oxamniquine costs way more than praziquantel, making it unfavorable for wider mass usage. Praziquantel was demonstrated to be way more effective as compared to oxamniquine, when used in a controlled trial cure rate for praziquantel was high (96.1%) while that of oxamniquine was low (42.4%) [66]. Praziquantel remains the first and only choice in all cases of schistosomiasis owing to its low cost, high efficacy, low toxicity and ease of administration. The acceptable attribute is mostly single oral doses that enhances compliance.

The mechanism of action of praziquantel is thought to involve the increased permeability to Ca^{2+} ions leading to uncontrollable contractions, paralysis and death of the worm. It is also suggested that it leads to vacuolation and blebbing of worm tegumental and subtegumental structures in adults but not juveniles worms [67, 68]. This leads to the exposure of surface antigens to host immune system thus Facilitating immune recognition and clearance of the worm [67]. The drug effect may be explained due to relative differences in sensitivities observed in some settings between adult and juvenile worms [67]. Praziquantel is well absorbed orally (80%), is subjected to first pass effect, metabolized by the liver and excreted via the kidneys [19]. Microsomal enzymes inducers like rifampicin interfere negatively with praziquantel efficacy as they lead to lower than minimum effective concentration of praziquantel in the blood. On the other hand, CYP450 inhibitors like cimetidine, ketoconazole, grape juice, etc. may lead to higher than normal blood levels. It is contraindicated in patients with history of epilepsy and those hypersensitive to it. Operation of machinery or driving by individual after intake is not recommended. There is no evidence linking praziquantel to mutagenesis or harmful effects to fetuses. But as a general rule drugs are best avoided in the first trimester and used during the rest of pregnancy when benefits outweighs risks [19]. The usual mild side effects of praziquantel which generally do not require treatment are malaise, headache, dizziness, abdominal discomfort with or without nausea and/or vomiting, fever and

urticarial. Some of these side effects may be altogether the effects of schistosomiasis. These and other side effects may be worse in patients with high worm burden. Resistance to praziquantel by schistosomes has not been reported as yet, as there are no substantiated clinical findings. Reports of resistance are usually misrepresentations of issues like noncompliance or very transient biological phenomena or effects [67, 68].

4.1.1. Management of soil-transmitted helminthiasis

In the management of STH, the WHO recommends any of the following drugs: albendazole (dose of 400 mg); mebendazole (dose of 500 mg); levamisole (dose of 2.5 $mgkg^{-1}$) and pyrantel (dose of 10 $mgkg^{-1}$). These drugs are effective against many helminthic infections, for example ascariasis, hookworms, lymphatic filariasis, trichuriasis, strongyloidiasis, zoonotic ancylostomiasis, enterobiasis, among others. Benzimidazoles (i.e., albendazole and mebendazole) are the mostly commonly used [58, 65] in the management of STHs owing to their efficacy, wider spectrum, safety and availability. Benzimidazoles are thought work through inhibiting tubulin polymerisation. Absorption of albendazole is usually very low and the absorbed is subjected to significant first pass effect by the liver. Mebendazole is absorbed almost fourfold better than albendazole, but the rest are similar. May cause bone marrow suppression if taken for a considerable long period as in hydatid disease management were the patient takes three 28 day cycles with 14 day breaks of albendazole. Benzimidazoles are best avoided in pregnancy especially during the first trimester unless good clinical advice benefits outweigh risks [19]. Without having the pharmacokinetic properties changed, praziquantel increases plasma concentration and area under the curve of albendazole sulfoxide (the most active metabolite) by about 50% in healthy subjects. This might be beneficial in coadministration as in MDAs, but also may lead to more side/adverse effects. Side/adverse effects of albendazole depending on the duration of therapy may include, abdominal pain, nausea and vomiting, fever, elevated hepatic enzymes, dizziness, headache, meningeal signs, raised intracranial pressure and vertigo hypersensitivity

Benzimidazoles are active against *Ascaris lumbricoides, Enterobius vermicularis, Necator americanus, Ancylostoma duodenale*, Trichuriasis, Strongyloidiasis, *Trichinella spiralis*, neurocysticercosis, cystic hydatid disease and microspiridiosis. Resistance to albendazole though rare occurs through alteration of the target site. The other drugs highlighted above are better reserved for drug-resistant worms. Levamisole is now in most guidelines reserved for veterinary use. Also, pyrantel has an inferior effective profile as compared to benzimidazoles. For long-term solutions, there is a need to combine MDA with various other strategies like improving the quality of the water supply, sanitation and hygiene, education and health promotion and intensify the search for vaccine development. Levamisole and pyrantel are not widely used, but since they are not in the same class as albendazole and mebendazole, they are usually reserved for drug-resistant forms of STHs. Thus, MDAs with praziquantel and a benzimidazole have a wide spectrum covering against important helminths. Coadministration has additional benefits that can be realized if regular MDAs are done in affected communities.

4.1.2. Safety of combining praziquantel and benzimidazoles

High safety profile has been observed, in a safety study of praziquantel – albendazole combined treatment of hydatidosis, which require a way more prolonged duration than schistosomiasis and/or STHs [69]. The mild side effects noted were not so different from when monotherapies were used and were transient, disappearing when treatment was withdrawn [69]. There may be need for more evaluations of the severity of side and/or adverse-effects versus worm burden, when worms are localized in the central nervous system and/or in eyes.

4.2. New chemotherapeutic avenues

Mathematical models suggest significant drug resistance by the helminths to current therapies in the new future [70], the need for new, safer and more effective drugs is apparent. It has been demonstrated that the use of praziquantel and other drugs may enhance the antischistosomal activity. An example of such drugs is lovastatin [65] (a hypolipidemic agent). Benzodiazepines such as clonazepam are known to have the ability to paralyze adult schistosomes (both males and females) and interfere with egg release [65]. Other promising molecules with antischistosomal activities are the artemisinins and related 1,2,4-trioxolanes [68]. Praziquantel and artemisinin derivatives combined offers better protection [69] and/or cure rates. Though not 100% effective, MDAs based on WHO guidelines are very important in the fight against many parasitic neglected tropical diseases like schistosomiasis and soil transmitted helminthiasis. MDAs has actually more benefits due to the wider spectrum of both praziquantel and albendazole/mebendazole, as the administration will cover other parasitic infections within targeted communities. Effectiveness is significantly improved if chemoprophylaxis is done together with education and promotion of hygiene and the use of safe water. While praziquantel and albendazole/mebendazole are very effective there is still need to develop new better pharmaceuticals and pursue other avenues like vaccines.

4.3. Schistosomiasis control and elimination: research priorities and capacity building needs

The WHO/TDR Special Program for Research and Training in Tropical Diseases convened diseases reference groups to examine and set research priorities for the neglected tropical diseases. The following research priorities were made: (i) to optimize existing intervention tools so as to maximize impact and sustainability, (ii) to develop novel control tools that will improve impact and sustainability, (iii) to improve diagnostic tests with good sensitivity, specificity, multiplex capacity, and ability to measure infection intensity, and detect drug resistance; especially useful at the current preventive treatment control initiative in which reinfection would be very low. There is also need (iv) to standardize and validate methodologies and cost effective protocols for diagnosis in monitoring and evaluation settings, (v) to develop delivery strategies of multiple interventions to maximize sustainability of control program and integrated neglected tropical diseases control. Recommendation also included the need to develop strategies to increase awareness of ill-health processes, community participation, ownership and empowerment, as well as equity in access to preventive chemotherapeutic control interventions. The application of epidemiological models is required to help monitoring of intervention efficacy including drug resistance tracing. Further to develop

new tools for parasite functional genomics in key species, this is believed to assist in vaccine development. A comprehensive research agenda need to be developed from basic sciences to emphasize implementation research and to ensure that control program could be implemented and evaluated based on rigorous scientific evidence. New tools, policies and strategies would lead to strengthened control programs that aim at disease elimination or eradication, where feasible.

4.4. Progress of schistosomiasis preventive chemotherapy in the African region: challenges and research needs

The African region has the highest burden of schistosomiasis, with 4 intermediate host species, endemic in 43 countries. According to WHO statistics at least 220 million people may have schistosomiasis infections. Ten sub-Saharan countries account for more than 70% of the global number of people requiring preventive chemotherapy for schistosomiasis. Prevalence of infection and morbidity are high in school-age children, but high prevalence has also been documented in children less than 5 years of age [71, 72]. The African region has adopted and recommends a comprehensive control strategy for schistosomiasis that includes preventive chemotherapy, health education, access clean water, sanitation and environmental control. These strategies, if implemented vigorously, would lead to the reduction of morbidity and possibly interruption of transmission. However treatment coverage is low in the region and many countries are not yet mapped. Scaling up to reach at least 75% of children is still a challenge because of access to praziquantel. Treatment of pre-school children is also limited by the lack of a pediatric formulation [52].

Research priorities for schistosomiasis control and elimination in endemic region include, better understanding of the epidemiology and surveillance of infections, implementation research, environmental and social ecology, better use of data and modeling and the basic biology of transmission and snail dynamics [73]. These priorities can only be met through widespread capacity strengthening and collaborative partnerships, transparent interactions between researchers and disease control program managers, learning from areas that have successfully controlled and have experience in research and control of schistosomiasis, for example, China, including intersectorial collaboration and technology transfer and political commitment and funding for disease control and research in each affected country. Conduct of the required research should also be done so as to increase capacity for advanced research as well as to improve disease control. Capacity strengthening should provide personnel able to address gaps from the laboratory to the field, and with skills to properly evaluate interventions, model likely progression and scenarios and quantify impacts of the control program. For schistosomiasis control and elimination, it will be important to rebuild capacity for malacology, which was not stressed when preventive chemotherapy was the main operational component. Other aspects to be strengthened are drug efficacy monitoring, and pharmacovigilance.

4.5. Monitoring and evaluation towards the elimination of schistosomiasis

Monitoring and evaluation (M&E) is a process that helps to improve performance and achieve planned targets. The goal should be to improve current and future management of out-

puts, outcomes and impact. The results of M&E should help control programs, governments and development partners assess the performance and progress towards schistosomiasis control and elimination. These processes should also document past and current interventions, as well as for planning future activities. Monitoring should be incorporated and implemented from the planning stage of a program as a periodic and recurring task. Documenting results, processes and experiences should steer decision-making and learning processes. Monitoring checks progress against plans. The data acquired through monitoring is used for evaluation.

Evaluations should help to draw conclusions about efficiency, effectiveness, impact, relevance and sustainability of the interventions. The process consolidates information and allows program managers to learn from each other's experiences, building on expertise and knowledge; generates reports that contribute to transparency and accountability of donated resources. Evaluation may reveal errors and offers alternative ways for improvements. Evaluation documentation provides means by which agencies consolidate and learn from their experiences making policy to guide control and monitoring activities. Evaluations also provide ways to assess the success of the program and the relationship between implementers, decision makers and beneficiaries. Evaluation results provide evidence for raising funds, influencing policy and tracking the success of the program. The assessments of activities depend to a large extent on the manner in which monitoring and evaluation is recommended. Assessment of performance is necessary to select indicators that permit rating of the targeted outputs and outcomes before the implementation of the project.

Parasitological indicators: This aspect using parasitology to determine number of people screened for infection, number of people positive, number of people requiring preventive chemotherapy, number of people treated and the positive numbers to be treated.

Malacological indicators: The indicators here show the number of areas that need survey, the number of areas that are high transmission, the number of areas that need molluscicides/snail control and the number of areas that have been treated/modified.

There should be indicators for other interventions such as health education, water supply and sanitation. Evaluation should inform whether planned tasks are completed or on-going. Quality control and effectiveness of all interventions should be assured.

5. Concluding remarks: mass drug administration for the control of helminthiasis

Tropical and subtropical areas have conducive environment for the flourishing of helminthiasis; these include appropriate temperature, wet and humid soils, abundant fresh flowing river waters and the human factor that continuously contaminates their environment and maintains the life cycle of the parasites. Vaccines are still a long way to be developed since we lack complete understanding of the host-parasite relationship. Host-parasite effects have been observed those leading into severe pathology, in some instances, during the

parasite colonization. The effects of helminthiasis are so diverse affecting the health of the host resulting in poor cognitive in school children, affecting reproductive health in child-bearing age and reduced work output in economically engaged workforce. The current control strategy is by removing the infection using preventive chemotherapy, ultimately anticipating cutting the life cycle of helminthiasis after several rounds of treatment using mass drug administration. While controlling the life cycle by treatment, much effort should be invested in health education to reduce contamination of the environment. The overall control strategies required should include health education, water and sanitation development, selective chemotherapy, snail control and passive treatment of cases. The options for consideration of water and sanitation development remain a major challenge since this is grossly neglected in most developing areas that are resource limited. While additional environmental and engineering measures for irrigation schemes particularly the small scale irrigation currently being developed require incorporation of the helminthiasis control strategy right from the onset of program development. Use of indigenous and locally available resources in vector control should be included in health education and basic health delivery services (e.g., plant molluscicide — *Phytolacca dodecandra)*. This can be grown as homestead or garden hedge whose berries can be crushed for local application at water contact sites for the control of snail vectors. Concerted efforts from all partners in human development need to be involved in the control of helminthiasis. Partnerships with other sectors in the farming, irrigation, health education and mining is required for the common goal to develop and improve human living standards in an effort to control helminthiasis from all angles.

Finally, recommendations are made for comprehensive, integrated and through multi-disciplinary intervention strategies that include preventive chemotherapy, environmental management, water conservancy, water supply and sanitation development in affected areas and snail control using locally available resources. Such strategies should be evidence-based from research component incorporated in the control activities and use of the most up to date technologies and tools in control. Collaboration would be a platform for capacity strengthening, technology transfer and expertise for the elimination of schistosomiasis from Africa. Above all there is need to obtain government political will for support and sustainability of the programs.

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